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$TiCl_3$-Mediated Reductive Cyclization of Tetrasubstituted Alkenes and Enol Esters Bearing a 2-Nitrophenyl Substituent

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par

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To my beloved parents...

« Dans la vie il faut oser, si tu n'oses pas – on va jamais savoir »

Mike Horn

"There is no shame in not knowing; the shame lies in not finding out"

Russian Proverb

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find this equilibrium to work for 200% but also have this French "joie de vivre"^^. You are such amazing friends, and I am so happy to know you and spend a few years together! Without you, LSPN wouldn't be the same; thank you for everything! I would like to also thank Claire for all our great discussions and support, I wish you a great future, you deserve it and you will manage it, gros bisous!!

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My dear brother, I know that when I left for France, it was hard for you, but believe me, it was hard for me as well, and you are my second half! You will always be number one in my life, even if I am far. You are the best present our parents ever gave me; I love you so much. I hope that soon you will join me, and we will make a great future as we dream; I am always there for you! My dear sister, we are pretty different, but as we get older, our connection becomes more profound, making me so happy. Thank you for being my older sister; you are the best! I hope you know that I love you a lot!

My dear mama and papa, as French would say: ça y est, I am finally crying writing these lines. You are my strength and my weakness. Everything I made in my live I owe to you. The distance that separates us, is so hard and cruel, but you are always in my thoughts and my heart, I am sure that you know how much I love you! Thank you for all the opportunities you gave to me, for your love and support, I hope to make you proud and happy! My biggest dream is to be reunited and we will manage it.

Abstract

Indole is one of the most important heterocycles widely present in bioactive natural products, pharmaceuticals, agrochemicals and materials. Being easily accessible, the 2-nitrostyrenes are attractive starting materials for the indole synthesis and the Cadogan-Sundberg reaction is one of the well-established methods exploiting the reductive cyclization of 2-nitrostyrene derivatives. The harsh reaction conditions associated with this named reaction [reflux in $P(OEt)_3$] limited, nevertheless, its synthetic applications. Consequently, alternative conditions combining different transition metal catalysts with a terminal reductant have been developed. Recently, our group demonstrated that aqueous $TiCl_3$ is a mild reductant capable of promoting the reductive cyclization of 2-nitrostyrene derivatives at room temperature leading to diversely substituted indoles or indolenines. The reaction was featured in the total synthesis of complex natural products such as (+)-1,2-dehydroaspidospermidine, (+)-condyfoline and (−)-tubifoline.

This thesis focuses on the development of $TiCl_3$-promoted reductive cyclization of previously unexploited substrates for the synthesis of important heterocycles and their applications in natural product synthesis.

In chapter 2, we describe a novel synthesis of 3-acyloxy-2,3-disubstituted indolenines *via* $TiCl_3$-mediated reductive cyclization of trisubstituted enol esters bearing a 2-nitrostyrene substituent. Mechanistically, a domino process involving a partial reduction of the nitro to nitroso group followed by a 5-center-6π-electrocyclization, 1,2-acyloxy migration and further reduction of the resulting nitrone intermediate accounts for the reaction outcome. This operationally simple reaction (aqueous $TiCl_3$ solution, MeCN, 0 °C to room temperature) tolerates a wide range of functional groups affording 3-acyloxy-2,3-disubstituted indolenines in good to high yields. Conceptually, this important heterocycle is accessed for the first time under reductive conditions.

Chapter 3 details our approach towards the total synthesis of trigonoliimine C, a pentacyclic bisindole alkaloid, featuring the reductive cyclization of enol esters as a key step. The requisite enol ester was synthesized following a two steps procedure: a) Ketone synthesis *via* the Liebeskind-Srogl coupling between *N*,*N*'-diBoc-2-tributylstannyltryptophane and *S*-phenyl 2-benzyloxyethyl-2-(4-bromo-2-nitro)phenyl acetylthioate; b) Enol ester formation by treatment of the ketone with LiHMDS at −78 °C followed by addition of anhydride. However, all attempts to generate the 3-acyloxy-2,3-disubstituted indolenines met with failure at the present stage of development.

Benzofuro[3,2-*b*]indoline is a key structural motif found in the natural product - phalarine. It is synthetically much more difficult to access than its isomer, the benzofuro[2,3-*b*]indoline. The few existing methods suffer from the low regioselectivity in the oxidative coupling of two selected building blocks. We describe in Chapter 4 a $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkenes bearing a 2-nitrophenyl substituent and a properly tethered nucleophile. The starting materials were prepared *via* a key Suzuki-Miyaura cross couping of tosyl enol ester with aryl boronic acid based on Gosselin's report. Treatment of a MeCN solution of tetrasubstituted alkenes with aqueous $TiCl_3$ and NH_4OAc afforded the desired (benzo)furo[3,2-*b*]indolines in good to high yield with excellent regioselectivities. Total synthesis of phalarine featuring this novel reductive cyclization methodology was exploited and is being pursued in our laboratory.

Keywords: Reduction, Nitro-group, Cadogan, Sundberg, Indole, Titanium, 3-Acyloxy-2,3-disubstituted indolenines, Furo[3,2-*b*]indolines, Trigonoliimine C, Phalarine

Zusammenfassung

Indole sind unter den wichtigsten Heterocyclen und in den Gebieten der bioaktiven Naturstoffe, Pharmazeutika, Agrochemikalien und Materialien weit verbreitet. Die einfach zu erhaltenen 2-Nitrostyrene sind attraktive Startmaterialien für die Indolsynthese, und die Cadogan-Sundberg Reaktion eine der gängigen Methoden, die reduktive Cyclisierung von 2-Nitrostyrenen ausnutzt. Die harschen Bedingungen der genannten Rektion – Reflux in $P(OEt)_3$ – limitierten stets deren synthetischen Nutzen. Aus diesem Grund wurden alternative Bedingungen, die verschiedene Übergangsmetalle zur Katalyse nutzen, und auch ein Reduktionsmittel involvieren, für diese Namensreaktion entwickelt. Neulich demonstrierte unsere Gruppe, dass wässriges $TiCl_3$ ein mildes Reduktionsmittel ist, welches die reduktive Cyclisierung von 2-Nitrostyrenderivaten bei Raumtemperatur vorantreiben kann, und letztlich zu divers substituierten Indolen und Indoleninen führt. Diese Reaktion findet ihren Nutzen in der Totalsynthese von Naturprodukten wie (+)-1,2-Dehydroaspidospermidine, (+)-Condyfoline und (−)-Tubifoline.

Diese Thesis ist auf die Entwicklung von $TiCl_3$-mediierten reduktive Cyclisierungen von vormals nicht berücksichtigten Substraten für die Synthese wichtiger Heterocyclen und deren Anwendung in der Naturstoffsynthese fokussiert.

Im zweiten Kapitel beschreiben wir die neue Synthese von 3-acyloxy-2,3-disubstituierten Indoleninen *via* einer $TiCl_3$-mediierten reduktiven Cyclisierung von trisubstituierten Enol estern, welche eine 2-Nitrostyrenesubstitution tragen. Der Mechanismus beinhaltet einen Dominoprozess mit partieller Reduktion der Nitrogruppe zu einer Nitrosofunktion, auf was eine 5-Zenter-6π-Electrocyclisierung, 1,2-Acyloxymigration und schließlich eine weitere Reduktion des Nitronintermediates folgt. Dadurch entsteht dann das finale Produkt. Von der Handhabung ist diese Technik relativ simpel (wässriges $TiCl_3$, MeCN und 0 °C bis Raumtemperatur), während sie eine weite Spanne von funktionellen Gruppen toleriert, und 3-acyloxy-2,3-disubstituierte Indolenine in guten Ausbeuten liefert. Das Konzept besticht, da es die erstmalige Erschließung dieses Heterocycluses unter reduktiven Bedingungen ermöglicht.

Kapitel drei präsentiert unseren Ansatz in Richtung der Totalsynthese von Trigonoliimin C – ein pentabicyclisches Bisindolalkaloid, welches die reduktive Cyclisierung von Enol estern als Schlüsselschritt in seiner Synthese einschließt. Die benötigten Ester wurden in den zwei folgenden Schritten gemacht. A) Ketonsynthese *via* der Liebeskind-Srogl Kupplung zwischen *N*,*N*'-DiBoc-2-tributylstannyltryptophan und *S*-Phenyl 2-benzyloxyethyl-2-(4-bromo-2-nitro)phenyl acetylthioat; B) Enolesterbildung durch Behandlung des Ketons mit LiHMDS bei –78 °C, gefolgt von der Addition von Anhydrid. Leider waren die bisherigen Versuche 3-acyloxy-2,3-disubstituierte Indolenine zu erzeugen allerdings bis zum jetzigen Zeitpunkt nicht erfolgreich.

Benzofuro[3,2-*b*]indolin ist eine Schlüsselunterstruktur, welche in Phalarin gefunden wird. Synthetisch ist diese viel schwerer als ihr korrespondierendes Isomer – das Benzofuro[3,2-*b*]indolin – zu erhalten. Die weniger, existierenden Methoden leiden an geringer Regioselektivität in der oxidativen Kupplung der zwei selektierten Bausteine. In Kapitel 4 beschreiben wir eine $TiCl_3$-mediierte reduktive Cyclisierung von tetrasubstituierten Alkenen, welche einen 2-Nitrophenyl Substituenten und ein angehangenes Nucleophil tragen. Die Startmaterialien wurden über eine Suzuki-Miyaura Kreuzkupplung von Tosylenolestern mit Arylboronsäure gemacht , wie es in Gosselins Bericht vermerkt ist. Behandlung einer MeCN-Lösung von tetrasubstituierten Alkenen mit wässrigem $TiCl_3$ und NH_4OAc brachte das gewünschte (Benzo)furo[3,2-

b]indolin dann in hoher Ausbeute und exzellenter Regioselektivität. Die Totalsynthese von Phalarin wurde mit dieser neuen Methodologie der reduktiven Cyclisierung geprobt und wird in diesem Augenblick in unserem Labor weiterverfolgt.

Stichworte: Reduktion, Nitrogruppe, Cadogan, Sundberg, Indol, Titan, 3-acyloxy-2,3-disubstituierte Indolenine, Furo[3,2-*b*]indoline, Trigonoliimin C, Phalarin

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List of Abbreviations

Ac	Acetyl
Alk	Alkyl
Ar	Aryl
aq	Aqueous
BINOL	1,1′-Bi(2-naphthol)
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
Bu	Butyl
Bz	Benzoyl
°C	Degree Celsius
c	Concentration
Cbz	Carboxybenzyl
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DBED	*N*,*N*′-Dibenzylethylenediamine
DBU	1,8-Diazabicycloundec-7-ene
1,2-DCE	1,2-Dichloroethane
DCC	N,N'-Dicyclohexylcarbodiimide
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-p-benzoquinone
DFT	Density functional theory
DIAD	Diisopropyl azodicarboxylate
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-Dimethylamino pyridine
DMEA	*N*,*N*-Dimethylethylamine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPP	Diphenylphosphinate
dr	Diastereomeric ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDG	Electron donating group
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
equiv	Equivalent
er	Enantiomeric ratio
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HFIP	Hexafluoro *iso*propanol
HOBt	1-Hydroxybenzotriazole
HRMS	High resolution mass spectrometry

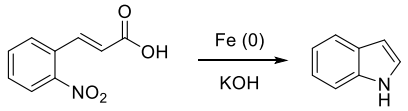
Hz	Hertz
IBX	2-Iodoxybenzoic acid
IR	Infrared radiation
LA	Lewis acid
LiHMDS	Lithium bis(trimethylsilyl)amide
m-CPBA	Meta-perbenzoic acid
mg	Milligram
mL	Milliliter
mmol	Millimole
MOM	Methoxymethyl ethers
NMP	1-Methyl-2-Pyrrolidone
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
PCET	Proton-coupled electron transfer
PIDA	Phenyliodide diacetate
PIFA	Phenyliodide ditrifluoroacetate
phen	Phenathroline
Phth	*N*-Phtalimiddoyl
Piv	Pivaloyl
ppm	Parts per million
Red-Al	Sodium bis(2-methoxyethoxy)aluminumhydride
Rf	Retardation factor
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
SDS	Sodium dodecyl sulfate
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBS	*Tert*-butyldimethylsilyl
TC	Thiophene-2-carboxylate
TEA	Triethylamine
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFAA	Trifluoroacetic anhydride
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Troc	Trichloroethyl chloroformate
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl

Chapter 1. Cadogan-Sundberg Indole Synthesis

1.1. Indole

Heterocycles are important structural motifs which can be found in a wide range of natural products, compounds of pharmaceutical interest and materials. Therefore, many methods have been developed to access almost every type of heterocyclic derivative.[1]

Among heterocycles, the indole moiety takes a particular place and is a fundamental fragment of many natural products with essential biological activities. The most active compounds possess various pharmacological activities, including anticancer, antibacterial, antiviral, antimalarial, antifungal, anti-inflammatory, antidepressant, analgesic, hypotensive, anticholinesterase, antiplatelet, antidiarrheal, spasmolytic, antileishmanial, lipid-lowering, antimycobacterial, and antidiabetic activities.[2] This skeleton can be found in the vital amino acid tryptophan and the key neurotransmitter - serotonin, as well as in several approved drugs on the market, such as vincristine and vinblastine (anticancer drugs), reserpine (antihypertensive agent), physostigmine (cholinesterase inhibitor), and ajmaline (anti-arrhythmic agent). Due to their biological importance, great attention was directed toward the synthesis of indoles. The first synthesis of indole **1.1.2** was reported by Baeyer in 1866 (Scheme 1).[3]



1.1.1 **1.1.2**

Scheme 1. The first indole synthesis by Baeyer

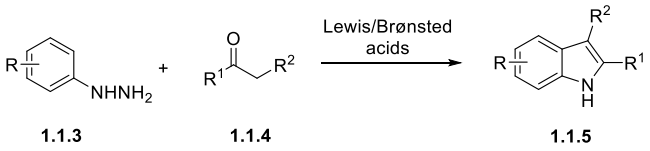
1.1.1. Synthesis of indole scaffolds

Since 1866, many methods have been developed for the synthesis of indoles, which all differ in the step responsible for the formation of the 5-membered ring.[4] Several named reactions are known for the synthesis of this type of scaffold, such as Fischer indole synthesis,[5] Bischler indole synthesis,[6] Reissert indole synthesis,[7] Madelung indole synthesis,[8] Nenitzescu indole synthesis,[9] Cadogan-Sundberg indole synthesis,[10] Hemetsberger indole synthesis,[11] Gassman indole synthesis,[12] Leimgruber–Batcho indole

[1] Baumann, M. ; Baxendale, I.R. *Beilstein J. Org. Chem.* **2013**, *9*, 2265 - 2319
[2] Omar, F. ; Tareq, A.M.; Alqahtani, A.M.; Dhama, K.; Sayeed, M.A.; Emran, T.B.; Simal-Gandara, J. *Molecules* **2021**, *26*, 2297 – 2323.
[3] Baeyer, A. *Justus Lieb. Ann. Chem*., **1866**, *140*, 295 – 313.
[4] Taber, D.F.; Tirunahari, P.K. *Tetrahedron* **2011**, *67*, 7195 – 7210.
[5] Fischer, E.; Jourdan, F. *Eur. J. Inorg. Chem.* **1883**, ***16***, 2241 – 2245.
[6] Bischler, A. *Eur. J. Inorg. Chem.* **1892**, ***25***, 2860 – 2879.
[7] Reissert, A. *Eur. J. Inorg. Chem.* **1897**, ***30***, 1030 – 1053.
[8] Madelung, W. *Eur. J. Inorg. Chem.* **1912**, ***45***, 1128 – 1134.
[9] Nenitzescu, C. *Bull. Soc. Chim. Romania* **1929**, ***11***, 37 – 43.
[10] Sundberg, R.J.; Yamazaki, T. *J. Org. Chem.* **1967**, ***32***, 290 – 294.
[11] Hemetsberger, H.; Knittel, D. *Monath. Chem.* **1972**, ***103***, 194 – 204.
[12] Gassman, P.G.; Van Bergen, T.; Gruetzmacher, G. *J. Am. Chem. Soc.* **1973**, ***95***, 6508 – 6509.

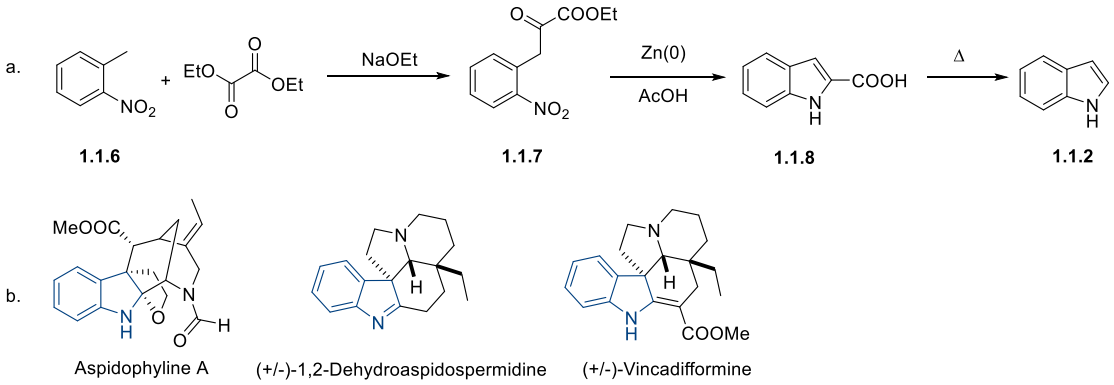
synthesis,[13] Julia indole synthesis,[14] Bartoli indole synthesis,[15] Larock indole synthesis,[16] and Fukuyama indole synthesis,[17] etc.

One of the first discovered and most known robust methods for the preparation of indoles **1.1.5** is based on the coupling of a non-activated ketone **1.1.3** with an aryl hydrazine **1.1.4**, known as the Fischer indole synthesis (Scheme 2). Typically, the reaction is performed under acidic conditions (Brønsted or Lewis acid). The benefits of this procedure include its operational simplicity and typically short reaction times. However, some limitations cannot be neglected (in particular, the use of toxic non-commercially available aryl hydrazines, high temperatures and regioselectivity issues for non-symmetric ketones).



Scheme 2. Fisher indole synthesis

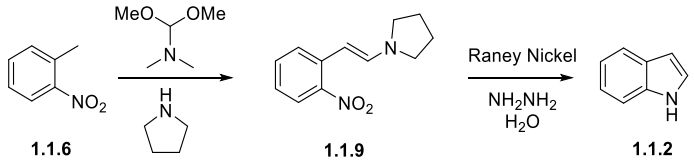
Nitro-substituted arenes are especially attractive starting materials for the synthesis of indoles because they are readily accessible and can be easily transformed. Different methods were explored by Reissert, Leimgruber and Batcho, Bartoli, Cadogan and Sundberg. The first synthesis of indoles from nitroarenes **1.1.6** was reported in 1897 by Reissert (Scheme 3, a).[18,19] The reaction begins with the base-catalyzed condensation of *o*-nitrotoluene **1.1.6** with ethyl oxalate to give *o*-nitrophenylpyruvate **1.1.7**. The hydrolysis of ester **1.1.7**, followed by a zinc-mediated reductive cyclization afford 1H-indole-2-carboxylic acid **1.1.8**. Simple alkoxides can be used as catalyst for the condensation step. Besides Zn, many other reducing systems have been explored, such as Zn-Hg/HCl, $FeSO_4/NH_4OH$, Fe/H_2, $TiCl_3$, etc. In our group, the Reissert method was applied for the total synthesis of some natural products: aspidophyline A,[20] (±)-1,2-dehydroaspidospermidine, (±)-vincadifformine (Scheme 3, b).[21]



Scheme 3. Reissert indole synthesis

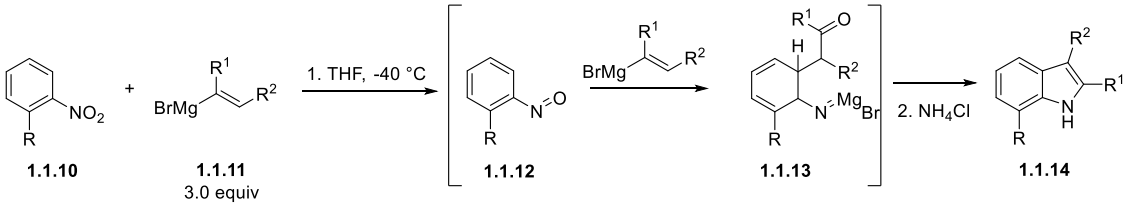
[13] Batcho, A.D.; Leimgruber, W. *Org. Synth.* **1985**, ***63***, 214 – 220.
[14] Baudin, J.-B.; Julia, S.A. *Tetrahedron Lett.* **1986**, ***27***, 837 – 840.
[15] Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, ***30***, 2129 – 2132.
[16] Larock, R.C.; Yum, E.K. *J. Am. Chem. Soc.* **1991**, ***113***, 6689 – 6690.
[17] Fukuyama, T.; Chen, X.; Peng, G. *J. Am. Chem. Soc.* **1994**, ***116***, 3127 – 3128.
[18] Sundberg, R. J. *The Chemistry of Indoles*; Acedemic Press: New York, 1970; Chapter 3.
[19] Brown, R. K. *Indoles*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Part 1, Chapter 2.
[20] Ren, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 1818 – 1821.
[21] Wagnières, O.; Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2014**, *136*, 15102 – 15108.

Another named transformation is the Leimgruber-Batcho reaction (Scheme 4). The reaction starts with the condensation of an *o*-nitrotoluene **1.1.6** with *N,N'*-dimethylformamide dimethyl acetal (DMF-DMA) to give intermediate *β*-(dimethylamino)-2-nitrostyrene. The formation of the enamine can be accelerated by the addition of amines, the dimethylamine is then displaced by the amine; in this case pyrrolidine, affording **1.1.9**. Reductive cyclization leads to indole **1.1.2**. Originally, *N,N*-dimethylformamide dimethyl acetal (DMF-DMA), *N*-formylpyrrolidine dimethyl acetal, and *N*-formylpiperidine dimethyl acetal were coupled with *o*-nitrotoluenes, however, DMF-DMA became the most used reagent.[22] Different reducing agents can be used to perform the last step: Pd/H_2, Raney Ni, Fe/HCl, $(NH_4)_2Fe(SO_4)_2$, $Na_2S_2O_4$, $SnCl_2$/HCl, $TiCl_3$. The possible hydrogenation of the double bond and isolation of hydroxylamines are the main disadvantages of this reaction. At the same time, the reaction tolerates a large range of ring substituents and was used in natural product synthesis.



Scheme 4. Leimgruber-Batcho indole synthesis

Vinyl Grignard reagents can be used as reducing agents for the synthesis of indoles. This recently developed transformation is known as the Bartoli indole synthesis (Scheme 5).[23] The reaction begins with the double attack of the Grignard reagent **1.1.11** on the nitroarene **1.1.10** followed by a [3,3]-sigmatropic rearrangement to give the carbonyl compound **1.1.13**. Intramolecular attack on the ketone, subsequent deprotonation and an acid work-up afford **1.1.14**. Three equivalents of the Grignard reagent are necessary to perform this reaction: one to reduce the nitro-group, another equivalent becomes a part of the indole ring, and a third equivalent serves as a base. This method gives rise to products with substituents at any position of the indole ring, which was sometimes challenging to achieve with other methods. The preparation of sensitive Grignard reagents and the fact that only one out of three equivalents of vinyl magnesium bromide is incorporated into indole structure limits, nevertheless, the practicability of this method.



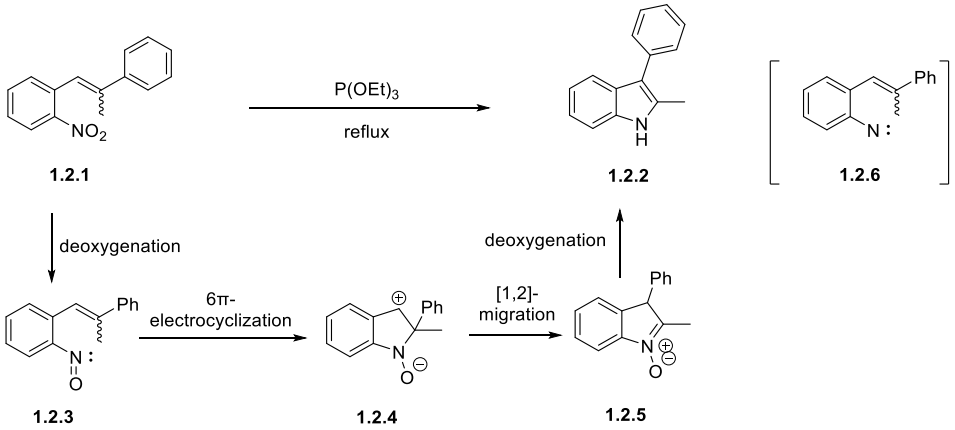
Scheme 5. Bartoli indole synthesis

1.2. **The Cadogan-Sundberg reaction**

The first report on indole synthesis through reductive electrocyclization process was published in 1962. Cadogan *et al.* demonstrated that *ortho*-nitrostyrene **1.2.1** could be transformed into indole **1.2.2** *via* deoxygenation mediated by triethyl phosphite at high temperatures (Scheme 6).[24] In a few years,

[22] Clark, R.D.; Repke, D.B. *Heterocycles* **1984**, *22*, 195 – 221.
[23] Bartoli, G.; Dalpozzo, R.; Nardi, M. *Chem. Soc. Rev.* **2014**, *43*, 4728 – 4750.
[24] Cadogan, J.I.G.; Cameron-Wood, M. *Proc. Chem. Soc.* **1962**, 361

independently Cadogan and Sundberg showed that this transformation could be applied to the synthesis of carbazoles, benzotriazoles, indazoles, indoles, phenothiazines and anthranil ring systems.[25,26,27,28] Based on the work of Cadogan and the isolation of some reaction intermediates: 1-hydroxyindole and 1-ethoxyindole; Sundberg *et al.* proposed that the reaction starts with a deoxygenation of the nitro group to form the corresponding nitroso species **1.2.3**.[29,30] All efforts to isolate nitroso-derivative failed, as the reductive electrocyclization of nitroso-derivatives proceeds efficiently even without heating. There are many debates about the reactive species, which proceeds in 5-center-6π-electrocyclization: either the nitrene **1.2.6** (derived from the reduction of nitroso-intermediate) or the nitroso-intermediate **1.2.3** are possible candidates for this electrocylization. Due to the similar product distribution for the reductive cyclization of aromatic nitro compounds and their analogous azides (Sundberg reaction), the mechanism *via* nitrene formation was considered predominant.[31,32] However, the isolation of 1-hydroxyindoles in some cases showed that the nitroso derivative **1.2.3** can indeed be the reactive specie, which proceeds in the cyclization. Based on computational studies, Houk and Davies could support the feasibility of nitroso-cyclization.[33,34] The last steps consist of the electrocyclization to form **1.2.4** and 1,2-migration. In the example shown in Scheme 6, the migration of the phenyl group prevailed over methyl group leading to nitrone **1.2.5**. Reduction of intermediate **1.2.5** delivers the desired product **1.2.2**. Though this reaction can be applied to a broad scope of *o*-nitrostyrenes, the harsh reaction conditions (heating at 150 °C), the use of an excess of triethyl phosphite (in general as solvent) and the formation of side-products (*N*-hydroxy and *N*-ethoxyindoles) limited its application scope.

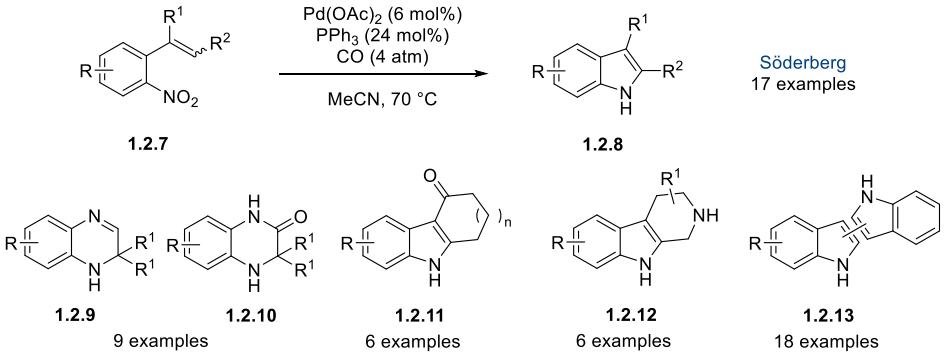


Scheme 6. Cadogan-Sundberg indole synthesis

The first alternative conditions for the Cadogan-Sundberg reaction were based on the use of transition metal catalysts along with CO as a stoichiometric reductant. Cenini *et al.* demonstrated that $Fe(CO)_5$, $Ru_3(CO)_{12}$ and $Rh_6(CO)_{16}$ could be used for the deoxygenation of *o*-nitrostyrenes. Although, most of the products were isolated with moderate yields under harsh reaction conditions (220 °C and 80 bar CO), it was

[25] Cadogan, J.I.G.; Cameron-Wood, M.; Mackie, R.K.; Searle, R.J.G. *J. Chem. Soc.* **1965**, 4831 – 4837.
[26] Sundberg, R.J. *J. Org .Chem.* **1965**, *30*, 3604 – 3610.
[27] Cadogan, J.I.G.; Mackie, R.K.; Todd, M.J. *J. Chem. Soc., Chem. Commun.* **1966**, 491.
[28] Cadogan, J.I.G.; Mackie, R.K. *Chem. Soc. Rev*. **1974**, *3*, 87 – 137.
[29] Sundberg, R. J. *J. Org. Chem.* **1965**, *30*, 3604 – 3610.
[30] Sundberg, R.J.; Tamazaki, T. *J. Org. Chem.* **1967**, *32*, 290 – 294.
[31] Sundberg, R.J.; Lin, L.S.; Blackburn, D.E. *Heterocycl. Chem.* **1969**, *6*, 441 – 441.
[32] Jana, N.; Driver, T.G. *Org. Biomol. Chem.* **2015**, *13*, 9720 – 9741.
[33] Davies, I.W.; Guner, V.A.; Houk, K.N. *Org. Lett.* **2004**, *6*, 743 – 746.
[34] Leach, A.G.; Houk, K.N.; Davies, I.W. *Synthesis* **2005**, *19*, 3463 – 3467.

the first working example.[35] In 1994, Watanabe and coworkers reported that the catalytic system $PdCl_2(PPh_3)_2/SnCl_2$ in combination with carbon monoxide could catalyze the reductive cyclization of 2-nitrostyrenes at lower temperatures (100 °C).[36] The group of Söderberg made a significant impact in this field (Scheme 7).[37] Based on a broad screening of the reaction conditions (Pd-source/ligand/solvent/temperature), a library of indoles **1.2.8** was synthesized with good to excellent yields. The scope was extended to 1,2-dihydroquinoxalines **1.2.9**, 3,4-dihydro-quinoxalinones **1.2.10**,[38] 1,2-dihydro-4(3*H*)-carbazolone **1.2.11**,[39] *β*-carbolines **1.2.12**,[40] bisindoles **1.2.13**,[41] and later applied for the synthesis of natural products.[42,43] The group of Davies at Merck reported the use of catalytic amounts of $Pd(TFA)_2$ with 3,4,7,8,-tetramethyl-1,10-phenanthroline in the presence of CO as reductant.[44,45]

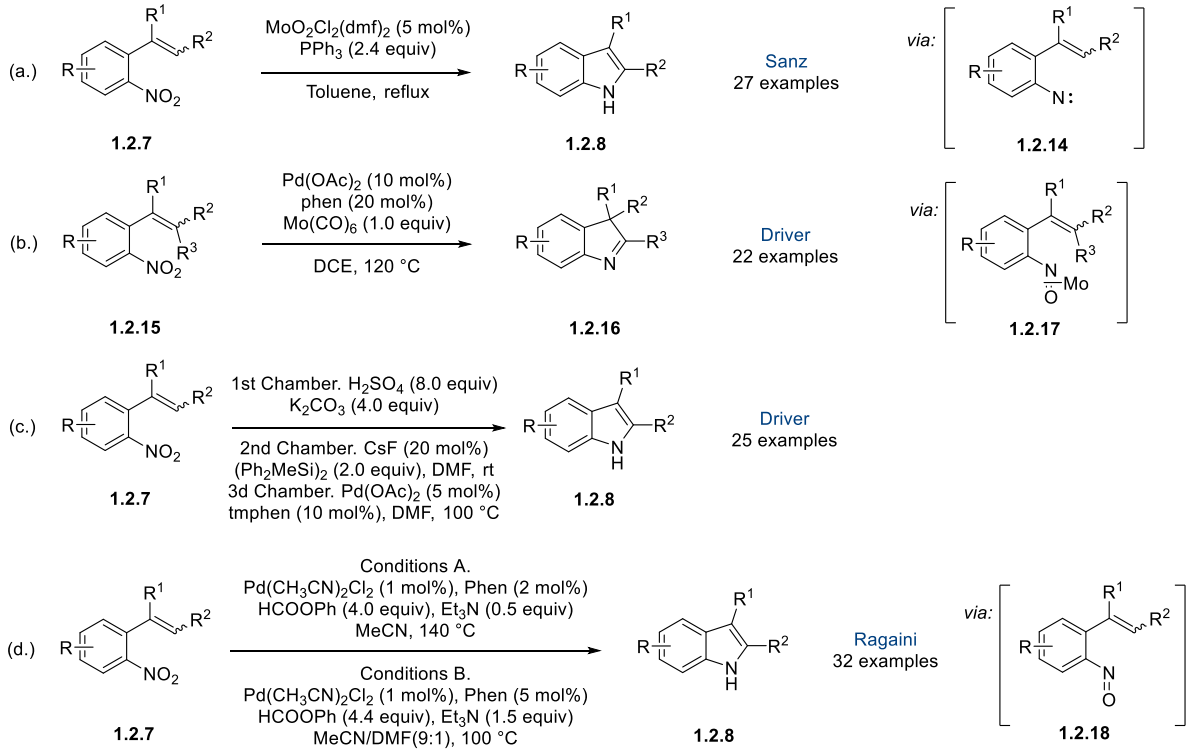


Scheme 7. Cadogan-Sundberg reaction under Söderberg conditions

The elevated levels of CO pressure, high temperatures, and high amounts of transition metals forced scientists to explore other types of reducing systems. Sonoda *et al.* reported that, alternatively, elemental selenium could catalyze the reductive cyclization of *o*-nitrostyrenes under 5-30 atm of CO gas. The authors proposed that the reaction begins with the formation of carbonyl selenide SeCO, which might be responsible for the reduction of the nitro group to the nitrene.[46] In 2007, Sanz *et al.* reported a dioxomolybdenum(VI)-catalyzed reductive cyclization of *o*-nitrostyrenes **1.2.7** using PPh_3 as a reductant (Scheme 8, a).[47] Under those mild conditions, the reaction showed high functional group compatibility and efficiency. The authors proposed that the deoxygenation of the nitro group is firstly achieved by a dinuclear Mo-complex, which is formed by the reduction with PPh_3. In contrast, the second deoxygenation step to form the nitrene **1.2.14** can be assisted by PPh_3. As an alternative source of CO, Driver and coworkers reported the transformation of 2-nitroarenes **1.2.15** into 3*H*-indoles **1.2.16** catalyzed by a combination of $Mo(CO)_6$ and $Pd(OAc)_2$

[35] Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1986**, 784 – 786.
[36] Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375 – 3380.
[37] Söderberg, B.C.; Shriver, J.A. *J. Org. Chem.* **1997**, *62*, 5838 – 5845.
[38] Söderberg, B.C.; Wallace, J.M.; Tamariz, J. *Org. Lett.* **2002**, *4*, 1339 – 1342.
[39] Scott, T. L.; Söderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621 – 1624.
[40] Dantale, S.W.; Söderberg, B.C. *Tetrahedron* **2003**, *59*, 5507 – 5514.
[41] Ansari, N.H.; Dacko, C.A.; Akhmedov, N:G.; Söderberg, B.C. *J. Org. Chem*. **2016**, *81*, 9337 – 9349.
[42] Söderberg, B.C.; Chisnell, A.C.; O'Neil, S.N.; Shriver, J.A. *J. Org. Chem.* **1999**, *64*, 9731– 9734.
[43] Zhang, Y.; Hubbard, J.W.; Akhmedov, N.G.; Petersen, J.L.; Söderberg, B. C. *J. Org. Chem.* **2015**, *80*, 4783−4790.
[44] Smitrovich, J.H.; Davies, I.W. *Org. Lett.* **2004**, *6*, 533 – 535.
[45] Davies, I.W.; Smitrovich, J.H.; Sidler, R.; Qu, C.; Gresham, V.; Bazaral, C. *Tetrahedron* **2005**, *61*, 6425 – 6437.
[46] Nishiyama, Y.; Maema, R.; Ohno, K.; Hirose, M.; Sonoda, N. *Tetrahedron Lett.* **1999**, *40*, 5717 – 5720.
[47] Sanz, R.; Escribano, J.; Pedrosa, M.R.; Aguado, R.; Arnaiz, F.J. *Adv. Synth. Catal.* **2007**, *349*, 713 – 718.

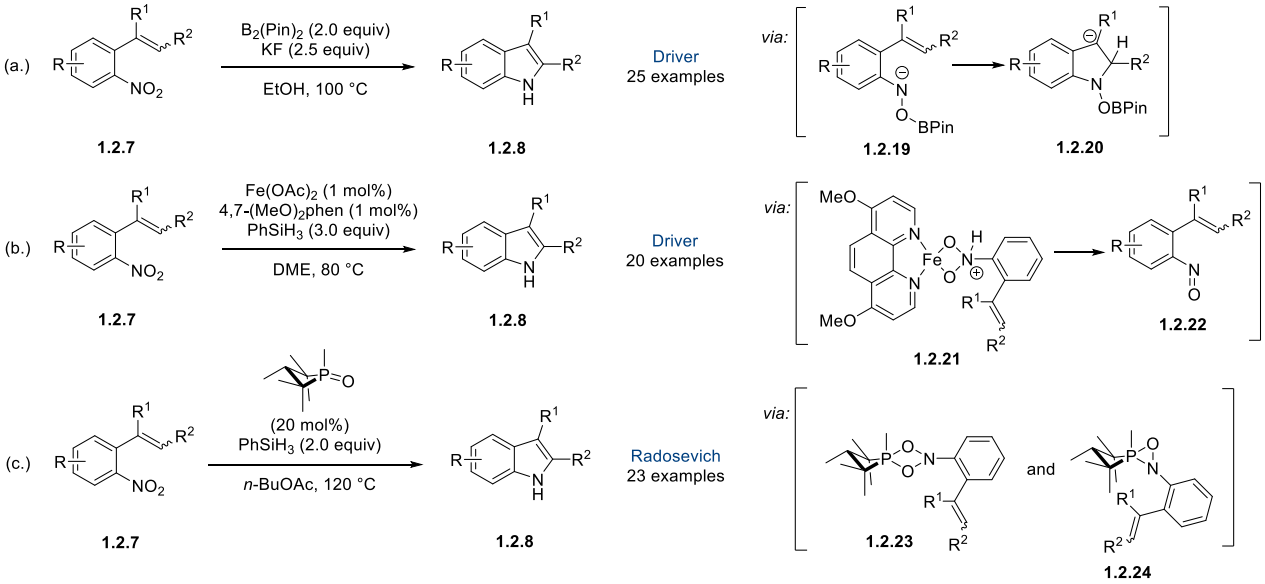
complexes (Scheme 8, b).[48,49,50] Based on control experiments, the authors postulated a dual role of Mo as a source of CO and metal which can coordinate to the nitroso group **1.2.17** to induce the cyclization. Later on, the authors explored the use of CO_2 as a precursor of CO, using CsF and $(Ph_2MeSi)_2$ as terminal reductants (Scheme 8, c).[51] A three-chamber process turned out to be efficient although it requires a special reactor. The group of Ragaini reported several applications of formate esters as reducing agents, which are commercially available and have low toxicity, compared to $Mo(CO)_6$ (Scheme 8, d). [52,53,54,55] Phenyl formate was the most effective source of CO, and the reaction could be performed in a single glass pressure tube avoiding special equipment. Fine-tuning of the reaction conditions allowed the employment of substrates containing sensitive groups. Furthermore, reactions worked well at 100 °C, the temperature could even be reduced to 80 °C. Control experiments were performed to determine if the base or the Pd were responsible for the release of CO, and showed that the base was responsible for decarbonylation process.[56] Isolation of oxazine from the reaction of nitrobenzene in the presence of butadiene, confirmed the formation of active nitroso-arene intermediate **1.2.18**.[57]



Scheme 8. Cadogan-Sundberg reaction with alternative sources of reducing agent

[48] Jana, N.; Zhou, F.; Driver, T.G. *J. Am. Chem. Soc.* **2015**, *137*, 6738 – 6741.
[49] Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582 – 9854.
[50] Zhou, F.; Wang, D.-S.; Driver, T.G. *Adv. Synth. Catal.* **2015**, *357*, 3463 – 3468.
[51] Guan, X.; Zhu, H.; Zhao, Y.; Driver, T.G. *Eur. J. Org. Chem.* **2020**, 57 – 60.
[52] Formenti, D.; Ferretti, F.; Ragaini, F. *ChemCatChem* **2018**, *10*, 148 – 152.
[53] Fouad, M.A.; Ferretti, F.; Formenti, D.; Milani, F.; Ragaini, F. *Eur. J. Org. Chem*. **2021**, 4876 – 4894.
[54] Ferretti, F.; Fouad, M.A.; Ragaini, F. *Catalysts* **2022**, *12*, 106 – 121.
[55] Ramadan, D.R.; Ferretti, F.; Ragaini, F. *Journal of Catalysis* **2022**, *409*, 41 – 47.
[56] Ueda, T.; Konishi, H.; K. Manabe, K. *Org. Lett*. **2012**, *14*, 3100 – 310.
[57] EL-Atawy, M.A.; Formenti, D.; Ferretti, F.; Ragaini, F. *ChemCatChem* **2018**, *10*, 4707 – 4717.

In 2016, Driver, Song and coworkers published a transition metal-free reductive cyclization of **1.2.17** catalyzed by B_2pin_2 and KF (Scheme 9, a). The formation of a strong B-O bond was assumed as a driving force in this transformation. A different mechanism was proposed *via* the formation of negatively charged intermediates **1.2.19-1.2.20**.[58] A year later, Driver *et al.* reported that $Fe(OAc)_2$ can catalyze reductive cyclization of *o*-nitrostyrenes **1.2.7** in the presence of 4,7-$(MeO)_2$phen as a catalytic system and phenylsilane as a terminal reductant (Scheme 9, b).[59] For this reaction, the turnover limiting step turned out to be the reduction of Fe-catalyst with silane and not the reduction of the nitro-group. The nitroso-intermediate **1.2.22** could be formed *via* an iron hydride-mediated reduction **1.2.21**. Radosevich and coworkers showed that hydrosilanes could be used as terminal reductants in the Cadogan reaction catalyzed by 1,2,2,3,4,4-hexamethylphosphetane (Scheme 9, c).[60,61] The ring strain of a catalyst plays a crucial role in the method's efficiency. Replacing 1,2,2,3,4,4-hexamethylphosphetane by acyclic phosphetanes or phosphacycle with bigger rings leads to a poor reactivity. The *in situ* reduction of a P^V═O with hydrosilane made this process catalytic in phosphorus. NMR and kinetics studies showed that the formation of P(III) is a relatively fast process and during the reaction phosphorus stays in this catalytic resting state. A library of carbazoles, indoles, 2*H*-indazoles, 2*H*-benzotriazoles was synthesized. Based on control experiments and computational studies, the authors concluded that the double deoxygenation could proceed *via* the formation of azadioxophosphetane **1.2.23** and oxazaphosphirane **1.2.24** intermediates. Finally, the electrocyclization goes through a nitrenoid pathway. In 2011, Peters *et al.* reported that indoles could be obtained from *o*-nitrostyrenes under electrochemical reduction. The addition of a proton donor changes drastically the cyclic voltammogram of the starting material and is responsible for the reactivity.[62]

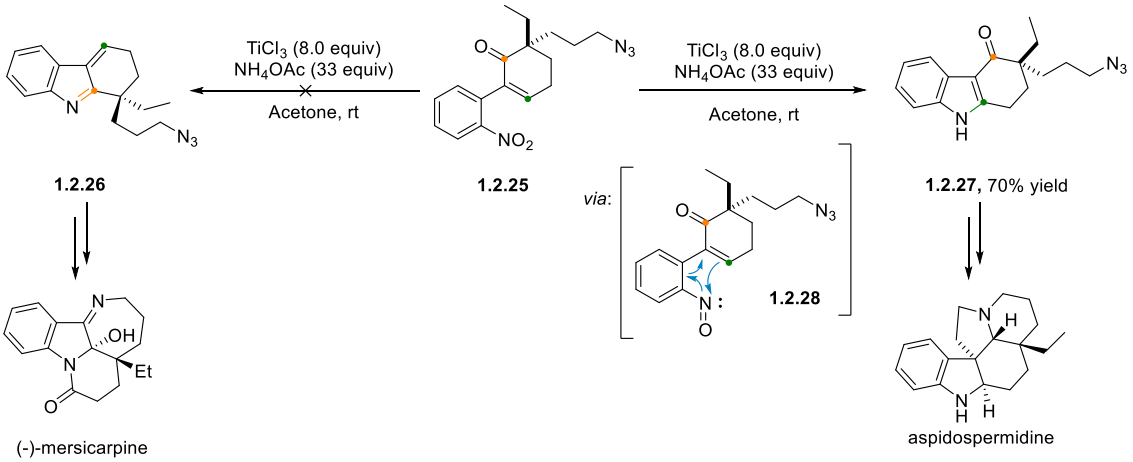


Scheme 9. Cadogan-Sundberg reaction with alternative reducing agents

[58] Yang, K.; Zhou, F.; Kuang, Z.; Gao, G.; Driver, T.G.; Song, Q. *Org. Lett.* **2016**, *18*, 4088 – 4091.
[59] Shevlin, M.; Guan, X.; Driver, T.G. *ACS Catal.* **2017**, *7*, 5518 – 5522.
[60] Nykaza, T.V.; Harrison, T.S.; Ghosh, A.; Putnik, R.A.; Radosevich, A.T. *J. Am. Chem. Soc.* **2017**, *139*, 6839−6842.
[61] Nykaza, T.V.; Ramirez, A.; Harrison, T.S.; Luzung, M.R.; Radosevich, A.T. *J. Am. Chem. Soc.* **2018**, *140*, 3103 – 3113.
[62] Du, P.; Brosmer, J.L.; Peters, D.G. *Org. Lett.* **2011**, *13*, 4072 – 4075.

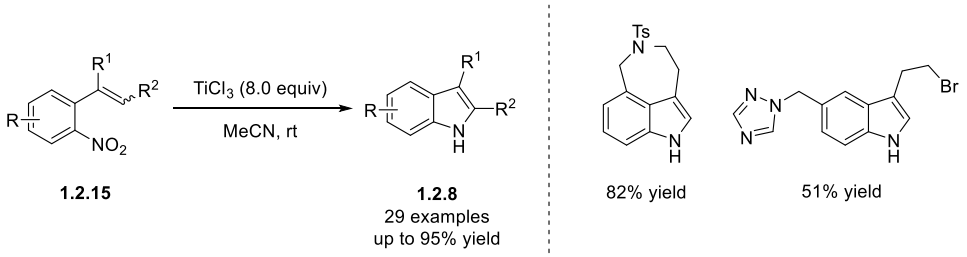
1.2.1. **$TiCl_3$-mediated Cadogan-Sundberg reaction**

In the context of continuous interest of our group in the total synthesis of natural products, one of the selected targets was (−)-mersicarpine (Scheme 10).[63] The synthesis was thought to be performed *via* the formation of *o*-nitrostyrene **1.2.25** and its subsequent reduction to form indolenine **1.2.26**.[64,65] Testing different reducing systems, it was found that $TiCl_3$-mediated reduction of the *o*-nitrostyrene **1.2.25** leads to the formation of indole **1.2.27** instead of indolenine **1.2.26**. The isolated product could be formed *via* the Cadogan-Sundberg reaction: reduction of the nitro-group to nitroso **1.2.28** followed by a 5-center-6π-electrocyclization.



*Scheme 10. $TiCl_3$-mediated reductive cyclization of o-nitrostyrene **1.2.25***

To further explore the synthetic potential of this reducing system, we became interested in addressing the same conditions for the synthesis of a library of indoles **1.2.8**. In this regard, in 2015, our group showed that aqueous titanium trichloride can be a suitable reducing agent for the cyclization of *ortho*-nitrostyrenes **1.2.15** (Scheme 11).[66] The reaction was done under mild conditions with a simple experimental protocol and readily accessible starting materials. High functional group tolerance allowed the synthesis of substrates containing halides (Cl, Br), carbonyl (ester, carbamate), cyano, hydroxy, and amino groups. Depending on the double bond substituents, migration of either the proton or the aryl group was observed.

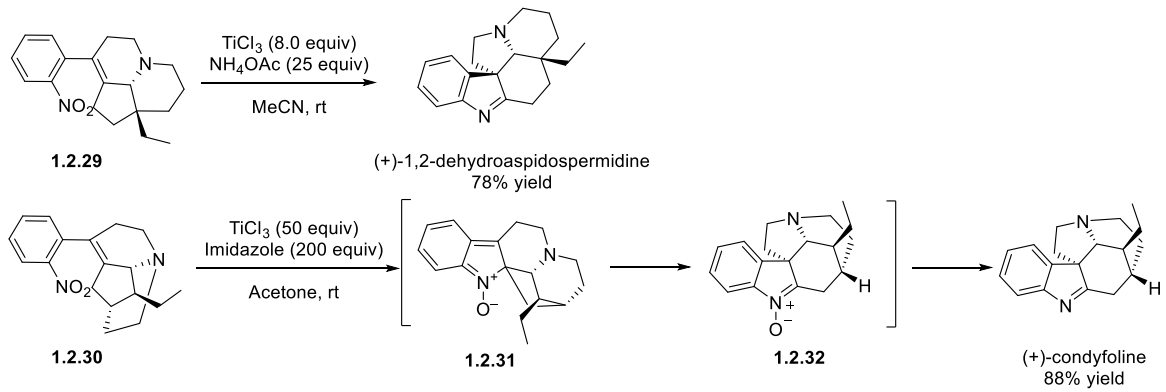


*Scheme 11. $TiCl_3$-mediated reductive cyclization of trisubstituted o-nitrostyrenes **1.2.15***

Inspired by this reactivity, the total synthesis of several natural products: (+)-1,2-dehydroaspidospermidine, (+)-condyfoline and (−)-tubifoline, was accomplished using these conditions

[63] Kam, T.-S.; Subramaniam, G.; Lim, K.-H.; Choo, Y.-M. *Tetrahedron Lett.* **2004**, *45*, 5995 – 5998.
[64] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 19127 – 19130.
[65] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137*, 6712 – 6724.
[66] Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 11809 – 11812.

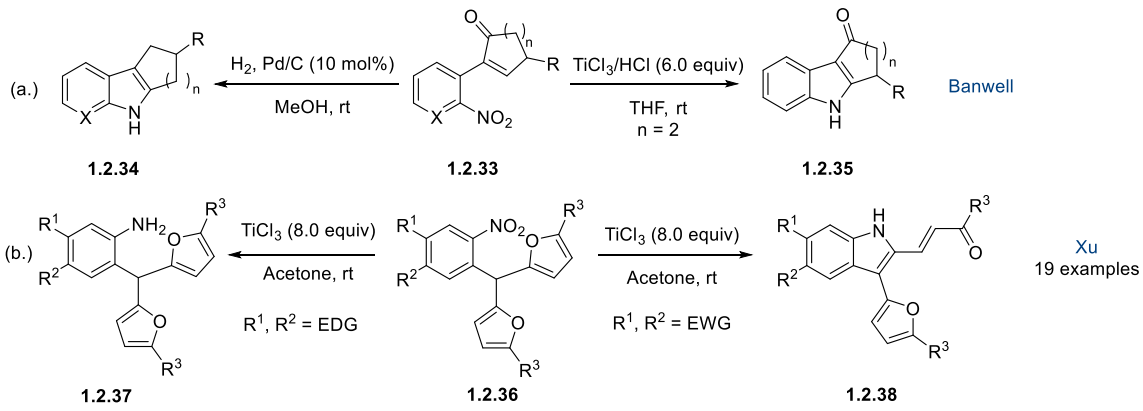
(Scheme 12).[67] These bioactive compounds contain 2,3,3-trisubstituted indolenine moiety. This scaffold was envisioned to be built from 2-nitroaryl substituted alkenes *via* the reduction of a nitro-group, 5-atom-6π-electrocyclization and subsequent 1,2-alkyl migration. The reductive cyclization was studied with both alkenes **1.2.29** and **1.2.30**. The treatment of alkene **1.2.29** in acetonitrile with $TiCl_3$ successfully provided (+)-1,2-dehydroaspidospermidine as a single diastereoisomer. Similar conditions were later applied for the synthesis of (+)-condyfoline, the desired product was isolated in 88% yield by treatment of an acetone solution of alkene **1.2.30** with $TiCl_3$. The isolation of the only desired product supported the concerted mechanism *via* Wagner-Meerwein 1,5-sigmatropic rearrangement for intermediate **1.2.31** and contradicted the potential retro-Mannich process. This observation constituted an unprecedented example of $TiCl_3$-mediated reduction of tetrasubstituted alkenes.



Scheme 12. Application of $TiCl_3$-mediated reductive cyclization for the synthesis of natural products

Banwell and coworkers showed that depending on the conditions, the nitro-group of the *o*-nitrostyrene **1.2.33** could either be fully reduced and react with the carbonyl group (treatment with Pd/H_2) or proceed in the electrocyclization with the double bond (treatment with aqueous $TiCl_3$, Scheme 13).[68] Last year, Xu *et al*. reported the $TiCl_3$-mediated reductive cyclization of bis(5-alkyl-2-furyl)(2-nitroaryl)methane **1.2.36**.[69] Depending on the substituents on the nitro-arene ring, different products were isolated. With electron-donating groups, the over-reduction could not be slowed down and mostly the corresponding aniline **1.2.37** was formed. However, in the presence of electron-withdrawing groups the desired indoles **1.2.38** were obtained.

[67] Delayre, B.; Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2020**, *59*, 13990 – 13997.
[68] Qiu, Y.; Dlugosch, M.; Liu, X.; Khan, F.; Ward, J.S.; Lan, P.; Banwell, M.G *J. Org. Chem.* **2018**, *83*, 12023 – 12033.
[69] Li, D.-K.; Tan, J.-Y.; Deng, W.; Xu, Z.-Y. *Tetrahedron* **2021**, *99*, 132407 – 132415.



Scheme 13. Recent application of $TiCl_3$-mediated reductive cyclization

The development of new methods for the synthesis of indoles remains a major area of focus due to the high prevalence of this heterocyclic ring in nature. In our laboratory, reductive cyclization of substituted *o*-nitrostyrenes with $TiCl_3$ was used in the total synthesis of natural products. This reaction is performed under mild conditions, showing good to excellent yields and good functional group tolerance. Aimed at exploiting the full synthetic potential of the $TiCl_3$-mediated Cadogan-Sundberg reaction, we became interested in investigating the reductive cyclization of previously unexploited *o*-nitrostyrene derivatives, our results will be shown in the next chapters.

1.3. **Nitro compounds**

Dieter Seebach highlighted nitro compounds as "ideal intermediates in organic synthesis",[70] due to their versatile reactivity. Since the beginning of the 19th century, the chemistry of nitro compounds is still under exploration. Nitro compounds act as synthetically useful building blocks to prepare aminated scaffolds with different purposes such as drugs, agricultural chemicals, dyes, optical/electronic materials and explosives. Thanks to the diverse potential of the nitro group (reactivity and functional group conversions), products possessing decorated structures can be synthesized.[71]

1.3.1. **Preparation**

Historically for aromatic compounds, conventional nitration processes involve the employment of HNO_3 in combination with different acids, for instance H_2SO_4. Although this process is still widely used in industry, the reaction generates toxic and corrosive nitrogen oxide gas. Since nitrating agents are also strong oxidants, nitro compounds are often accompanied by oxidation products. In order to avoid the formation of byproducts and regioisomers, other nitrating agents have been developed, which are briefly summarized in Scheme 14. The oxidation of **1.3.1** can be performed by employing stoichiometric amounts of reagents such

[70] Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1 – 18.
[71] Ono, N. "*The Nitro Group in Organic Synthesis*" **2001**, Wiley-VCH.

as: HNO_3 with zeolite-β (as a solid acid catalyst),[72] lanthanide(III) triflates,[73] vanadium oxytrinitrate,[74] potassium nitrate along with $AlCl_3$,[75] dinitrogen pentoxide,[76] nitrogen dioxide together with ozone,[77] etc. During the last decade, several reviews were published dedicated to the use of alternative nitrating agents; a significant impact was made by Katayev and coworkers.[78,79,80] At the same time, electrophilic nitration of alkanes **1.3.3** is a more complicated process compared to aromatic compounds. The process can generally be highlighted by low selectivity and efficiency, unless specific substrates are used as starting materials.[81] The situation changes when activated C-H bonds are nitrated. Most commonly, the reaction proceeds *via* the formation of carbanion, which is then trapped with an electrophilic nitrating agent: alkyl nitrates,[82] N_2O_4,[83] etc. Alkenes like aromatic compounds are prone to react in electrophilic reactions. Similar conditions, as described before can be applied to alkenes.[84] The obtained nitroalkenes can later be reduced to nitro-alkanes **1.3.4** if necessary. However, one of the most used methods for the synthesis of nitro compounds is based on the oxidation of preformed amines **1.3.5** and oximes. Different oxidizing reagents can be used for these purposes, for example: ozone,[85] oxone,[86] peracids,[87] potassium permanganate,[88] etc.

[72] Smith, K.; Musson, A.; DeBoos, G.A. *J. Org. Chem.* **1998**, *63*, 8448 – 8454.
[73] Waller, F.J.; Barrett, A.G.M.; Braddock, D.C.; Ramprasad, D. *Chem. Commun.* **1997**, 613 – 614.
[74] Dove, M.F.A. ; Manz, B.; Montogomery, J.; Pattenden, G.; Wood, S.A. *J. Chem. Soc., Perkin Trans 1* **1998**, 1589 – 1590.
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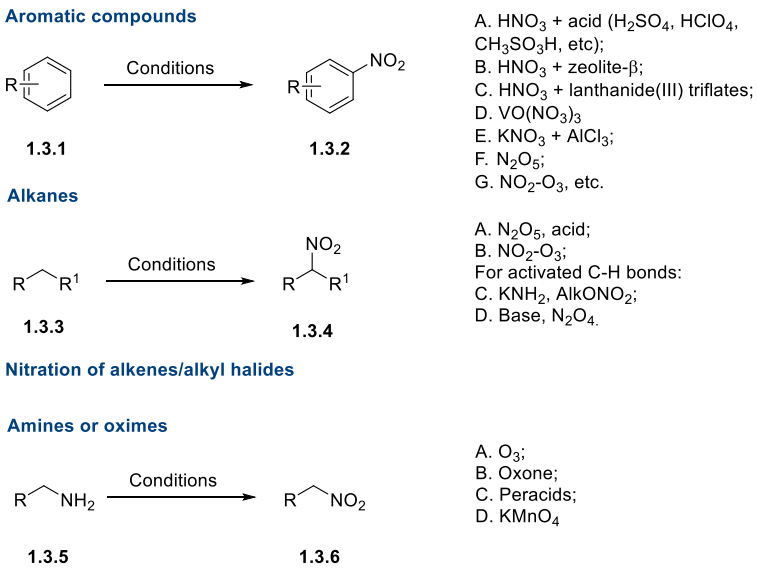
[76] Fisher, J.W. "*The chemistry of dinitrogen pentoxide in nitro compounds"* **1990**, VCH, New York by Feuer, H. and Nielsen, A.T.
[77] Mori, T.; Suzuki, H. *Synlett* **1995**, 383 – 392.
[78] Patra,S.; Mosiagin, I.; Giri, R.; Katayev, D. *Synthesis* **2022**, *54*, 3432 – 3472.
[79] Calvo, R.; Zhang, K.; Passera, A.; Katayev, D. *Nat. Commun.* **2019**, *10*, 3410-3418.
[80] Zhang, K.; Jelier, B.; Passera, A.; Jeschke, G.; Katayev, D. *Chem. Eur. J.* **2019**, *25*, 12929-12939.
[81] Suzuki, H.; Nonomiya, N. *Chem. Commun.* **1996**, 1783 – 1784.
[82] Feuer, H.; Lawrence, J.P. *J. Org. Chem.* **1972**, *37*, 3662 – 3670.
[83] Lukin, K.; Li, J.; Gilardi, R.; Eaton, P.E. *Angew. Chem. Int. Ed.* **1996**, *35*, 864 – 866.
[84] Olah, G.A.; Malhotra, R.; Narang, S.C. "*Nitration : methods and mechanism"* **1989**, VCH, New Your.
[85] Bailey, P.S.; Keller, J.E. *J. Org. Chem.* **1968**, *33*, 2680 – 2684.
[86] Murray, R.W.; Jeyaraman, R.; Mohan, L. *Tetrahedron Lett.* **1986**, *27*, 2335 – 2336.
[87] Gilbert, K.E.; Borden, W.T. *J. Org. Chem.* **1973**, *44*, 659.
[88] Calder, A.; Forrester, A.R.; Hepburn, S.O. *Org. Synth.* **1988**, *6*, 803.



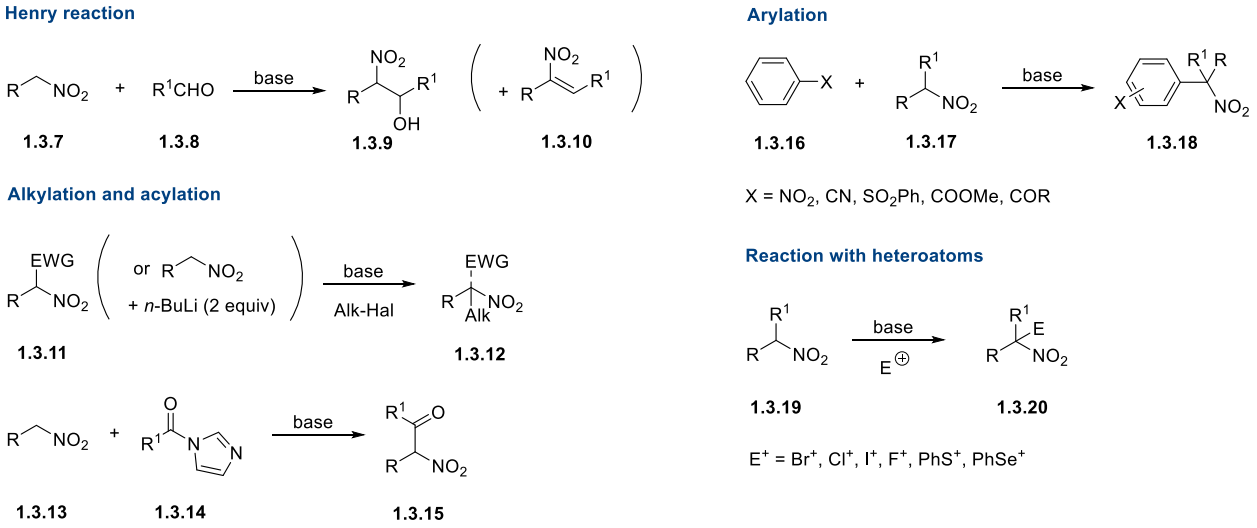
Scheme 14. Synthesis of nitro-compounds

1.3.2. **Chemical properties**

The strong electron-withdrawing properties of the nitro group *via* inductive and mesomeric effects allow nitro-compounds to undergo reactions with nucleophiles or single-electron transfer reagents. At the same time, the α-hydrogen is highly acidic and can be abstracted by bases, making the molecule a potential nucleophile. One of the most famous transformations is the Henry reaction (the nitro-aldol, Scheme 15).[89,90] Various bases can be used to perform the reaction between nitroalkane **1.3.7** and aldehyde **1.3.8**, even in catalytic amounts: NaOR, Et_3N, DBU, TMG, etc. The Henry reaction, followed by the reduction of the nitro group, can be an alternative way for the synthesis of *β*-amino alcohols. To render the reaction stereoselective, various catalytic systems were discovered: chiral metal catalysts; chiral ligands such as Schiff bases, tetrahydrosalens, amino alcohols, and diamines; and small organic molecules such as guanidine, cinchona alkaloid-derived organocatalysts and quaternary ammonium salts.[91] Similarly to the Henry reaction, nitro compounds can be alkylated and acylated, though the problem of O/C-selectivity arises.[92] To avoid the *O*-alkylation, either substrates with two electron-withdrawing groups **1.3.11** need to be used or the starting material could be doubly deprotonated.[93] Selective C-acylation works well with soft acylating agents such as: acyl imidazoles **1.3.14**, phenyl esters, acyl nitriles and enol-lactones.[94] Arylation of nitro compounds is possible *via* aromatic nucleophilic substitution.[95] Apart from carbon electrophiles,

[89] Rosini, G. *Comprehensive Organic Synthesis*, ed. By B.M. Trost, **1992**, *2*, Pergamon, New York.
[90] Shvekhgeimer, M.C.A. *Russ. Chem. Rev.* **1998**, *67*, 35 – 68.
[91] Dong, L.; Chen, F.-E. *RSC Adv.* **2020**, *10*, 2313 – 2326.
[92] Zen, S.; Kaji, E. *Org. Synth.* **1988**, *4*, 503.
[93] Seebach, D.; Henning, R.; Lehr, F.; Widdowson, D.a. *Tetrahedron Lett.* **1977**, 1161.
[94] Jager, V.; Seidel, B.; Guntrum, E. *Synthesis* **1991**, 629 – 632.
[95] Terrier, F. "*Nucleophilic Aromatic Displacement. The influence of the Nitro Group*" **1991**, VCH, New York.

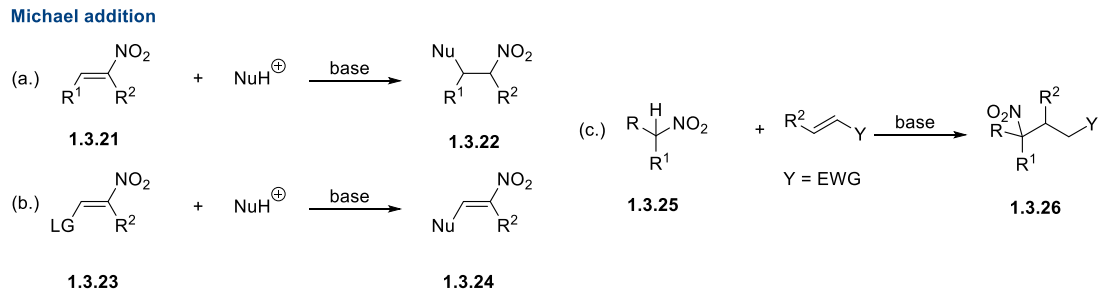
nitro-compounds can react with other types of electrophiles: halogens, sulfur, selenium.[96] Some products of these transformations show high antimicrobial and insecticide activities.[97]



Scheme 15. Reactions of nitro-compounds as nucleophiles

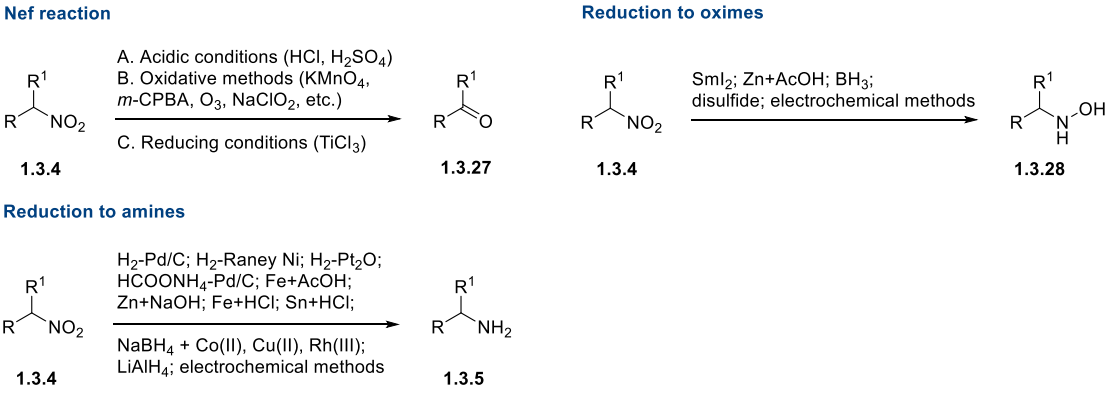
For the substrates containing a nitro-alkene fragment **1.3.21**, the nitro group activates the carbon–carbon double bond, which serves as an excellent Michael acceptor (Scheme 16).[98] Although, the products of the Michael reaction **1.3.22** are not always stable, due to the reversibility of the process, the final products can be subsequently transformed into more stable derivatives such as amines (reduction), ketones (Nef reaction), etc. In the case of substrates **1.3.23** which contain a leaving group in the β-position of the double bond, the elimination of the leaving group affords alkenes **1.3.24**. As aforementioned, the *α*-proton of nitroalkanes **1.3.25** is acidic and therefore can be deprotonated, the obtained carbanion can itself be a good Michael donor (Scheme 16, c). During the last decades, enantioselective versions of this transformation were reported, apart from the use of chiral starting materials, different chiral organocatalysts were applied (i.e. cinchona alkaloids, prolines).[99] The application of nitro-compounds as Michael donors and acceptors was shown in different papers by Rodriguez *et al.*[100,101,102,103,104,105,106]

[96] Nielsen, A.T. "*The Chemistry of Nitro and Nitroso Groups; Chemistry of Functional Groups*" **1969**, *Part I*, 349 – 486.
[97] Metcalf, R.L. "*Organic Insecticides; Their Chemistry and Mode of Action*" **1955**, *134*.
[98] Ballini, R.; Araujo, N.; Gil, M.V.; Roman, E.; Serrano, J.A. *Chem. Rev.* **2013**, *113*, 3493 – 3515.
[99] Faisca Phillips, A.M. *Curr. Org. Synth.* **2016**, *13*, 687 – 725.
[100] Giorgi, G.; Lopez-Alvarado, P.; Miranda, S.; Rodriguez, J.; Carlos Menendez, C. *Eur. J. Org. Chem.* **2013**, *7*, 1327 – 1336.
[101] Fofana, M.; Dudognon, Y.; Bertrand, L.; Constantieux, T.; Rodriguez, J.; Ndiaye, I.; Bonne, D.; Bugaut, X. *Eur. J. Org. Chem.* **2020**, *23*, 3486 – 3490.
[102] Mailhol, D.; del Mar Sanchez Duque, M.; Raimondi, W.; Bonne, D.; Constantieux, T.; Coquerel, Y.; Rodriguez, J. *Adv. Synth. Cat.* **2012**, *354*, 3523 – 3532.
[103] Du, H. ; Rodriguez, J.; Bugaut, X.; Constantieux, T. *Chem. Eur. J.* **2014**, *20*, 8458 – 8466.
[104] Quintard, A.; Rodriguez, J. *Adv. Synth. Cat.* **2016**, *358*, 3362 – 3367.
[105] Raut, V.S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. *J. Am. Chem. Soc.* **2017**, *139*, 2140–2143
[106] Zhou, Y.; Wei, Y.-L.; Rodriguez, J.; Coquerel, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 456 – 460.



Scheme 16. Michael addition with nitro-compounds

The nitro-group **1.3.4** can easily be transformed into a carbonyl group **1.3.27** under acidic, oxidative or reducing conditions, this reaction is known as the Nef reaction (Scheme 17).[107] For the reaction under acidic conditions, HCl and H_2SO_4 are commonly used.[108] Different oxidants showed good reactivity, such as $KMnO_4$, *m*-CPBA, CAN, ozone, oxone, $NaClO_2$, etc. At the same time, $TiCl_3$ can efficiently reduce the nitro group into an oxime, which can be subsequently hydrolyzed into carbonyl group **1.3.27**.[109] However, the most used transformation of the nitro group is the reduction to nitroso, oxime and amino groups, which is highly used in pharmaceutical-oriented organic syntheses.[110,111] Various combinations of reducing agents have been developed for this purpose.



Scheme 17. Transformations of nitro-compounds

The replacement of the nitro-group by nucleophiles or hydrogen is well studied (Scheme 18). One of the methods bases on a radical process.[112] The alternative ionic replacement works well for allylic nitro-compounds, through three major pathways: a) *via* the assistance of transition metal;[113] b) *via* the activation with Lewis acid;[114] c) *via* the assistance of proton.[115] Denitrohydrogenation can be achieved *via* radical and

[107] Nef, J.U. *Justus Liebigs Annalen der Chemie*. **1894**, *280*, 263 – 291.
[108] Pinnick, H.W. *"Organic reactions"*, ed. By Paquette, L.A., **1990**, *38*, Chapter 3.
[109] McMurry, J.E.; Melton, J. *J. Am. Chem. Soc.* **1971**, *93*, 5309 – 5311.
[110] Formenti, D.; Ferretti, F.; Scharnagl, F.K.; Beller, M. *Chem. Rev.* **2019**, *119*, 2611 – 2680.
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[112] Kornblum, N. *Angew. Chem. Int. Ed.* **1975**, *14*, 734 – 745.
[113] Tamura, R.; Kato, K.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1987**, *52*, 4121 – 4124.
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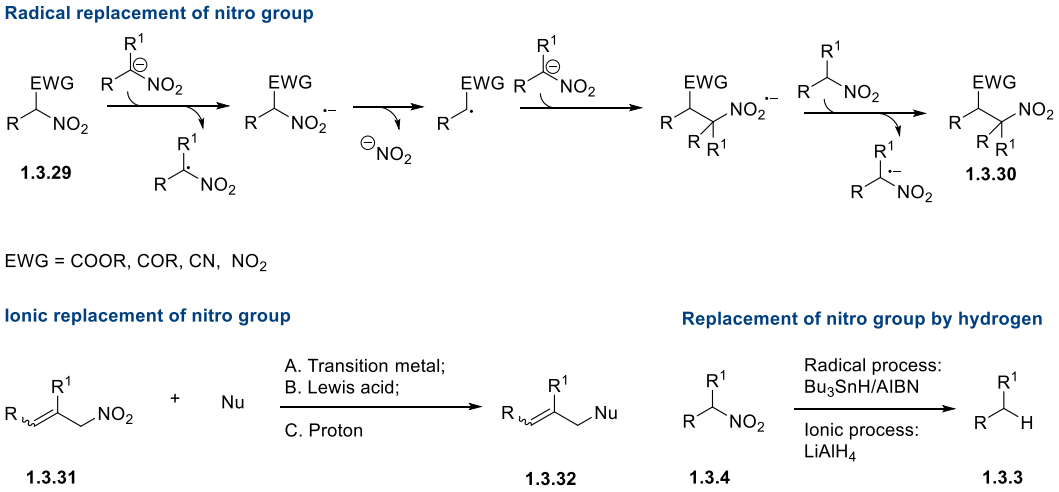
[115] Chung, J.Y.L.; Grabowski, E.J.J.; Reider, P.J. *Org. Lett.* **1999**, *1*, 1783 – 1785.

ionic processes. For radical transformations, a combination of Bu_3SnH with a radical initiator (such as AIBN) is commonly used,[116] for ionic process – reduction with $LiAlH_4$ can be performed.[117]

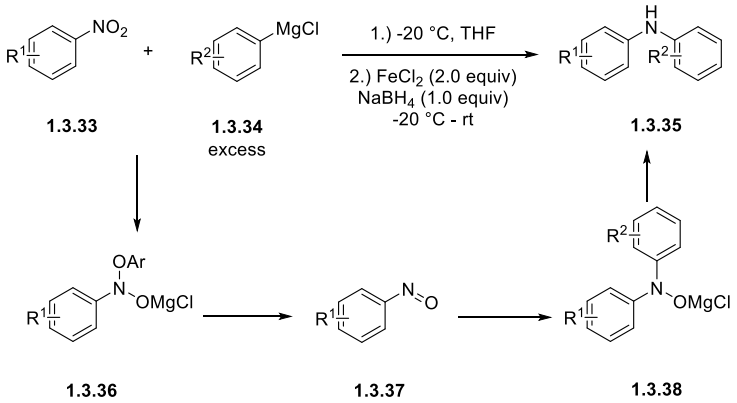


Scheme 18. Replacement of the nitro-group

The partially reduced nitro group (nitroso intermediate) is a highly active species and can participate in subsequent transformations, for example, cyclization (Cadogan-Sundberg reaction), alkylation or arylation. The Cadogan-Sundberg reaction was discussed previously in this chapter and only related reactions would be mentioned here. The main difficulties arise from the competitive over-reduction to aniline/amine or dimerization and tautomerization to oxime.

In 2002, Knochel *et al.* reported a nucleophilic C-N addition of aryl magnesium reagents **1.3.34** to nitroarenes **1.3.33** (Scheme 19).[118] This was the first example of a reductive transformation of nitro-compounds into diarylamines **1.3.35**. Unfortunately, an excess of the Grignard reagent was necessary and the reaction showed limited functional group tolerance. As for the mechanism of this transformation, the authors proposed that the first equivalent of Grignard reagent adds to the oxygen of the nitro-group affording nitroso derivative **1.3.37**. The addition of the second equivalent leads to the formation of desired C-N bond **1.3.38**, subsequent reductive work-up delivers the desired product **1.3.35**.[119]

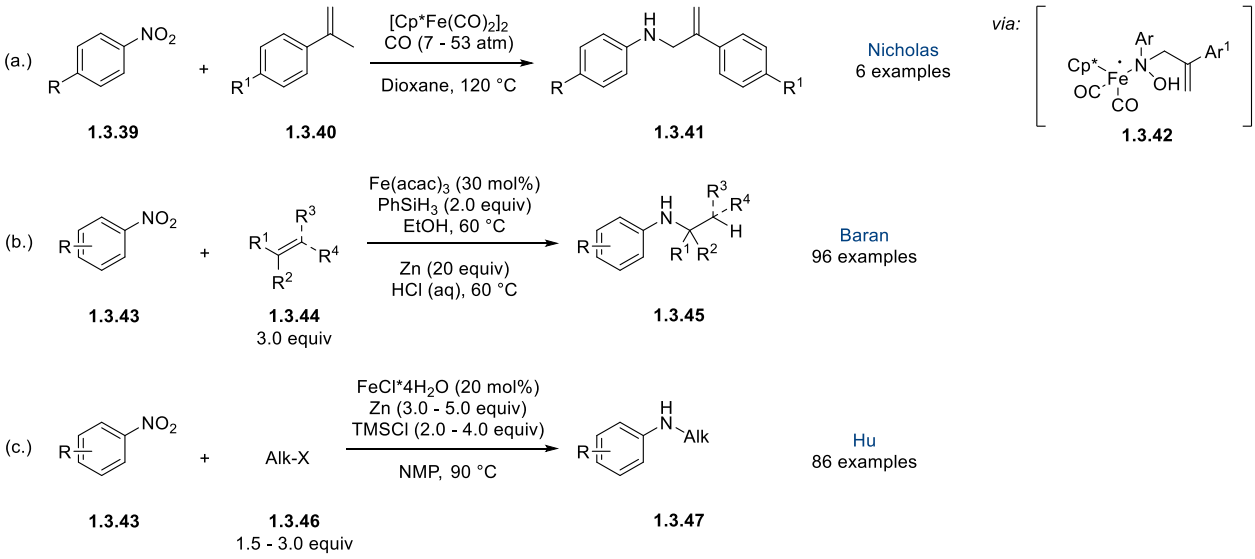
[116] Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705 – 1708.
[117] Rosini, G.; Ballini, R.; Zanotti, V. *Synthesis*, **1983**, 137 – 139.
[118] Sapountzis, I.; Knochel, P. *J. Am. Chem. Soc.* **2002**, *124*, 9390 – 9391.
[119] Dhayalan, V.; Knochel, P. *Synthesis* **2015**, *47*, 3246 – 3256.



Scheme 19. A nucleophilic C-N addition of aryl magnesium reagents to nitroarenes

In 2005, Nicholas and coworkers presented the iron-catalyzed reductive coupling of nitro-compounds **1.3.39** with alkenes, in the presence of CO gas as co-reductant (Scheme 20, a).[120] Based on control experiments and kinetic studies, the authors proposed that the coordination of alkene to the metal center followed by deoxygenation of the nitro-group and metal-assisted ene reaction, could lead to hydroxylamine complex **1.3.42**. Finally, the second deoxygenation would give allyl amine **1.3.41**. Ten years later, Baran *et al.* reported an iron-catalyzed synthesis of alkylamines **1.3.45** starting with nitroarenes **1.3.43** and alkenes **1.3.44** (di-, tri- and tetrasubstituted olefins), in the presence of silanes as hydrogen donors and Zn as reductant (Scheme 20, b).[121] A single electron transfer to the nitro-group was proposed to deliver nitroso-intermediate, which can be trapped by *in situ* formed reactive radical. Under these conditions, dimerization can be avoided due to the fast recombination of the radical. This direct transformation of the nitro-group into the amine is tolerant towards many functional groups (i.e. amines, alcohols, thiols, eliminating the need for protection). Unfortunately, only nitroarenes could be used with an excess of alkene. Inspired by the work of Baran group, Hu *et al.* showed an alternative coupling of nitroarenes **1.3.43** with alkyl halides **1.3.46** (Scheme 20, c).[122] Under optimized conditions, not only tertiary, but primary and secondary alkyl halides could be used. However, for the primary alkyl halides, elevated amounts of reducing agents and Lewis acid were used to avoid double alkylation. The active Fe(I)-species was generated by the reduction of Fe(II)-salt by Zn, this Fe(I)-specie subsequently generates an alkyl radical from alkyl halides. At the same time, the nitro-group is reduced by Zn to the nitroso intermediate, which is directly attacked by the radical. The reactivity was later expanded to the Ni-catalyzed transamidation of esters,[123] amides[124] and aminocarbonylation of alkyl halides starting with nitroarenes.[125] Related transformations were reported by the groups of Thomas[126] and Wang.[127]

[120] Srivastava, R.S.; Nicholas, K.M. *Organometallics* **2005**, *24*, 1563 – 1568.
[121] Gui, J.H.; Pan, C.M.; Jin, Y. ; Qin, T.; Lo, J.L.C.; Lee, B.J.; Spergel, S.H.; Mertzman, M.E.; Pitts, W.J.; La Cruz, T.E.; Schmidt, M.A.; Darvatkar, N.; Natarajan, S.R.; Baran, P. *Science* **2015**, *348*, 886 – 891.
[122] Cheung, C.W.; Hu, X. *Nat. Commun.* **2016**, *7*, 12494.
[123] Cheung, C.W.; Ploeger, M.L.; Hu, X. *Nat. Commun.* **2017**, *8*, 14878 – 14888.
[124] Cheung, C.W.; Ploeger, M.L.; Hu, X. *ACS Catalysis* **2017**, *7*, 7092 – 7096.
[125] Cheung, C.W.; Ploeger, M.L.; Hu, X. *Chem. Sci.* **2018**, *9*, 655 – 659.
[126] Zhu, K.; Shaver, M.P.; Thomas, S.P. *Chem. Sci.* **2016**, *7*, 3031 – 3035.
[127] Song, H.; Yang, Z.; Tung, C.-H.; Wang, W. *ACS Catal.* **2020**, *10*, 276 – 281.

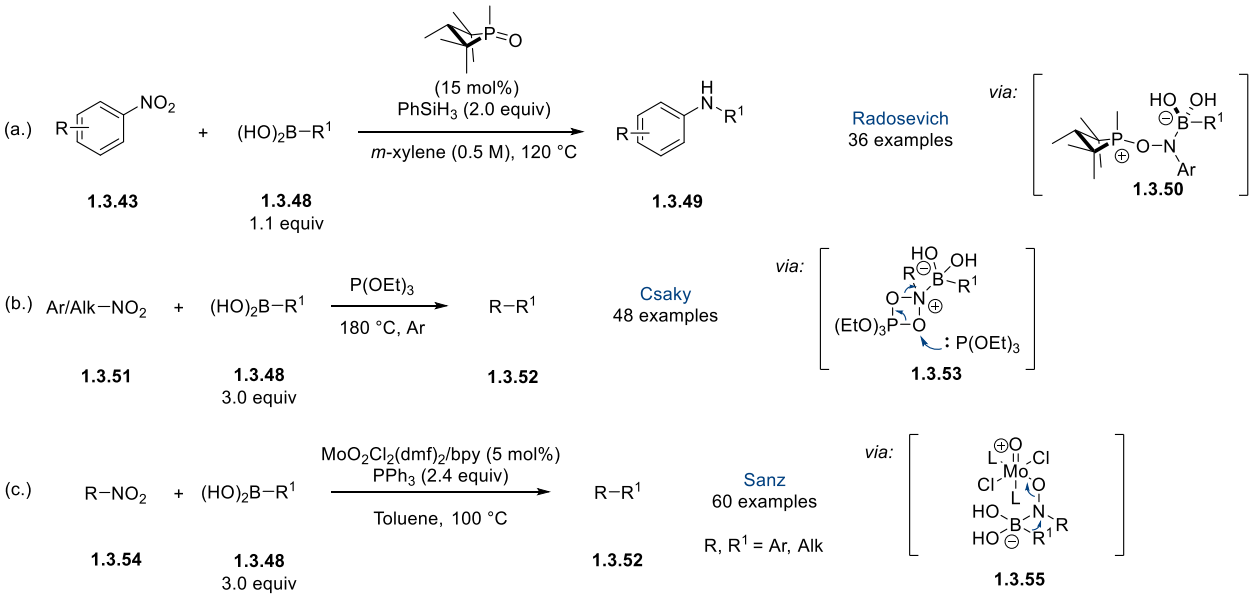


Scheme 20. Radical-mediated coupling of nitroarenes

Boronic acids can be convenient coupling partners for the reactions with nitro compounds, due to the ease of installation, functional group compatibility and synthetic versatility. At the same time, these substrates are less nucleophilic than, for example, Grignard reagents. Their reactivity can be enhanced by nucleophilic addition and the formation of an *ate*-complex. In 2018, Radosevich and coworkers applied their conditions for the intramolecular Cadogan-Sundberg reaction to the intermolecular coupling of nitroarenes **1.3.43** with organoboranes **1.3.48** (Scheme 21, a).[128] They showed that 1,2,2,3,4,4-hexamethylphosphetane can catalyze the reaction using phenylsilane as a terminal reductant. For the elucidation of the mechanism, the authors performed a deep analysis of the mechanism based on experimental data and DFT calculations.[129] They proposed that the process begins with the reduction of phosphetane catalyst to P(III), which can reduce the nitro-group to afford nitroso intermediate. The second deoxygenation leads to the formation of oxazaphosphirane, which reacts intermolecularly with boronic acid before the elimination of phosphetane oxide. The 1,2-metalate rearrangement of *ate*-complex **1.3.50** followed by hydrolysis delivers desired product **1.3.49**. Both arylboronic and alkylboronic acids can be used in this transformation. Csaky *et al*. later reported that an excess of triethyl phosphite can be used for the same purposes (Scheme 21, b).[130] The absence of oxime (product of tautomerization of nitrosoalkane) excluded the formation of nitroso-intermediate. The authors proposed that the reaction goes through the formation of the zwitterion **1.3.53**, which then proceeds through a ring-opening mediated by the coordination of the second molecule of triethyl phosphite. Although different amines, anilines and α-amino esters can be obtained with good yields, harsh reaction conditions limit the application of this transformation. Sanz and coworkers discovered an alternative method based on oxo-molybdenum catalyzed phosphine-mediated reductive coupling of nitro-compounds **1.3.54** with boronic acids **1.3.48** (Scheme 21,

[128] Nykaza, T.V.; Cooper, J.C.; Li, G.; Mahieu, N.; Ramirez, A. ; Luzung, M.R.; Radosevich, A.T. *J. Am. Chem. Soc.* **2018**, *140*, 15200 – 15205.
[129] Li, G.; Nykaza, T.V.; Cooper, J.C.; Ramirez, A. ; Luzung, M.R.; Radosevich, A.T. *J. Am. Chem. Soc.* **2020**, *142*, 6786 – 6799.
[130] Roscales, S.; Csaky, A.G. *Adv. Synth. Catal.* **2020**, *362*, 111 – 117.

c).[131] Both aromatic and alkyl nitro-compounds reacted well with arylboronic and alkylboronic acids. For the mechanism, the authors proposed that Mo(IV)-complex could reduce the nitro group to the nitroso, which could then either proceed in the formation of intermediate **1.3.51** (with PPh_3, similarly to work by Radosevich) or nitrenoid **1.3.55** to give the desired amine at the end.

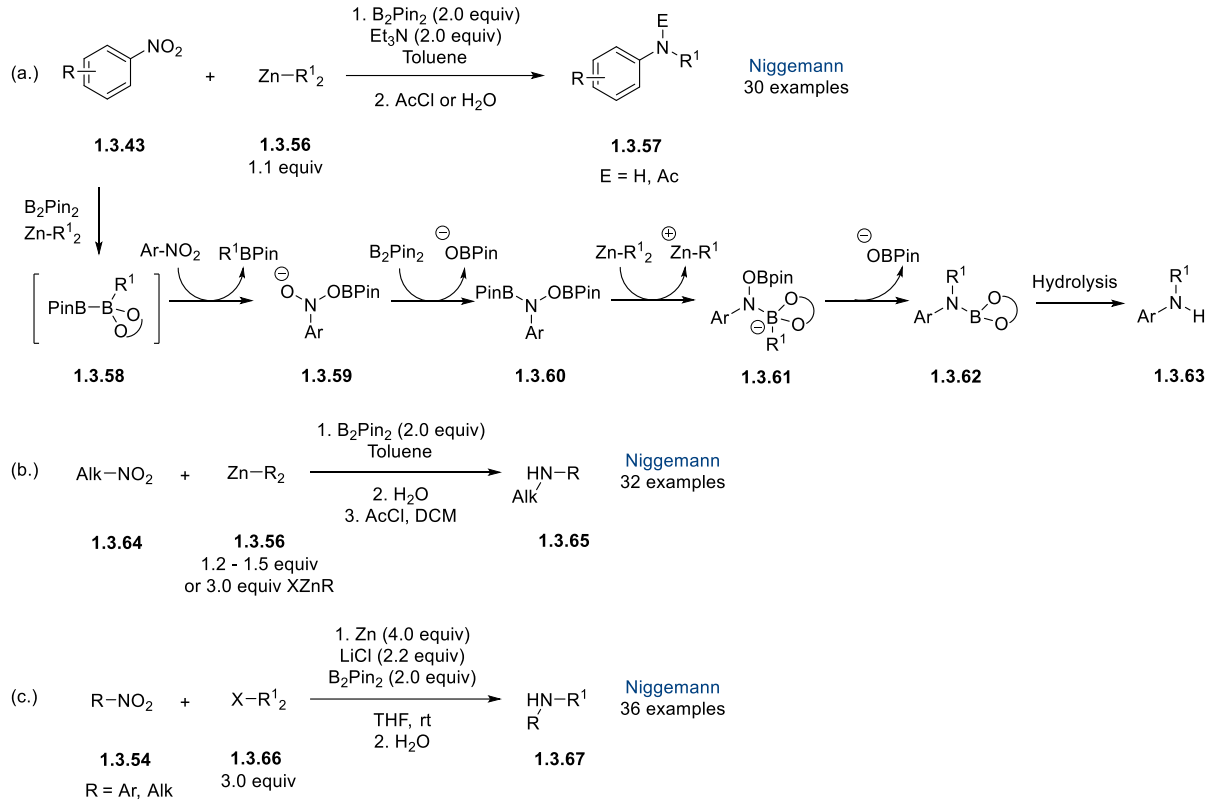


Scheme 21. Phosphine-mediated coupling of nitro-compounds with boronic acids

Nitrosoalkanes can easily proceed in side-reactions, such as dimerization and tautomerization into oximes. Niggemann *et al*. proposed an alternative method for the reductive coupling of nitro-compounds **1.3.43** *via* formation of more stable nitrenoid species **1.3.60** (Scheme 22, a).[132] The synthetic hypothesis was that if partially reduced O-alkylated nitronate **1.3.59** could react with B_2Pin_2, the nitroso-intermediate would be avoided, and instead, nitrenoid **1.3.60** would be obtained. In more details, the organozinc reagent would react with B_2Pin_2 to produce an active anion **1.3.58**. This anion attacks the oxygen atom of the nitro group **1.3.43** to form the nitronate **1.3.59**, which can react with B_2Pin_2 to form nitrenoid **1.3.60**. This intermediate **1.3.60** can be attacked by another molecule of organozinc leading to an "ate"-complex **1.3.61**. Subsequent alkyl transfer (1,2-migration) provides the desired aminoboranes **1.3.62**, which can be readily hydrolyzed to give free amines. A library of secondary amines and amides was synthesized in good yields and with good functional group compatibility. A year later, the authors expanded the scope and showed that primary, secondary and tertiary aliphatic nitro-compounds are well tolerated under the optimized conditions (Scheme 22, b).[133] This methodology was later applied to the reductive cross-coupling of nitro compounds with organohalides (Scheme 22, c).[134] Under metal-free conditions, an unprecedented coupling was achieved, based on the mechanism shown above, starting with the preformation of organozinc species from alkyl halides. The *in-situ* formation of organozinc was simplified by addition of LiCl, which is known to be responsible for the activation of zinc surface.[135] Both aliphatic and aromatic nitro compounds can be

[131] Suarez-Pantiga, S.; Hernandez-Ruiz, R.; Virumbrales, C.; Pedrosa, M.R.; Sanz, R. *Angew. Chem. Int. Ed.* **2019**, *58*, 2129 – 2133.
[132] Rauser, M.; Ascheberg, C.; Niggemann, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11570 – 11574.
[133] Rauser, M.; Ascheberg, C.; Niggemann, M. *Chem. Eur. J.* **2018**, *24*, 3970 – 3974.
[134] Rauser, M.; Eckert, R.; Gerbershagen, M.; Niggemann, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 6713 – 6717.
[135] Feng, C.; Cunningham, D.W.; Easter, Q.T.; Blum, S.A. *J. Am. Chem. Soc.* **2016**, *138*, 11156 – 11159.

efficiently used. The presented methodologies tolerate an increased steric environment around the nitro group and a variety of functional groups. As a complementary method for the known metal-catalyzed cross-coupling reactions, one of the advantages of this work is that electron-poor nitroarenes were particularly efficient. Similarly, hydroxylamines can be synthesized starting with nitro compounds *via* oxidation of aminoboranes **1.3.62** with molecular oxygen.[136]

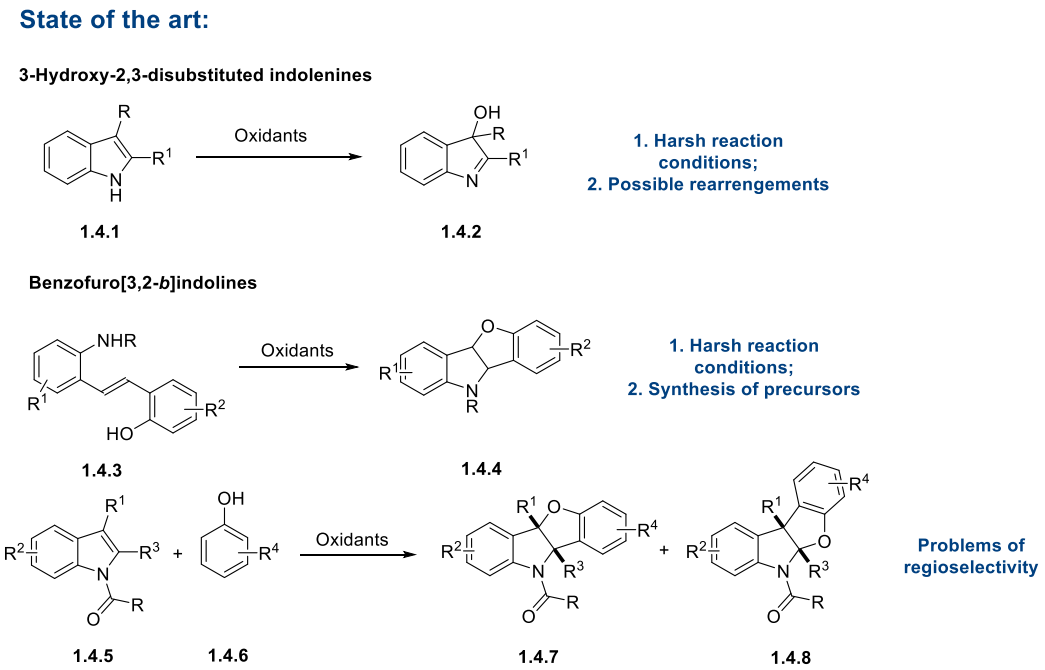


Scheme 22. Synthesis of anilines and amines from nitro-compounds via formation of nitrenoid species

1.4. Aims of the thesis

The development of new methods for the synthesis of indoles remains an important topic due to the prevalence of these scaffolds in bioactive compounds and materials. 3-Hydroxy-2,3-disubstituted indolenines **1.4.2** and benzofuro[3,2-*b*]indolines **1.4.4** are motifs found in different natural products: voacangine hydroxyindolenine, 7-hydroxymitragynine, terengganensine A, phalarine, etc. Most of the methods for the synthesis of these two types of "oxidized indoles" relied on oxidative conditions (Scheme 23). However, the harsh reaction conditions and the lack of regioselectivity are often associated with the existing synthetic methodologies.

[136] Rauser, M.; Warzecha, D.P.; Niggemann, M. *Angew. Chem. Int. Ed.* **2018**, *57*, 5903 – 5907.

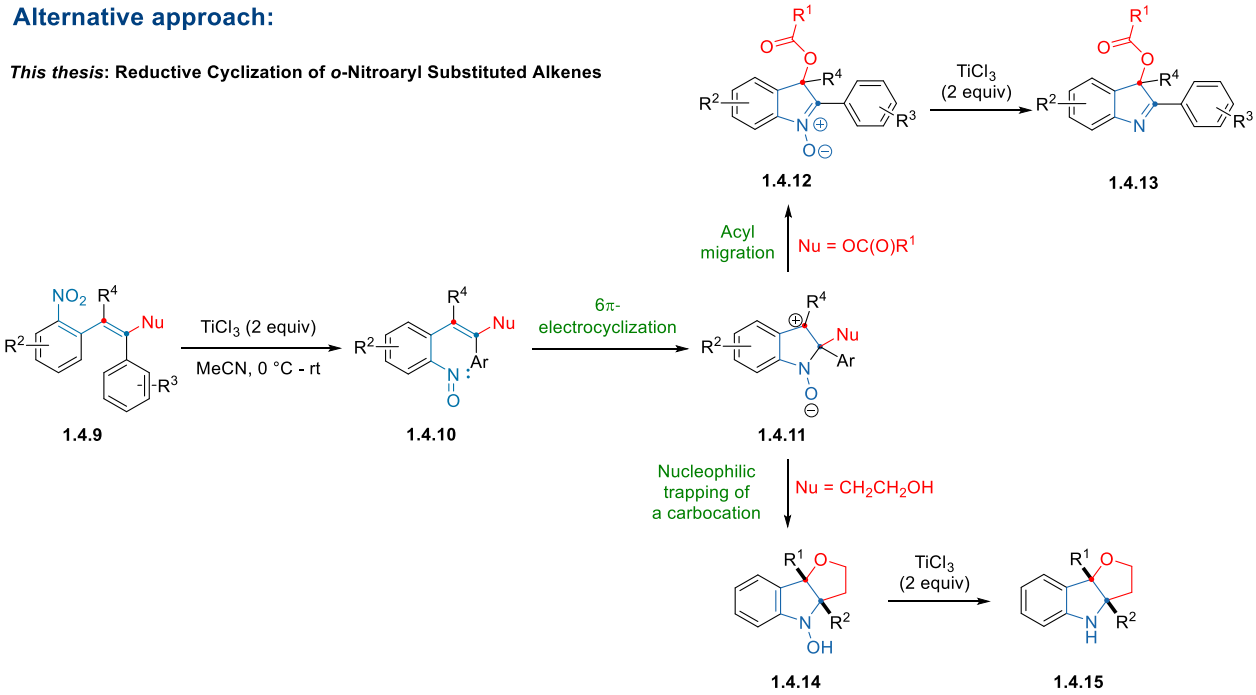


Scheme 23. State of the art: synthesis of 3-hydroxy-2,3-disubstituted indolenines and benzofuro[3,2-b]indolines

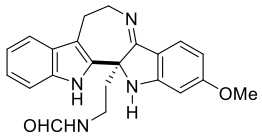
Our group has recently developed a $TiCl_3$-mediated reductive cyclization of functionalized *o*-nitrostyrenes and applied it to the total syntheses of a number of complex natural products. Aimed at exploiting the full synthetic potential of the $TiCl_3$-mediated Cadogan-Sundberg reaction, we became interested in investigating the reductive cyclization of previously unexplored 2-nitroaryl substituted alkenes. Towards this end, we developed novel syntheses of 3-acyloxy-2,3-disubstituted indolenines (**Chapter 2**) and (benzo)furo[3,2-*b*]indolines (**Chapter 4**) *via* reductive cyclization of the corresponding trisubstituted enol esters and tetrasubstituted alkenes bearing an internal nucleophile, respectively (Scheme 24). Conceptually, these important heterocycles are accessed for the first time under reductive cyclization conditions. Approaches towards the total synthesis of trigonoliimine C and phalarine featuring these two transformations as key steps are detailed in **Chapter 3** and **4** respectively (Scheme 24).

Alternative approach:

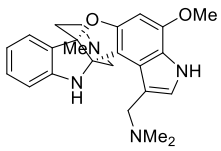
***This thesis*: Reductive Cyclization of *o*-Nitroaryl Substituted Alkenes**



Natural products synthesis:



(–)-Trigonoliimine C (**1.4.16**)



(–)-Phalarine (**1.4.17**)

Scheme 24. Goals of the thesis

Chapter 2. Synthesis of 3-Acyloxyindolenines by $TiCl_3$-Mediated Reductive Cyclization of 2-(*ortho*-nitro)aryl Substituted Enol Esters

2.1. Introduction

2.1.1. 3-Hydroxy-2,3-disubstituted indolenine

The 3-hydroxy-2,3-disubstituted indolenine **2.1.1** is an interesting structural motif in the drug discovery and is found in many bioactive molecules such as voacangine hydroxyindolenine,[137] 7-hydroxymitragynine,[138] terengganensine A[139] and alsmaphorazine D,[140] etc. (Figure 1, a). This scaffold is readily converted *via* an *aza*-pinacol rearrangement to indolinone which is another important bicyclic skeleton widely present in natural products. We note that this 1,2-rearrangement could nevertheless be a side reaction when one aims towards the synthesis of 3-hydroxyindolenine. In addition, the rearrangement could afford different products **2.1.2 – 2.1.4** depending on the reaction conditions which could further complicate the synthesis of 3-hydroxyindolenine (Figure 1, b).

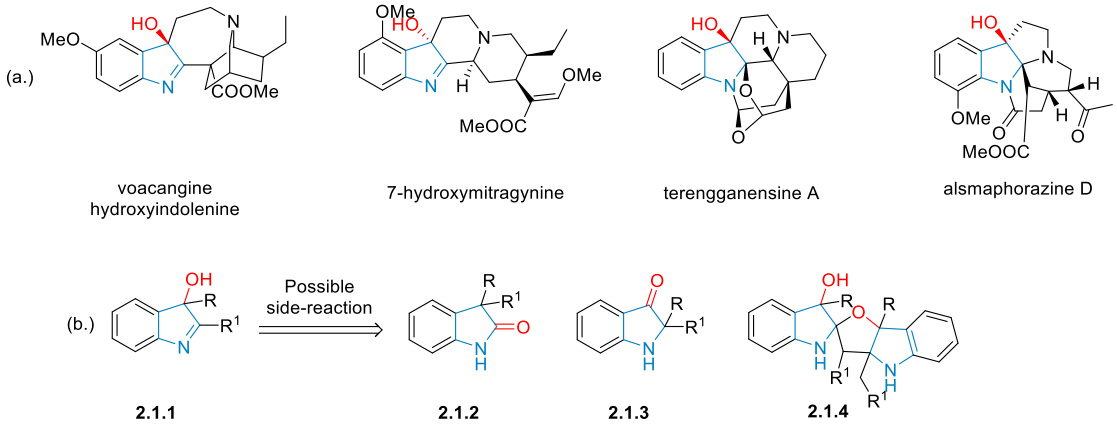
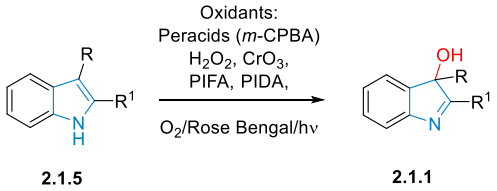


Figure 1. Natural products containing 3-hydroxy-2,3-disubstituted indolenine moiety

Most of the synthetic methods for the synthesis of 3-hydroxy indolenines **2.1.1** relied on the oxidation of preformed indoles **2.1.5** under harsh conditions (Scheme 25).[141] The oxidation can be performed by

[137] (a) Thomas, D. W.; Biemann, K. *Tetrahedron* **1968**, *24*, 4223 – 4231; (b) Madinaveitia, A.; de la Fuente, G.; González, A. *Helv. Chim. Acta* **1998**, *81*, 1645 – 1653.
[138] (a) Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Kikuchi, M.; Kurihara, M.; Kitajima, M.; Aimi, N.; Sakai, S.-I. *Planta Med.* **1994**, *60*, 580 – 581; (b) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L.T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949 – 1956.
[139] (a) Isolation, see: Uzir, S.; Mustapha, A.M.; Hadi, A.H.A.; Awang, K.; Wiart, C.; Gallard, J.-F.; Païs, M. *Tetrahedron Lett.* **1997**, *38*, 1571 – 1574; (b) Total synthesis, see: Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556 – 6560.
[140] Koyama, K.; Hirasawa, Y.; Nugroho, A.E.; Kaneda, T.; Hoe, T.C.; Chan, K.-L.; Morita, H. *Tetrahedron* **2012**, *68*, 1502 – 1506.
[141] Witkop, B.; Patrick, J.B. *J. Am. Chem. Soc.* **1951**, *73*, 2188 – 2195.

employing stoichiometric oxidants such as peracids,[142] oxaziridines,[143] hypervalent iodine(III) reagents,[144] Mo-complexes,[145] dimethyldioxirane,[146] or photooxidation.[147] Furthermore, problems of chemoselectivity arise under oxidative conditions since products of competing C2, C3 and N-oxidation, as well as the Witkop oxidation could take place.[148,149]



2.1.5 **2.1.1**

Scheme 25. Synthesis of 3-hydroxy-2,3-disubstituted indolenines via oxidative conditions

During the last decade, enantioselective versions of this process were also reported. The first example of highly chemoselective and stereoselective oxidation of indoles was developed by Miller *et al.*[150] In the presence of aspartyl peptide catalyst and H_2O_2, diversely substituted indoles **2.1.6** were converted to 3-hydroxy-2,3-disubstituted indolenines **2.1.7** in good yields with high enantioselectivities (Scheme 26, a). Enantioselective epoxidation of the indole ring followed by intramolecular epoxide opening is a powerful means to access hydroxyfuroindolines. In 2014, You *et al.* reported a vanadium mediated enantioselective epoxidation of the tryptofols **2.1.8** (Scheme 26, b).[151] Chiral BHA (bis-hydroxamic acid) ligand **L1** was responsible for high level of enantioselectivity. A year later, the authors expanded the scope using a tethered phenol **2.1.10** as a nucleophile (Scheme 26, c).[152] In 2018, Knowles *et* al. reported the first enantioselective oxidation of indoles **2.1.12** *via* noncovalent stabilization (Scheme 26, d).[153] The authors hypothesized that the formation of a hydrogen bond between chiral phosphate and indole NH may reduce the oxidation potential of starting material **2.1.12**. Single-electron oxidation would produce a tryptamine radical cation **2.1.14** which, upon enantioseletive nucleophilic attack on the iminium cation would be converted to radical.

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[142] Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 6556– 6560; *Angew. Chem.* **2016**, *128*, 6666 – 6670; b) Williams, R. M.; Glinka, T.; Kwast, E. *J. Am. Chem. Soc.* **1988**, *110*, 5927 – 5929; c) Guller, R.; Borschberg, H.-J. *Helvetica Chimica Acta* **1993**, *76*, 1847 – 1862.

[143] a) Han, S.; Morrison, K.C.; Hergenrother, P.J.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 473 – 486; b) Liu, S.; Scotti, J.S.; Kozmin, S.A. *J. Org. Chem.* **2013**, *78*, 8645 – 8654; c) Mercado-Marin, E.V. Garcia-Reynaga, P.; Romminger, S.; Pimenta, E.F.; Romney, D.K.; Lodewyk, M.W.; Williams, D.E.; Andersen, R.J.; Miller, S.J.; Tnatillo, D.J.; Berlinck, R.G.S.; Sarpong, R. *Nature* **2014**, *509*, 318 – 324.

[144] Kruegel, A. C.; Gassaway, M.M.; Kapoor, A.; Varadi, A.; Majumdar, S.; Filizola, M.; Javitch, J.A.; Sames, D. *J. Am. Chem. Soc.* **2016**, *138*, 6754 – 6764; b) Takayama, H.; Misawa, K.; Okada, N.; Ishikawa, H.; Kitajima, M.; Hatori, Y.; Murayama, T.; Wongseripipatana, S.; Tashima, K.; Matsumoto, K.; Horie, S. *Org. Lett.* **2006**, *8*, 5705 – 5708.

[145] Kawasaki, T.; Chiem, C.-S.; Sakamoto, M. *Chem. Lett.* **1983**, 855 – 858.

[146] a) Zhao, G.; Hie, X.; Sun, H.; Yuan, Z.; Zhong, Z.; Tang, S.; She, X. *Org. Lett.* **2016**, *18*, 2447 – 2450; b) Movassaghi, M.; Schmidt, M.A.; Ashenhurst, J.A. *Org. Lett.* **2008**, *10*, 4009 – 4012; c) Zhu, C.; Liu, Z.; Chen, G.; Zhang, K.; Ding, H. *Angew. Chem.* **2015**, *127*, 893 – 896.

[147] a) Lerch, S.; Unkel, L.-N.; Brasholz, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 6558 – 6562; *Angew. Chem.* **2014**, *126*, 6676 – 6680; b) Ferroud, C.; Rool, P. *Heterocycles* **2000**, *55*, 545 – 555.

[148] Xu, J.; Liang, L.; Zheng, H.; Chi, Y. R.; Tong, R. *Nat. Commun.* **2019**, *10*, 4754 – 4765 and references cited therein.

[149] a) Witkop, B.; Patrick, J. B.; Rosenblum, M. *J. Am. Chem. Soc.* **1951**, *73*, 2641 – 2647; b) Ihara, M.; Noguchi, K.; Fukumoto, K. *Tetrahedron* **1985**, *41*, 2109 – 2114.

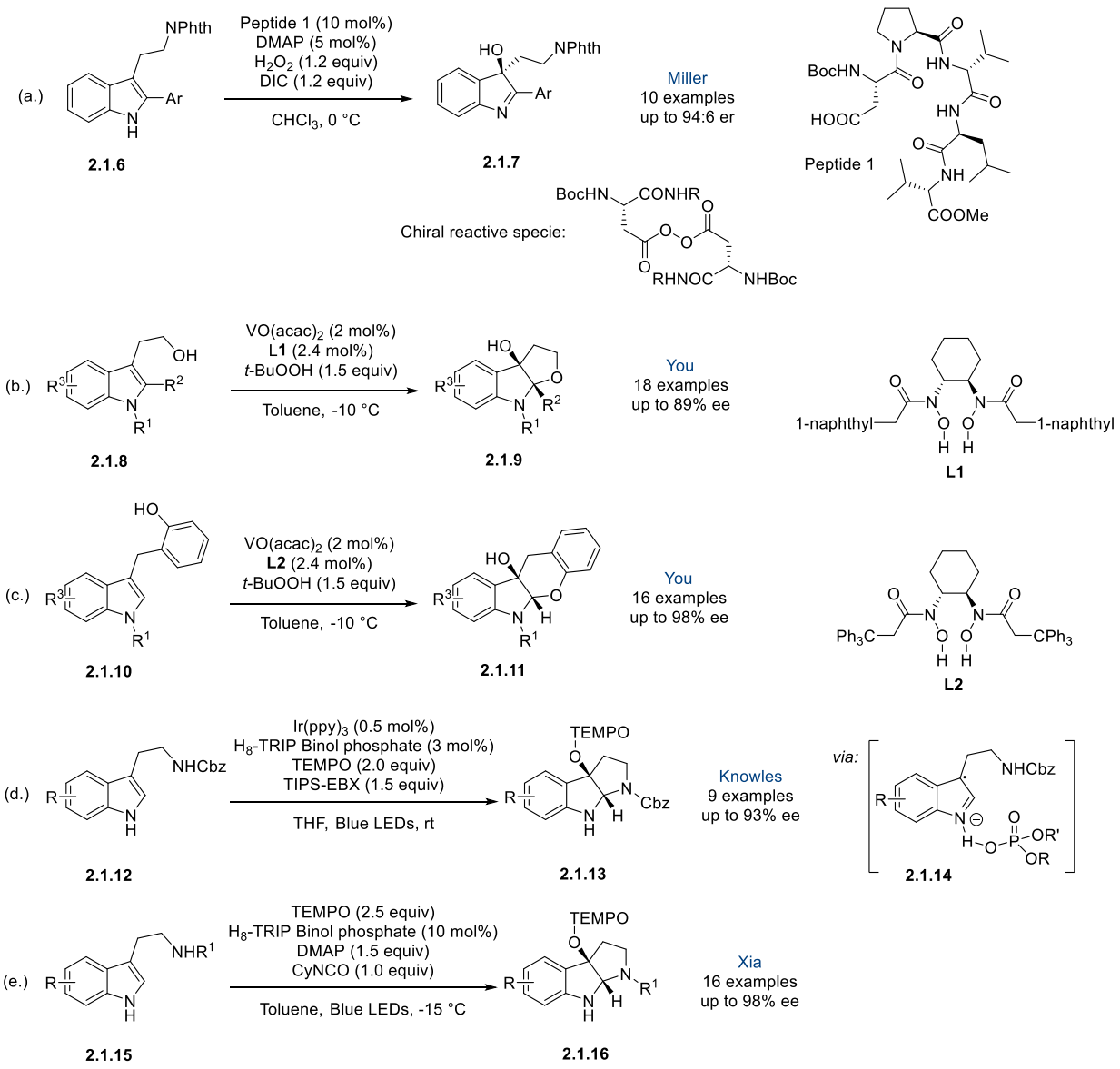
[150] Kolundzic, F.; Noshi, M.N.; Tjandra, M.; Movassaghi, M.; Miller, S.J. J. Am. Chem. Soc. 2011, 133, 9104 – 9111.

[151] Han, L.; Liu, C.; Zhang, W.; Shi, X.-X.; You, S.-L. *Chem. Commun.* **2014**, *50*, 1231 – 1233.

[152] Han, L.; Zhang, W.; Shi, X.-X., You, S.-L. *Adv. Synth. Catal.* **2015**, *357*, 3064 – 3068.

[153] Gentry, E.C.; Rono, L.J.; Hale, M.E.; Matsuura, R.; Knowles, R.R. *J. Am. Chem. Soc.* **2018**, *140*, 3394 – 3402.

Trapping of the formed radical with TEMPO delivers pyrroloindoline **2.1.13**. The whole process is known as reductive proton-coupled electron transfer (PCET). Precise tuning of catalytic system can ensure the selectivity of the process, due to the hydrogen-bonding stabilization. In this paper an Ir-redox catalyst was used in combination with TRIP-BINOL phosphate as a chiral base, while few months later Xia *et al.* showed that the process can be performed by visible light excited TEMPO (Scheme 26, e).[154]

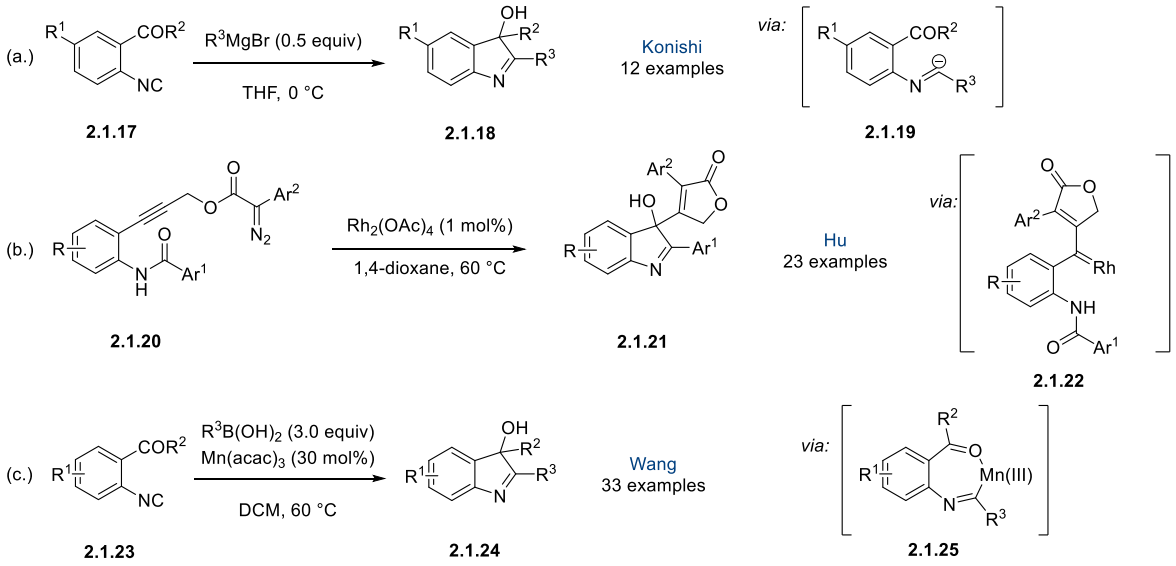


Scheme 26. Stereoselective synthesis of 3-hydroxy-2,3-disubstituted indolenines

On the other hand, methods for the direct synthesis of 3-hydroxy-2,3-disubstituted indolenines have also been developed during the last decade. In 2010, Konishi and coworkers showed that nucleophilic addition of Grignard reagents to 2-isocyanophenyl ketones **2.1.17** leads to the formation of imidoyl anion intermediate **2.1.19**, which can cyclize to give 3-hydroxy-2,3-disubstituted indolenine **2.1.18** (Scheme 27,

[154] Liang, K.; Tong, X.; Li, T.; Shi, B.; Wang, H.; Yan, P.; Xia, C. *J. Org. Chem.* **2018**, *83*, 10948 – 10958.

a).[155] Though the reaction worked with good yields, an excess of ketone was necessary to avoid side-products and decomposition of the starting material **2.1.17**. Later, Hu and coworkers disclosed a Rh-catalyzed conversion of diazo compound **2.1.20** to various 3-hydroxy-2,3-disubstituted indolenines **2.1.21**. A domino process involving carbene formation followed by carbene-alkyne metathesis, C-O bond insertion and oxygen atom transfer was proposed to account for the reaction outcome (Scheme 27, b).[156] Wang and coworkers reported a Mn-catalyzed reaction of 2-acyl aromatic isocyanides **2.1.23** with boronic acids for the synthesis of **2.1.24** (Scheme 27, c).[157] The coordination of Mn to the isocyanide followed by transmetalation and nucleophilic addition delivered intermediate **2.1.25** which, upon cyclization, was converted to 3-hydroxy-2,3-disubstituted indolenines **2.1.24** in good yields and with excellent functional group compatibility.



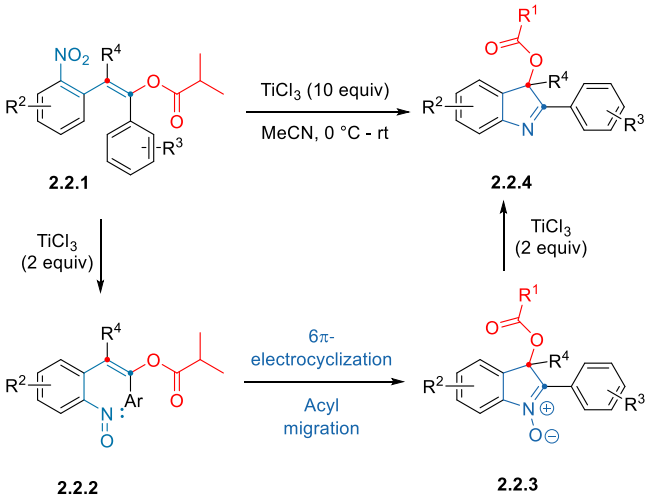
Scheme 27. Metal-mediated synthesis of 3-hydroxy-2,3-disubstituted indolenines

2.2. **Goal of the chapter**

As we discussed in the previous section, oxidation of indoles is the most general method to access 3-hydroxy-2,3-disubstituted indolenines. However, this method suffers from functional group compatibility and competitive side-reactions. Therefore, development of new and convenient method for the synthesis of this heterocycle is of considerable merit. To the best of our knowledge, synthesis of 3-hydroxyindolenines under reductive conditions has not been reported yet. In connection with our laboratory's earlier work on $TiCl_3$-mediated reductive cyclization of *o*-nitrostyrene derivatives,[66,67] we became interested in $TiCl_3$-mediated reductive cyclization of 2-(*ortho*-nitroaryl)-substituted enol esters **2.2.1** (Scheme 28). Assuming that the acyloxy group has a higher migratory aptitude than the aryl group, we hypothesized that the chemoselective reduction of the nitro group would generate a nitroso intermediate **2.2.2** that could then

[155] Kobayashi, K.; Okamura, Y.; Fukamachi, S.; Konishi, H. *Tetrahedron* **2010**, *66*, 7961 – 7964.
[156] Jia, S.; Dong, G.; Ao, C.; Jiang, X.; Hu, W. *Org. Lett.* **2019**, *21*, 4322 – 4326.
[157] Liu, J.; Li, L.; Bu, X.; Yuan, Y.; Wang, X.; Sun, R.; Zhou, M.-D.; Wang, H. *Org. Chem. Front.* **2022**, *9*, 2486 – 2490.

undergo a 5-atom-6π-electrocyclization followed by a 1,2-acyl migration forming the nitrone intermediate **2.2.3**. Subsequent reduction of **2.2.3** could then deliver indolenine **2.2.4** in a single operation.

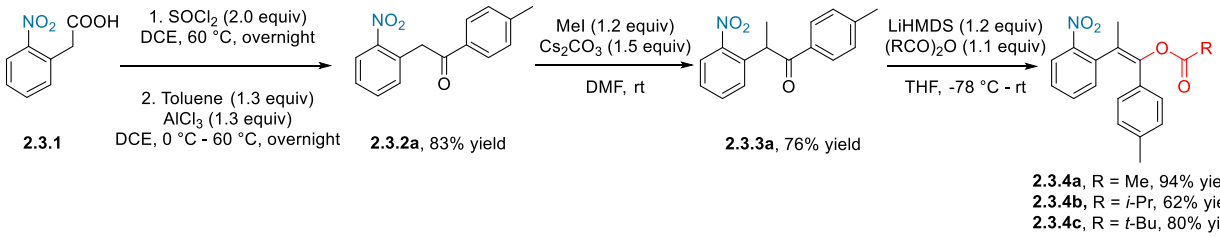


*Scheme 28. Reductive cyclization of o-nitroaryl substituted enol ester **2.2.1***

2.3. $TiCl_3$-Mediated Reductive Cyclization of 2-(*ortho*-nitro)aryl Substituted Enol Esters

2.3.1. Synthesis of starting materials

The model substrates **2.3.4a-c** were synthesized from 2-(2-nitrophenyl)acetic acid **2.3.1** (Scheme 29). Conversion of 2-nitrophenylacetic acid **2.3.1** to the acyl chloride followed by Friedel-Crafts reaction with toluene afforded ketone **2.3.2** in 83% yield.[158] Alkylation of **2.3.2** with MeI provided **2.3.3** in 76% yield. From ketone **2.3.3,** three different enol esters were synthesized by deprotonation of starting material followed by quenching with different anhydrides.

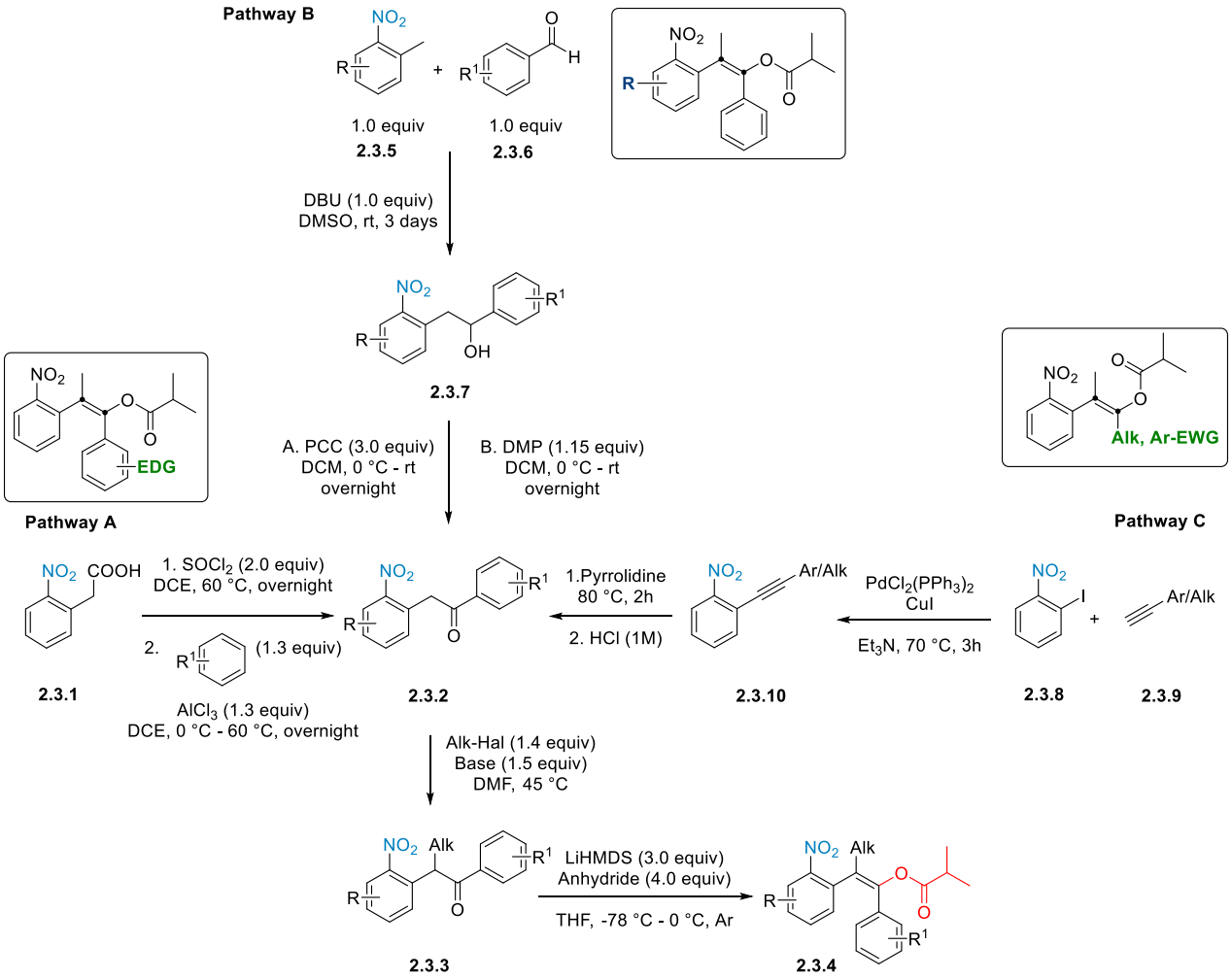


*Scheme 29. Synthesis of model substrates – 2-(o-nitro)aryl substituted enol ester **2.3.4a-c***

Different synthetic routes were subsequently developed for the synthesis of ketones **2.3.2** as it is shown in Scheme 30. A) Friedel-Crafts reaction for the preparation of ketones bearing an electron-rich aromatic ring (pathway A); b) aldol/oxidation sequence for the synthesis of substrates containing different functional groups on the nitro-arene ring (pathway B); c) Sonogashira coupling followed by regioselective

[158] Xu, J.; Xia, J.; Lan, Y. *Synthetic Comm.* **2005**, *35*, 2347 – 2353.

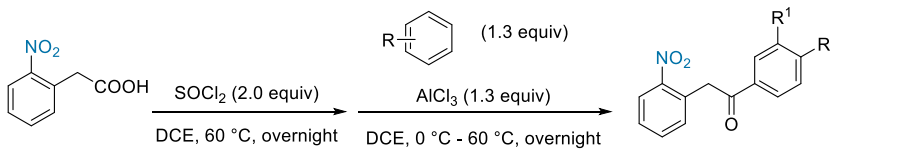
hydrolysis of the resulting internal alkynes **2.3.10** to access substrates bearing an electron poor aromatic rings or alkyl chains (pathway C).



*Scheme 30. General scheme for the synthesis of 2-(o-nitro)aryl substituted enol ester **2.1.33***

Pathway A

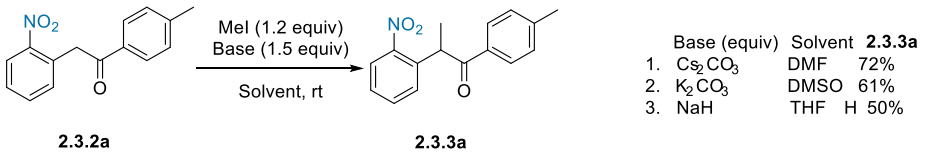
The $AlCl_3$-promoted Friedel-Crafts reaction of 2-(2-nitrophenyl)acetyl chloride with toluene, anisole and 1,2-dimethoxybenzene afforded the corresponding ketones **2.3.2a**, **2.3.2m**, **2.3.2o** in moderate to good yields (Scheme 31).



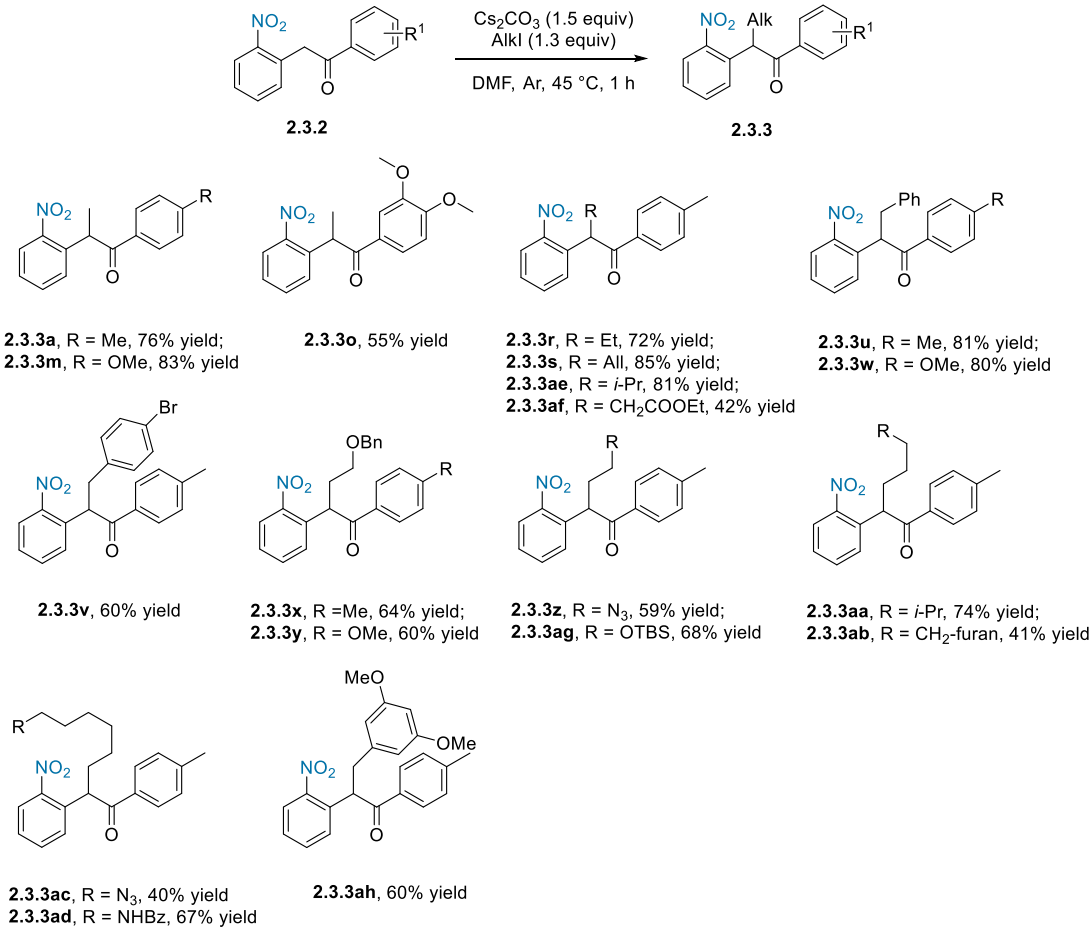
2.3.2a, R = Me, R^1 = H, 83% yield;
2.3.2m, R = OMe, R^1 = H, 77% yield;
2.3.2o, R = OMe, R^1 = OMe, 45% yield

*Scheme 31. Synthesis of ketone **2.3.2** via Friedel-Crafts reaction*

For the alkylation step 3 different conditions were tested on substrate **2.3.2a**, results are shown in Scheme 32. Combination of Cs_2CO_3/DMF turned out to be the most efficient and was applied for all subsequent reactions. When NaH was used as a base, the reaction became messy providing product in 50% isolated yield. With these conditions in hand, *C*-alkylation of ketone **2.3.2** with different alkyl halides gave corresponding ketones in good to excellent yields (Scheme 33). While methylation occurred at room temperature, alkylation with other alkyliodides needed to be performed at 45 °C to ensure that the reaction proceeded in a reasonable timeframe (under 3 hours). Different functional groups were incorporated such as: Allyl (**2.3.3s**), ester (**2.3.3af**), ethers (**2.3.3x**, **2.3.3y**), N_3 (**2.3.3z**, **2.3.3ac**), furanyl (**2.3.3ab**), amide (**2.3.3ad**). *O*-alkylation was observed in some cases, however, the *O*-alkylated product could be easily separated from the desired ketone **2.3.3** *via* purification by column chromatographic.

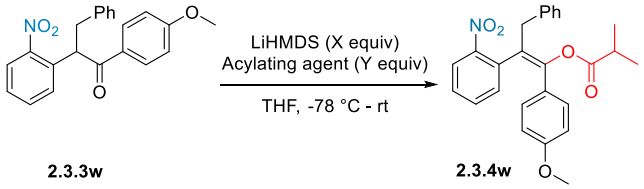


*Scheme 32. Optimization of the conditions for the alkylation of ketone **2.1.3***



*Scheme 33. Synthesis of ketone **2.1.32** via alkylation*

O-Acylation of in situ formed enolate was optimized with the substrate **2.3.3w**, results are presented in Table 1. In the case of substrates **2.3.3a**, **2.3.3m**, **2.3.3o** with Me-substituent the reaction worked well within few hours. However, replacement of Me-group by any bigger substituent led to lower reactivity. Firstly, it was found, that ketones underwent decomposition slowly at ambient temperatures in the presence of a strong base (LiHMDS, NaH, *t*-BuOK, entry 1). Decreasing the reaction temperature to -78 °C solved the problem as starting material could be totally recovered after quenching with water. Time of prestirring of ketone and base was increased to 1 h, due to the slow deprotonation at low temperature (entries 2-3). Upon deprotonation the solution slowly changes the color from orange to purple. With low loadings of base and acylating agent – only starting material is recovered (entries 2-4). The desired product was isolated in an excellent 90% yield when the amount of base and anhydride were increased to 3.0 and 4.0 equiv accordingly (entry 6). An excess of the acylating agent is probably necessary due to the low reactivity of the starting material. Replacement of anhydride by acyl chloride leads to a lower conversion (entry 7).



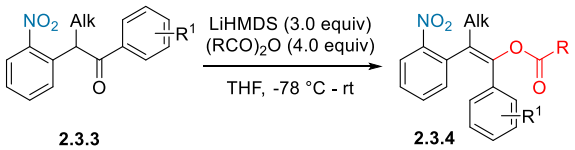
2.3.3w **2.3.4w**

	LiHMDS	Acylating agent	t (SM+base), min/h	T °C	**Results**[a]
1.	1.2 equiv	Anhydride (1.1 equiv)	5 min	0 °C - rt	Slow decomposition
2.	1.2 equiv	Anhydride (1.1 equiv)	5 min	-78 °C - rt	SM
3.	1.2 equiv	Anhydride (1.1 equiv)	1 h	-78 °C - rt	SM
4.	1.5 equiv	Anhydride (1.4 equiv)	1 h	-78 °C - rt	SM
5.	1.5 equiv	Anhydride (2.0 equiv)	1 h	-78 °C - rt	SM : **2.3.4w** (65:35)
6.	3.0 equiv	Anhydride (4.0 equiv)	1 h	-78 °C - rt	90% yield
7.	3.0 equiv	Acyl chloride (4.0 equiv)	1 h	-78 °C - rt	Low converison

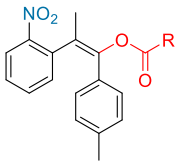
[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 1. Optimization of the conditions for the synthesis of 2-(o-nitro)aryl substituted enol ester **2.1.32w** from ketone **2.1.31w***

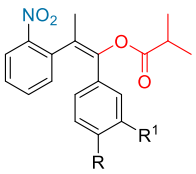
With the optimized conditions in hand, enol esters **2.3.4** were synthesized (Scheme 34). Except for one enol ester **2.3.4d**, which was obtained as a mixture of *E*- and *Z*- isomers (*E*/*Z* = 1:1), all the other enol esters were synthesized as a single *E*-isomer, the X-ray structures of three substrates confirms the preferred *E*-configuration (Figure 2). The exceptional low stereoselectivity for the formation of the enol ester **2.3.4d** can be explained by π-stacking between the aromatic rings. Ketones bearing an α-secondary alkyl chains failed to participate in the reaction. Substrate **2.3.3af** gave a side-product, where the double bond was conjugated between the nitro arene and ester. Carbamate **2.3.4e** was synthesized in a similar way using triphosgene and dipropyl amine as trapping reagents.



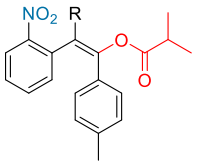
2.3.3 **2.3.4**



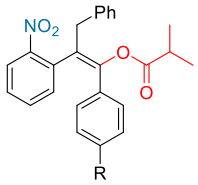
2.3.4a, R = Me, 94% yield;
2.3.4b, R = *i*-Pr, 62% yield;
2.3.4c, R = *t*-Bu, 80% yield;
2.3.4d, R = Ph, 32% yield;
2.3.4e, R = NPr_2, 82% yield



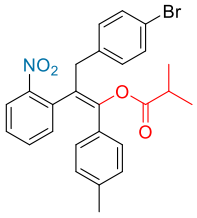
2.3.4m, R = OMe, R^1 = H, 90% yield;
2.3.4o, R = OMe, R^1 = OMe, 57% yield



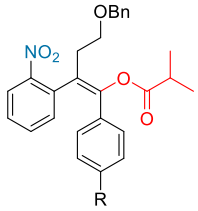
2.3.4r, R = Et, 42% yield;
2.3.4s, R = Allyl, 84% yield;
2.3.4ae, R = *i*-Pr, SM;
2.3.4af, R = CH_2COOEt, SP



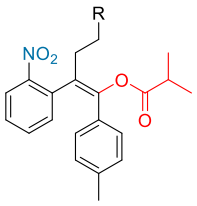
2.3.4u, R = Me, 68% yield;
2.3.4w, R = OMe, 51% yield



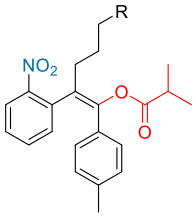
2.3.4v, 52% yield



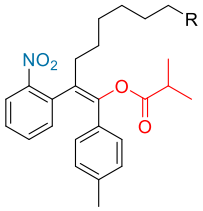
2.3.4x, R =Me, 96% yield;
2.3.4y, R = OMe, 74% yield



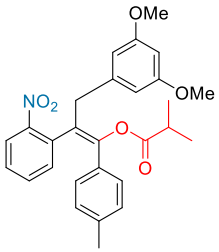
2.3.4z, R = N_3, 46% yield;
2.3.4ag, R = OTBS, 52% yield



2.3.4aa, R = *i*-Pr, 83% yield;
2.3.4ab, R = CH_2-furan, 85% yield



2.3.4ac, R = N_3, 62% yield
2.3.4ad, R = NHBz, 56% yield



2.3.4ah, 82% yield

*Scheme 34. Synthesis of 2-(o-nitro)aryl substituted enol esters **2.3.4** from ketones **2.3.3***

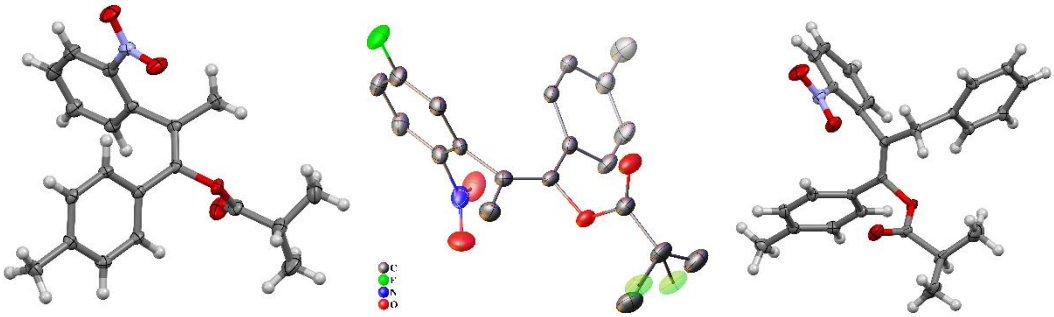
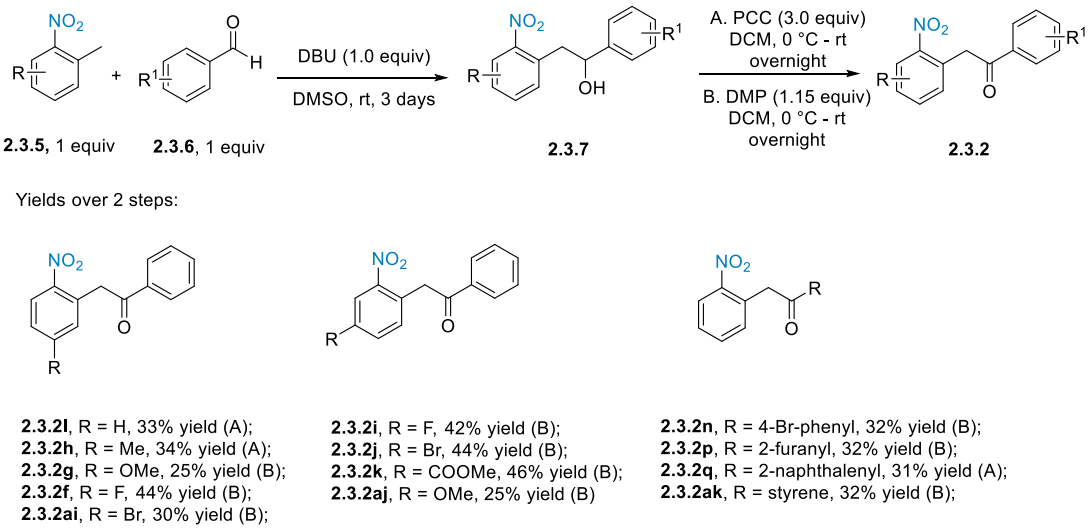


*Figure 2. X-ray structures of 2-(o-nitro)aryl substituted enol esters **2.3.4a, 2.3.4f** and **2.3.4u***

Pathway B

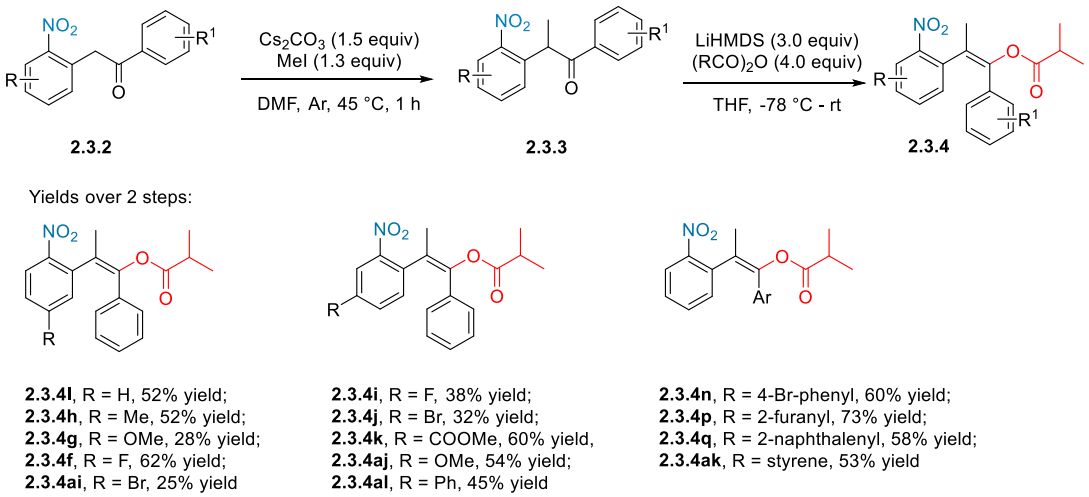
Due to the low availability of substituted nitroarenes and the fact that Friedel-Crafts reaction works efficiently with only electron-rich aromatics, a second synthetic route was developed based on the literature reports.[159,160,161] The deprotonation of 2-nitro-toluene **2.3.5** followed by nucleophilic attack on the aldehyde **2.3.6** delivered alcohols **2.3.7** in moderate yields (Scheme 35). Substrates with electron-donating groups on the nitroarene ring were isolated in low yields, due to the higher pK_a of the methyl C-H of *o*-nitro-toluene. The yields could be increased by increasing the temperature. Oxidation of the secondary alcohol to ketone **2.3.2** was realized with either PCC or DMP as oxidant.[162,163]



*Scheme 35. Synthesis of the ketones **2.3.2** from 2-nitrotoluenes and aldehydes*

Ketones **2.3.2** were transformed into enol esters **2.3.4** following a similar procedure as the one reported in Scheme 34: alkylation and acylation (Scheme 36).

[159] Izumi, T.; Yokota, T. *J. Heterocyclic Chem.* **1992**, *29*, 1085 – 1090.
[160] Coffman, K.C.; Keith, C.; Palazzo, T.A.; Hartley, T.P.; Fettinger, J.C.; Tantillo, D.J.; Kurth, M.J. *Org. Lett.* **2013**, *15*, 2062 – 2065.
[161] Kim, H.; Lee, S.H. *Heterocycles* **2016**, *92*, 2004 – 2017.
[162] Floresta, G.; Cilibrizzi, A.; Abbate, V.; Spampinato, A.; Zagni, C.; Rescifina, A. *Bioorg. Chem.* **2019**, *84*, 276 – 284.
[163] Li, Y.; Brand, J.P.; Waser, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 6743 – 6747.

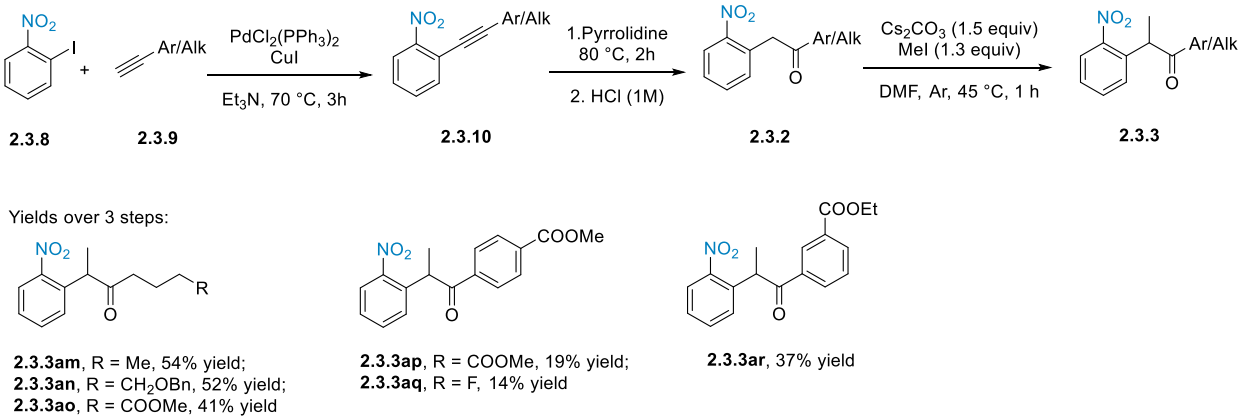


*Scheme 36. Synthesis of 2-(o-nitro)aryl substituted enol ester **2.3.4** from ketones **2.3.3***

Pathway C

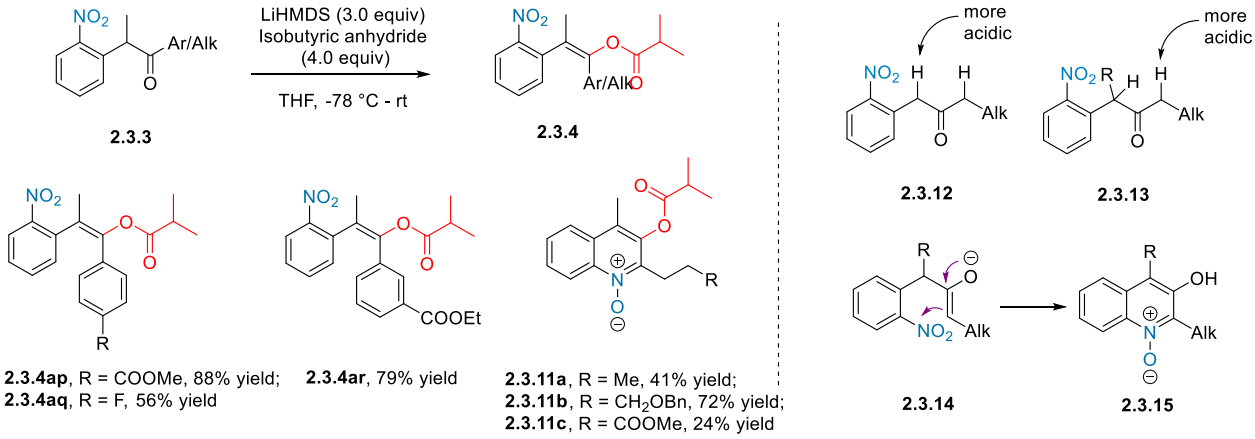
In 2007, Fukuyama showed that *ortho*-nitrophenylacetylenes can be hydrolyzed into ketones *via* conjugate addition of pyrrolidine onto the triple bond, followed by acidic hydrolysis of enamine.[164] The efficiency of this reaction was later proved in the total synthesis of natural products.[165,166] *o*-Nitrophenylacetylenes **2.3.10** were synthesized *via* Sonogashira reaction between 1-iodo-2-nitrobenzene **2.3.8** and different acetylenes **2.3.9** (Scheme 37). The desired acetylenes **2.3.10** could be synthesized in quantitative yields by performing reaction in triethylamine at 70 °C with 2.5 mol% of $PdCl_2(PPh_3)_2$ and 4 mol% of CuI.[167,168] Heating *o*-nitrophenylacetylenes **2.3.10** in pyrrolidine for 2 h gave the corresponding enamine, which could be isolated, purified and characterized. Acidic work-up of enamines afforded corresponding ketones **2.3.2**. Following this two-step sequence, ketones **2.3.2** were prepared in moderate to good overall yields. Alkylation step worked with good to excellent yields without a problem of regioselectivity.

[164] Tokuyama, H.; Makido, T.; Han-ya, Yu.; Fukuyama, T. *Heterocycles* **2007**, *72*, 191 – 197.
[165] Yamakawa, T.; Ideue, E.; Iwaki, Yu.; Sato, A.; Tokuyama, T.; Shimokawa, J.; Fukuyama, T. *Tetrahedron* **2011**, *67*, 6547 – 6560.
[166] Suzuki, M.; Kambe, M.; Tokuyama, T.; Fukuyama, T. *J. Org. Chem.* **2004**, *69*, 2831 – 2843.
[167] Grigg, R.; Sansano, J.M.; Santhakumar, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1994**, *50*, 11803 – 11812.
[168] Hamze, A.; Provot, O.; Alami, M. ; Brion, J.-D. *Org. Lett.* **2005**, *7*, 5625 – 5628.



*Scheme 37. Synthesis of ketones **2.3.3** via Sonogashira reaction and hydrolysis of triple bond*

Aryl ketones **2.3.3ap-ar** were easily transformed into enol esters **2.3.4ap-ar** using previously established conditions (Scheme 38). However, in the case of alkyl ketones **2.3.3am-ao** 3-acyloxyquinoline *N*-oxides **2.3.11a-c** were isolated. This transformation is known in the literature.[169] Authors explained this reactivity by the fact, that the benzylic proton in unsubstituted ketone **2.3.12** delivers more stable enolate than α-proton on the other side of ketone due to conjugation of nitroarene ring with formed enolate. For substituted ketone **2.3.13** the steric repulsion between substitutent and nitroarene ring prevents the formation of conjugated enolate. Upon deprotonation, intramolecular addition of enolate to the nitro group **2.3.14** followed by elimination of water gave hydroxyquinoline *N*-oxides **2.3.15**. Addition of isobutyric anhydride delivered 3-acyloxyquinoline *N*-oxides **2.3.11**.

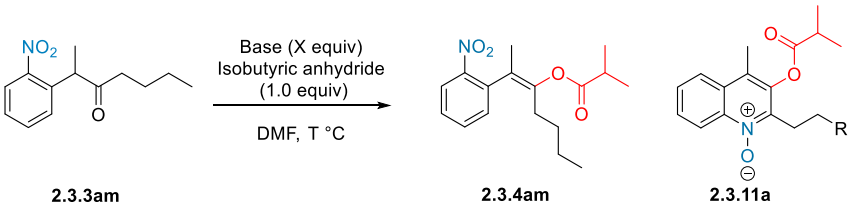


*Scheme 38. Synthesis of 2-(o-nitro)aryl substituted enol ester **2.3.4***

To avoid the formation of 3-acyloxyquinoline *N*-oxides **2.3.11**, different bases were screened. We believed that under milder conditions the nucleophilic addition to the nitro group could be avoided. Firstly, inorganic bases were tested, however, no reaction was observed even with the increased reaction temperatures (Table 2). Weak organic bases with reversible deprotonation led to the same results. At this moment, it became obvious that for our reaction irreversible deprotonation is necessary and stronger bases such as *t*-BuOK and LiHMDS were used (Table 3). To determine the relate rate between cyclization and *O*-

[169] Hattori, H.; Yokoshima, S.; Fukuyama, T. *Angew. Chem. Int. Ed.* **2017**, *56*, 6980 – 6983.

acylation, anhydride was added 5, 15, 30 min and 1 h after the addition of base at -78 °C (entries 1-4). Deprotonation of ketone **2.3.3am** is not a fast process, after 30 min only 40% of starting material is deprotonated (entries 1-3). However, after 1 h with a base a competing cyclization of ketone **2.3.3am** into hydroxyquinoline *N*-oxides **2.3.11a** takes place (entry 4). Slow increase of the reaction temperature to ambient does not enhance the conversion (entry 6). Higher yields can be obtained when the amount of base and anhydride are increased to 1.5 and 1.4 equiv accordingly (entry 7). Turning to LiHMDS, similar results and tendencies can be observed (entries 8-10). LiHMDS showed higher activity and reaction can be done in 83% NMR yield (entry 10). Applying conditions from entry 10 on a bigger scale – enol ester **2.3.4am** was isolated in 52% yield.



2.3.3am **2.3.4am** **2.3.11a**

	Base	T °C	Results
1.	K_2CO_3 (1.0 equiv)	0 °C	No reaction
2.	K_2CO_3 (1.0 equiv)	rt	
3.	Cs_2CO_3 (1.0 equiv)	0 °C	
4.	Cs_2CO_3 (1.0 equiv)	rt	
5.	Cs_2CO_3 (1.0 equiv)	35 °C	
6.	Cs_2CO_3 (1.0 equiv)	50 °C	
7.	Cs_2CO_3 (1.0 equiv)	70 °C	
8.	DIPEA (1.0 equiv)	rt	
9.	Et_3N (1.0 equiv)	rt	
10.	DBU (1.0 equiv)	rt	

*Table 2. Optimization of the conditions for the synthesis of 2-(o-nitro)aryl substituted enol ester **2.3.4am** - weak bases*

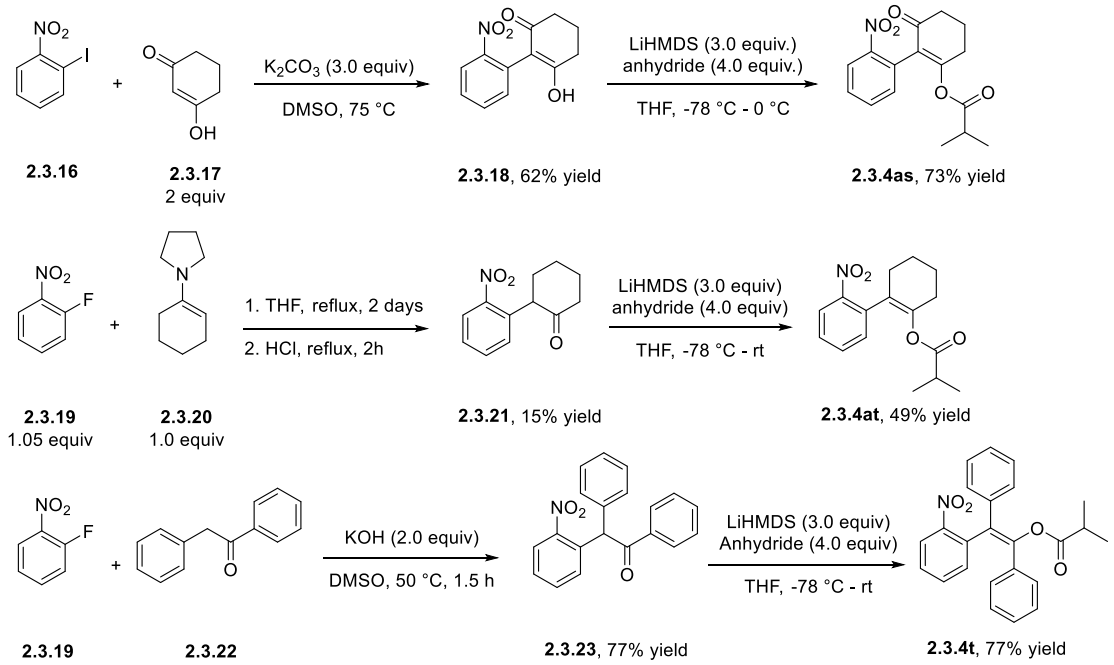
	Base	Anhydride addition, time	Solvent	T °C	Overall time	Results (ratio)		
						2.3.4[a]	**2.3.11**[a]	SM[a]
1.[b]	*t*-BuOK (1.0 equiv)	5 min	THF	- 78°C – 0 °C	6 h			100 %
2.[b]	*t*-BuOK (1.0 equiv)	15 min	THF	- 78°C – 0 °C	6 h	40%		60%
3.[b]	*t*-BuOK (1.0 equiv)	30 min	THF	- 78°C – 0 °C	6 h	36%		64%
4.[b]	*t*-BuOK (1.0 equiv)	1 h	THF	- 78°C – 0 °C	6 h	37%	11%	52%
5.[b]	*t*-BuOK (1.0 equiv)	20 min	THF	- 78°C – 0 °C	1 day	38%	6%	56%
6.[b]	*t*-BuOK (1.0 equiv)	15 min	THF	- 78°C – rt	6 h	32%	9%	59%
7.[c]	*t*-BuOK (1.5 equiv)	30 min	THF	- 78°C	6 h	65%	10%	25%
8.[b]	LiHMDS (1.0 equiv)	15 min	THF	- 78°C – rt	6 h	43%	6%	51%
9.[d]	LiHMDS (1.0 equiv)	30 min	THF	- 78°C	4 h	66%	-	34%
10.[e]	LiHMDS (1.2 equiv)	30 min	THF	- 78°C	4 h	83%	-	17%
11.[e]	LiHMDS (1.2 equiv)	30 min	THF	- 78°C	4 h	52%		

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard. [b]Temperature was gradually increased to 0 °C. [c]Quenching at -78 °C, 1.4 equiv of anhydride. [d]Quenching at -78 °C. [e]Quenching at -78 °C, 1.2 equiv of anhydride.

*Table 3. Optimization of the conditions for the synthesis of 2-(o-nitro)aryl substituted enol ester **2.3.4am** - strong bases*

Pathway D

The last three trisubstituted enol esters **2.3.4as-at** and **2.3.4t** were synthesized *via* a sequence of nucleophilic aromatic substitution[170,171,172] and enol ester formation under conditions previously optimized (Scheme 39).



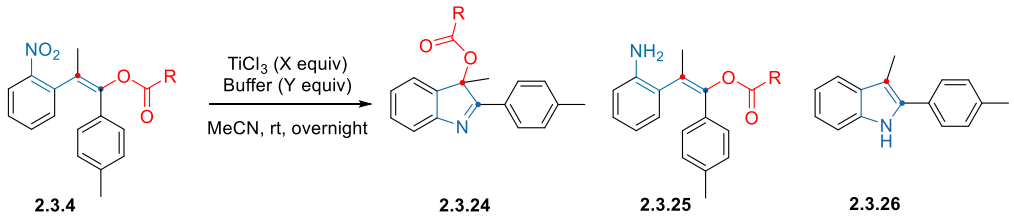
*Scheme 39. Synthesis of the 2-(o-nitro)aryl substituted enol ester **2.3.4as-at** and **2.3.4t** via nucleophilic aromatic substitution and enol ester-formation*

2.3.2. **Optimization of the reaction conditions**

We commenced our investigation using *o*-nitroaryl substituted enol ester **2.3.4a**. Aqueous titanium trichloride (in 2.0N HCl), which already has been shown to be an efficient reducing agent for the reductive cyclization of *o*-nitrostyrenes, was as well effective in our transformation (Table 4). In the presence of 50 equiv of $TiCl_3$ and NH_4OAc (200 equiv) in CH_3CN at room temperature, indolenine **2.3.24a** was formed in approximately 35% NMR yield along with aniline **2.3.25a** (17% yield) and indole **2.3.26a** (50% yield) (entry 1). The elevated amounts of $TiCl_3$-reagent and buffer were used to accelerate the reduction of the nitro group to the nitroso-intermediate, a process which is harder compare to the second reduction step. For the Cadogan-Sundberg reaction, the starting material should be reduced to nitroso-intermediate, which should have time to proceed in electrocyclization before the second reduction. Upon optimization of the reaction conditions the rate of the first reduction step should be accelerated while the second reduction step should be slow down. Reducing the amount of $TiCl_3$ to 20 equiv and 8.0 equiv leads to a poor reactivity (entries 1-3). Hydrolysis of the enol ester to the ketone and over-reduction of the nitroarene to the aniline

[170] Sole, D.; Bosch, J.; Bonjoch, J. *Tetrahedron* **1996**, *52*, 4013 – 4028.
[171] Ye, L.; Lo, K.-Y.; Gu, Q.; Yang, D. *Org. Lett.* **2017**, *19*, 308 – 311.
[172] Jawdosiuk, M.; Kmiotek-Skarzynska, I.; Wilczynski, W. *Can. J. Chem.* **1978**, *56*, 218 – 220.

are our concerns at the outset of this reseach. Formation of indole **2.3.26** as a major product indicated that these side reactions are indeed occurring. To avoid this, different enol esters were tested in the reaction. Fortunately, enol isobutyrate and enol pivalate ester function were stable under these reductive conditions since formation of indole was not observed with these two substrates (entries 4-5).



2.3.4 **2.3.24** **2.3.25** **2.3.26**

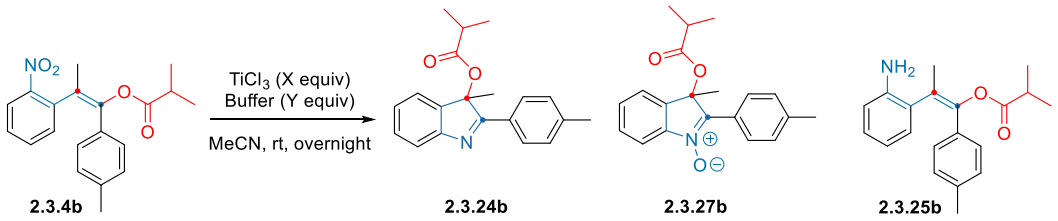
	R	$TiCl_3$	NH_4OAc	c [M]	**2.3.24**[a]	**2.3.25**[a]	**2.3.26**[a]	**2.3.4**[a]
1.	Me	50 equiv	200 equiv	0.01	35%	17%	50%	-
2.	Me	20 equiv	80 equiv	0.01	10%	55%	20%	-
3.	Me	8 equiv	32 equiv	0.1	6%	16%	-	70%
4.	*i*-Pr	50 equiv	200 equiv	0.01	65%	26%	-	-
5.	*t*-Bu	50 equiv	200 equiv	0.01	60%	35%	-	-

Conditions: enol ester (0.1 mmol), $TiCl_3$ (X equiv), buffer (Y equiv) in MeCN at rt, overnight. [a]NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 4. Optimization of the conditions for the reductive cyclization of 2-(o-nitro)aryl substituted enol ester **2.3.4a-c***

The optimization of the reactions conditions was continued with the enol isobutyrate **2.3.4b**, as with enol pivalate ester **2.3.4c** the reaction took more time and gave the desired product in slightly lower yield. The $TiCl_3$-loading was firstly lowered from 50 to 20 (Table 5, entries 1-2). The order of addition played an important role on the reactivity. The desired product **2.3.24b** was formed in 62% yield when $TiCl_3$ was slowly added to a solution of starting material and additive at 0 °C (entries 1-2). Fast addition of $TiCl_3$ or addition at rt can oxidize our reducing agent to Ti^{IV}. This can be observed through discoloration of the Ti-solution to yellow-grey and no reaction was observed. Similar results were obtained when 15 equiv of $TiCl_3$ were used (entries 3-4). Titanium trichloride is commercially available and stored in a 2.0 N solution of HCl, to prevent its oxidation to Ti^{IV}. In order to partially neutralize the strong acidity derived from the $TiCl_3$ different weak bases were tested into the reaction mixture: NH_4OAc, NH_4OOCH, NH_4Cl, HCOONa and imidazole. Screening of additives showed that the best results can be obtained with HCOONa and $HCOONH_4$ (entries 5-10). To understand the importance of the pH, we slowly increased the amount of additive to basify the reaction (entries 11-15). In the case of $HCOONH_4$ as a buffer, the 1 to 4 ratio between Ti and buffer was found to be optimal. In

Table 6, we showed that the reaction mixture's pH indeed increases with the addition of NH_4OAc. Dilution of the reaction mixture leads to a drop in the yields, as well as, increased concentrations (entries 16-17). This can be explained by the fact that with higher concentrations the reaction does not work well delivering aniline **2.3.25** in higher yields, while in the case of dilution, the extension of the reaction time is necessary.



	$TiCl_3$	Additive (equiv)	c [M]	**2.3.24b**[a]	**2.3.27b**[a]	**2.3.25b**[a]	**2.3.4b**[a]
1.[b]	20 equiv	NH_4OAc (80 equiv)	0.1	33	9	28	28
2.	20 equiv	NH_4OAc (80 equiv)	0.1	62	-	37	-
3.[b]	15 equiv	NH_4OAc (60 equiv)	0.1	30	4	19	42
4.	15 equiv	NH_4OAc (60 equiv)	0.1	65	-	32	-
5.	10 equiv	NH_4OAc (20 equiv)	0.1	65	-	13	
6.	10 equiv	NH_4Cl (40 equiv)	0.2	18	-	-	70
7.	10 equiv	NaOOCH (40 equiv)	0.2	26	32	9	33
8.	10 equiv	NaOOCH (20 equiv)	0.2	70	-	9	-
9.	10 equiv	Imidazole (20 equiv)	0.2	20	9	30	29
10.	10 equiv	NH_4OOCH (40 equiv)	0.2	69	7	23	-
11.	10 equiv	NH_4OOCH (10 equiv)	0.2	33	5	11	49
12.	10 equiv	NH_4OOCH (20 equiv)	0.2	50	16	7	27
13.[c]	10 equiv	NH_4OOCH (20 equiv)	0.2	70	-	21	-
14.	10 equiv	NH_4OOCH (30 equiv)	0.2	61	-	26	13
15.	10 equiv	NH_4OOCH (60 equiv)	0.2	-	71	18	-
16.	10 equiv	NH_4OOCH (40 equiv)	0.1	24	2	24	50
17.	10 equiv	NH_4OOCH (40 equiv)	0.3	26	4	4	66

Conditions: enol ester (0.1 mmol), $TiCl_3$ (X equiv), buffer (Y equiv) in MeCN at rt, overnight. [a] NMR yields with 1,3,5-trimethoxybenzene as a standard. [b] Addition of $TiCl_3$ to additive. [c] Reaction was performed under Ar.

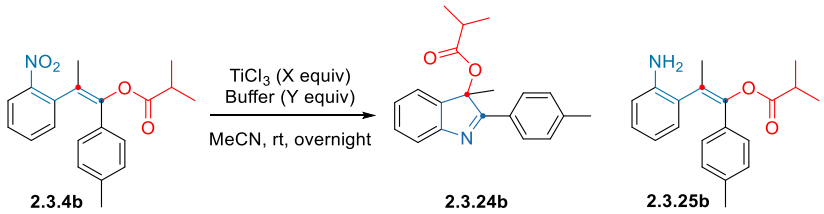
*Table 5. Optimization of the conditions for the reductive cyclization of 2-(o-nitro)aryl substituted enol ester **2.3.4b***

	Additive	$TiCl_3$ / additive	pH
1.	NH_4OAc	1:1	0-1
2.	NH_4OAc	1:2	
3.	NH_4OAc	1:3	
4.	NH_4OAc	1:4	
5.	NH_4OAc	1:5	2-3
6.	NH_4OAc	1:6	4
7.	NH_4OAc	1:8	5
8.	NH_4OAc	1:10	6
9.	Bu_4NOAc	1:6	1
10.	NH_4OAc, Et_3N	1:6:1	2-3
11.	Et_3N	1:6	2-3

Table 6. Dependence of pH from the amount of additive

Unfortunately, at this moment, our problems with reproducibility remained unsolved. We noticed that when changing the bottles of $TiCl_3$ different results were obtained. Two possible explanations can be

proposed. On the one hand, basification of Ti-solution makes it more sensitive to the oxygen of the atmosphere. Indeed, performing the reaction under an argon atmosphere improved the yield (Table 5, entry 13). On the other hand, with elevated amounts of additives, the reaction mixture became heterogeneous due to their low solubility. To avoid this problem, we decided to turn our attention towards optimization of the reaction conditions without additive. Key results are summarized in Table 7. We first screened the concentration of the reaction with 15 equiv of $TiCl_3$ suggesting that 0.2 M is optimal (entries 1-3). We then screened the concentration of the reaction with 10 equiv of $TiCl_3$ (entries 4-7) and were pleased to see that at 0.2 M the desired 3-acyloxyindolenine could be obtained in 70 % yield. Among solvents screened (MeCN, acetone, THF, methanol, PrCN), MeCN remained the best (entries 8-13). Low conversion was observed when the reaction was performed at 15 °C, while the reaction was shut down at 0 °C (entries 14-15). Heating of the reaction mixture to 30-40 °C led to a faster reaction decreasing the yield of the desired product with while increasing the yield of aniline (entries 16-17). As it will be shown later, some starting materials showed a low solubility in the reaction mixture, to render the reaction mixture more homogeneous different phase transfer agents were examined (entries 18-26): SDS, TBAI, Bu_4NOAc. Similar results were obtained when SDS was used though with slightly lower yields, changing the amount of transfer agent did not improve the results. However, when TBAI and Bu_4NOAc were used, the aniline **2.3.25b** was formed predominantly.



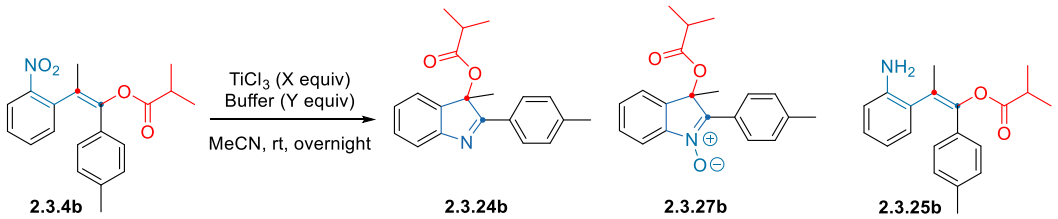
2.3.4b 2.3.24b 2.3.25b

	$TiCl_3$ (equiv)	Solvent (M)	T °C	Transfer agent	**2.3.24b**[a]	**2.3.25b**[a]	**2.3.4b**[a]
1.	15	MeCN (0.2 M)	rt	-	63	19	7
2.	15	MeCN (0.3 M)	rt	-	25	64	-
3.	15	MeCN (0.4 M)	rt	-	17	77	-
4.	10	MeCN (0.1 M)	rt	-	30	21	28
5.	10	MeCN (0.2 M)	rt	-	70	12	-
6.	10	MeCN (0.3 M)	rt	-	45	5	36
7.	10	MeCN (0.4 M)	rt	-	15	2	74
8.	10	Acetone (0.2 M)	rt	-	56	31	-
9.	10	Acetone (0.3 M)	rt	-	33	5	41
10.	10	Acetone (0.4 M)	rt	-	8	-	82
11.	10	THF (0.1 M)	rt	-	66	8	-
12.	10	MeOH (0.2 M)	rt	-	16	-	69
13.	10	PrCN (0.3 M)	rt	-	-	-	100
14.	10	MeCN (0.2 M)	0 °C	-	-	-	100
15.	10	MeCN (0.2 M)	15 °C	-	8	7	59
16.	10	MeCN (0.2 M)	30 °C	-	67	18	-
17.	10	MeCN (0.2 M)	40 °C	-	65	21	-
18.	10	MeCN (0.2 M)	rt	SDS (10 mol%)	65	10	16
19.	10	MeCN (0.2 M)	rt	SDS (1 equiv)	56	13	20
20.	10	MeCN (0.2 M)	rt	SDS (2 equiv)	58	16	-
21.	10	MeCN (0.2 M)	rt	SDS (5 equiv)	55	23	-
22.	10	MeCN (0.2 M)	rt	SDS (10 equiv)	53	13	-
23.	10	Acetone (0.2 M)	rt	SDS (5 equiv)	49	32	-
24.	10	Acetone (0.2 M)	rt	SDS (10 equiv)	53	26	-
25.	10	MeCN (0.2 M)	rt	TBAI (20 equiv)	37	63	-
26.	10	MeCN (0.2 M)	rt	Bu_4NOAc (20 equiv)	-	100	-

Conditions: enol ester (0.1 mmol), $TiCl_3$ (X equiv), buffer (Y equiv) using the indicated solvent, concentration and temperature, overnight. [a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 7. Optimization of the conditions for the reductive cyclization of 2-(o-nitro)aryl substituted enol ester **2.3.4b***

Overall, the optimized reaction conditions consisted in the addition of $TiCl_3$ solution (10 equiv, 1.3M in 2.0N HCl) to the solution of starting material **2.3.4b** in MeCN (0.2 M) at 0 °C, the reaction mixture was then stirred at rt overnight. Under these conditions, indolenine **2.3.24b** was obtained in 70% isolated yield. Monitoring the reaction progress indicated a linear relationship between conversion and time (Table 8, entries 1-5) with full conversion being reached after 14-16 h.



	$TiCl_3$ (equiv)	Solvent (M)	T °C	t, h	**2.3.24b**[a]	**2.3.27b**[a]	**2.3.25b**[a]	**2.3.4b**[a]
1.	10	MeCN (0.2 M)	rt	2 h	7%	5%	2%	75%
2.	10	MeCN (0.2 M)	rt	4 h	15%	5%	4%	64%
3.	10	MeCN (0.2 M)	rt	6 h	24%	4%	6%	55%
4.	10	MeCN (0.2 M)	rt	8 h	35%	4%	7%	38%
5.	10	MeCN (0.2 M)	rt	16 h	70%	-	12%	-

Conditions: enol ester (0.1 mmol), $TiCl_3$ (X equiv), buffer (Y equiv) in MeCN at rt, overnight. [a]NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 8. Time evaluation of the reductive cyclization of 2-(o-nitro)aryl substituted enol ester **2.3.4b***

2.3.3. **Scope of the 3-acyloxyindolenines**

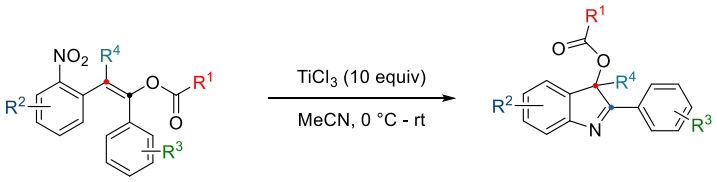
With the optimized conditions in hand, we proceeded to the scope of the transformation (Scheme 40). At the beginning, the influence of the acyl part of the enol esters was examined. The best results were observed with the model substrate **2.3.4b**. This can be explained by lower stability of acetyl derivative **2.3.4a** which is more prone to hydrolysis and higher steric hindrance for substrates with substituents: *t*-Bu **2.3.4c** and phenyl **2.3.4d**. Enol carbamate **2.3.4e** can also be used in the reaction, albeit with a lower yield (45%). A gram-scale experiment was performed with enol esters **2.3.4b** showing that indolenine **2.3.24b** can be obtained in an increased yield of 86%.

Varying the substituents on the nitro-aryl ring showed that substrates bearing electron-withdrawing (fluorine, bromine, ester group, **2.3.24f, i-k**) and electron-donating groups deliver the desired products in moderate to good yields, with electron-withdrawing groups giving better results. In the case of compound **2.3.24h**, 2 equiv of transfer agent were necessary due to a low solubility of the starting material under optimized conditions. The structure of compound **2.3.24f** was confirmed by X-ray crystallographic analysis.

Furthermore, the influence of R^3 group on the reaction outcome was next examined. While compounds **2.3.24l-m**, **2.3.24o** with electron-donating groups were isolated in high yields (71 – 79% yield), the close analogous product **2.3.24n** was obtained in moderate yield (45% yield). All attempts to perform the reaction with substrates containing electron-withdrawing groups on this aryl ring were unsuccessful. Heteroarene such as furan and naphthalene were compatibale with the reaction conditions affording products **2.3.24p** and **2.3.24q** in yields of 50% and 63%, respectively.

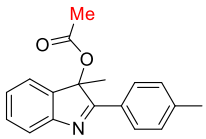
Finally, substrates with different R^4 groups were examined. The efficiency of the transformation is affected by the steric hindrance of α-substituent R^4 of *o*-nitrostyrenes. In fact, replacing Me-group by sterically more hindered groups led to a progressive drop of the yield. Thus starting material with an ethyl

group gave indolenine **2.3.24r** in similar yield (70%), while compound **2.3.24aa** with long alkyl chain was isolated in 63% yield (2 equiv of transfer agent were added). Replacing the alkyl chain by phenyl group led to a poor reactivity, the desired product **2.3.24t** was obtained in 31% yield. Similarly, substrates bearing a benzyl group (substrates **2.3.24u-w**), an allyl group (**2.3.24s**), alkyl chains with benzyl ether (**2.3.24x-y**), azide (**2.3.24z** and **2.3.24ac**), furan (**2.3.24ab**) and protected amine (**2.3.24ad**) were converted to products in yields ranging from 30% to 68%. Comparing the results for compounds **2.3.24u** vs **2.3.24w** and **2.3.24x** vs **2.3.24y**, we can see that while changing the Me- group to a MeO- as R^3-substituent the yields were increased.

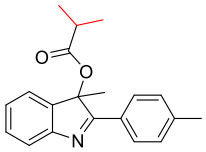


2.3.4 **2.3.24**

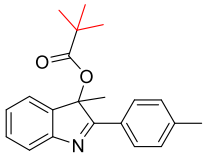
R^1 - substituents



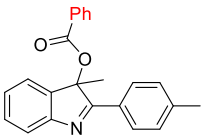
2.3.24a, 55% yield[a]



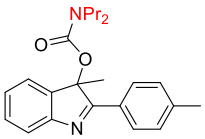
2.3.24b, 70% yield[a] (86% yield on gram scale)



2.3.24c, 65% yield[b]

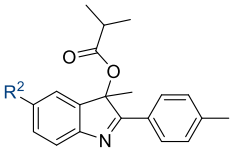


2.3.24d, 62% yield[b]

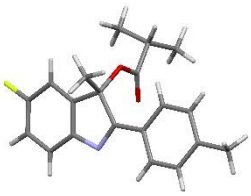


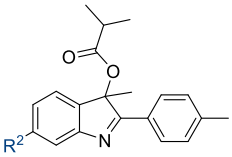
2.3.24e, 45% yield[b]

R^2 - substituents



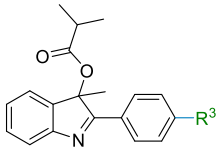
2.3.24f, R = F, 75% yield;[a]
2.3.24g, R = OMe, 53% yield;[b]
2.3.24h, R = Me, 77% yield[c]



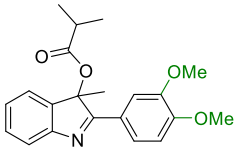


2.3.24i, R = F, 50% yield;[b]
2.3.24j, R = Br, 42% yield;[b]
2.3.24k, R = COOMe, 64% yield;[a]

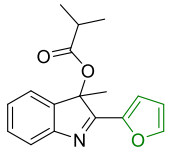
R^3 - substituents



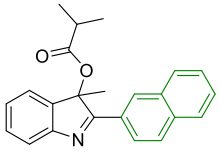
2.3.24l, R^3 = H, 71% yield;[a]
2.3.24m, R^3 = OMe, 72% yield;[a]
2.3.24n, R^3 = Br, 45% yield;[a]



2.3.24o, 79% yield[a]

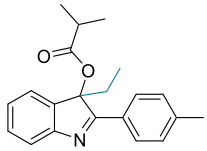


2.3.24p, 50% yield[b]

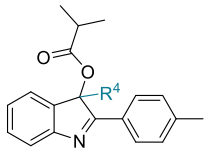


2.3.24q, 63% yield[b]

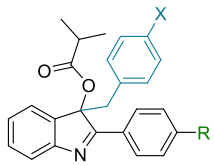
R^4 - substituents



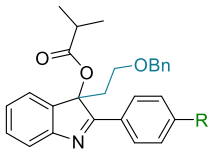
2.3.24r, 70% yield[b]



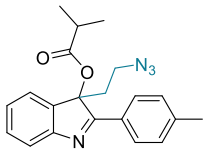
2.3.24s, R^4 = Allyl, 48% yield;[b]
2.3.24t, R^4 = Ph, 31% yield[b]



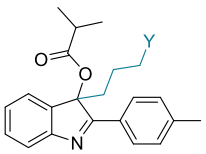
2.3.24u, R = Me, X = H, 47% yield;[b]
2.3.24v, R = Me, X = Br, 32% yield;[b]
2.3.24w, R = OMe, X = H, 52% yield;[b]



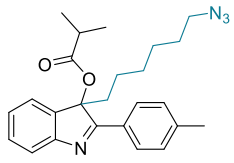
2.3.24x, R = Me, 50% yield;[b]
2.3.24y, R = OMe, 68% yield[b]



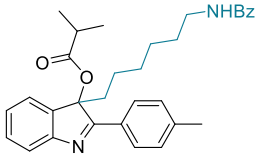
2.3.24z, 40% yield[b]



2.3.24aa, Y = *i*-Pr, 63%[c]
2.3.24ab, Y = furan-2-yl, 30%[b]



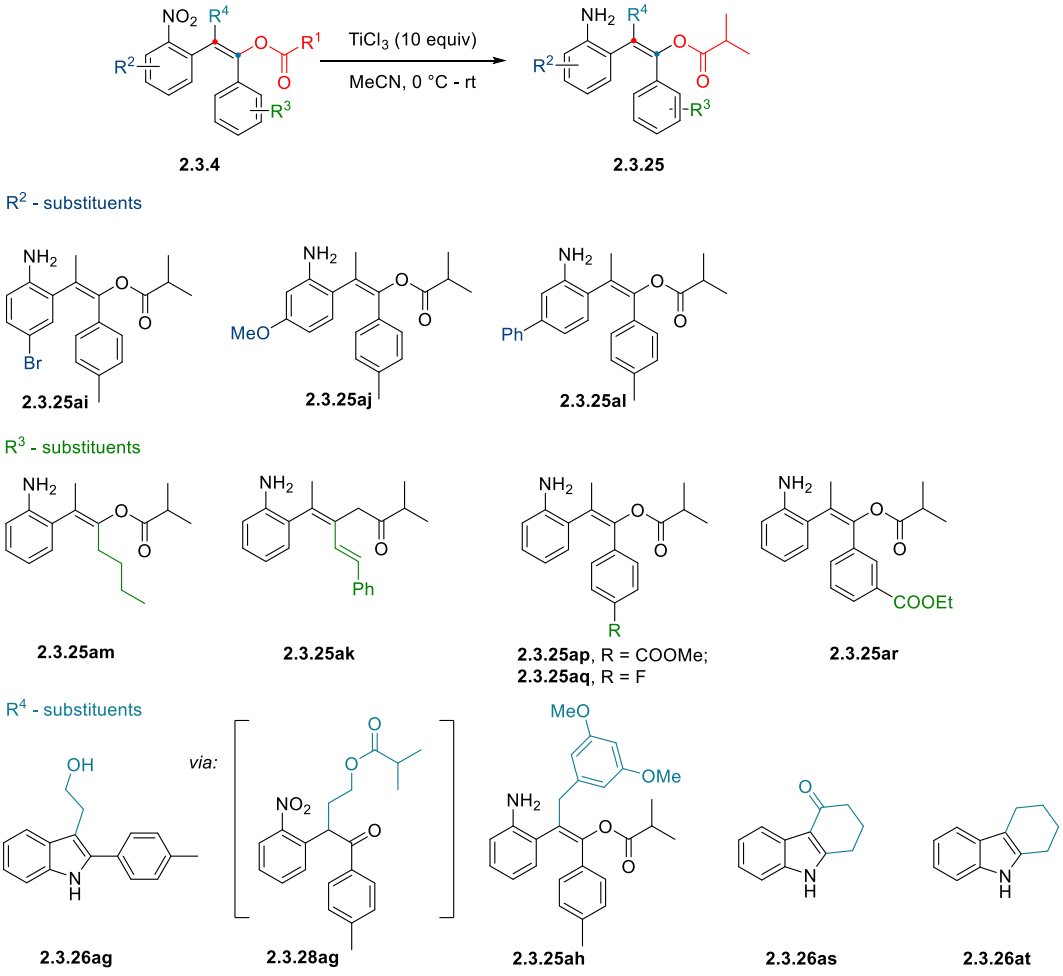
2.3.24ac, 46% yield[b]



2.3.24ad, 51% yield[c]

Scheme 40. Scope of the reductive electrocyclization of 2-(o-nitro)aryl substituted enol esters ***2.3.4***

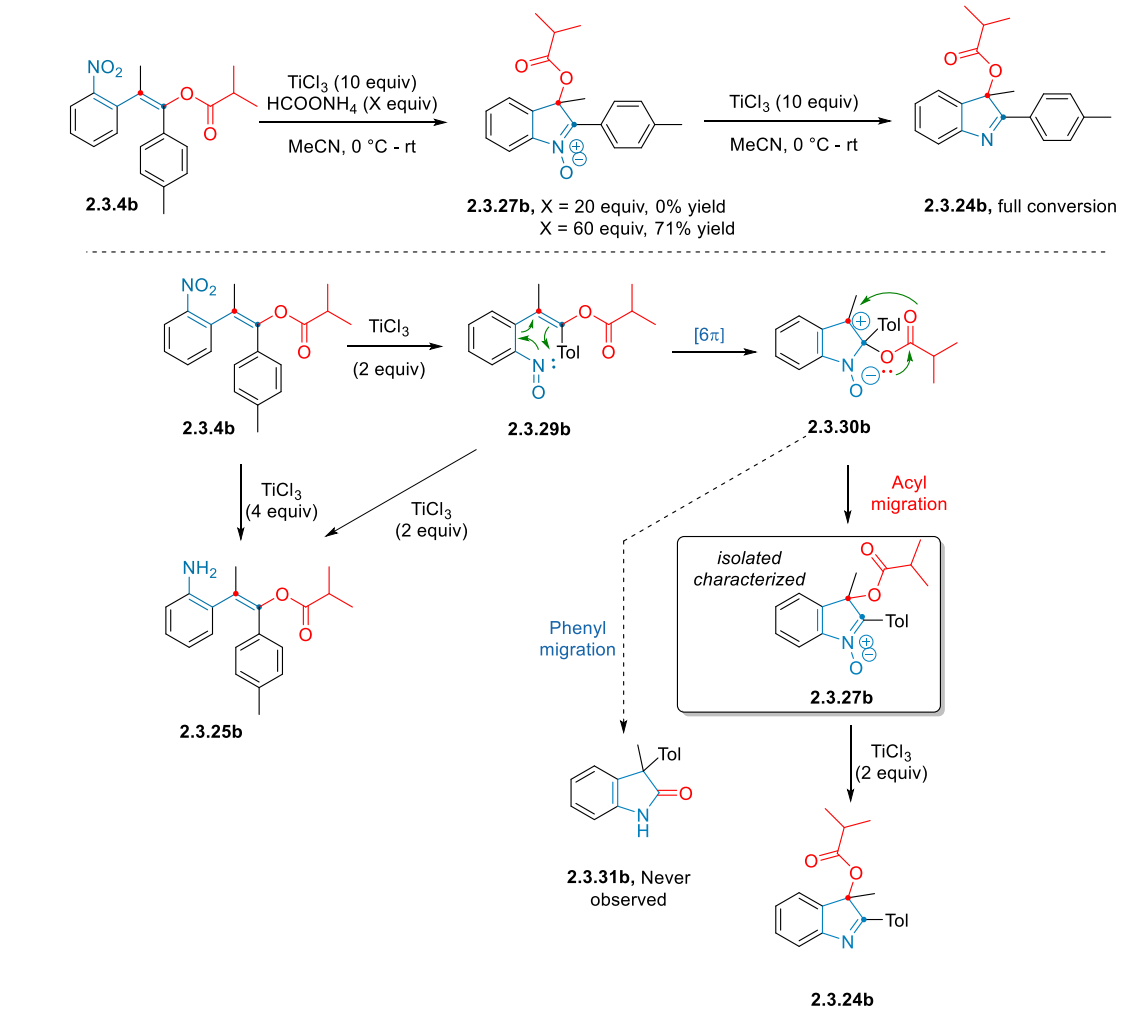
Unfortunately, some substrates failed to undergo the reductive cyclizaiton. Instead anilines **2.3.25** resulting from the over-reduction of nitro group were isolated (Scheme 41). As aforementioned variation of R^2-substituents showed that starting materials containing electron-withdrawing groups on nitroarene ring showed higher reactivity. Accordingly, substrates **2.3.4ai, 2.3.4aj, 2.3.4al** were converted into anilines **2.3.25ai, 2.3.25aj, 2.3.25al**. Replacement of electron-rich arene ring as R^3-substituent by an alkyl chains or electron-poor aromatic ring leads to an over-reduction, anilines **2.3.25am, 2.3.25ak, 2.3.25ap-ar** were isolated from reaction mixtures. Variation of R^4-substituents showed undesired transformation of compounds **2.3.4ag, 2.3.4ah, 2.3.4as, 2.3.4at** into indoles and aniline. The substrate with TBS-protected alcohol **2.3.4ag** was subjected several times to the reaction; however, the TBS-group turned out to be labile under our acidic conditions. It is possible that the free alcohol can proceed in an intramolecular transesterification to form a ketone **2.3.28ag**, as a result, the 6π-electrocyclization cannot take place due to absence of a double bond, and instead Reissert reaction takes place. For substrate **2.3.4ah** we believe that increased steric hindrance around the double bond is responsible for undesired reactivity.

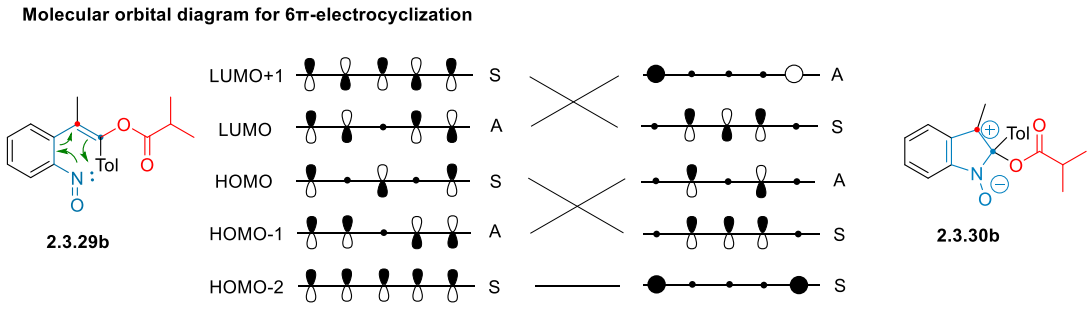


*Scheme 41. Limitations of the scope of the reductive cyclization of 2-(o-nitro)aryl substituted enol ester **2.3.4***

2.3.4. **Mechanism**

During the optimization of reaction conditions, it was found that the ratio between Ti(III) and additive had pronounced impact on the reaction outcome (Scheme 42). Interestingly, nitrone **2.3.27b** was isolated as a major product when the reaction was performed with 1 to 6 ratio between Ti and NH_4OOCH. Resubmitting **2.3.27b** to the standard conditions afforded product **2.3.24b** in 80% yield indicating that nitrone **2.3.27b** could indeed be an intermediate for the conversion of **2.3.4** to **2.3.24** (Scheme 42, a). A possible mechanism that is consistent with our experimental data is proposed in Scheme 42, b. Accordingly, the first two equivalents of $TiCl_3$ reduce the nitro group to nitroso **2.3.29b**. The major competing pathway is the further reduction of nitroso compound **2.3.29b** to aniline **2.3.25b**, which was indeed observed in most of the reactions listed in Scheme 40. In our case, the nitroso group can either be reduced to aniline **2.3.25b** or it can react with the double bond through a 6π-electrocyclization to form zwitterion **2.3.30b**. Based on the Woodward-Hoffmann role a molecular orbital diagram can be drawn, the reaction proceeds *via* a disrotatory process. To obtain the desired product the cyclization step needs to be faster than the reduction to aniline **2.3.25b**. From nitrone **2.3.30b** two possible pathways are possible: either aryl shift or migration of acyl group. The product of aryl shift oxindole **2.3.31b** has not been observed during our studies. We envisage that with the assistance of lone pair of oxygen, the acyl group migrates faster than the aryl group to form nitrone **2.3.27b**, which is finally reduced by $TiCl_3$ to indolenine **2.3.24b**. The final product is obtained as a racemate, as nitroso-group can approach the double bond from both sides.





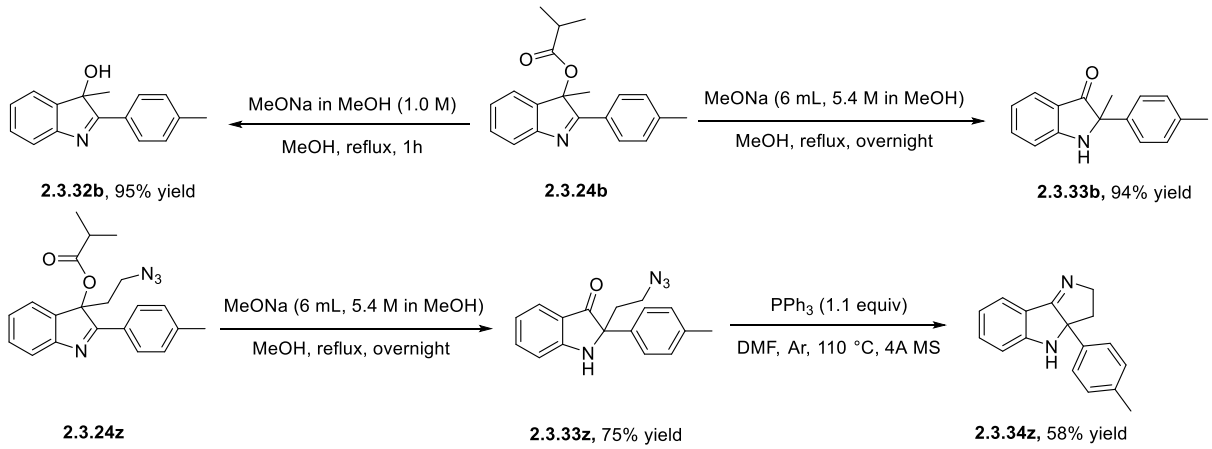
Scheme 42. Plausible mechanism for the reductive cyclization of 2-(o-nitro)aryl substituted enol ester ***2.3.4***

2.3.5. **Post-transformations**

Indolenines **2.3.24b** and **2.3.24z** were further submitted to the α-iminol rearrangement to form 3-indolinone (Scheme 43).[173] Heating to reflux indolenines **2.3.24b** and **2.3.24z** under basic conditions gave

[173] Paquette, L.A.; Hofferberth, J.E. *Org. React.* **2003**, *62*, 477.

the 3-indolinones **2.3.33b** and **2.3.3z** with excellent yields. By shortening the reaction time and decreasing the amount of base, 3-hydroxyindolenine **2.3.32b** can be isolated as the major product. In the case of 3-indolinone **2.3.33z** a subsequent aza-Wittig reaction affords tricyclic indoline **2.3.34z** in 58% yield.[174] Consequently, the present methodology can also be considered as a new method for the generation of 3-indolinones starting from *o*-nitrostyrenes.



Scheme 43. Post-transformations

2.4. **Conclusion**

A new method for the synthesis of 3-acyloxy-2,3-disubstituted indolenines **2.3.24** by a Ti(III)-mediated reductive cyclization of 2-(*ortho*-nitroaryl)-substituted enol esters **2.3.4** has been developed (Scheme 40). The obtained indolenines were readily transformed into 3-indolinones **2.3.33**. The simple experimental procedure, easy accessibility of starting materials and good functional group compatibility made this reaction an interesting alternative for the synthesis of this type of bicyclic heterocycle.

[174] Benalil, A.; Guerin, A.; Carboni, B. ; Vaultier, M. *J. Chem. Soc., Perkin Transactions 1* **1993**, *9*, 1061 – 1064.

Chapter 3. Studies towards the total synthesis of trigonoliimine C

3.1. Introduction

3.1.1. Isolation and Structure

(–)-Trigonoliimine C was isolated in 2010 along with two other members of the same family (+)-trigonoliimines A and B from the leaves of *Trigonostemon lii* by Hao and coworkers (Figure 3).[175] Trigonoliimines A **3.1.1** and C **3.1.3** were tested for their bioactivity, and the former has shown to possess anti-HIV activity (EC_{50} = 0.95 μg/mL). (–)-Trigonoliimine C, a light yellow gum, is a pentacyclic 2,2'-bisindole alkaloid. The dissymmetry in the molecule comes from methoxy-group in 6th-position of one of the trypatamine units.

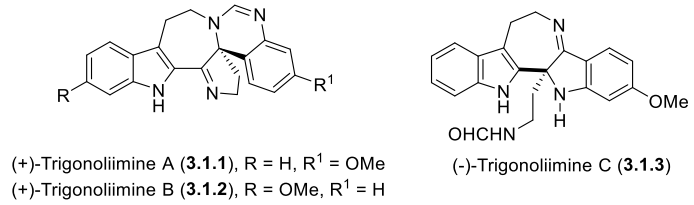


Figure 3. Trigonoliimine family of natural products

The structure of (–)-trigonoliimine C was elucidated by NMR spectroscopy. Based on 2D-NMR analyses, it was possible to identify three parts of natural product **3.1.4a-c**, which could be connected to each other based on HMBC correlations (Figure 4, HMBC correlations are shown as green arrows). The absolute configuration was assigned based on circular dichroism (CD) spectrum.

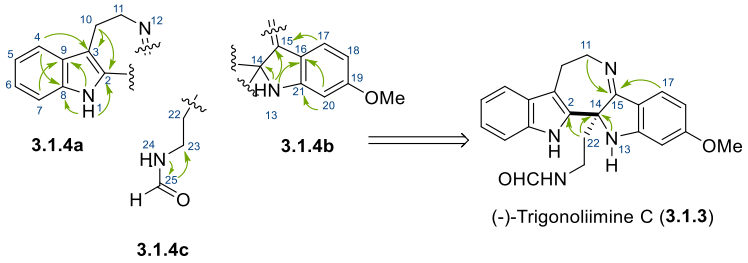


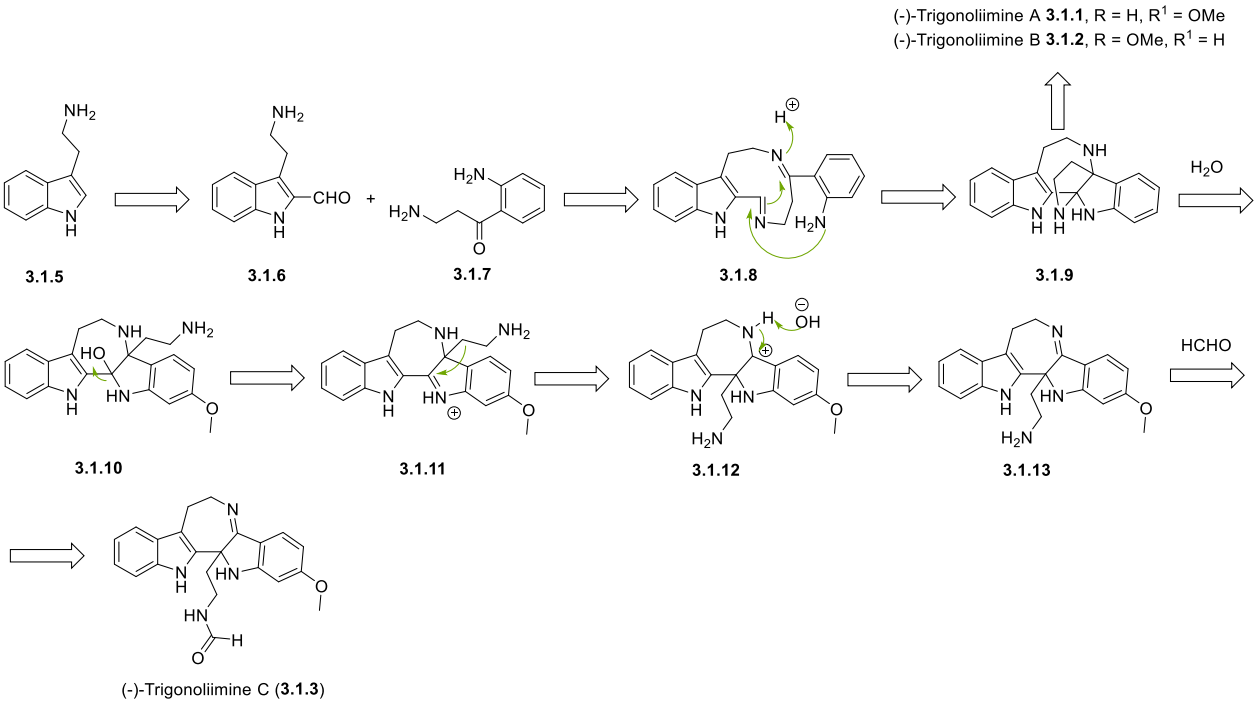
Figure 4. Determination of the structure of trigonoliimine C

3.1.2. Biosynthesis

In the isolation paper the authors proposed a biosynthetic route to the natural product which is depicted in Scheme 44. A putative synthesis begins with the double condensation of tryptamine derivative

[175] Tan, C.-J.; Di, Y.-T.; Wang, Y.-H.; Zhang, Y.; Si, Y.-K.; Zhang, Q.; Gao, S.; Hu, X.-J.; Fang, X.; Li, S.-F.; Hao, X.-J. *Org. Lett.* **2010**, *12*, 2370 – 2373.

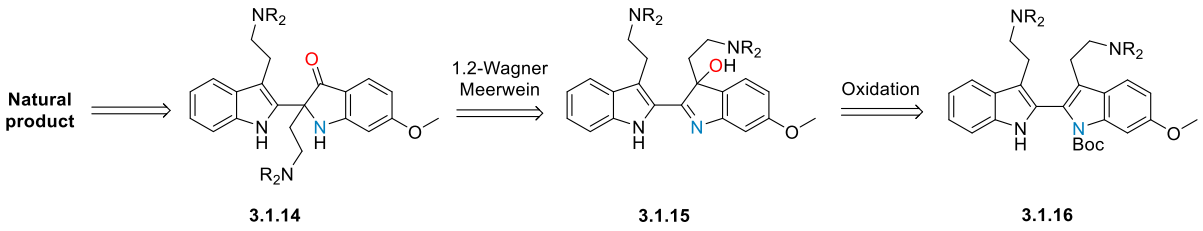
3.1.6 with kynuramine **3.1.7** to form intermediate **3.1.8** with a 10-membered ring. Under acidic conditions, intramolecular cyclization would form bridged [5.3.3] bicyclic scaffold **3.1.9**, from which (+)-trigonoliimine A **3.1.1** and B **3.1.2** would be obtained in 2 steps. At the same time, hydrolysis of intermediate **3.1.9** could deliver 2-hydroxyindoline **3.1.10**, which would lose a molecule of water and proceed through a semipinacol rearrangement to form indoline **3.1.13**. Subsequent formylation of amine could furnish the natural product (−)-trigonoliimine C **3.1.3**. In addition, the selective oxidation of the C-6 position of indole is speculated to proceed enzymatically.



Scheme 44. First possible route for the biosynthesis of trigonoliimine C from tryptamine

In 2011, two independent total syntheses of (−)-trigonoliimine C were published by the groups of Tambar and Movassaghi. [176,177] Both groups hypothesized that 2,2'-bisindole **3.1.16** could be a precursor for all the natural products of this family contradicting the proposed biosynthesis in the isolation paper (Scheme 45). The key transformation for both syntheses was based on the chemoselective oxidation of 2,2'-bisindole **3.1.16** to form hydroxyindolenine **3.1.15**, which then proceeded in Wagner-Meerwein [1,2]-shift to give oxindole **3.1.14**. The chemoselectivity was expected to be achievable, because the electron rich 6-methoxyindole system should be oxidized faster than unsubstituted one. Few months later the biomimetic synthesis of the skeleton of trigonoliimine C was investigated by the group of Hao, testifying the proposed biosynthesis by Tambar and Movassaghi.[178]

[176] Han, S.; Movassaghi, M. *J. Am. Chem. Soc.* **2011**, *133*, 10768 – 10771.
[177] Qi, X.; Bao, H.; Tambar, U.K. *J. Am. Chem. Soc.* **2011**, *133*, 10050 – 10053.
[178] Liu, S.; Hao, X.-J. *Tetrahedron Lett* **2011**, *52*, 5640 – 5642.

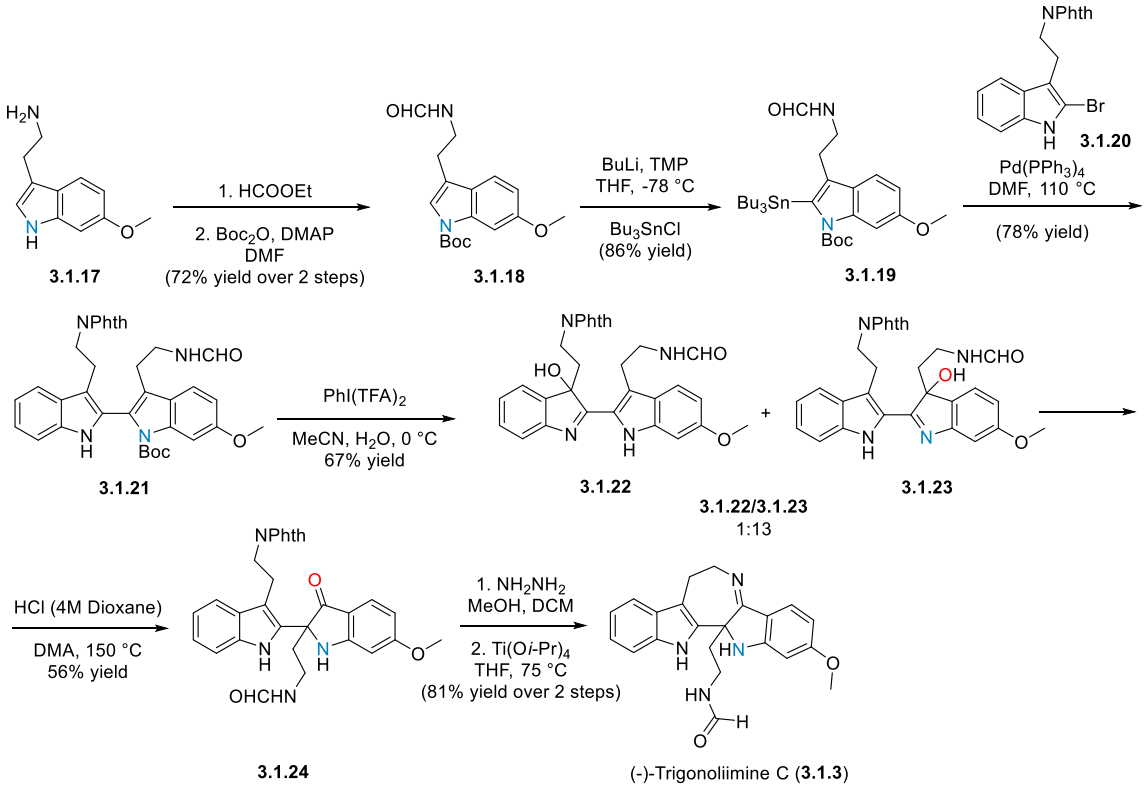


Scheme 45. Proposed route for the biosynthesis of trigonollimine C by Tambar and Movassaghi

3.1.3. **Previous syntheses**

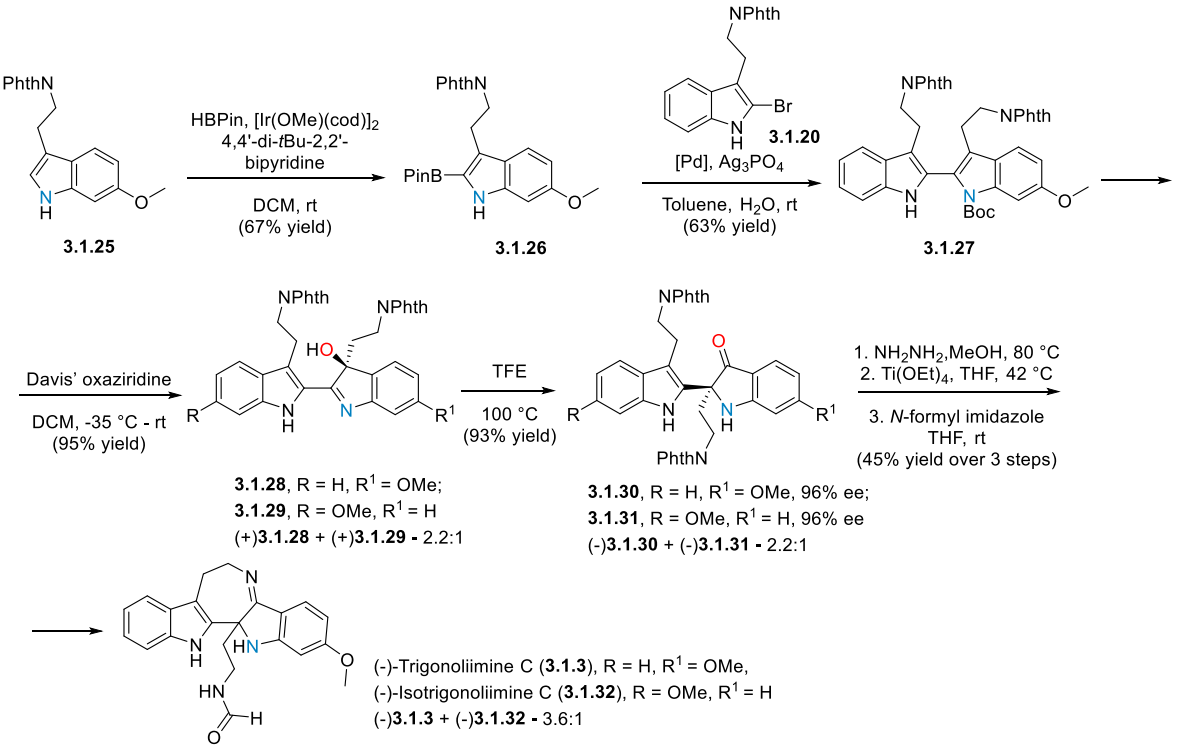
3.1.3.1. Total synthesis by Tambar and Movassaghi

Tambar's synthesis began with the Stille coupling of stannylindole **3.1.19** with bromoindole **3.1.20** affording bisindole **3.1.21** in excellent yields (Scheme 46). At first, the seemingly obvious chemoselectivity of oxidation turned out to be more complicated. Oxidation of bisindole **3.1.21** with oxidants such as: oxone, oxaziridine, *m*-CPBA, OsO_4 or oxygen of the air gave **3.1.22** as a major product. However, using the Ley–Griffith reagent or hypervalent iodine reagents, the selectivity could be turned into the desired one, and with $PhI(TFA)_2$, the desired product **3.1.23** was formed in good yields and chemoselectivity. Under acidic conditions, hydroxyindolenine **3.1.23** was efficiently transformed into indoxyl **3.1.24**. However, the replacement of Brønsted acids by Lewis acid leads to transfer of the hydroxyl group from the 6-methoxyindole to the unfunctionalized indole. Deprotection of amine followed by imine formation delivered the natural product **3.1.3** in 81% yield over 2 steps.



Scheme 46. Formal total synthesis of (–)-trigonoliimine C by Tambar

In Movassaghi's enantioselective synthesis, bisindole **3.1.27** was synthesized *via* the Suzuki-Miyaura cross-coupling of boronylindole **3.1.26** and bromoindole **3.1.20**, though in slightly lower yields than in Tambar's synthesis (Scheme 47). The oxidation with Davis's oxaziridine of bistryptamine **3.1.27** was done with high stereoselectivity (96% ee), but with no chemoselectivity. As a result, a 2.2 to 1.0 mixture of two hydroxyindolenines **3.1.28** and **3.1.29** was obtained which was used without separation. The formation of two regioisomers during the oxidation step is practical for the synthesis of (+)-trigonoliimine A **3.1.1** and B **3.1.2**, however, for the synthesis of (−)-trigonoliimine C **3.1.3,** this leads to a loss of starting material. Similarly as aforementioned, Lewis acids showed low selectivity for Wagner-Meerwein-type 1,2-alkyl rearrangement. The major side-product observed with Lewis acids was oxindole. Good results were obtained with trifluoroethanol, a mixture of indoxyls **3.1.30** and **3.1.31** was isolated in 93% yield. Upon deprotection of the two amines, the subsequent cyclization was quite selective and only product with seven-membered cycle was formed. DFT calculations (B3LYP, 6.31G*) showed that the formation of the five-membered imine is unfavorable as final product would be 9.4 kcal/mol higher in energy than the product with 7-membered cycle. Finally, formylation of free amine gave natural product **3.1.3** in good yields. A more detailed synthesis of the Trigonoliimine family was published few years later.[179]

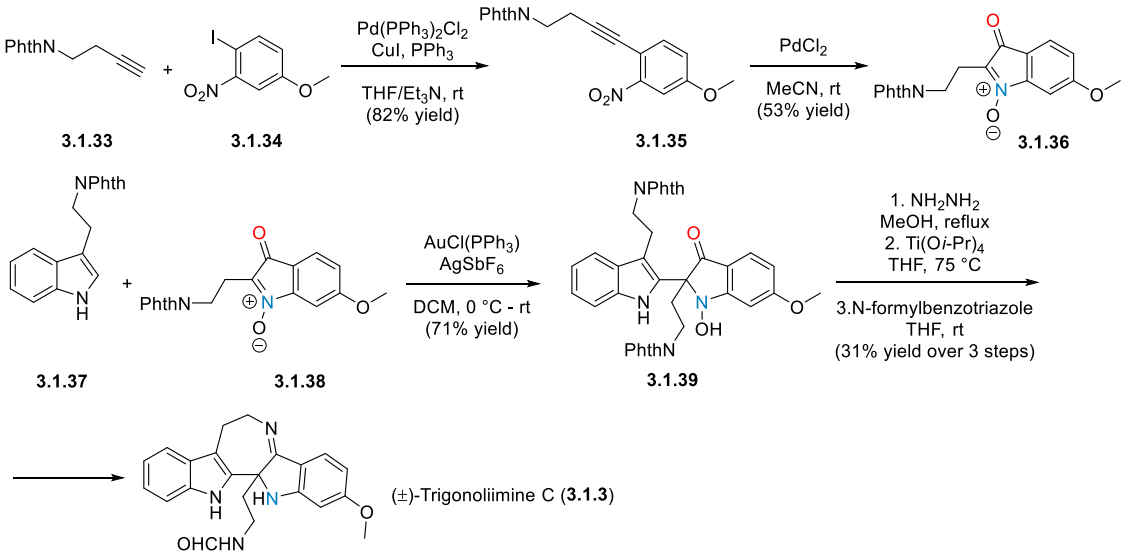


Scheme 47. Formal total synthesis of (−)-trigonoliimine C by Movassaghi

[179] Han, S.; Morrison, K.C.; Hergenrother, P.J.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 473 – 486.

3.1.3.2. Total synthesis by Ramana and Smith

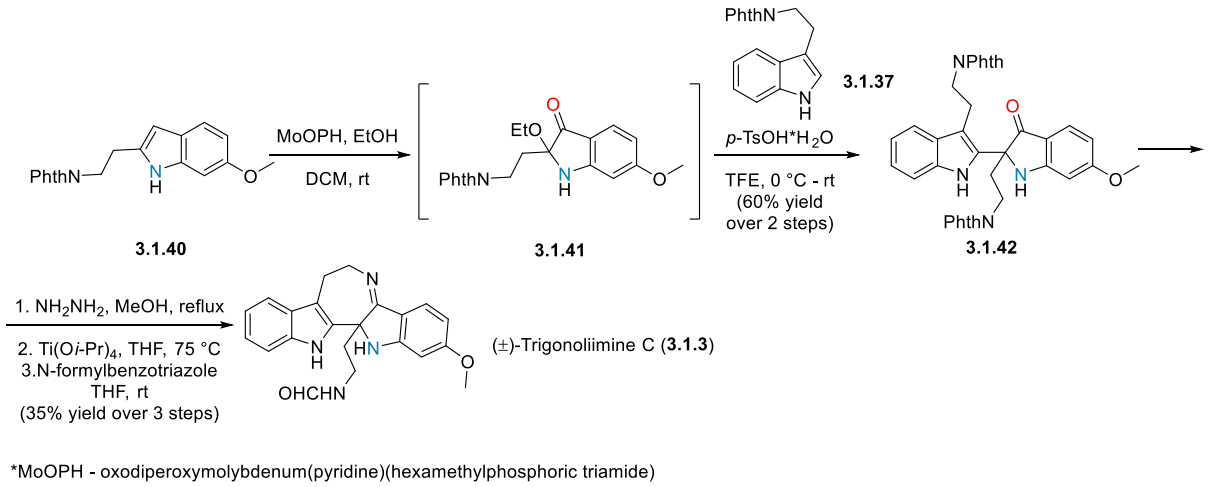
The alternative racemic total synthesis of (±)-trigonoliimine C was disclosed by Ramana *et al.* in 2013 featuring the [Au]-catalyzed C-2 addition of protected tryptamine to **3.1.38** (Scheme 48).[180] Authors proposed an efficient, six-step synthetic route to access the natural product. The synthesis began with the Sonogashira reaction to give alkyne **3.1.35**, which was then transformed into isatogen **3.1.36** *via* Pd-catalyzed cycloisomerization. In the early studies, Ramana and Degterev proposed that the cyclization takes place through a 5-exo-dig insertion of oxygen of the nitro group into the triple bond activated by Pd, followed by liberation of a nitroso and reclosure of the 5-membered ring.[181] The selective C-2 addition of tryptamine to isatogen was tested in the presence of different Brønsted and Lewis acids, *N*-hydroxyindol-3-one **3.1.39** could only be obtained with $AuCl(PPh_3)$ in combination with $AgSbF_6$. Concurrent deprotection of phthalimides and reduction of N-OH bond was realized with an excess of hydrazine. Formation of Shiff base and formylation was carried out according to the procedures developed by Tambar and Movassaghi.



Scheme 48. Formal total synthesis of (±)-trigonoliimine C by Ramana

Recently, Smith and coworkers presented another racemic formal total synthesis of (±)-trigonoliimine C featuring similar key-step as shown before – the nucleophilic C-2 coupling of tryptamine **3.1.37** with a 3-oxoindolenine, in this case with a 2-alkoxyindoxyl **3.1.41** (Scheme 49).[182] Oxidation of 2-substituted indole **3.1.40** with Mo-complex delivered 2-alkoxyindoxyl intermediate **3.1.41**, which was directly coupled with protected tryptamine **3.1.37** to give indoxyl **3.1.42** in 60% yield over 2 steps. Authors showed a broad substrate scope for the nucleophilic addition of different nucleophiles to 2-monosubstituted indoxyls.

[180] Reddy, B.N.; Ramana, C.V. *Chem. Commun.* **2013**, *49*, 9767 – 9769.
[181] Ramana, C.V.; Patel, P.; Vanka, K.; Miao, B.; Degterev, A. *Eur. J. Org. Chem.* **2010**, 5955 – 5966.
[182] Xu, F.; Smith, M.W. *Chem. Sci.* **2021**, *12*, 13756 – 13763.



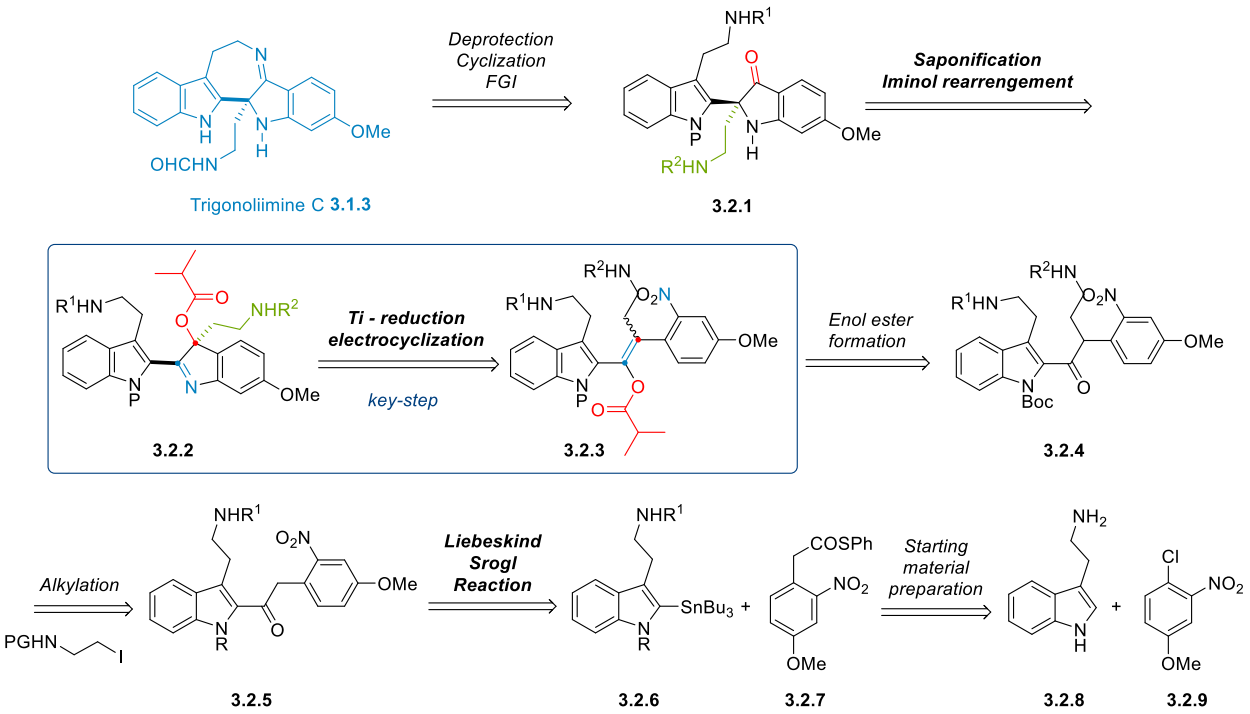
Scheme 49. Formal total synthesis of (±)-trigonoliimine C by Smith

3.2. **Retrosynthetic Pathway and Background**

3.2.1. **General Retrosynthetic Scheme**

Based on our work on the synthesis of 2,2-disubstituted 3-oxindoles *via* titanium trichloride-mediated reductive cyclization of trisubstituted enol esters bearing a 2-(*ortho*-nitroaryl) substituent **2.3.4**, we developed a retrosynthetic plan for the synthesis of trigonoliimine C (Scheme 50). Trigonoliimine C was planned to be synthesized from 2,2-disubstituted 3-oxindole **3.2.1**. The closure of the last 7-membered ring would be done *via* similar sequence of steps as in previous total syntheses: deprotection, Shiff-base formation and functional group interconversion. Compound **3.2.1**, in its turn, would be obtained *via* saponification and iminol rearrangement of 3-acyloxyindolenine **3.2.2**.[183] Intermediate **3.2.2** would be formed by key-transformation – reductive cyclization of *o*-nitrostyrene **3.2.3**. The latter would be prepared from the stannyl derivative of tryptamine **3.2.6** and thioester **3.2.7** *via* Liebeskind-Srogl reaction, followed by alkylation and enol ester formation.[184]

[183] Paquette, L.A.; Hofferberth, J.E. *Org. React.* **2003**, *62*, 477.
[184] Cheng, H.-G.; Chen, H.; Liu, Y.; Zhou, Q. *Asian J. Org. Chem.* **2018**, *7*, 490 – 508.

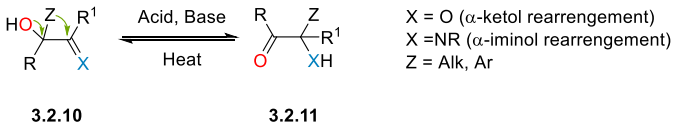


Scheme 50. General retrosynthetic scheme for the total synthesis of trigonoliimine C

3.2.2. **Iminol rearrangement**

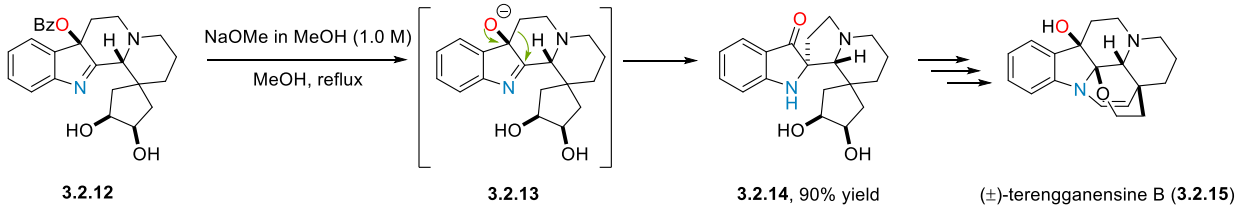
α-Iminol rearrangement together with α-ketol rearrangement belongs to a class of 1,2-nucleophilic rearrangements, in which the migrating group (alkyl/aryl) undergoes 1,2-shift with its electron pair (Scheme 51).[185,186] During this process hydroxy group on one of the two vicinal carbon atoms in **3.2.10** is transformed into ketone, while on the other side the carbonyl or imine are converted into an alcohol or amine, respectively. This reaction can be initiated by base,[187] acid[188] or heat.[189] The main advantage of an iminol rearrangement is that the process does not need a driving force unlike in the case of α-ketol migration (the use of aldehydes, α-carbonyls or ring expansion), due to the formation of more stable α-amino ketone **3.2.11**. For α-iminol rearrangement as for other 1.2-migration processes, the migrating group should be antiperiplanar to the double bond for the better orbital overlap.

[185] Zhang, X.-M.; Tu, Y.-Q.; Zhang, F.-M.; Chen, Z.-H.; Wang, S.-H. *Chem. Soc. Rev.* **2017**, *46*, 2272 – 2305.
[186] Benz, S.; Murkin, A.S. *Beilstein J. Org. Chem.* **2021,** *17*, 2570 – 2584.
[187] Kawamura, M.; Kamo, S.; Azuma, S.; Kubo, K.; Sasamori, T.; Tokitoh, N.; Kuramochi, K.; Tsubaki, K. *Org. Lett.* **2017**, *19*, 301 – 303.
[188] Serusi, L.; Cuccu, F.; Secci, F.; Aitken, D. J.; Frongia, A. *Synthesis* **2021**, *53*, 673 – 681.
[189] Stevens, C.L.; Treat, T.A.; Pillai, P.M. *J. Org. Soc.* **1972**, *37*, 2091.



Scheme 51. Iminol rearrengement

The synthetic application of this transformation was recently showcased in our group's total synthesis of natural products: (±)-eburnamonine, (±)-larutensine, (±)-terengganensine B and (±)-melokhanine E (Scheme 52).[190,191] Heating 3-benzoyloxyindolenine **3.2.12** with NaOMe in MeOH leads to hydrolysis of ester **3.2.13** and 1,2-rearrangement to give spiroindolin-3-one **3.2.14** in 90% yield. From this intermediate the desired natural products were synthesized in few steps.



Scheme 52. Iminol rearrangement as a key-step for the total synthesis of terengganensine B

Closely related transformations based on semipinacol type rearrangements can also be found in different total syntheses, selected examples are presented in Scheme 53. In 1979, the group of Kishi applied this transformation in the late stage of total synthesis of (±)-austamide **3.2.19**.[192] Stereoselective oxidation of the 2,3-disubstituted indole **3.2.16** was followed by a pinacol-type rearrangement to provide *spiro*-indoxyl **3.2.18**. The diastereoselective version of this synthesis was done by Corey and Baran in 2002 starting from (*S*)-tryptophan.[193] In 1990, a similar approach was used for the synthesis of natural product brevianamide B **3.2.23** by the group of Williams.[194,195] The group of Heathcock showed another application for the (–)-alloaristoteline **3.2.27** synthesis.[196] McWhorter worked on the addition of Grignard reagents to 3*H*-indol-3-ones **3.2.28** and rearrangements of the resulting tertiary alcohols.[197] He showed that the semipinacol type rearrangement of 3*H*-indol-3-ol **3.2.29** can be efficiently performed to give diverse 2,2-disubstituteted-3*H*-indol-3-one **3.2.30** starting from simple starting materials. Synthesis of 8-desbromohinckdentine A **3.2.31** was done following similar approach.[198]

[190] Li, G.; Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2019**, *58*, 2870 – 2874.
[191] Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2016**, *55*, 6556 – 6560.
[192] Hutchison, A.J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786 – 6788.
[193] Baran, P.S.; Corey, E.J. *J. Am. Chem. Soc.* **2002**, *124*, 7904 – 7905.
[194] Williams, R.M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J.K. *J. Am. Chem. Soc.* **1990**, *112*, 808 – 821.
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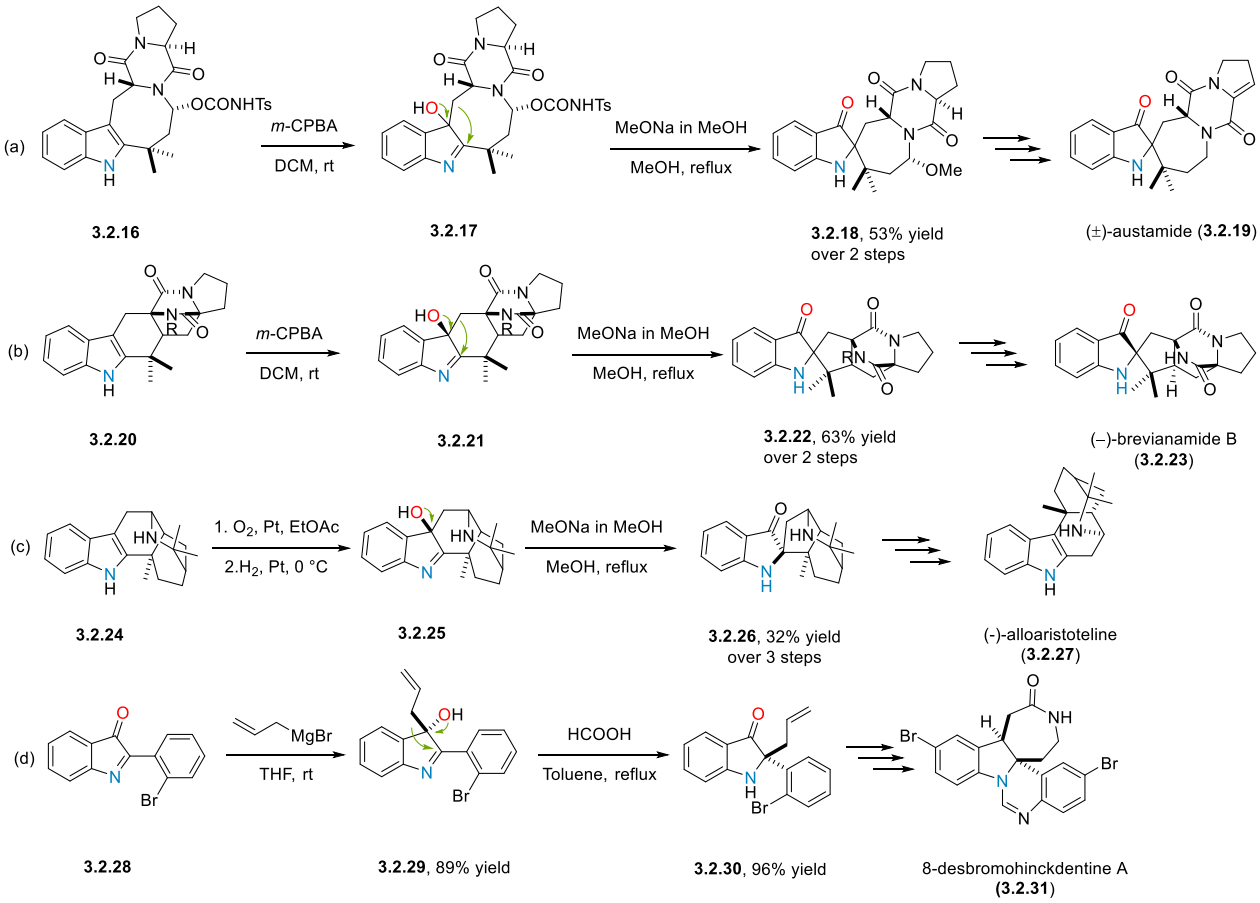
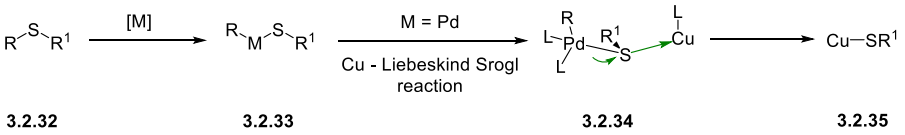
[196] Stoermer, D.; Heathcock, C.H. *J. Org. Chem.* **1993**, *58*, 564 – 568.
[197] Liu, Y.; McWhorter, W.W. Jr. *J. Org. Chem.* **2003**, *68*, 2618 – 2622.
[198] Liu, Y.; McWhorter, W.W. Jr. *J. Am. Chem. Soc.* **2003**, *125*, 4240 – 4252.



Scheme 53. Semipinacol rearrengements in total syntheses

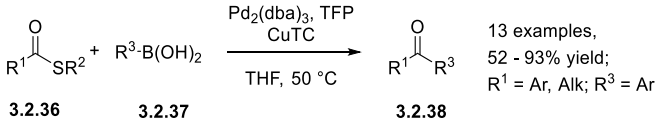
3.2.3. **Liebeskind-Srogl cross coupling reaction**

The Liebeskind-Srogl reaction is an efficient alternative cross-coupling method for the synthesis of different organic compounds starting with bench-stable thioesters as electrophiles. Sulfides can be easily introduced from simple substrates and several thioesters are even commercially available. Due to the low polarization of the C-S bond, this bond is relatively stable to ionic processes, however, it is characterized by the low bond dissociation enthalpies allowing transition metal complexes to easily fragilize and insert to this bond. Thanks to the low dissociation energy, this bond can be selectively cleaved in the presence of other C-X bonds. Formation of a donor-acceptor bond between the sulfur atom in thioesters and Lewis acids leads to the formation of positive charge on the sulfur and can lead sometimes to C-S bond cleavage. Soft transition metals (which are generally used as catalysts) make a strong M-S bonds with the soft sulfur atom **3.2.33**, which can be broken by the addition of another metal center, Cu – in the case of the Liebeskind-Srogl reaction (Scheme 54).



Scheme 54. Activation of thioethers with transition metals

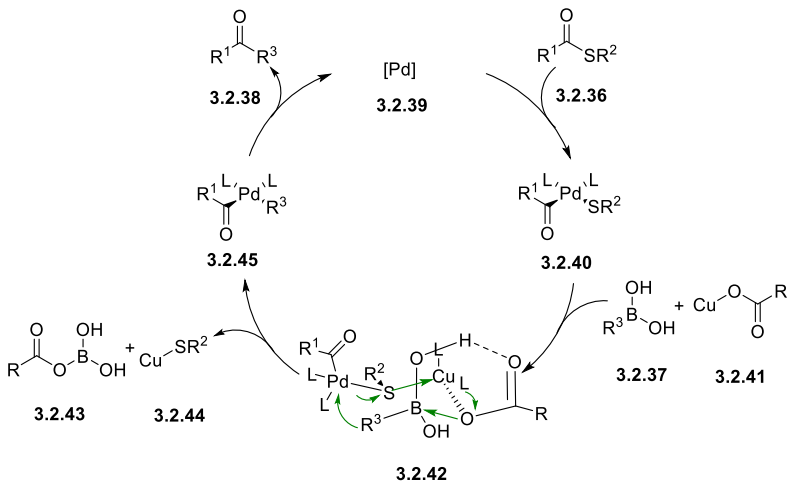
The first report about coupling of thioesters **3.2.36** and boronic acids **3.2.37** under mild base-free conditions was published in 2000 by Liebeskind and Srogl (Scheme 55).[199] At the beginning, it was seen as efficient and complementary way for the synthesis of ketones **3.2.38**, avoiding highly reactive and sensitive reagents and basic conditions. Nevertheless, since 2000, this reaction became a valuable C-C bond-forming method for the synthesis of different types of substrate, including its application for the synthesis of natural products, peptides, etc. Due to the difference of the reaction conditions from other cross-coupling reactions and orthogonal reactivity, it is possible to perform a sequence of cross-coupling reactions with high chemoselectivity.[200] Another important advantage of this transformation is the fact that both reaction partners (thioesters and boronic acids) are commercially available, stable and have low toxicity. In the case when the organoboron reagent is not accessible, the organostannane derivative can be an efficient replacement.[201]



Scheme 55. Liebeskind-Srogl reaction

Initially this reaction was developed with catalytic amounts of Pd in combination with stoichiometric amounts of copper(I) **3.2.41**. Cu salts can polarize the Pd-S bond and liberate Pd, to regenerate the catalyst, serving as a scavenger for thiolates **3.2.44**.[202] At the same time, the Cu counterion plays an important role in the reaction, replacement of carboxylate anion by halides or cyanides can completely shut down the reactivity. As it was shown later, carboxylate can activate the boronic acid during the transmetalation with Pd. Copper(I) thiophene-2-carboxylate (CuTC) and copper(I) diphenylphosphinate (CuDPP) are the most used reagents. A 6-membered transition state **3.2.42** is proposed, which shows the involvement of each reagent in the process (Scheme 56).[203] The reaction must be performed under inert atmosphere to avoid oxidation of Cu(I) to Cu(II), resulting in catalyst poisoning and the consumption of the organoboron reagent *via* protodeborylation. Any highly coordinating solvents, ligands or bases, can block Cu from coordination to sulfur.

[199] Liebeskind, L.S.; Srogl, J. *J. Am. Chem. Soc.* **2000,** *122*, 11260 – 11261.
[200] Kusturin, C.; Liebeskind, L.S.; Rahman, H.; Sample, K.; Schweitzer, B.; Srogl, J.; Neumann, W. L. *Org. Lett.* 2**003**, *5*, 4349 – 4352.
[201] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* **2003**, *5*, 3033 – 3035.
[202] Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979 – 981.
[203] Yu, Y.; Liebeskind, L.S. *J. Org. Chem.* **2004**, *69*, 3554 – 3557.



Scheme 56. Mechanism of Liebeskind-Srogl reaction

Since its discovery, different organosulfur compounds have been used in Liebeskind-Srogl reaction: thioesters, heteroaromatic thioethers, cyclic thioamides, thioalkynes, benzylthiocyanates, and diaryl disulfides, etc; proving the efficiency and broad applicability of this method. In terms of catalysts loading some progress was achieved during the last decade. For example, the Cu-free reaction can be performed with an organoindium coupling partner, which can scavenge thiol in place of copper to make the process catalytic.[204] The first example of a Cu(I)-catalyzed Pd-free anaerobic desulfitative cross-coupling reaction was published in 2007, however, in this reaction one additional equivalent of boronic acid was necessary to close the catalytic cycle.[205] To reduce the amount of organoboron coupling reagent new anaerobic conditions were investigated, where a special type of thioester could scavenge the formed thiol through the formation of cyclic side-product.[206]

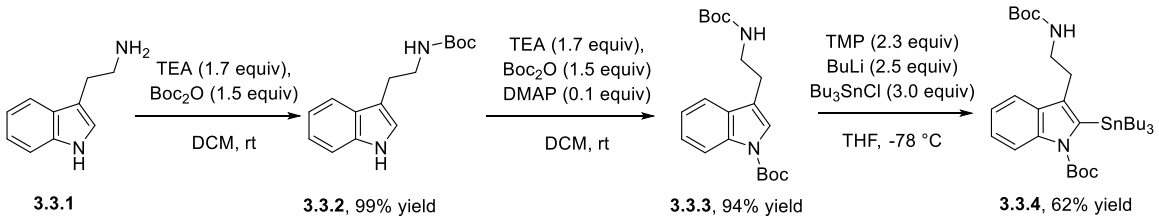
3.3. Synthetic studies

3.3.1. Synthesis of the precursors 3.3.4 and 3.3.10 for the key-step

We started the synthesis of (±)-trigonoliimine C by preparing coupling partners for the Liebeskind-Srogl reaction. Both organoboron and organotin compounds have been used in this cross-coupling reaction. Based on the work from our lab on the synthesis of (+)-peganumine A, we knew that in our case, it was necessary to use organotin derivative **3.3.4**, because organoboron derivative did not work in a similar reaction.[207,208] Boc-protection of both nitrogens of tryptamine **3.3.1** afforded **3.3.3** in 93% yield over two

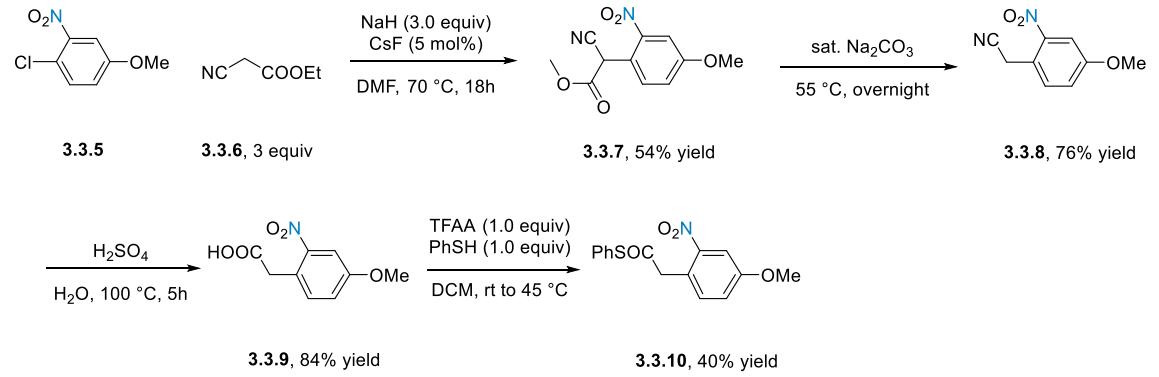
[204] Fausett, B.W.; Liebeskind, L.S. *J. Org. Chem.* **2005**, *70*, 4851 – 4853.
[205] Villalobos, J. M.; Srogl, J.; Liebeskind, L.S. *J. Am. Chem. Soc.* **2007**, *129*, 15734 – 15735.
[206] Zhang, Z.H.; Lindale, M.G.; Liebeskind, L.S. *J. Am. Chem. Soc.* **2011**, *133*, 6403 – 6410.
[207] Piemontesi, C.; Zhu, J. *Thesis EPFL* **2018**.
[208] Piemontesi, C.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2016**, 11148 – 11151.

steps (Scheme 57).[209] Deprotonation of indole with *n*-BuLi at -78 °C followed by trapping the resulting organolithium species with Bu_3SnCl gave the desired compound **3.3.4** in 62% yield.[210]



Scheme 57. Synthesis of organostanne coupling partner for the Liebeskind-Srogl reaction

The synthesis of the second coupling partner for the Liebeskind-Srogl reaction, thioester **3.3.10** started with the preparation of the known carboxylic acid **3.3.9**.[211] Nucleophilic aromatic substitution (S_NAr) of 4-chloro-3-nitroanisole **3.3.5** with ethyl cyanoacetate **3.3.6** delivered the α-arylated product **3.3.7** in 54% yield (Scheme 58). Saponification of ester **3.3.7** followed by decarboxylation gave nitrile **3.3.8** in 76% yield. Hydrolysis of nitrile group in a solution of sulfuric acid (1.0 N) afforded carboxylic acid **3.3.9** in 70% isolated yield. Finally, reaction of carboxylic acid **3.3.9** with TFAA and PhSH furnished thioester **3.3.10** in moderate 40% yield. Arylacetic acid **3.3.9** is commercially available but cannot be purchased at a reasonable price.



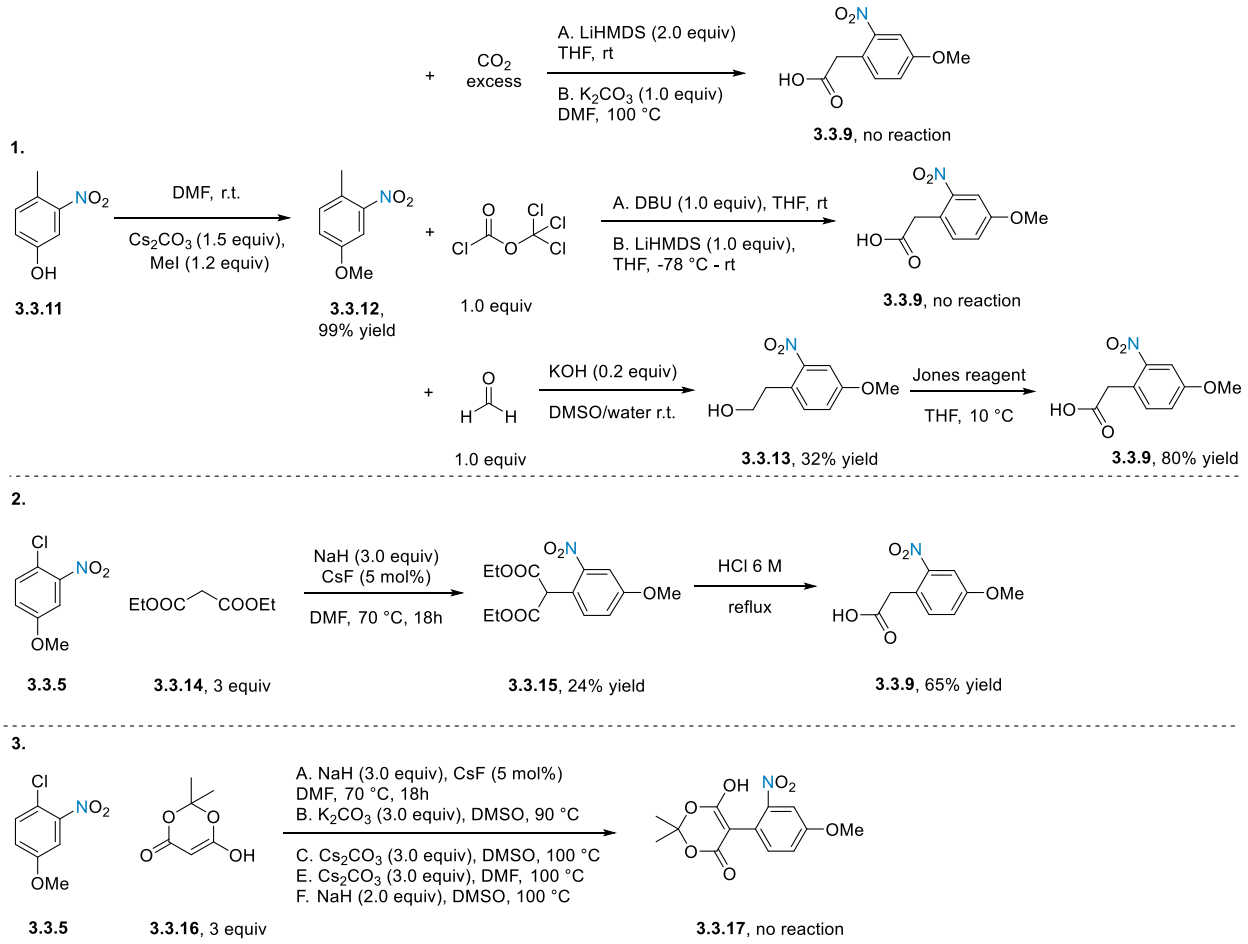
*Scheme 58. Synthesis of organosulfur coupling partner **3.3.10** for the Liebeskind-Srogl reaction*

In the meantime, we tried to find a more straightforward and efficient synthesis of compound **3.3.9**, and different approaches were tested. The results are summarized in Scheme 59. The first route consisted of the carboxylation of 4-methoxy-2-nitrotoluene **3.3.12**, prepared by methylation of the corresponding phenol **3.3.11** in quantitative yields (Scheme 59.1). Unfortunately, in the presence of different bases (LiHMDS, DBU and K_2CO_3), no reaction was observed between *o*-nitrotoluene **3.3.12** and CO_2 or diphosgene. CO_2 gas was formed *in situ* in a connected flask by the slow addition of concentrated HCl to Na_2CO_3. When formaldehyde was used as an electrophile, desired alcohol **3.3.13** was isolated in 32% yield and directly transformed into the acid **3.3.9** under Jones oxidation conditions. Increasing amount of base

[209] Jacquemard, U.; Beneteau, V.; Lefoix, M.; Routier, S.; Merour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039 – 10047.
[210] Qi, X.; Bao, H.; Tambar, U.K. *J. Am. Chem. Soc.* **2011**, *133*, 10050 – 10053.
[211] Lowe, W.; Witzel, S.; Tappmeyer, S.; Albuschat, R. *J. Heterocyclic Chem.* **2004**, *41*, 317 – 326.

and temperature did not improve the yield of the first step. The overall 25% yield for the three steps starting from phenol **3.3.11** was not higher than those described in the literature.

The second route was based on S_NAr reaction between diethyl malonate **3.3.14** and 4-chloro-3-nitroanisole **3.3.5**. However, this reaction afforded the desired product in only 24% yield (Scheme 59.2).[212] This route is therefore not competitive with the previous ones. Finally, Meldrum's acid failed to participate in the S_NAr reaction with 4-chloro-3-nitroanisole **3.3.5** under diverse sets of conditions varying the bases and the temperature (Scheme 59.3).



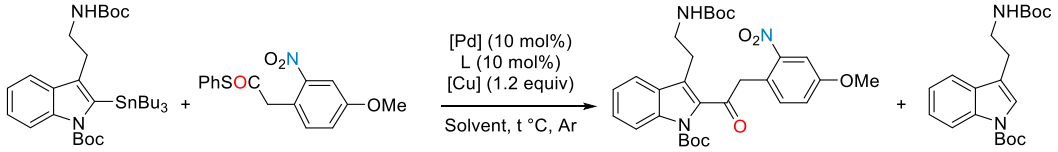
*Scheme 59. Different approaches for the synthesis of organosulfur cross coupling partner **3.3.10***

3.3.2. **Synthesis of enol ester 3.3.36**

With both coupling partners in hand, the optimization of the reaction conditions for the Liebeskind-Srogl reaction was undertaken. From the beginning, all reactions were performed under an inert atmosphere of argon with a Freeze-pump-Thaw degassing of all the liquids. By applying classical coupling conditions: $Pd_2(dba)_3$ (catalyst), CuTC (as co-catalyst) in THF at 40 °C, we could already isolate the desired product

[212] Sun, Li; Tran, N. ; App, H.; Hirth, P.; McMahom, G.; Tang, C. *J. Med. Chem.* **1998**, *41*, 2588 – 2603.

3.3.18 in 39% yield ($P(OEt)_3$ as ligand, Table 9, entries 1-3).[213] Using TFP and $AsPh_3$ as ligands gave slightly lower yields. The main side-product of this transformation is a destannylated indole **3.3.19**, which is probably formed through competing transmetalation of the organotin derivative with Cu. A similar yield was obtained when the reaction was performed at 50 °C (entry 6). However, the yield of **3.3.18** dropped to 11% when the reaction was carried out at 0 °C (entry 4). Using a mixture of solvents THF/hexane with different proportion didn't improve significantly the yield of the desired product (entries 7-11). Varying the Cu cocatalyst (CuDPP), ligand ($AsPh_3$),[214] temperature and Pd source failed to improve the reaction outcome.



3.3.4, 1.1 equiv **3.3.10**, 1.0 equiv **3.3.18** **3.3.19**

	[Pd]	L	Cu	Solvent	T, °C	**3.3.18**[a]	**3.3.19**[a]
1.	$Pd_2(dba)_3$	TFP	CuTC	THF	40 °C	20%	50%
2.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF	40 °C	39%	31%
3.	$Pd_2(dba)_3$	$AsPh_3$	CuTC	THF	40 °C	32%	53%
4.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF	rt	11%	55%
5.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF	30 °C	35%	23%
6.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF	50 °C	42%	41%
7.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF/Hexane 1:1	40 °C	25%	58%
8.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF/Hexane 2:1	40 °C	15%	54%
9.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF/Hexane 4:1	40 °C	21%	34%
10	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF/Hexane 1:2	40 °C	32%	47%
11.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	THF/Hexane 1:4	40 °C	43%	36%
12.	$Pd_2(dba)_3$	$AsPh_3$	CuDPP	THF/Hexane 1:3	rt	37%	26%
13.	$Pd_2(dba)_3$	$AsPh_3$	CuDPP	THF/Hexane 1:3	40 °C	33%	33%
14.	$Pd_2(dba)_3$	$P(OEt)_3$	CuDPP	THF/Hexane 1:4	40 °C	16%	64%
15.	$Pd(PPh_3)_4$	-	CuTC	THF	40 °C	3%	64%
16.	$Pd(PPh_3)_4$	-	CuDPP	THF	40 °C	30%	30%

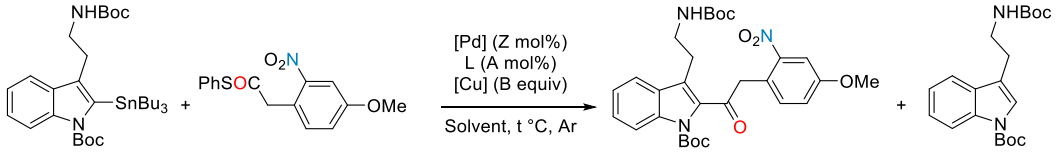
[a] NMR yields determined using 1,3,5-trimethoxybenzene as internal reference.

Table 9. Optimization of the Liebeskind-Srogl cross-coupling reaction

Entry 12 in Table 9 seemed to be promising, delivering desired product in 37% yield at ambient temperature with catalytic system, which was efficient in previous studies.[208] Based on these conditions we decided to do a second round of optimization (Table 10). The main observations are summarized as follows. a) solvent: A mixture of solvents THF/hexane = 1:3 is optimum (Table **10**, entries 1-5); b) stoichiometry: Since protodestannylation is a competing process, the amount of [Sn] coupling partner was varied (entries 3-5). The yield of the desired coupling product was improved to 46% with 2.5 equiv of organotin **3.3.4**. On the other hand, performing the reaction with an excess of thioester **3.3.10** had no positive influence (entry

[213] Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L.S. *Org. Lett.* **2003**, *5*, 3033 – 3035.
[214] Huang, Y.-Z.; Shi, L.-L.; Zhou, Z.-L.; Espinet, P.; Genov, M., Triphenylarsine. In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd, **2001**.

12); c) catalyst loading: Increasing the loading of Pd and ligand reduced the yield of the product (entries 6-7). However, the yield was increased when the amount of CuDPP was increased from 1.2 to 1.6, 2.0 and 3.0 equivalents. It is necessary to mention that the quantity of organotin **3.3.4** partner should also be increased in order to get the improved product yield (entries 8-11); d) temperature: 40 °C seemed to be optimum. Performing the reaction at 40 °C afforded the desired product in 68% yield (entries 13-14). Overall, the optimal conditions consisted of performing the coupling reaction of **3.3.10** with organotin compound **3.3.4** (2.0 equiv) in a solution of THF/hexane (1:3, c 0.07 M) at room temperature in the presence of CuTC (1.6 equiv), a catalytic amount of $Pd_2(dba)_3$ (10 mol%) and $P(OEt)_3$ (10 mol%) under argon atmosphere. Under these conditions, **3.3.18** was isolated in 70% yield.



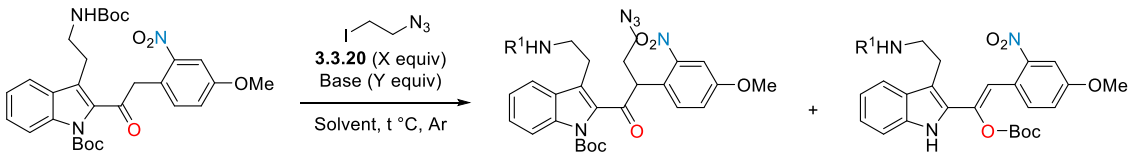
3.3.4, X equiv **3.3.10**, Y equiv **3.3.18** **3.3.19**

	COSPh (equiv)	[Sn] (equiv)	$Pd_2(dba)_3$ (mol%)	$AsPh_3$ (mol%)	CuDPP (equiv)	Solvent	T, °C	**3.3.18**	**3.3.19**
1.	1.0	1.1	10	10	1.2	THF/Hexane 1:4	rt	23%	41%
2.	1.0	1.1	10	10	1.2	THF/Hexane 1:7	rt	18%	33%
3.	1.0	1.2	10	10	1.2	THF/Hexane 1:3	rt	30%	32%
4.	1.0	2.0	10	10	1.2	THF/Hexane 1:3	rt	44%	30%
5.	1.0	2.5	10	10	1.2	THF/Hexane 1:3	rt	46%	64%
6.	1.0	1.2	20	20	1.2	THF/Hexane 1:3	rt	25%	17%
7.	1.0	1.2	40	40	1.2	THF/Hexane 1:3	rt	21%	31%
8.	1.0	1.2	10	10	1.6	THF/Hexane 1:3	rt	40%	27%
9.	1.0	1.6	10	10	1.6	THF/Hexane 1:3	rt	60%	65%
10	1.0	2.0	10	10	2.0	THF/Hexane 1:3	rt	54%	43%
11.	1.0	2.0	10	10	3.0	THF/Hexane 1:3	rt	67%	15%
12.	1.5	1.0	10	10	1.2	THF/Hexane 1:3	rt	30%	35%
13.	1.0	2.0	10	10	1.6	THF/Hexane 1:3	30 °C	40%	47%
14.	1.0	2.0	10	10	1.6	THF/Hexane 1:3	40 °C	68%	81%
15.[b]	1.0	1.2	10	10	1.2	THF/Hexane 1:3	rt	38%	39%
16.	1.0	2.0	10	$P(OEt)_3$	1.6	THF/Hexane 1:3	rt	60%	30%
17.	1.0	2.0	10	$P(OEt)_3$	CuTC	THF/Hexane 1:3	rt	70%	91%

[a] NMR yields determined using 1,3,5-trimethoxybenzene as internal reference; [b] Reaction was stopped after one day.

Table 10. Optimization of the Liebeskind-Srogl cross-coupling reaction (2nd round of optimization)

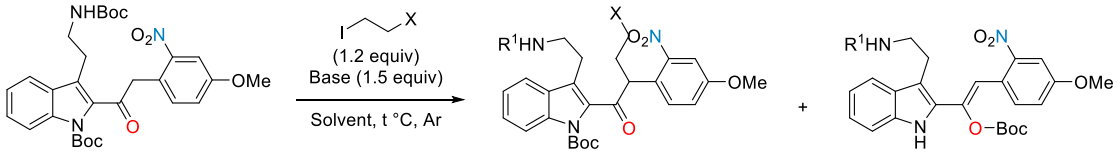
After the Liebeskind-Srogl coupling, the α-alkylation of ketone was investigated (Table 11). Initially, 1-azido-2-iodoethane **3.3.20** was used as an electrophilic alkylating agent. Unfortunately, instead of the formation of alkylated ketone **3.3.21**, the Boc-transfer product **3.3.22** or starting material **3.3.18** were obtained under a variety of conditions. Only side-product **3.3.22** was formed when weak bases K_2CO_3, K_3PO_4 and Cs_2CO_3 were used (Table **11**, entries 1-5). Performing the alkylation reaction with strong base (LHMDS) at low temperature (-78 °C, -40 °C, 0 °C) led to the recovery of the starting materials (entries 6-9). Increasing the amount of alkyl iodide had no positive effect on the reaction (entry 10). Finally, similar results were obtained when KHMDS was used as a base (entry 11).



	Alk-I (equiv)	Base (equiv)	Solvent	T °C	Results
1.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	rt	
2.	1.4	Cs_2CO_3 (2.5 equiv)	DMF	rt	
3.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	rt	**3.3.22**
4.	1.2	K_2CO_3 (1.5 equiv)	DMF	rt	
5.	1.2	K_3PO_4 (1.5 equiv)	DMF	rt	
6.	1.2	LiHMDS (1.5 equiv)	THF	-78 °C	
7.	1.2	LiHMDS (1.5 equiv)	THF	-78 – (-40) °C	**3.3.18**
8.	1.2	LiHMDS (1.5 equiv)	THF	-78 – 0 °C	
9.	1.2	LiHMDS (1.5 equiv)	THF	-78 °C – rt	**3.3.22**
10	3.0	LiHMDS (1.5 equiv)	THF	-78 °C	**3.3.18**
11.	1.2	KHMDS (1.5 equiv)	THF	-78 °C	**3.3.22**

*Table 11. Attempted alkylation of ketone **3.3.18***

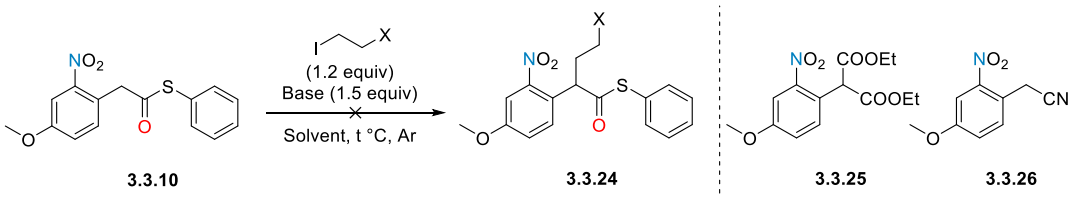
Other alkylating agents (X = OTBS, NPhth and -NHBoc) were next examined (Table 12). In all cases, only the Boc transfer product **3.3.22** was formed.



	Alk-X (1.2 equiv)	Base (1.5 equiv)	Solvent	T °C	Results
1.	-OTBS	LiHMDS	THF	-78 °C – rt	**3.3.22**
2.	-NPhth	LiHMDS	THF	-78 °C – rt	
3.	-NHBoc	LiHMDS	THF	-78 – (-40) °C	**3.3.18**
4.	-NHBoc	LiHMDS	THF	-78 – 0 °C	
5.	-NHBoc	LiHMDS	THF	-78 °C – rt	**3.3.22**
6.	-NHBoc	LiHMDS	THF	-78 – 40 °C	

*Table 12. Attempted alkylation of ketone **3.3.18** with different alkylating reagents*

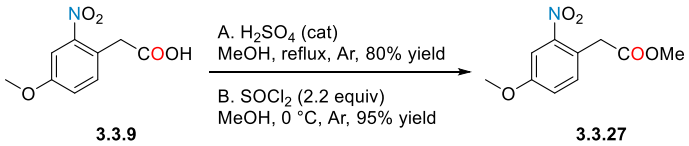
To reach the desired compound and to avoid Boc-migration, one can either change the order of the reaction sequence by preforming the alkylation at any step before the Liebeskind-Srogl coupling or to replace the Boc-protecting group by other non-migrating group. Alkylation of thioester **3.3.10** with alkyl iodides containing azido or –NPhth groups was examined without any success (Table 13). Malonate **3.3.25** and cyanide **3.3.26** did not work as well.



	Alk-X (equiv)	Base (1.5 equiv)	Solvent	t °C	Results
1.	-N_3	Cs_2CO_3	DMF	rt – 55 °C	
2.	-N_3	LiHMDS	THF	-78 °C – rt	Slow
3.	-N_3	*t*-BuOK	THF	-78 °C – rt	decomposition
4.	-NPhth	LiHMDS	THF	-78 – 0 °C	of **3.3.10**
5.	-NPhth	LiHMDS	THF	-78 °C – rt	

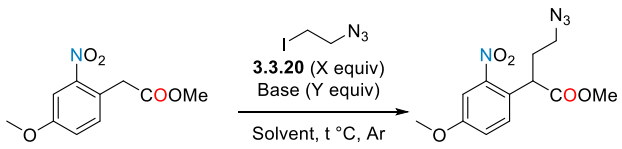
*Table 13. Attempted alkylation of thioester **3.3.10***

Acid **3.3.9** was not tested in this α-alkylation reaction to avoid double deprotonation of starting material and complication of reaction. However, another potential option was to use methyl ester **3.3.27**, which was synthesized in 80% yield under acidic conditions with a catalytic amount of H_2SO_4 (Scheme 60). Later, the yields were improved when $SOCl_2$ was used as activating agent.



*Scheme 60. Esterification of acid **3.3.9***

Alkylation of methyl ester **3.3.27** with alkyl azide **3.3.20** was examined firstly. From the first try Cs_2CO_3/DMF system showed to be efficient (Table 14, entries 1-6). After 7h, half of starting material was converted (entry 5), after 12h the reaction was stopped and desired product was obtained in only 43% yield (entry 6). To improve the yield, higher temperatures and higher amounts of the alkylating agent were applied without improving the results (entries 7-9). With K_2CO_3 and K_3PO_4 as bases, only starting material **3.3.27** was recovered. The use of strong base such as LiHMDS leads to only decomposition of ester **3.3.27**.

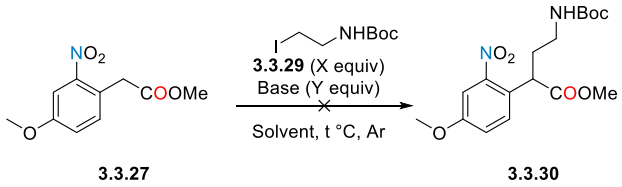


	Alk-N_3 (equiv)	Base (equiv)	Solvent	Time	T °C	Results[a]
1.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	5 min	rt	**SM**
2.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	30 min	rt	**SM**
3.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	1h	rt	**SM**
4.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	2h	rt	**3.3.28/SM** 40/60
5.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	7h	rt	**3.3.28/SM** 50/50
6.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	12h	rt	**3.3.28** 43%
7.	1.2	Cs_2CO_3 (1.5 equiv)	DMF	12h	rt – 50 °C	**3.3.28** <5%
8.	1.5	Cs_2CO_3 (1.5 equiv)	DMF	12h	rt	**3.3.28** 23%
9.	1.6	Cs_2CO_3 (1.5 equiv)	DMF	12h	rt	**3.3.28** <10%
10	1.5	K_2CO_3 (1.5 equiv)	DMF	12h	rt	**SM**
11.	1.5	K_3PO_4 (1.5 equiv)	DMF	12h	rt	**3.3.28** <10%
12.	1.2	LiHMDS (1.5 equiv)	THF	12h	-78 °C – rt	Slow decomposition of SM
13.	1.2	LiHMDS (1.5 equiv)	THF	12h	-78 °C – rt	
14.	1.2	LiHMDS (1.0 equiv)	THF	12h	-78 – (-20) °C	

[a] NMR yields determined using 1,3,5-trimethoxybenzene as internal reference.

*Table 14. Optimization of alkylation of ester **3.3.27** with alkyl iodide **3.3.20***

The previously obtained results did not seem ideal; to improve them the azide was replaced by –NHBoc **3.3.29**. The same conditions were applied but no conversion was observed, an increasing amount of alkylating agent did not affect the reaction (Table 15).

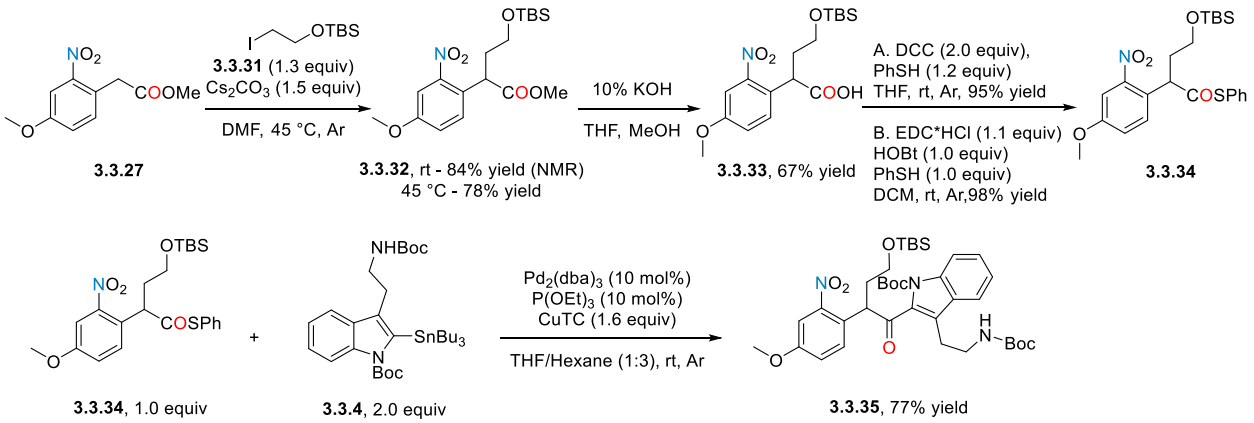


	3.3.29 (equiv)	Base (1.5 equiv)	Solvent	T °C	Results
1.	1.0 + 1.0	Cs_2CO_3	DMF	rt	No conversion
2.	1.5	Cs_2CO_3	DMF	rt	
3.	2.4	Cs_2CO_3	DMF	rt	
4.	4.8	Cs_2CO_3	DMF	rt	

*Table 15. Attempted alkylation of ester **3.3.27** with alkyl iodide **3.3.29***

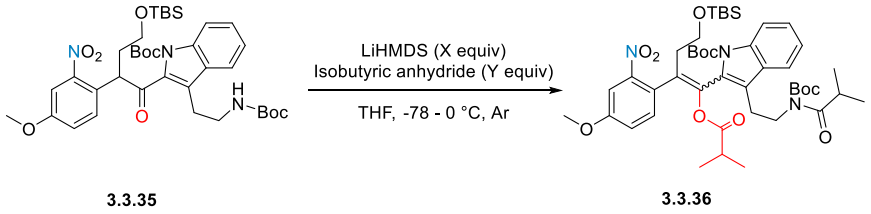
Finally, excellent results were obtained using *tert*-butyl(2-iodoethoxy)dimethylsilane **3.3.31** as alkylating reagent. Simply stirring a DMF solution of methyl 2-(4-methoxy-2-nitrophenyl)acetate **3.3.27** and *tert*-butyl(2-iodoethoxy)dimethylsilane **3.3.31** at 45 °C afforded product **3.3.32** in 78% isolated yield (Scheme 61). Saponificaiton of ester (KOH, THF-MeOH) gave acid **3.3.33** (97% yield), which was

converted to thioester **3.3.34** in quantitative yields under Steglich conditions. Gratefully, Liebeskind-Srogl coupling between organotin **3.3.4** and thioester **3.3.34** afforded ketone **3.3.35** in 77% yield.



*Scheme 61. Synthesis of ketone **3.3.35***

From compound **3.3.35**, the ketone moiety needed to be converted into enol ester. Conditions for enol ester formation presented in Chapter 2 turned out to be incompatible with this substrate. Only decomposition of ketone **3.3.35** was observed when it was treated with 2.5 equiv of LiHMDS and 3.0 equiv of anhydride at -78 °C (Table 16, entry 1). The formation of product **3.3.36** resulting from the *N*,*O*-double acylation of the starting material was observed when the amount of anhydride was reduced to 2.0 or to 1.2 equiv (entries 2-3). With 2.0 equiv of base, a slightly better result was obtained (entries 4-5). When LiHMDS (2.0 equiv) and anhydride (2.0 equiv) were used in equal amounts, the di-acylated product was formed in 32% yields. Further decreasing the amount of LiHMDS and anhydride leads to slow decomposition or no reaction (entries 6-7). Since double acylation product was formed even with 1.2 equivalent of anhydride, the N-acylation of carbamate might be faster than the enol ester formation (entry 5). Finally, when conditions from entry 4 were used on a bigger scale, the desired product was isolated in 40% yield (entry 8).



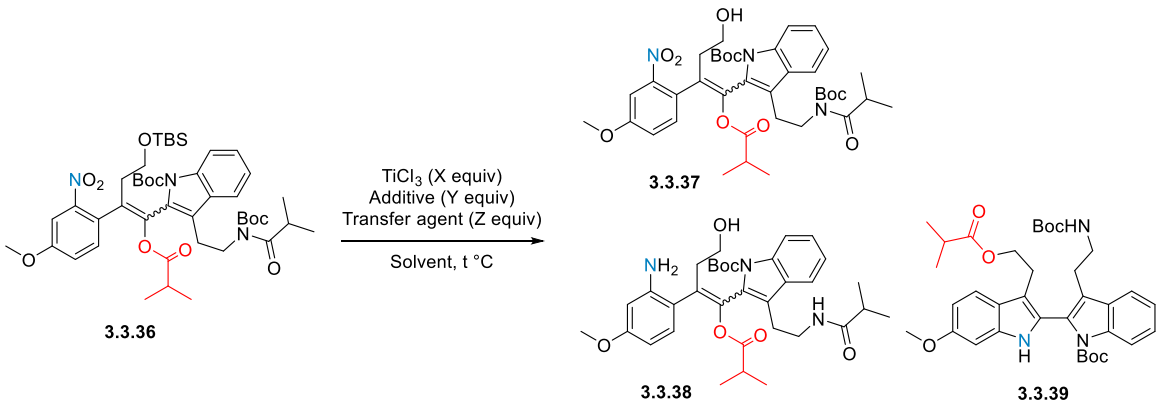
	LiHMDS (equiv)	Anhydride (equiv)	Results
1.	2.5 equiv	3.0 equiv	Decomposition
2.	2.5 equiv	2.0 equiv	**3.3.36** + Decomposition
3.	2.5 equiv	1.2 equiv	**3.3.36** + SM
4.	2.0 equiv	2.0 equiv	**3.3.36** – 32%
5.	2.0 equiv	1.2 equiv	Decomposition
6.	1.5 equiv	1.5 equiv	Decomposition + SM
7.	1.2 equiv	1.2 equiv	SM
8.[a]	2.0 equiv	2.0 equiv	**3.3.36** – 40% yield

[a] 1.1 mmol scale

*Table 16. Optimization of the formation of enol ester **3.3.36***

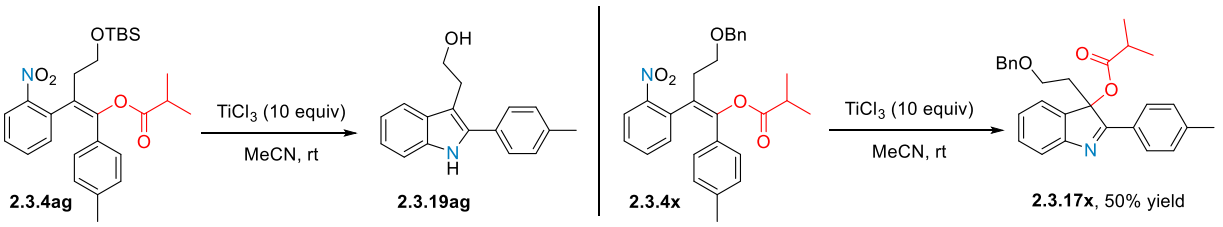
3.3.3. **Ti-mediated reductive cyclization of enol ester 3.3.36**

At this stage, we could finally test our key-step – the $TiCl_3$-mediated reductive cyclization of 2-(*ortho*-nitro)aryl substituted enol ester **3.3.36**. Under optimized conditions detailed in chapter 2, the reaction turned out to be messy with low conversion of the starting material (Table 17). The TBS-protecting group was quickly cleaved under all the applied conditions shown in Table 17, and may be the reason why the reaction became messy. The reaction conditions were therefore re-optimized by varying the stoichiometry of $TiCl_3$, the solvents (MeCN, Me_2CO, MeOH), the additives (NH_4OAc, NaOOCH, imidazole), the temperature (rt, 25 °C, 45 °C) and the phase transfer reagent (SDS). As it is seen from Table 17, no desired product was isolated from all these experiments. In addition to products **3.3.37** and **3.3.38** resulting from the removal of TBS ether and N-Boc from the imide function, 2,2'-bisindole **3.3.39** was isolated. Compound **3.3.39** might be generated from the *E*-enol ester through a sequence of reduction of the nitro group to aniline, OTBS-deprotection, transesterification and intramolecular condensation between the newly generated amino and ketone functions. From these results, we suspected that the free hydroxyl group generated in situ might be responsible to the failure. Indeed, working on the scope of our methodology, enol ester **2.3.4ag** was tested, and indole **2.3.19ag** was isolated as a main product with no traces of indolenine **2.3.17ag** (Scheme 62). At the same time, Bn-protected alcohol **2.3.4x** delivered desired product **2.3.17x** in 50% yield. Based on these results we decided to synthesize an enol ester in which the TBS-protecting group was replaced by a benzyl group.



	$TiCl_3$ (X equiv)	Additive (Y equiv)	Transfer agent (Z equiv)	Solvent (0.2 M)	T °C	Results
1.	10 equiv	-	-	MeCN	rt	Almost no reaction, **3.3.37**
2.	10+10 equiv	-	-	MeCN	rt	
3.	10+10 equiv	NH_4OAc (40 equiv)	-	MeCN	rt	
4.	10+10 equiv	-	SDS (2 equiv)	MeCN	rt	
5.	10+10 equiv	-	SDS (2 equiv)	Acetone	rt	
6.	20 equiv	NH_4OAc (40 equiv)	-	MeCN	rt	**3.3.37, 3.3.38, 3.3.39**
7.	20 equiv	-	SDS (2 equiv)	MeCN	rt	
8.	20 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.1 M)	rt	
9.	20 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.4 M)	rt	
10.	20 equiv	Imidazole (80 equiv)	-	Acetone	rt	
11.	20 equiv	Imidazole (80 equiv)	SDS (2 equiv)	Acetone	rt	
12.	50 equiv	-	-	MeCN	rt	
13.	50 equiv	NH_4OAc (200 equiv)	-	MeCN	rt	
14.	50 equiv	HCOONa (200 equiv)	-	MeCN	rt	
15.	50 equiv	Imidazole (200 equiv)	-	Acetone	rt	
16.	50 equiv	NH_4OAc (100 equiv)	-	MeCN	rt	
17.	50 equiv	NH_4OAc (200 equiv)	-	MeCN	35 °C	
18.	50 equiv	NH_4OAc (200 equiv)	-	MeCN	45 °C	
19.	50 equiv	NH_4OAc (200 equiv)	SDS (2 equiv)	MeCN	rt	
20.	50 equiv	NH_4OAc (200 equiv)	SDS (2 equiv)	MeCN	45 °C	
21.	50 equiv	NH_4OAc (200 equiv)	SDS (2 equiv)	MeOH	rt	
22.	50 equiv	Imidazole (200 equiv)	SDS (2 equiv)	Acetone	rt	

*Table 17. Attempted Ti-mediated cyclization of enol ester **3.3.36***

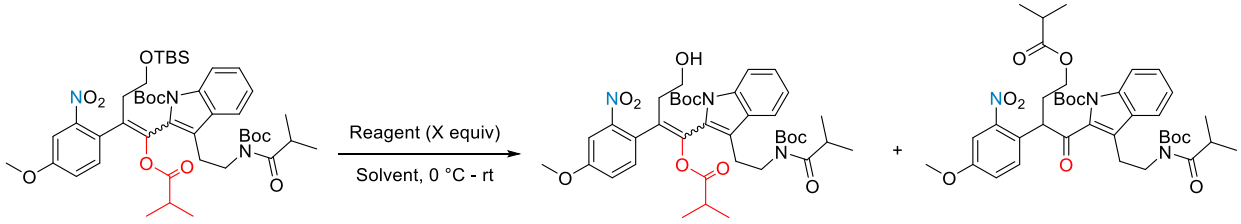


*Scheme 62. Examples of reductive cyclization of enol esters **2.3.4***

3.3.4. **Synthesis of Bn-protected enol ester 3.3.47**

Removal of the TBS-ether from **3.3.36** was tested under different conditions (

Table 18). With TBAF in THF and DMF, the *Z*-isomer was deprotected smoothly to give **3.3.40**. However, the *E*-isomer converted slowly to ketone **3.3.41** *via* deprotection and transesterification cascade (Table 18, entries 1-2). The addition of 1.1 equiv of acetic acid leads to the slow formation of desired product **3.3.40**. Finally, we were able to avoid the occurrence of the transesterification step by performing the deprotection under acidic conditions. The desired alcohol **3.3.40** was isolated in quantitative yields with 2.0 equiv of HCl (1.0 N).

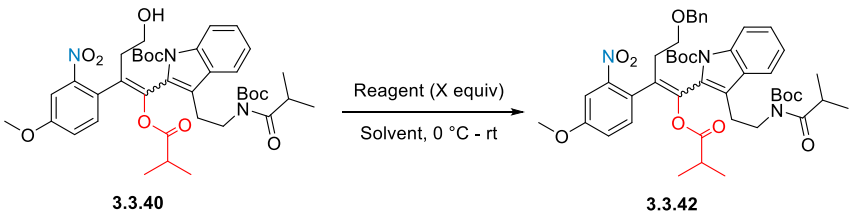


	Reagent (X equiv)	Solvent	Results
1.	TBAF (1.1 equiv)	THF	Not a full conversion, **3.3.41**
2.	TBAF (1.1 equiv)	DMF	
3.	TBAF (1.1 equiv), Acetic acid (1.1 equiv)	THF	**3.3.40** + SM
4.	HCl (1.0N, 2.0 equiv)	THF	Quantitative formation **3.3.40**

*Table 18. Optimization of the deprotection of enol ester **3.3.36***

Basic conditions turned out to be inefficient in transforming free alcohol of compound **3.3.40** to its benzyl ether **3.3.42** (Table 19). Sodium hydride led to the decomposition of enol ester **3.3.40** (Table 19, entry 1). No reaction was observed with K_2CO_3 (entries 2-3) or Ag_2O (entry 4).[215,216] Finally, reaction of **3.3.40** with benzyl 2,2,2-trichloroacetamide in the presence of a catalytic amount of TfOH afforded the benzyl ether **3.3.42** in quantitative yields (entry 6).[217]

[215] Bouzide, A.; Sauvé, G. *Tetrahedron Lett.*, **1997**, *38*, 5945 – 5948.
[216] Wang, L.; Hashidoko, Y.; Hashimoto, M. *J. Org. Chem.* **2016**, *81*, 4464 – 4474.
[217] Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49*, 1619 – 1624.

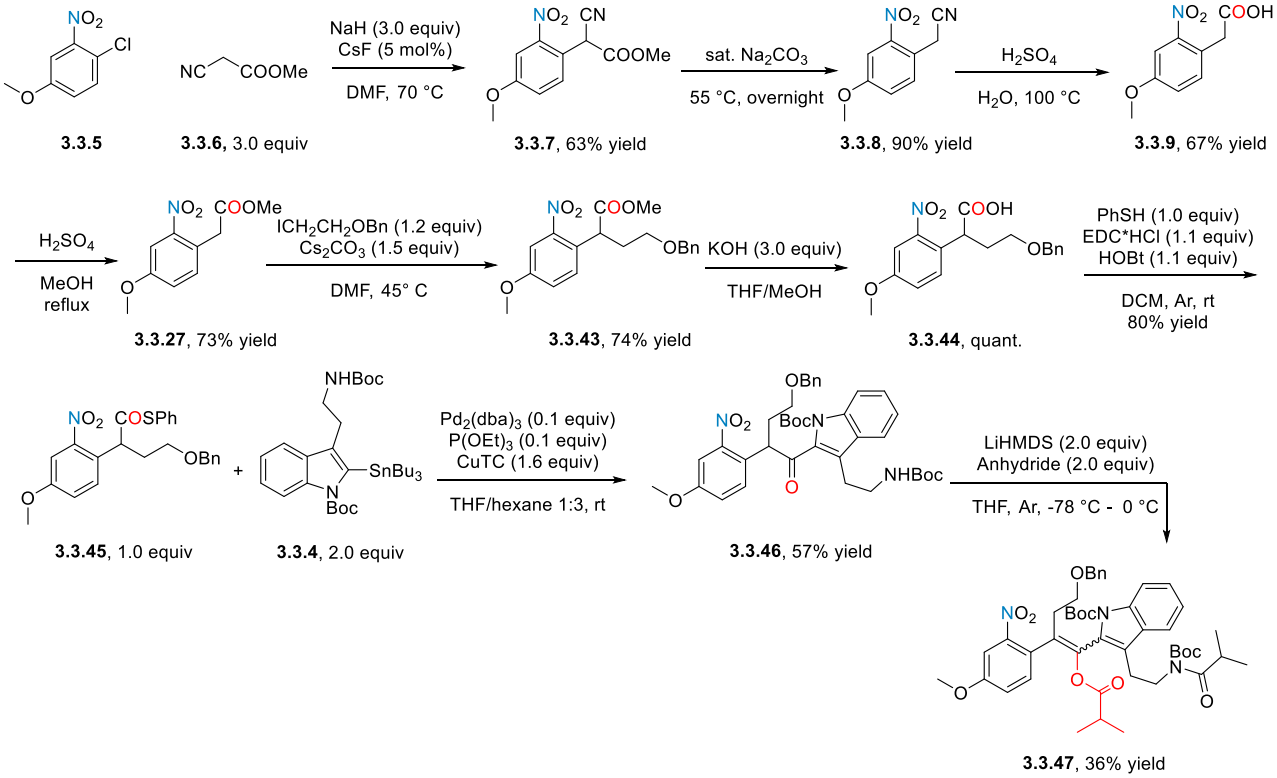


3.3.40 3.3.42

	Reagent (X equiv)	Solvent	Results
1.	NaH (1.2 equiv), BnBr (1.5 equiv)	DMF	Decomposition
2.	K_2CO_3 (1.2 equiv), BnBr (1.5 equiv)	DMF	
3.	K_2CO_3 (1.2 equiv), BnBr (1.5 equiv)	Acetone	No reaction
4.	Ag_2O (1.0 equiv), BnBr (1.5 equiv)	DCM	
5.	$CCl_3C(NH)OBn$ (4.0 equiv), TfOH	DCM	Decomposition
6.	$CCl_3C(NH)OBn$ (4.0 equiv), TfOH (cat.)	DCM	**3.3.42**, quantitative

*Table 19. Optimization of Bn-protection of alcohol **3.3.40***

As an alternative, we started the synthesis from the beginning to obtain starting material **3.3.42** on a bigger scale (Scheme 63). The first four steps of the synthesis gave similar results as aforementioned; ester **3.3.27** was isolated in 28% overall yield. Alkylation of **3.3.27** with ((2-iodoethoxy)methyl)benzene afforded alkylated product **3.3.43** in 74% yield, which was directly hydrolyzed to produce free acid **3.3.44** in quantitative yields. The thioester formation from acid **3.3.44** followed by the Liebeskind-Srogl coupling with organotin compound **3.3.4** gave ketone **3.3.46** in 46% overall yield. Enol ester **3.3.47** was formed as mixture of *E*- and *Z*- isomers in 36% yield.



3.3.5 **3.3.6,** 3.0 equiv **3.3.7**, 63% yield **3.3.8**, 90% yield **3.3.9**, 67% yield

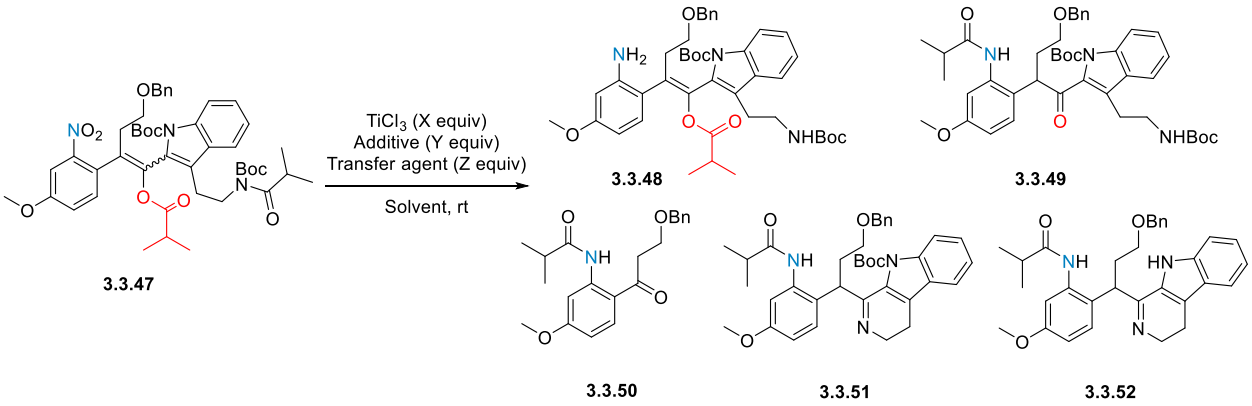
3.3.27, 73% yield **3.3.43**, 74% yield **3.3.44**, quant.

3.3.45, 1.0 equiv **3.3.4**, 2.0 equiv **3.3.46**, 57% yield **3.3.47**, 36% yield

*Scheme 63. Synthesis of enol ester **3.3.47***

3.3.5. **Ti-mediated reductive cyclization of Bn-protected enol ester 3.3.47**

The key-step of the total synthesis was then explored with Bn-protected enol ester **3.3.47**. Due to the low solubility of the starting material, SDS was added as a phase transfer agent. Performing the reaction in acetonitrile with 10 equiv of $TiCl_3$, the influence of the amount of NH_4OAc was examined. Unfortunately, none of the conditions examined afforded the desired product (Table 20). In all these cases, aniline **3.3.48** together with compounds **3.3.49**, **3.3.50**, **3.3.51** and **3.3.52** was formed in varied amount depending on the reaction time, the prolongation of the reaction time leads to slow decomposition of aniline to give **3.3.49**, **3.3.50**, **3.3.51** and **3.3.52**. Mechanistically, ketone **3.3.49** resulted from the intramolecular transesterification between aniline and *Z*-enol ester, while dihydrocarbazole **3.3.51** was formed *via* *N*-Boc deprotection followed by intramolecular condensation. Further deprotection of the indole N-Boc group from **3.3.51** would afford compound **3.3.52**. Compound **3.3.50** was formed *via* oxidative cleavage of a double bond. The formation of the only product of over-reduction can be explained by the relatively fast reduction of nitroso-intermediate compared to electrocyclization due to either electronic properties of our starting material or steric hindrance around the double bond. To solve this problem, we tried to adjust the reaction conditions to slow down the side-reaction.



	$TiCl_3$ (X equiv)	Additive (Y equiv)	Transfer agent (2.0 equiv)	Solvent	Results
1.	10 equiv	-	-	MeCN (0.1 M)	
2.	10 equiv	NH_4OAc (40 equiv)	-	MeCN (0.1 M)	
3.	10 equiv	NH_4OAc (40 equiv)	SDS	MeCN (0.1 M)	
4.	10 equiv	NH_4OAc (40 equiv)	SDS	MeCN (0.2 M)	
5.	10 equiv	NH_4OAc (40 equiv)	SDS	MeCN (0.05 M)	
6.	10 equiv	NH_4OAc (40 equiv)	SDS	MeCN (0.025 M)	**3.3.48 – 3.3.52**
7.	10 equiv	NH_4OAc (10 equiv)	SDS	MeCN (0.1 M)	
8.	10 equiv	NH_4OAc (20 equiv)	SDS	MeCN (0.1 M)	
9.	10 equiv	NH_4OAc (30 equiv)	SDS	MeCN (0.1 M)	
10.	10 equiv	NH_4OAc (60 equiv)	SDS	MeCN (0.1 M)	
11.[a]	10 equiv	NH_4OAc (40 equiv)	SDS	MeCN (0.1 M)	

[a] Reaction was done at 0 °C

*Table 20. Attempted reductive cyclization of enol ester **3.3.47***

We then turned our attention to different additives: NaOOCH, NH_4OOCH, NH_4Cl, Imidazole (MeCN, acetone), Rochelle salt, NaOAc, NaI, NaBr. The results are summarized in Table 21. Only aniline **3.3.48** and products of its transformation were isolated (entries 1-18). Different phase transfer agents were subsequently examined. Addition of SDS and tetrabutylammonium salts with different counter anion: TBAB, TBACl, TBAI, TBAOTf, $TBAPF_6$ failed to trigger the desired domino process (entries 19 – 25). Finally, variation of solvents was investigated. Only side-products **3.3.48 - 3.3.52** were formed in MeOH, THF and NMP, whereas no reaction occurred in DCM and toluene (entries 26 – 30). For all these reactions, crude NMRs and MS-analysis of combined crude mixtures were performed, however no traces of desired product were detected. After analysis of obtained results, we tried to find an explanation for the over-reduction. We turned back to the scope of our methodology and noted that our key-transformation worked less efficiently with substrates containing electron-donating groups on the nitro-arene ring (Figure 5). Indeed, compound **2.3.17aj** with methoxy group in the 6-position of indolenine was isolated in 15% yield, while substrates bearing an electron withdrawing group at the 5- and 6-position were formed in higher yields. At this moment, it was decided to exchange methoxy group on the nitro arene ring with a bromine atom and synthesize precursor **3.3.53** (Figure 5).

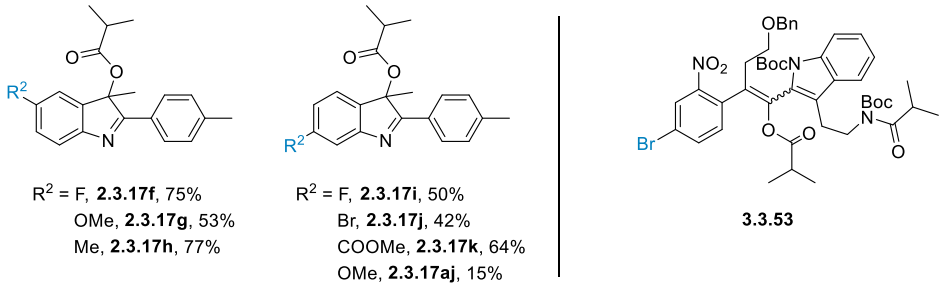
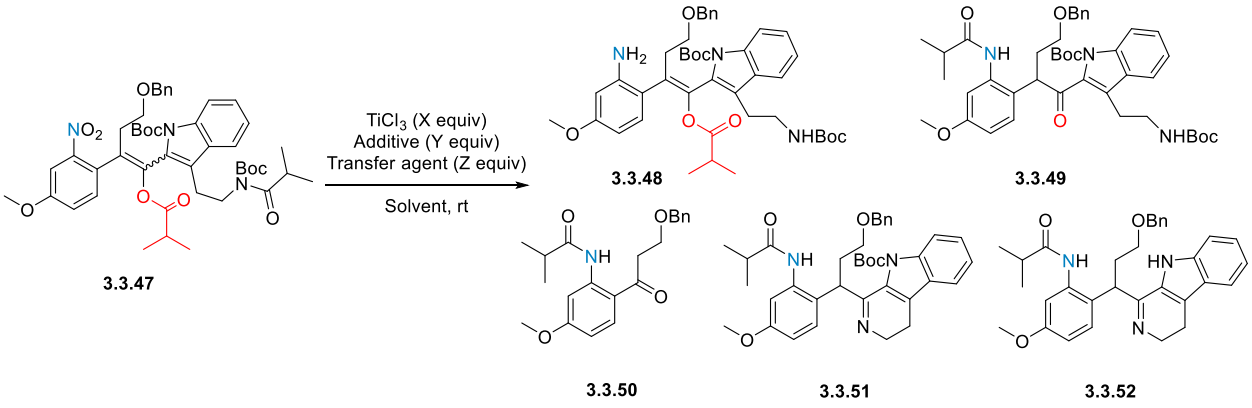


*Figure 5. Influence of the substituents on the nitro-arene ring on the efficiency of reductive cyclization of enol esters **2.3.4***



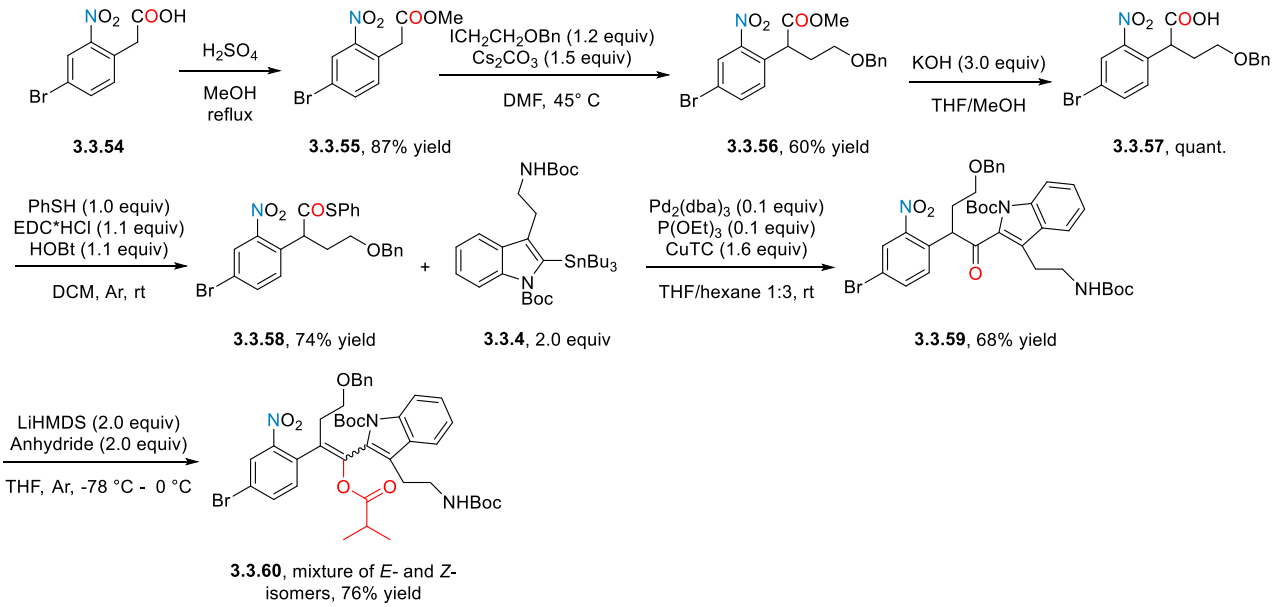
	$TiCl_3$ (X equiv)	Additive (Y equiv)	Transfer agent (Z equiv)	Solvent	Results
1.	10 equiv	NaOOCH (20 equiv)	-	MeCN (0.1 M)	
2.	10 equiv	NaOOCH (40 equiv)	-	MeCN (0.1 M)	
3.	10 equiv	NH_4OOCH (20 equiv)	-	MeCN (0.1 M)	
4.	10 equiv	NH_4OOCH (40 equiv)	-	MeCN (0.1 M)	
5.	10 equiv	NH_4Cl (20 equiv)	-	MeCN (0.1 M)	
6.	10 equiv	NH_4Cl (40 equiv)	-	MeCN (0.1 M)	
7.	10 equiv	Imidazole (20 equiv)	-	MeCN (0.1 M)	
8.	10 equiv	Imidazole (40 equiv)	-	MeCN (0.1 M)	
9.	10 equiv	Imidazole (20 equiv)	-	Acetone (0.1 M)	
10.	10 equiv	Imidazole (40 equiv)	-	Acetone (0.1 M)	
11.	10 equiv	Rochelle salt (20 equiv)	-	MeCN (0.1 M)	
12.	10 equiv	Rochelle salt (40 equiv)	-	MeCN (0.1 M)	
13.	10 equiv	NaOAc (20 equiv)	-	MeCN (0.1 M)	
14.	10 equiv	NaOAc (40 equiv)	-	MeCN (0.1 M)	
15.	10 equiv	NaI (20 equiv)	-	MeCN (0.1 M)	
16.	10 equiv	NaI (40 equiv)	-	MeCN (0.1 M)	**3.3.48 - 3.3.52**
17.	10 equiv	NaBr (20 equiv)	-	MeCN (0.1 M)	
18.	10 equiv	NaBr (40 equiv)	-	MeCN (0.1 M)	
19.	10 equiv	-	SDS (1 equiv)	MeCN (0.1 M)	
20.	10 equiv	-	SDS (4 equiv)	MeCN (0.1 M)	
21.	10 equiv	-	TBAB (2 equiv)	MeCN (0.1 M)	
22.	10 equiv	-	TBACl (2 equiv)	MeCN (0.1 M)	
23.	10 equiv	-	TBAI (2 equiv)	MeCN (0.1 M)	
24.	10 equiv	-	TBAOTf (2 equiv)	MeCN (0.1 M)	
25.	10 equiv	-	$TBAPF_6$ (2 equiv)	MeCN (0.1 M)	
26.	10 equiv	-	-	MeOH (0.1 M)	
27.	10 equiv	-	-	THF (0.1 M)	
28.	10 equiv	-	-	NMP (0.1 M)	
29.	10 equiv	-	-	Toluene (0.1 M)	No reaction
30.	10 equiv	-	-	DCM (0.1 M)	

*Table 21. Attempted reductive cyclization of enol ester **3.3.47***

3.3.6. **Synthesis of enol ester 3.3.60**

The synthesis began with 2-(4-bromo-2-nitrophenyl)acetic acid **3.3.54**, which is commercially available. The esterification followed by alkylation with alkyl iodide produced ester **3.3.56** in 52% yield over two steps (Scheme 64). The submission of compound **3.3.56** to hydrolysis and thioester formation afforded coupling partner **3.3.58** in approximately 74% yield over two steps. The Liebeskind-Srogl cross-

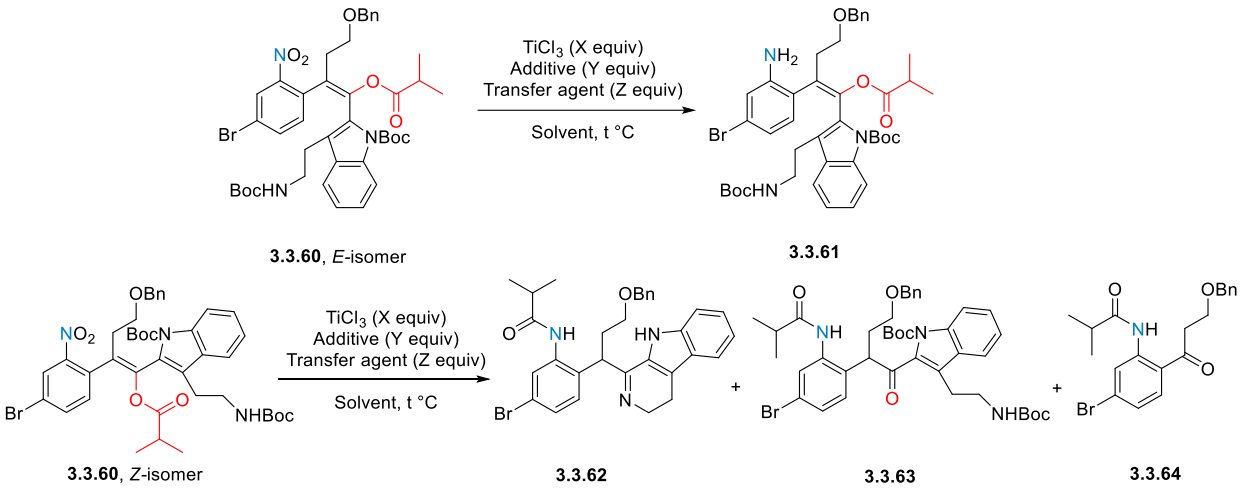
coupling between **3.3.58** and **3.3.4** afforded ketone **3.3.59** in 68% yield. Deprotonation of the latter with LiHMDS followed by addition of anhydride furnished enol ester **3.3.60** in 76% yield as a mixture of *E/Z* isomers (1:1).



*Scheme 64. Synthesis of enol ester **3.3.60***

3.3.7. **$TiCl_3$-mediated reductive cyclization of enol ester 3.3.60**

Typical reductive cyclization conditions were applied to enol ester **3.3.60** (Table 22). However, addition of different buffers, phase transfer agents, as well as variation in concentration, temperatures and solvents failed to produce the desired 3-acyloxy-2,3-disubstituted indolenine (entries 1 – 24). Same results were obtained with reduced loading of $TiCl_3$ (entries 25-27). Depending on the geometry of the double bond, either aniline **3.3.61** (from *E*-isomer) or acetamide **3.3.63** resulting from the transamidation (*Z*-isomer) were formed.

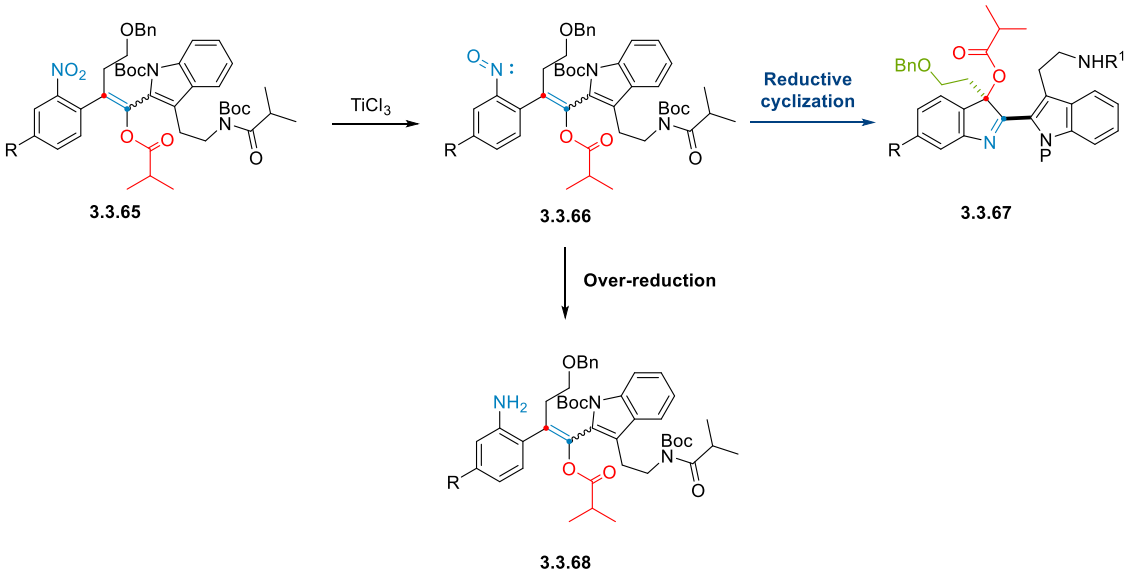


	$TiCl_3$ (X equiv)	Additive (Y equiv)	Transfer agent (Z equiv)	Solvent	Results
1.	10 equiv	-	-	MeCN (0.1 M)	
2.	10 equiv	-	-	MeCN (0.2 M)	
3.	10 equiv	NH_4OAc (20 equiv)	-	MeCN (0.1 M)	
4.	10 equiv	NH_4OAc (40 equiv)	-	MeCN (0.1 M)	
5.	10 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.1 M)	
6.	10 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.2 M)	
7.	10 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.05 M)	
8.	10 equiv	NH_4OAc (10 equiv)	SDS (2 equiv)	MeCN (0.1 M)	
9.	10 equiv	NH_4OAc (20 equiv)	SDS (2 equiv)	MeCN (0.1 M)	
10.[a]	10 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.1 M)	
11.	10 equiv	-	SDS (1 equiv)	MeCN (0.1 M)	
12.	10 equiv	-	SDS (2 equiv)	MeCN (0.1 M)	**3.3.61 – 3.3.64**
13.	10 equiv	-	SDS (4 equiv)	MeCN (0.1 M)	
14.	10 equiv		TBAI (2 equiv)	MeCN (0.1 M)	
15.	10 equiv	NH_4OAc (40 equiv)	TBAI (2 equiv)	MeCN (0.1 M)	
16.	10 equiv	NaOOCH (40 equiv)	-	MeCN (0.1 M)	
17.	10 equiv	NH_4OOCH (40 equiv)	-	MeCN (0.1 M)	
18.	10 equiv	NaOAc (40 equiv)	-	MeCN (0.1 M)	
19.	10 equiv	NaI (40 equiv)	-	MeCN (0.1 M)	
20.	10 equiv	Imidazole (40 equiv)	-	MeCN (0.1 M)	
21.	10 equiv	Imidazole (40 equiv)	-	Acetone (0.1 M)	
22.	10 equiv	NH_4Cl (40 equiv)	-	MeCN (0.1 M)	
23.	10 equiv	-	-	MeOH (0.1 M)	
24.	10 equiv	-	-	THF (0.1 M)	
25.	5 equiv	-	-	MeCN (0.1 M)	
26.	5 equiv	NH_4OAc (40 equiv)	-	MeCN (0.1 M)	
27.	5 equiv	NH_4OAc (40 equiv)	SDS (2 equiv)	MeCN (0.1 M)	

[a] Reaction was done at 0 °C

*Table 22. Attempted reductive cyclization of enol ester **3.3.60***

One of the main steps of reductive cyclization of 2-(*ortho*-nitro)aryl substituted enol ester **3.3.65** is 5-center-6π-electrocyclization of nitroso intermediate **3.3.66** (Scheme 65). In our methodology studies, we have observed that the yield of the indolenines decreased as the size of the substituent increased. In the case of enol esters **3.3.36**, **3.3.47** and **3.3.60** the steric hindrance around the double bond could probably prevent the free rotation of nitrosoarene around the double bond to reach the coplanarity, hampering therefore the electrocyclization. Consequently, further reduction of nitroso occurs affording anilines **3.3.68**.



*Scheme 65. Mechanism of reductive cyclization of enol ester **3.3.65***

3.4. **Conclusion**

In our synthetic studies towards trigonoliimine C, we successfully developed a synthetic route to reach a key intermediate – enol ester **3.3.36** in 9 steps from commercially available starting materials. Our preliminary studies showed that over-reduction of nitroarene to aniline prevails over the desired sequence involving partial reduction of nitro to nitroso followed by 6π-electrocyclization in the case of enol esters **3.3.36**, **3.3.47** and **3.3.60**. Despite our efforts, we were not able to find conditions to overturn this kinetic preference.

Chapter 4. Synthesis of furo[3,2-*b*]indolines by $TiCl_3$-mediated reductive cyclization of tetrasubstituted *ortho*-nitrostyrene derivatives

4.1. Introduction

4.1.1. (–)-Phalarine

(–)-Phalarine is an indole alkaloid isolated in 1999 from the perennial grass *Phalaris coerulescens* by Colegate and co-workers (Figure 6).[218] The natural product was obtained through extraction of the grass with DCM and purification by basified column chromatography. The propellerane structure of the natural product containing an unusual benzofuro[3,2-*b*]indoline moiety was determined based on detailed spectroscopic studies.

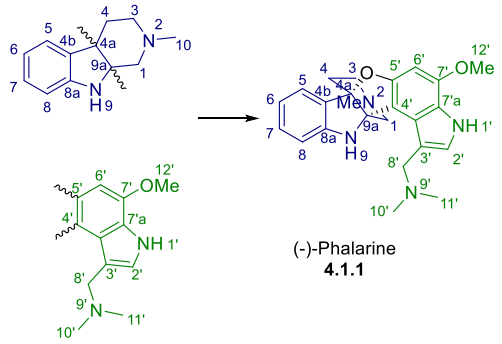
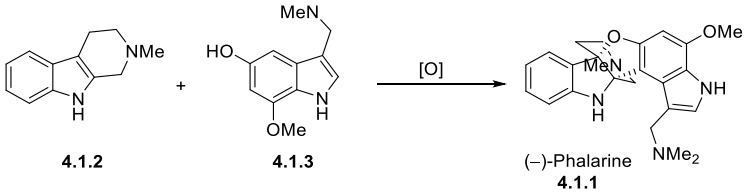


Figure 6. Structure of the natural product (–)-phalarine

The authors proposed that (–)-phalarine alkaloid could be formed from tetrahydro-*β*-carboline **4.1.2** and 5-hydroxy-7-methoxygramine **4.1.3**, as phalarine was isolated together with carboline **4.1.2** from the same plant (Scheme 66). The absolute configuration of the natural product was determined by Danishefsky in 2010 through an enantioselective total synthesis of this natural product.

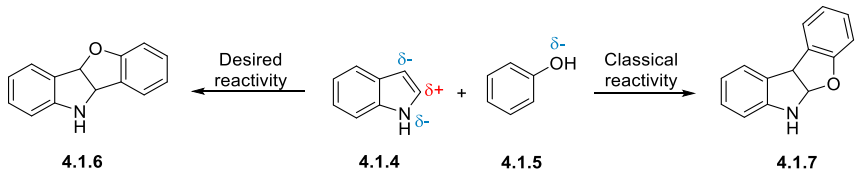


Scheme 66. Proposed biosynthetic route to (–)-phalarine

Although no bioactivity was found at the moment, the structure of phalarine is especially interesting for synthetic chemists due to the unprecedented benzofuro[3,2-*b*]indoline moiety **4.1.6**. The difficulty associated with the synthesis of this natural product is the mismatched reactivity of two potential starting

[218] Anderton, N.; Cockrum, P.A.; Colegate, S.M.; Edgar, J.A.; Flower, K.; Gardner, D.; Willing, R.I. *Phytochemistry* **1999**, *51*, 153 – 157.

materials: indole **4.1.4** and phenol **4.1.5**. By contrast, many natural products contain a benzofuro[2,3-*b*]indoline scaffold **4.1.7** (e.g. diazonamide A,[219,220] azonazine).[221] A common way for the synthesis of benzofuro[2,3-*b*]indoline scaffolds is the [3+2] heteroannulation between phenol and indole under oxidative conditions. Thus, the umpolung of phenol followed by intermolecular nucleophilic addition of indole C3 to the *ortho* position of phenol and intramolecular trapping of the resulting iminium by phenol oxygen would afford the tricyclic scaffold **4.1.7** (Scheme 67). Unfortunately, this approach could not be applied to the synthesis of benzofuro[3,2-*b*]indoline **4.1.6** found in phalarine.

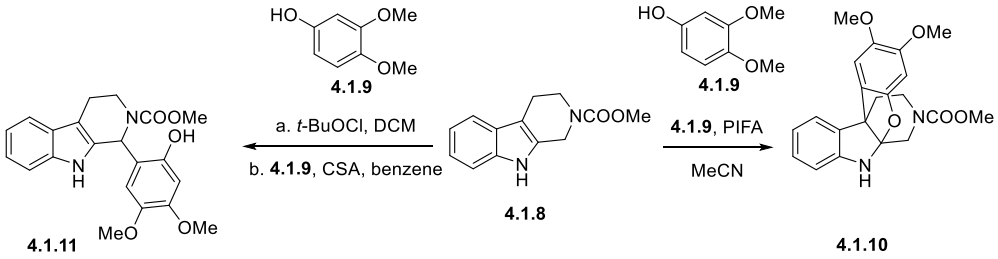


*Scheme 67. Coupling of indole **4.1.4** with phenol **4.1.5***

4.1.1.1. Total synthesis of Phalarine

Danishefsky's Total synthesis

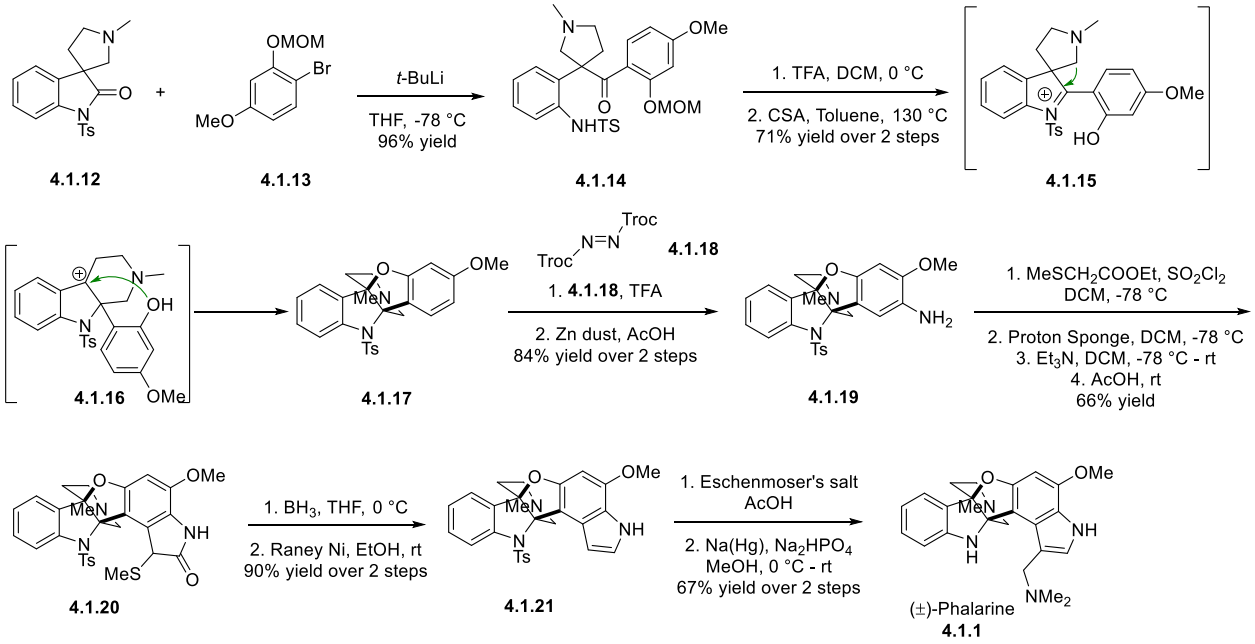
The first total synthesis of Phalarine was published in 2007 by the group of Danishefsky.[222,223] In their first paper, the authors achieved the racemic synthesis of phalarine **4.1.1**, unveiling and solving many synthetic problems associated with the structure of the natural product. The authors initially explored the synthesis of phalarine *via* biomimetic oxidative coupling of tetrahydro-*β*-carboline **4.1.8** with phenol **4.1.9** (Scheme 68).[224] Two approaches based on the umpolung of either phenol or indole reactivity were examined. Unfortunately, upon oxidation of phenol **4.1.9** with (bis(trifluoroacetoxy)iodo)benzene (PIFA), the opposite regioisomer of the natural product **4.1.10** was isolated. On the other hand, pre-oxidation of carboline **4.1.8** with *t*-BuOCl to chloroindolenine followed by the addition of phenol **4.1.9** afforded C-2 arylated tetrahydro-*β*-carboline **4.1.11**.



Scheme 68. Initial oxidative strategy towards phalarine attempted by Danishefsky

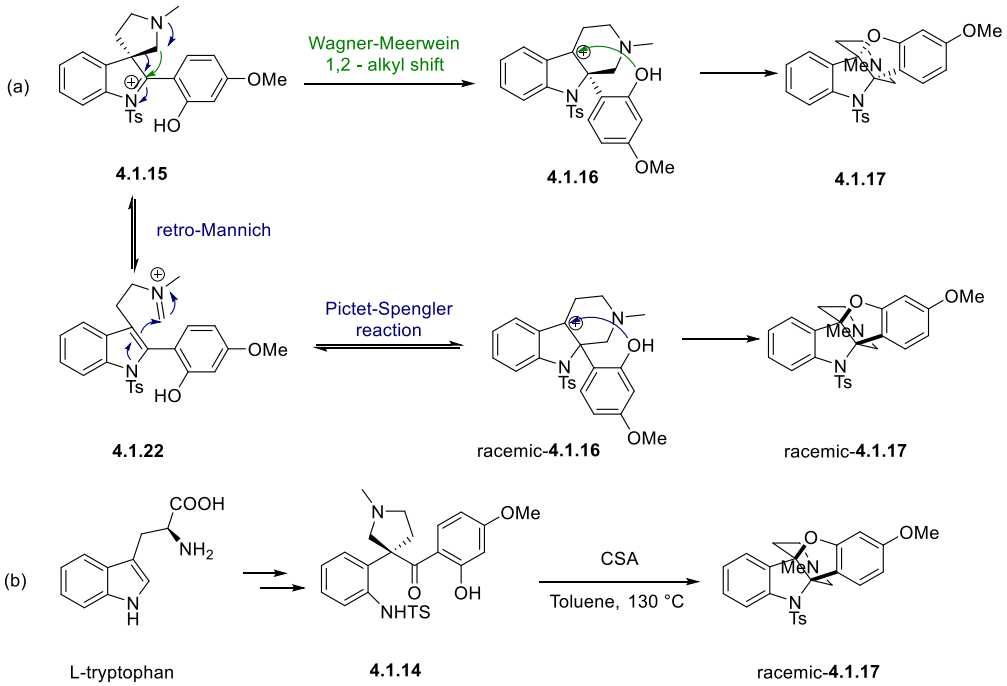
[219] Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303 – 2304.
[220] Li, J.; Burgett, A.W.G.; Esser, L.; Amezcua, C.; Harran, P.G. *Angew. Chem. Int. Ed.* **2001**, *40*, 4770–4773; *Angew. Chem.* **2001**, *113*, 4906 – 4909.
[221] Wu, Q.X.; Crews, M.S.; Draskovic, M.; Sohn, J.; Johnson, T.A.; Tenney, K.; Valeriote, F.A.; Yao, X.J.; Bjeldanes, L.F.; Crews, P. *Org. Lett.* **2010**, *12*, 4458 – 4461.
[222] Li, C.; Chan, C.; Heimann, A.C.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1444 – 1447.
[223] Li, C.; Chan, C.; Heimann, A.C.; Danishefsky, S.J. *Angew. Chem. Int. Ed.* **2007**, *46*, 1448 – 1450.
[224] Chan, C.; Li, C.; Zhang, F.; Danishefsky, S.J. *Tetrahedron Lett.* **2006**, *47*, 4839 – 4841.

A new synthetic route was developed *via* the preformation of a C-C bond between the indole and the phenol moieties (Scheme 69). Nucleophilic addition of aryl lithium reagent derived from **4.1.13** to *N*-Ts-spirooxindole **4.1.12** afforded 3,3-disubstituted *N*-methylpyrrolidine **4.1.14**. Chemoselective removal of the MOM protecting group (TFA, DCM, 0 °C) followed by heating a solution of the resulting phenol in toluene at 130 °C in the presence of camphosulfonic acid (CSA) furnished the desired tetracyclic compound **4.1.17** in 71% yield over 2 steps. The reaction of **4.1.17** with bis(2,2,2-trichloroethyl) (*E*)-diazene-1,2-dicarboxylate **4.1.18** in the presence of TFA followed by the reduction of the N-N bond and removal of the *N*-troc group, afforded the aniline **4.1.19** in excellent yields. Next, this compound was subjected to Gassman's oxindole synthesis affording oxindole **4.1.20** in 66% yield. Subsequent reduction of the amide and methyl thioester produced indole **4.1.21**. Finally, alkylation at the C3 position of indole with Eschenmoser'salt followed by *N*-tosyl deprotection gave (±)-phalarine **4.1.1** in 11 steps.



Scheme 69. Racemic synthesis of phalarine by Danishefsky

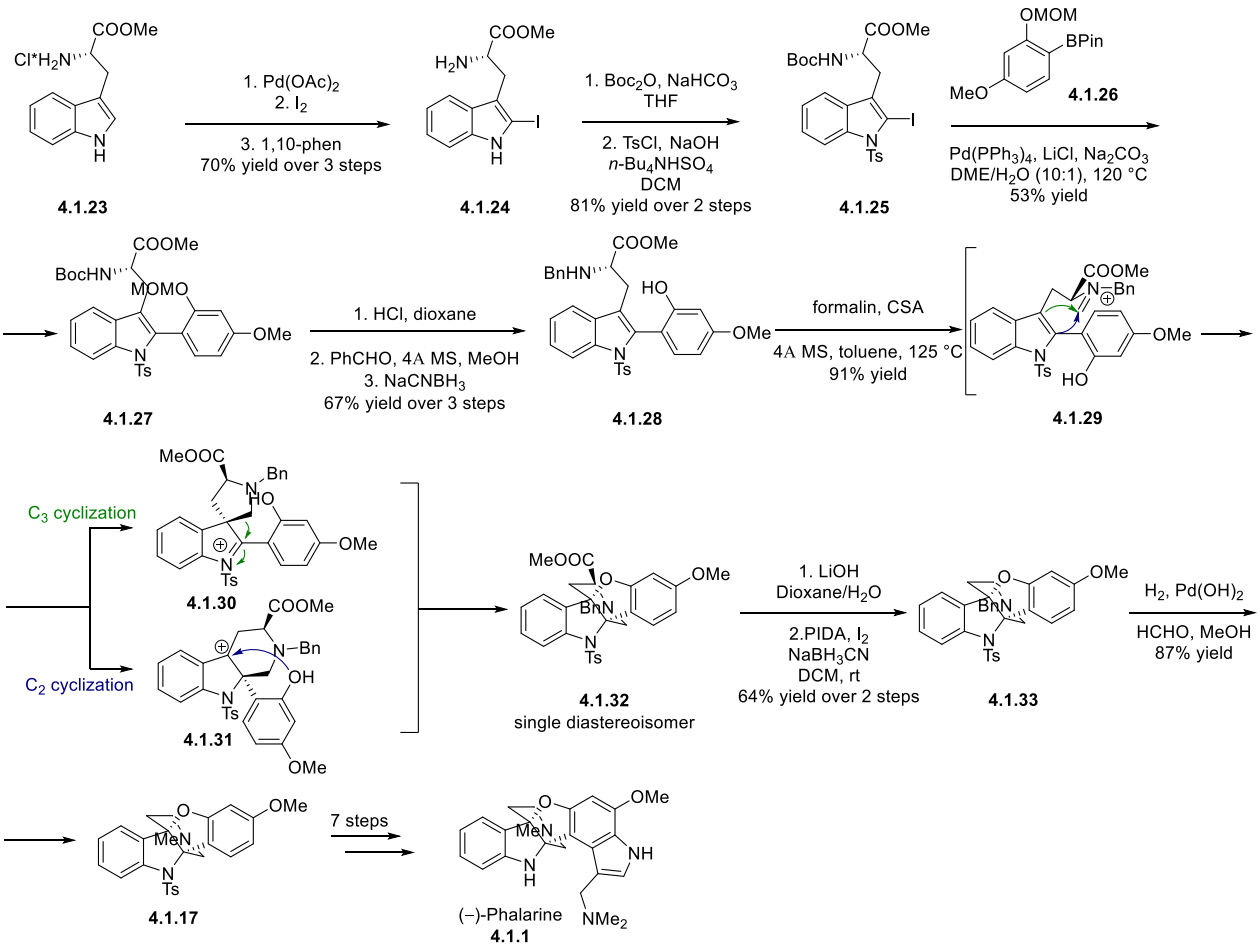
To rationalize the formation of **4.1.17** from **4.1.14**, two mechanisms were proposed. One was based on the Wagner-Meerwein 1,2-alkyl shift, where the retention of the stereochemistry and a chirality transfer was expected. While the second mechanism was based on a retro-Mannich/Pictet-Spengler sequence with loss of the chiral information (Scheme 70). To explore the mechanism of this rearrangement, the enantiopure ketone **4.1.14** was synthesized starting from L-tryptophan. Applying the previously developed conditions to enantiopure **4.1.14** led to the formation of benzofuro[3,2-*b*]indoline **4.1.17** as a racemate. Control experiments showed that: a.) The unconsumed starting material at the end of the reaction was enantiopure, which means that the first step (imine formation) proceed with retention of the stereochemistry; b.) Subjecting the enantiopure product benzofuro[3,2-*b*]indoline **4.1.17** to the reaction conditions resulted in its slow racemization, nevertheless with a lower rate. The racemization of the final product probably arises from the formation of intermediate **4.1.22** *via* retro-Mannich reaction. From intermediate **4.1.22**, both a direct Mannich reaction and a Pictet-Spengler pathway would give rise to the same racemic intermediate **4.1.16** leading to racemic product **4.1.17**.



Scheme 70. Plausible mechanism for the key-transformation in Danishefsky's total synthesis

The enantioselective synthesis started with L-tryptophane methyl ester **4.1.23** as a chiral precursor to transfer the chiral information during the rearrangement.[225] First, a Pd-mediated C2-iodination of tryptophan methyl ester delivered **4.1.24** in 70% yield (Scheme 71). Protection of the primary amine with a Boc-protecting group followed by tosylation of the indole nitrogen afforded compound **4.1.25**. Iodoindole **4.1.25** was next coupled with aryl pinacol borane **4.1.26** *via* the Suzuki-Miyaura cross-coupling reaction to form biaryl **4.1.27**. The deprotection of the MOM- protecting group and reductive amination with benzaldehyde gave a precursor for the key-step **4.1.28**. Fortunately, submitting compound **4.1.28** to the previously optimized conditions led to the formation of the desired product **4.1.32** as a single diastereoisomer. The structure of **4.1.32** was confirmed by single-crystal X-ray diffraction. Saponification of the ester group, followed by its decarboxylation and functional group interconversion on the tertiary amine, gave intermediate **4.1.17,** which was converted to (−)-phalarine following the same route developed for the racemic synthesis.

[225] Trzupek, J.D.; Lee, D.; Crowley, B.M.; Marathias, V.M.; Danishefsky, S.J. *J. Am. Chem. Soc.* **2010**, *132*, 8506 – 8512.



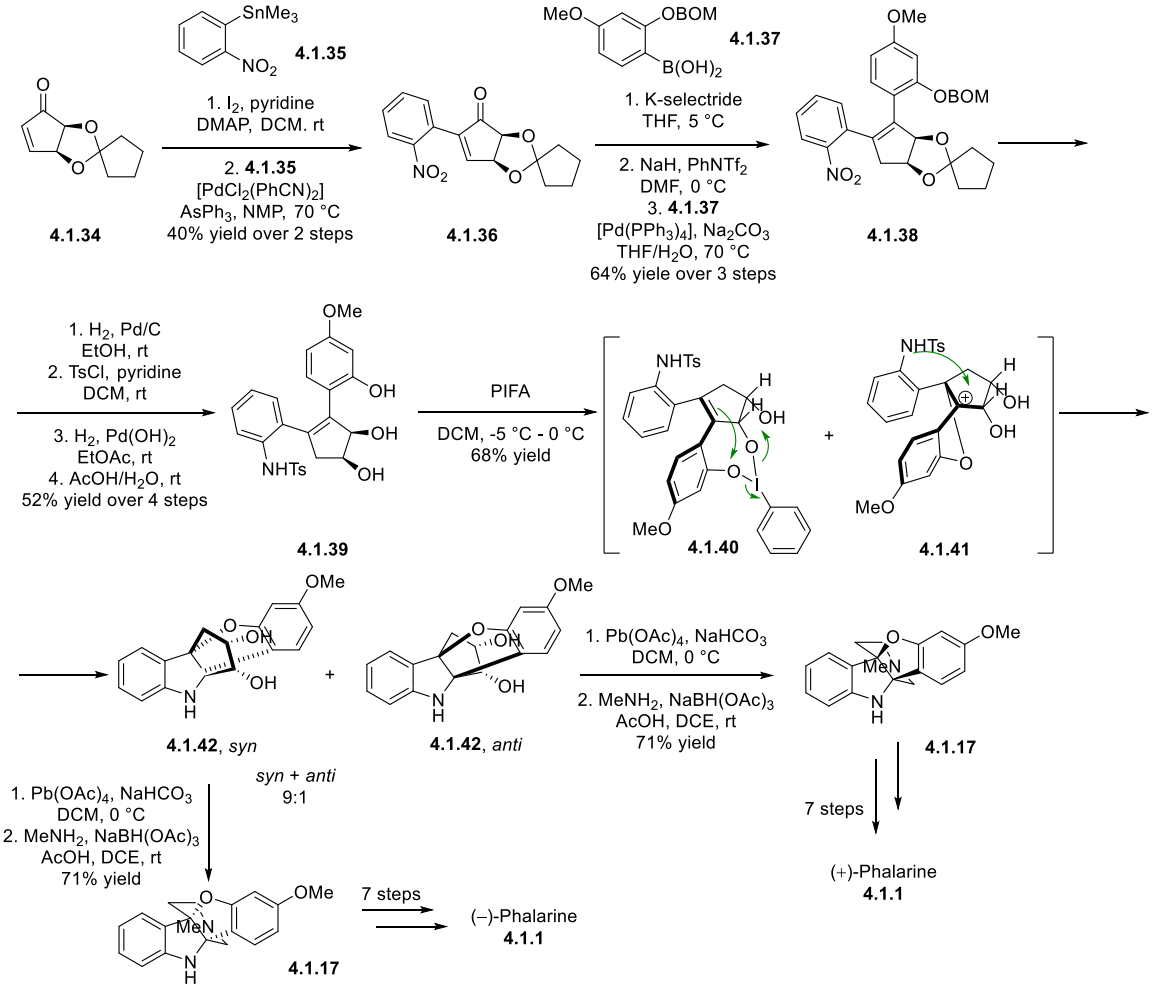
Scheme 71. Enantioselective synthesis of (−)-phalarine by Danishefsky

Recent total syntheses

In 2010, the second asymmetric total synthesis of (−) and (+)-phalarine was published by the group of Chen (Scheme 72).[226] It was inspired by the oxidative double cyclization of stilbenes reported by Muniz.[227] Starting from cyclopentenone **4.1.34**, iodination and Stille cross-coupling with organostannane **4.1.35** afforded compound **4.1.36**. Reduction of the double bond followed by triflate formation gave enol triflate. The latter was submitted to a Suzuki-Miyaura cross-coupling with arylboronic acid **4.1.37** to give tetrasubstituted alkene **4.1.38**. Upon reduction of the nitro group, the formed aniline was protected with TsCl. Deprotection of the phenolic hydroxyl group and diol afforded triol **4.1.39**. Oxidative coupling of phenolic tosylamide **4.1.39** worked with good yields and diastereoselectivity using PIFA as an oxidant. A mixture of diastereoisomers was obtained with a 9:1 ratio between *syn*- and *anti*-products **4.1.42**. To rationalize the obtained results, the authors proposed the precoordination of PIFA to the hydroxyl groups of the aromatic ring and the cyclopentanediol to form chelate **4.1.40**. The nucleophilic attack of the double bond to phenol oxygen led to the formation of intermediate **4.1.41**, which, after the second cyclization, was converted to benzofuro[3,2-*b*]indoline **4.1.42**. Indeed, performing the same transformation with protected

[226] Ding, H.; Chen, D.Y.-K. *Angew. Chem. Int. Ed.* **2011**, *50*, 676 – 679.
[227] Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542 – 14543.

diol led to an erosion of the diastereoselectivity. The oxidative cleavage of the cyclopentanediol moiety and reductive amination with methyl amine afforded Danishefsky's intermediate **4.1.17**. Following the literature procedure described by Danishefsky, both enantiomers of the natural product were synthesized.

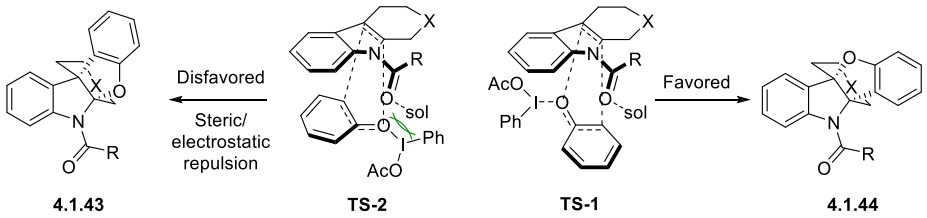


Scheme 72. Enantioselective total synthesis of phalarine by Chen

In 2019, Jia group reported a bioinspired total synthesis of phalarine *via* oxidative coupling of tetrahydro-β-carboline **4.1.46** with phenol **4.1.47** (Scheme 74).[228] The choice of protecting group on the indole nitrogen was found to be critical for the success of this transformation. Indeed, the presence of an acyl-protecting group was essential to direct the regioselectivity of the formal [3+2] cycloaddition both by steric and electronic repulsion (Scheme 73). Two transition states were proposed to explain the favoured regioselectivity. Depending on the size of the acyl-protecting group, the coplanarity between the carbonyl group and the indole scaffold was meant to be broken due to steric repulsion. Indeed, a pronounced effect of the N-acyl-protecting group was observed. Since the size of the C=O group is smaller than the R group, the hypervalent iodine specie, formed *in situ via* ligand exchange between PIDA and phenol, would approach indole from the side of the carbonyl group rather than the R substituent. Among two possible

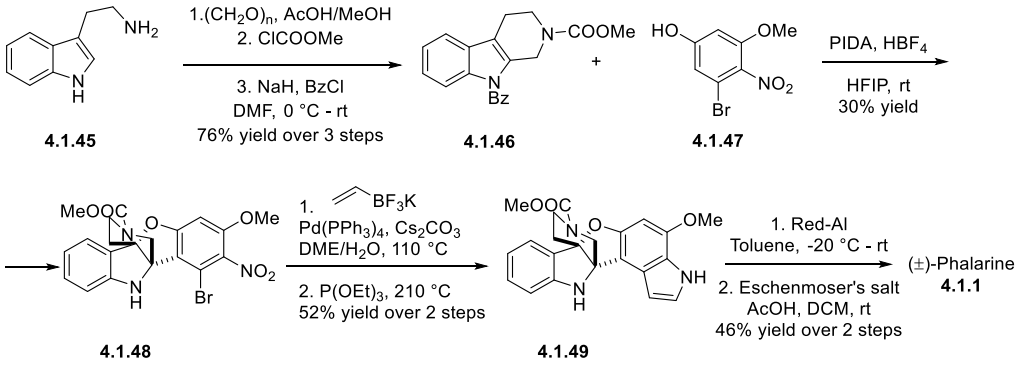
[228] Li, L.; Yuan, K.; Jia, Q.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 6074 – 6078.

transition states shown in Scheme 73, **TS-1** was favored over **TS-2** for steric reasons, affording, therefore, the desired benzofuro[3,2-*b*]indoline moiety.



Scheme 73. Rationalization of the key step in the total synthesis by Jia

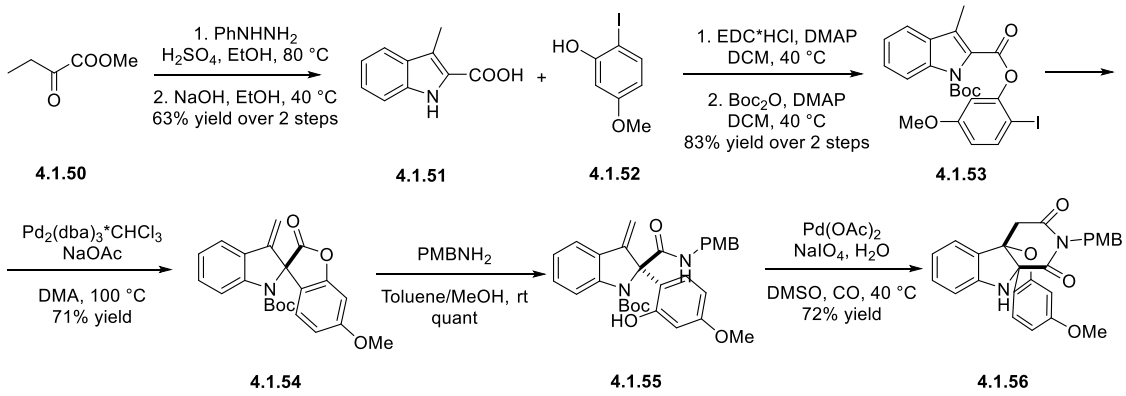
The synthesis begins with a Pictet-Spengler reaction using tryptamine **4.1.45**, followed by double protection of the two nitrogens to give carboline **4.1.46** (Scheme 74). The product was then submitted to an oxidative coupling with phenol **4.1.47** under the optimized conditions to afford prephalarine **4.1.48** as a sole product, albeit in a low yield. A two-step transformation of **4.1.48** *via* the Suzuki-Miyaura cross-coupling and the Cadogan-Sundberg reaction afforded indole **4.1.49**. Reduction of carbamate with Red-Al followed by alkylation with Eschenmoser's salt provided (±)-phalarine **4.1.1**. The racemic total synthesis was performed in 8 steps starting from commercial tryptamine, however, the low yield for the key step diminished the efficiency of the overall synthesis.



Scheme 74. Racemic total synthesis of phalarine by Jia

The same year, a synthesis of the core structure of phalarine was published by Kitamura and coworkers (Scheme 75).[229] A transition metal-catalyzed dearomatization reaction and Wacker-carbonylative cyclization were applied as key-transformations to build the tricyclic propeller skeleton **4.1.56**. The synthesis begins with the transformation of ketoester **4.1.50** to 1*H*-indole-2-carboxylic acid **4.1.51** under Fischer indole synthesis conditions. Coupling of this compound with iodophenol **4.1.52** *via* activation with EDC carbodiimide and Boc-protection of the indole nitrogen delivered ester **4.1.53**. The aryliodide **4.1.53** then underwent palladium-catalyzed dearomative spirocyclization to afford spirocycle **4.1.54** in 71% yield. Transamidation of **4.1.54** with *p*-methoxybenzylamine gave access to compound **4.1.55**, which was then subjected to a Wacker-carbonylative cyclization cascade to construct the core structure of phalarine in 72% yield. The precursor **4.1.56** was obtained on a 500 mg scale in 7 steps starting from commercially available starting materials.

[229] Douki, K.; Shimokawa, J.; Kitamura, M. *Org. Biomol. Chem.* **2019**, *17*, 1727 – 1730.



Scheme 75. Racemic total synthesis of phalarine by Kitamura

4.1.2. **Synthesis of benzofuro[3,2-*b*]indolines and relative scaffolds**

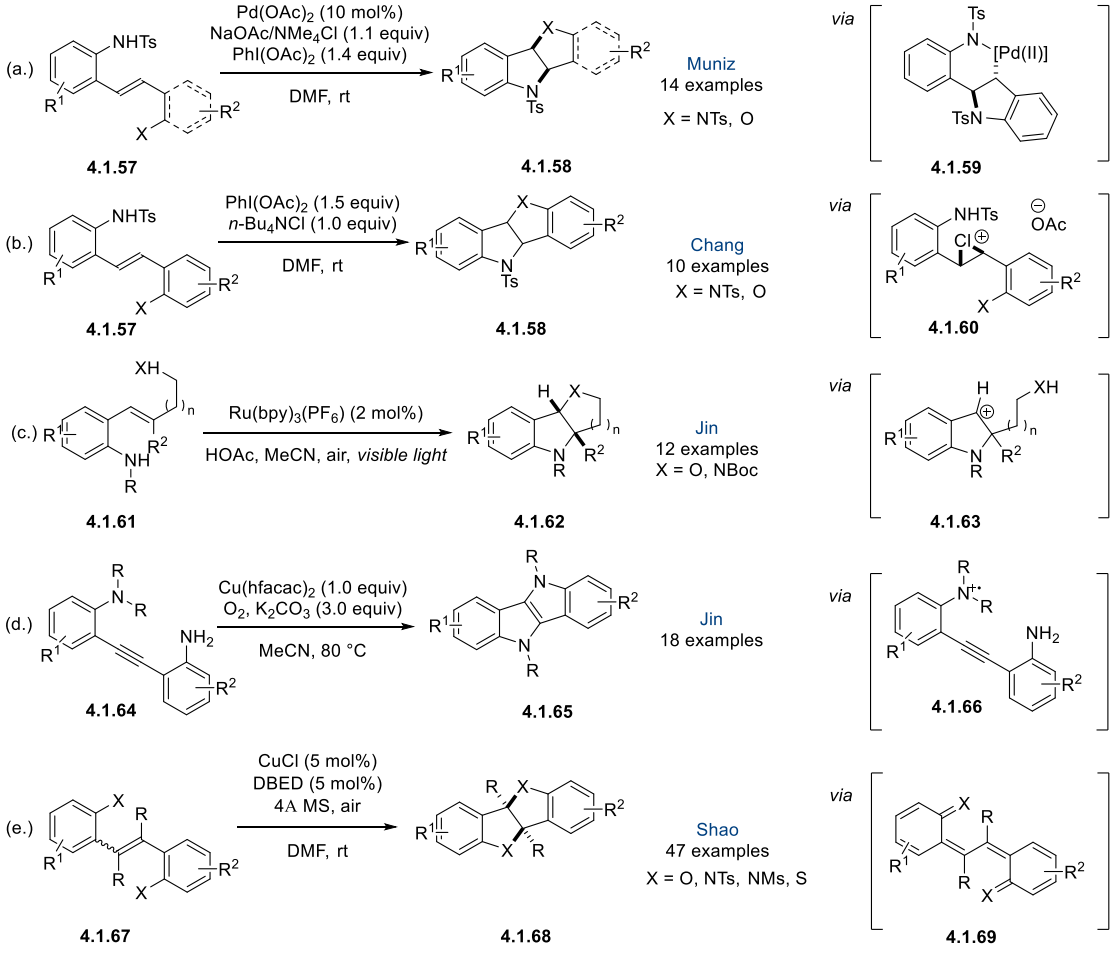
Since the first isolation of (−)-phalarine many research groups have been interested in finding efficient routes for the synthesis of the core structure of this natural product. Most of these methods are based on oxidative conditions, though metal based transformations, as well as reactions under acidic conditions are also known.

4.1.2.1. Synthesis of benzofuro[3,2-*b*]indolines and relative scaffolds *via* oxidative transformations

The synthesis of benzofuro[3,2-*b*]indolines *via* direct oxidative coupling of indoles and phenols has turned out to be highly challenging. The C3-position of indole is, in fact, the most nucleophilic and most reactive site for electrophilic substitution. Under oxidative conditions, the regioisomer - benzofuro[2,3-*b*]indoline is preferentially formed instead of the desired product. One solution to avoid the problem of regioselectivity was discovered by Muniz, who showed that under oxidative conditions bisindolines **4.1.58** can be constructed starting from stilbene **4.1.57** (Scheme 76.a).[230] The reaction goes through the coordination of the Pd catalyst to a tosylamide, followed by an *endo*-selective *anti*-aminopalladation, oxidation and *anti*-amination/depalladation sequence. The scope mainly consisted of bisindolines, however, two examples of benzofuro[3,2-*b*]indolines synthesis were shown. Since the pioneer work of Muniz and its application in Chen's total synthesis of phalarine, several reports on relative transformations have been published in the last 10 years. In 2012, Chang and coworkers showed that a similar reaction could be done under hypervalent iodine catalysis (Scheme 76.b). [231] An *in situ* formation of acetyl hypohalite starting from $PhI(OAc)_2$ and n-Bu_4NCl can explain the observed reactivity. This highly reactive specie could coordinate and activate the alkene by the formation of a chloronium intermediate **4.1.60**. In 2015, Zheng and coworkers described the synthesis of benzofuro[3,2-*b*]indoline and benzopyrrolo[3,2-*b*]indolines **4.1.62** from trisubstituted alkenes **4.1.61** under visible light photoredox catalysis (Scheme 76.c).[232] The oxidation of the nitrogen atom generates an amine radical cation, which would react with the double bond to form

[230] Muniz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542 – 14543
[231] Kim, J.H.; Cho, S.H., Chang, S. *Org. Lett.* **2012**, *14*, 1424 – 1427
[232] Morris, S.A.; Nguyen, T.H.; Zheng, N. *Adv. Synth. Catal*. **2015**, *357*, 2311 – 2316

intermediate **4.1.63**. The authors proposed that tethering a nucleophile to the styrene moiety might enable intramolecular trapping of the benzylic cation. Gratifyingly, both oxygen and nitrogen were shown to efficiently trap the photogenerated benzylic cation. In this methodology, all the substrates were mono-substituted at the 2-position of the indoline ring. In 2016, a Cu-mediated intramolecular oxidative diamination of alkynes **4.1.64** was applied for the synthesis of 5,10-dihydroindolo[3,2-*b*]indoles **4.1.65** using oxygen as oxidant (Scheme 76.d).[233] The reaction proceeds *via* formation of an amine radical cation **4.1.66** by oxidation of nitrogen atom with a stoichiometric amount of copper and oxygen followed by *N*-methyl transfer and radical addition to the alkyne. In the same year, a similar transformation was reported by the group of Du.[234] Shao and coworkers showed a catalytic variant of this transformation for the synthesis of less developed benzofuro[3,2-*b*]benzofurans and some examples of benzofuro[3,2-*b*]indolines **4.1.68** (Scheme 76.e).[235] Upon deprotonation of the heteroatom (O or N) and oxidation of stilbene **4.1.67**, a fully conjugated intermediate **4.1.69** was formed, which underwent a spontaneous antarafacial [4+4] cyclization to give the desired product.

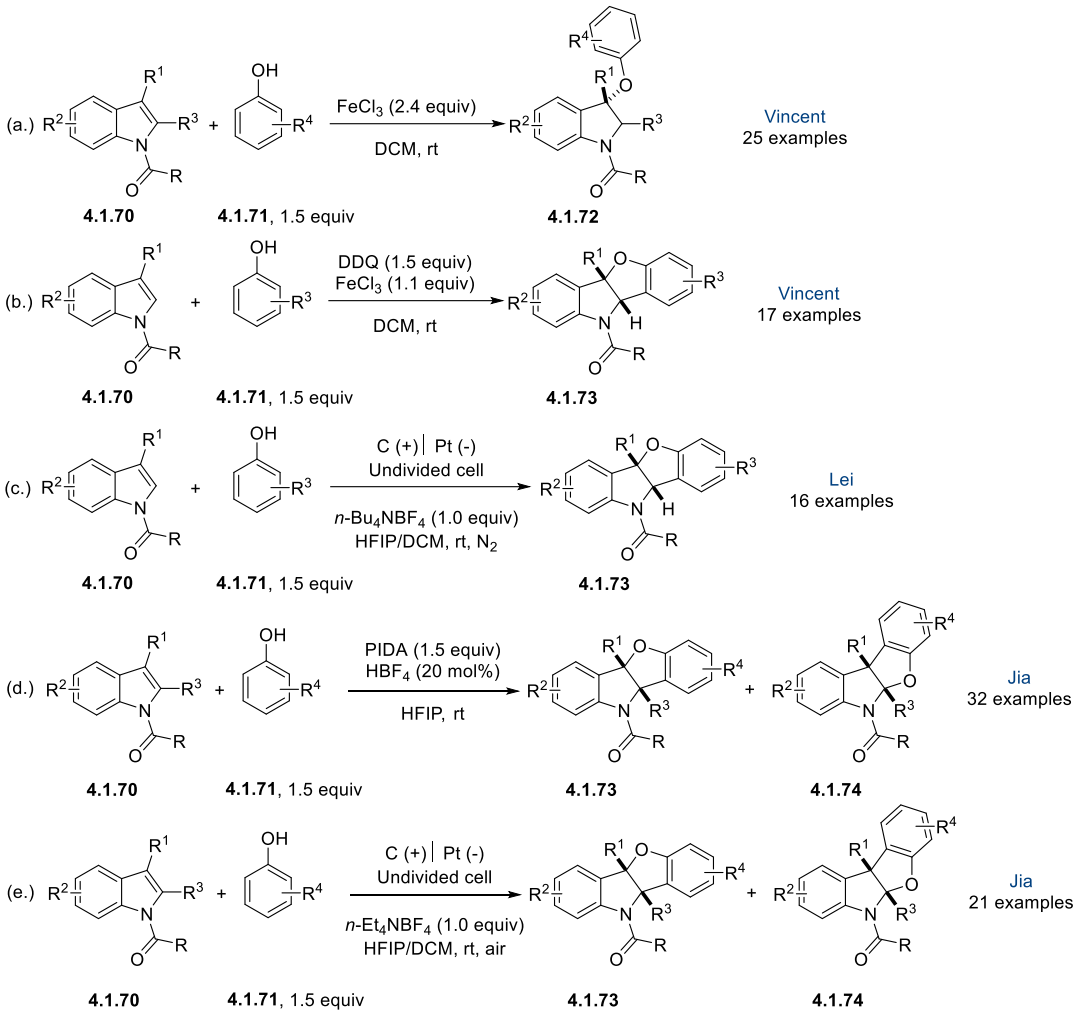


Scheme 76. Synthesis of benzofuro[3,2-b]indolines and relative scaffolds from stilbenes

[233] Ho, H.E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2016**, *18*, 2487 – 2490.
[234] Yu, J.; Zhang-Negrerie, D.; Du, Y. *Org. Lett.* **2016**, *18*, 3322 – 3325.
[235] Zhang, Z.-J.; Zhou, X.; Li, D.; Chen, Y.; Xiao, W.-W.; Li, R.-T.; Shao, L.-D. *J. Org. Chem.* **2021**, *86*, 7609 – 7624.

The first successful example of intermolecular oxidative coupling of indoles **4.1.70** and phenols **4.1.71** for the selective synthesis of benzofuro[3,2-*b*]indolines **4.1.73** was published by Vincent and coworkers.[236] In 2012, authors showed that coordination of $FeCl_3$ to indole **4.1.70** could change the reactivity of N-acetylindole by making the C-3 position electrophilic and available for regioselective nucleophilic attack. This rare umpolung of the indole nucleus can be explained by the broken aromaticity of the indole ring through the delocalization of the nitrogen lone pair in the carbonyl π system. It was then successfully applied for C-3 hydroarylation of indoles using different heteroaromatic compounds (Scheme 77.a).[237,238] Inspired by their previous results, the authors proposed that the direct oxidative [3+2] coupling of a phenol **4.1.71** and an indole **4.1.70** can be performed *via* coordination of $FeCl_3$ to the indole nitrogen and oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 77.b). Although the yields were low, it was an encouraging proof of concept. Following their landmark achievement, others have reported similar transformations. A few years later, Lei *et al.* presented an alternative electrocatalysis approach (Scheme 77.c).[239] The reaction proceeded *via* anodic oxidation of both reagents followed by the cross-coupling of the transient phenol carbon radical and the stabilized cation radical of indole. Interestingly, depending on the substituents on the indole ring (C-2 or C-3) different regioisomers of benzofuroindolines can be formed. Thereby, starting with 3-substituted N-acetylindoles benzofuro[3,2-*b*]indolines **4.1.73** were obtained, while 2-substituted N-acetylindoles gave benzofuro[2,3-*b*]indolines **4.1.74**, probably, substituents at C-2 position block the addition of electrophilic phenol carbon radical. Following their total synthesis of phalarine in 2019, Jia and coworkers expanded the scope of benzofuro[3,2-*b*]indolines synthesis by applying their developed conditions (i.e. PIDA, HBF_4) to various indoles and phenols (Scheme 77.d).[240] Desired products were obtained with moderate yields along with their regioisomers, however, it remained the first example of benzofuro[3,2-*b*]indolines synthesis starting with 2,3-disubstituted indoles. The same group lately reported that similar reactivity can be achieved *via* electrooxidative conditions (Scheme 77.e).[241]

[236] Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 11881 – 11885.
[237] Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Angew. Chem.* **2012**, *124*, 12714 – 12718; *Angew. Chem. Int. Ed.* **2012**, *51*, 12546 – 12550.
[238] Beaud, R.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Eur. J.* **2014**, *20*, 7492 – 7500.
[239] Liu, K.; Tang, S.; Huang, P.; Lei, A. *Nature Commun.* **2017**, *8*, 775 – 782.
[240] Li, L.; Yuan, K.; Jia, Q.; Jia, Y. *Angew. Chem. Int. Ed.* **2019**, *58*, 6074 – 6078.
[241] Li, K.; Wang, Y.; Chen, L.; Li, L.; Jia, Y. *Tetrahedron Lett.* **2021**, *63*, 152603 – 152606.

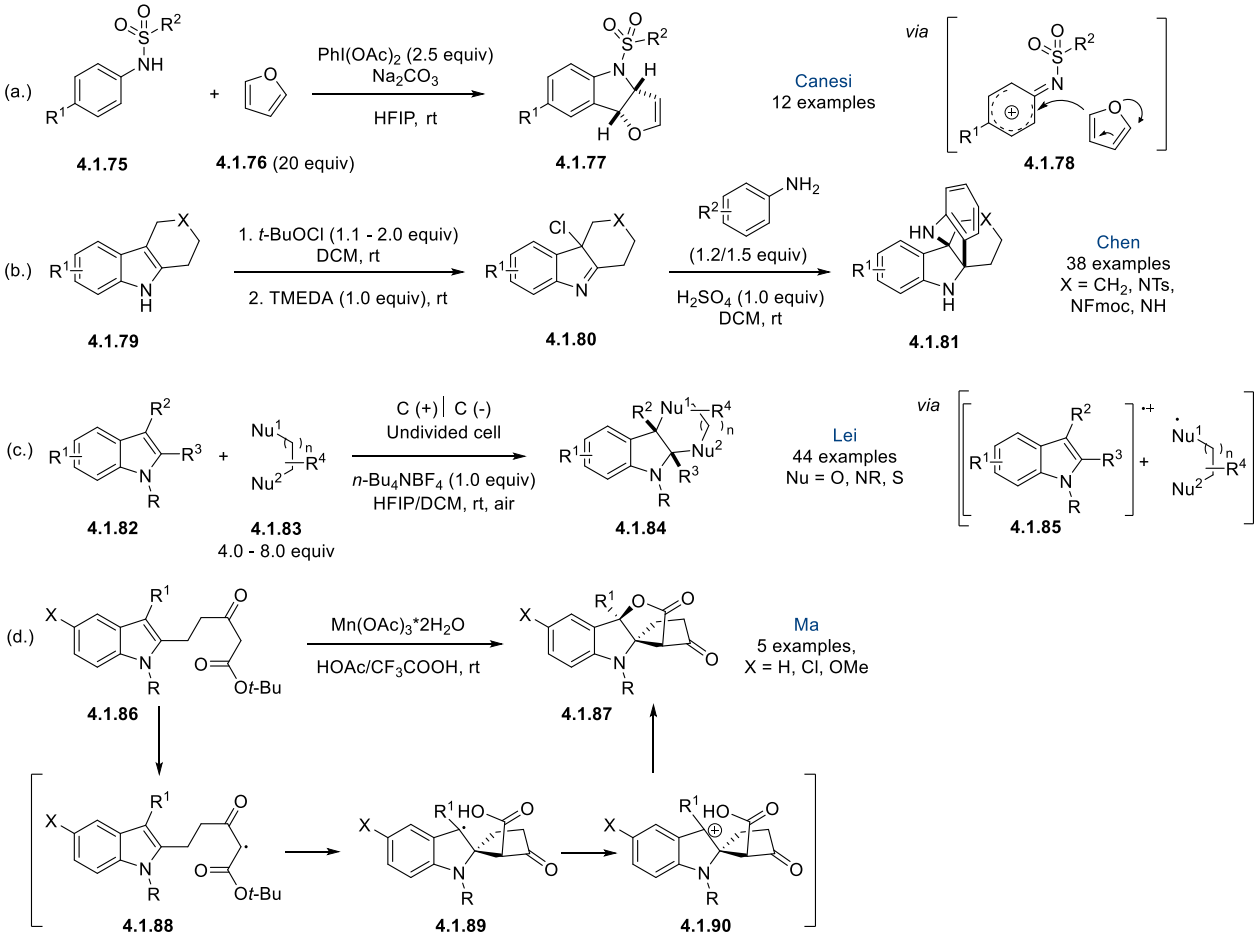


Scheme 77. Synthesis of benzofuro[3,2-b]indolines and relative scaffolds via oxidative coupling of indole and phenol

At the same time, different reports were published concerning the synthesis of similar scaffolds (Scheme 78). In 2017, Deruer and Canesi showed that under oxidative conditions, sulfonamides **4.1.75** can be coupled with furan **4.1.76** to afford dihydrofurano[3,2-*b*]indolines **4.1.77** (Scheme 78.a).[242] The reaction proceeds *via* the oxidation of sulfonamide with (diacetoxyiodo)benzene (DIB), which is then trapped with furan. Unfortunately, products were obtained in only moderate to good yields and 20 equivalents of furan were necessary to ensure a smooth reaction. The replacement of furan by electron-rich or electron-poor analogues showed poor reactivity, due to the easy oxidation of electron-rich furans and the low reactivity of electron-poor furans. Regardless of the disadvantages, this procedure affords dihydrofuranoindolines **4.1.77** from simple precursors. An alternative method for the synthesis of bisindolines was discovered by Chen and coworkers, who showed that oxidation of tetrahydro-γ-carbolines **4.1.79** with *t*-BuOCl affords 3-chloroindolenines **4.1.80**. These compounds can then be easily converted into bisindolines **4.1.81** *via* intermolecular coupling with anilines under acid catalysis (Scheme 78.b).[243] Desired products are formed with good to excellent yields with a broad scope of starting materials. We note that these two steps can be

[242] Deruer, E. ; Canesi, S. *Org. Biomol. Chem*. **2017**, *15*, 3736 – 3741.
[243] Cui, R.; Ye, J.; Li, J.; Mo, W.; Gao, Y.; Chen, H. *Org. Lett.* **2020**, *22*, 116 – 119.

integrated into a one-pot process. Almost at the same time, Lei *et al.* presented the synthesis of five to eight-membered heterocycle-2,3-fused indolines and dihydrobenzofurans **4.1.84** through electrooxidative dearomatization of indoles and benzofurans **4.1.82** (Scheme 78.c).[244] Similarly to the previous works by Lei and Jia, anodic oxidation of the indole is accountable for the observed reactivity. This procedure should be highlighted for its ease of operation and the good functional group compatibility, however, only a few examples of 2,3-disubstituted indoles were presented as starting materials. The natural product lapidilectine B contains a furano[3,2-*b*]indoline moiety. In 2018, Ma and coworkers showed that this kind of scaffold could be constructed through a manganese(III)-mediated oxidative cyclization of indole **4.1.86** (Scheme 78.d).[245] The authors proposed that the oxidation of β-ketoester **4.1.86** would give electrophilic radical **4.1.88**, which could attack the C-2 position of indole followed by cleavage of *t*-Bu ester to afford intermediate **4.1.89**. The oxidation of the radical would produce carbocation **4.1.90**, which would be trapped intramolecularly to give the desired pentacyclic product **4.1.87**. To show the practicality of this method, 5 different substrates were synthesized with excellent yields and this methodology was then applied for the synthesis of the natural product.

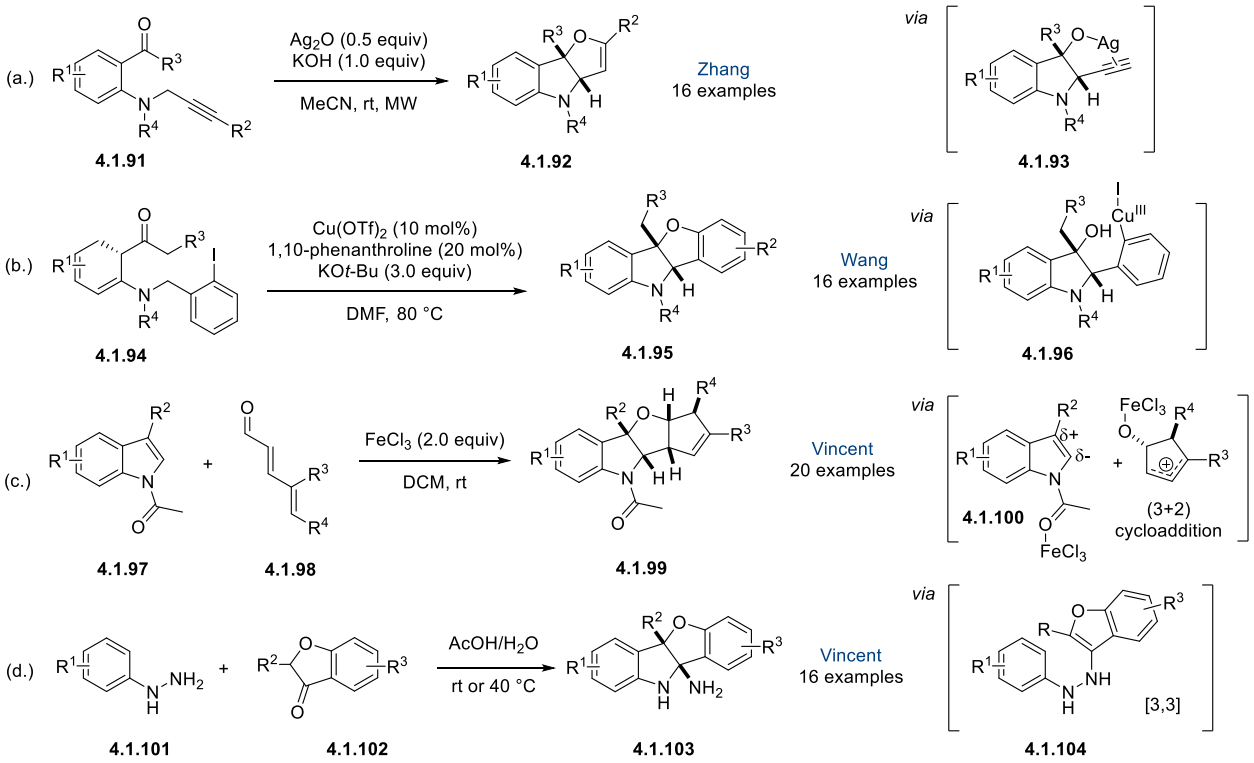


Scheme 78. Synthesis of relative scaffolds to furo[3,2-b]indolines via oxidative conditions

[244] Liu, K.; Song, W.; Deng, Y. ; Yang, H. ; Song, C.; Abdelilah, T.; Wang, S.; Cong, H.; Tang, S.; Lei, A. *Nature Commun.* **2020**, *11*, 3.
[245] Gao, Y.; Fan, M.; Geng, Q.; Ma, D. *Chem. Eur. J.* **2018**, *24*, 6547 – 6550.

Metal-catalyzed methods have as well been reported in the literature. In this regard, Zhang and coworkers published the first example of a silver-catalyzed intramolecular cycloaddition reaction for the synthesis of furo[3,2-*b*]indolines **4.1.92** (Scheme 79.a).[246] Analysis of the reaction crude showed that at the end of the reaction elemental silver could be recovered, indicating the dual-role of Ag_2O as base and oxidant. The reaction is initiated by the coordination of Ag_2O to the triple bond of **4.1.91**, enhancing the acidity of the alpha proton. The deprotonation of this hydrogen, followed by the cyclization onto the tethered carbonyl, would form cis intermediate **4.1.93**. Single electron transfer (SET) from oxygen to Ag(I), 5-*endo*-dig radical cyclization, second SET from Ag(0) to vinyl radical and protonation would afford the desired product **4.1.92**. In 2015, Wang and co-workers showed that depending on the transition metal, either benzofuro[3,2-*b*]indolines **4.1.95** or dihydro[1,2-b]indenoindole-9-ol can be synthesized starting from the same starting material **4.1.94** (Scheme 79.b).[247] The reaction begins with an intramolecular nucleophilic addition to the carbonyl group to afford intermediate **4.1.96**. The intramolecular Ullman cross-coupling of the latter delivers the tetracyclic compound **4.1.95**. Almost at the same time, Vincent and coworkers reported the reaction of 2,4-dienals **4.1.98** with N-acetylindoles **4.1.97** to access the core of furo[3,2-*b*]indoles **4.1.99** *via* a (3+2)-cycloaddition.[248] In the presence of a stoichiometric amount of $FeCl_3$, dienal **4.1.98** underwent an iron-catalyzed 4π electrocyclization to produce allylic cation **4.1.100** which reacted with the activated indole to afford **4.1.99**. The complexation of $FeCl_3$ to the indole ring accounts for the umpolung of the classical reactivity. The same group showed that an interrupted Fischer indolization could be an efficient alternative method for the synthesis of substrate **4.1.103** (Scheme 79.d).[249] Under acidic conditions, aromatic hydrazines **4.1.101** were coupled with benzofuran-3-one **4.1.102** to give intermediate **4.1.104**. [3,3]-Sigmatropic rearrangement afforded only benzofurano[3,2-*b*]indolines **4.1.103**.

[246] Zhang, Z.; Fang, S.; Liu, Q.; Zhang, G. *Adv. Synth. Catal*. **2012**, *354*, 927 – 932.
[247] Boominathan, S.S.K.; Wang, J.-J. *Chem. Eur. J.* **2015**, *21*, 17044 – 17050.
[248] Marques, A.S.; Coeffard, V.; Chataigner, I.; Vincent, G.; Moreau, X. *Org. Lett.* **2016**, *18*, 5296 – 5299.
[249] Tomakinian, T.; Guillot, R.; Kouklovsky, C.; Vincent, G. *Chem. Commun.* **2016**, *52*, 5443 – 5446.



Scheme 79. Non-oxidative methods for the synthesis of furo[3,2-b]indolines

4.2. Goal of the project

Most of the aforementioned methodologies are limited to the preparation of furo[3,2-*b*]indolines **4.2.1-4.2.3** where only one or no carbon of the fused ring is quaternary (Figure 7). Synthesis of fully substituted two vicinal quaternary carbon centres remains a challenging task.

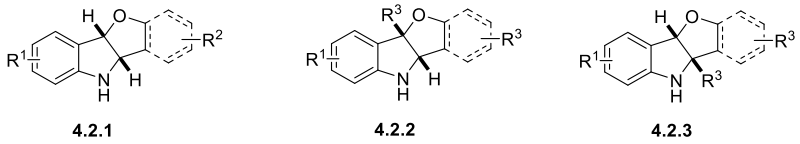
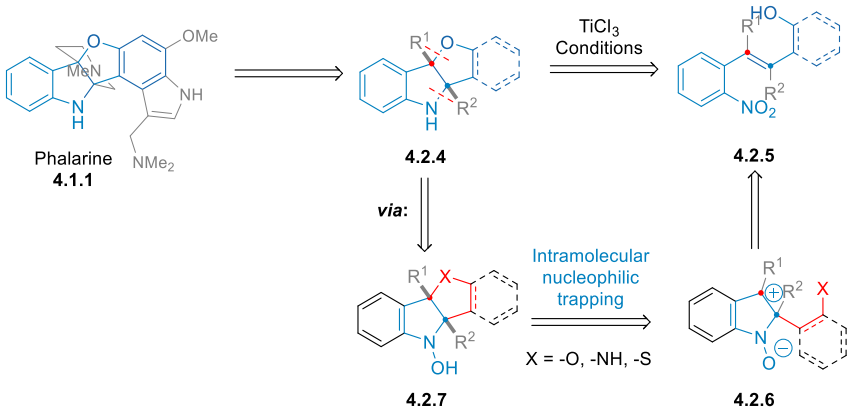


*Figure 7. Furo[3,2-b]indolines **4.2.1** – **4.2.3***

Being aware of the difficulties associated with the synthesis of benzofuro[3,2-*b*]indoline scaffold, we thought to investigate an alternative reductive condition for the synthesis of fully substituted benzofuro[3,2-*b*]indolines applicable to the total synthesis of phalarine. As aforementioned, most of the methods for the synthesis of this kind of scaffold are based on oxidative conditions delivering products in either low yields or with poor regioselectivity. The $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkenes bearing a *o*-nitrophenyl substituent **4.2.5** could be an interesting alternative to access furo[3,2-*b*]indolines (Scheme 80). We hypothesized that under appropriate reductive conditions, the **4.2.5** could be converted to zwitterion **4.2.6** *via* selective reduction of nitro to nitroso group followed by the 6π-electrocyclization. Trapping the benzylic carbocation by tethered nucleophile (alcohol, thiol or amine) would afford regioselectively the *N*-

hydroxyfuroindoline **4.2.7** which, upon further reduction, would be converted to the desired product **4.2.4**. Herein, we would like to present the discovery of a $TiCl_3$-mediated reductive cyclization of tetrasubstituted *o*-nitrostyrene derivatives, as well as our synthetic studies toward total synthesis of (±)-phalarine.



Scheme 80. Synthesis of furo[3,2-b]indolines by $TiCl_3$-mediated reductive cyclization of o-nitrostyrenes

4.3. Synthesis of a model-substrate

At the beginning of our studies, we focused on the synthesis of starting materials for the key-transformation. Alkene **4.3.1** was chosen as a model substrate. The main challenge with this substrate is that it contains an all-carbon tetrasubstituted triphenylethylene scaffold bearing a 2-nitroaryl substituent. Tetrasubstituted olefins can be found in numerous natural products and drugs (e.g. Tamoxifen, Ospemifene, Miproxifene, Idoxyfene) showing high bioacivity and have attracted much attention in the past decades (Figure 8).[250,251,252,253]

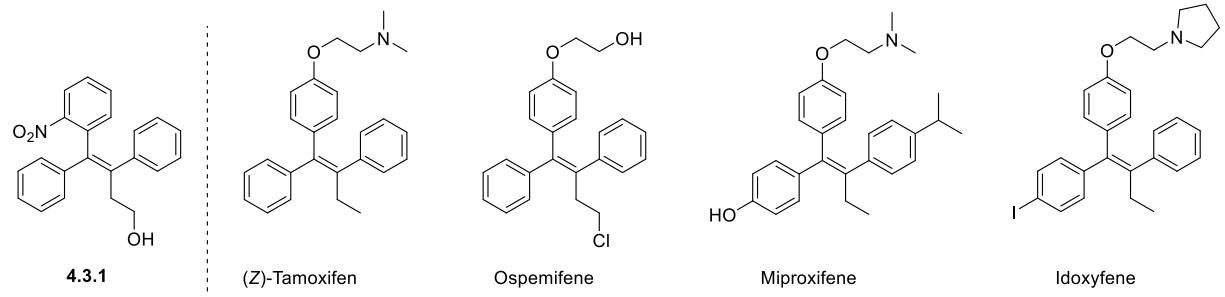
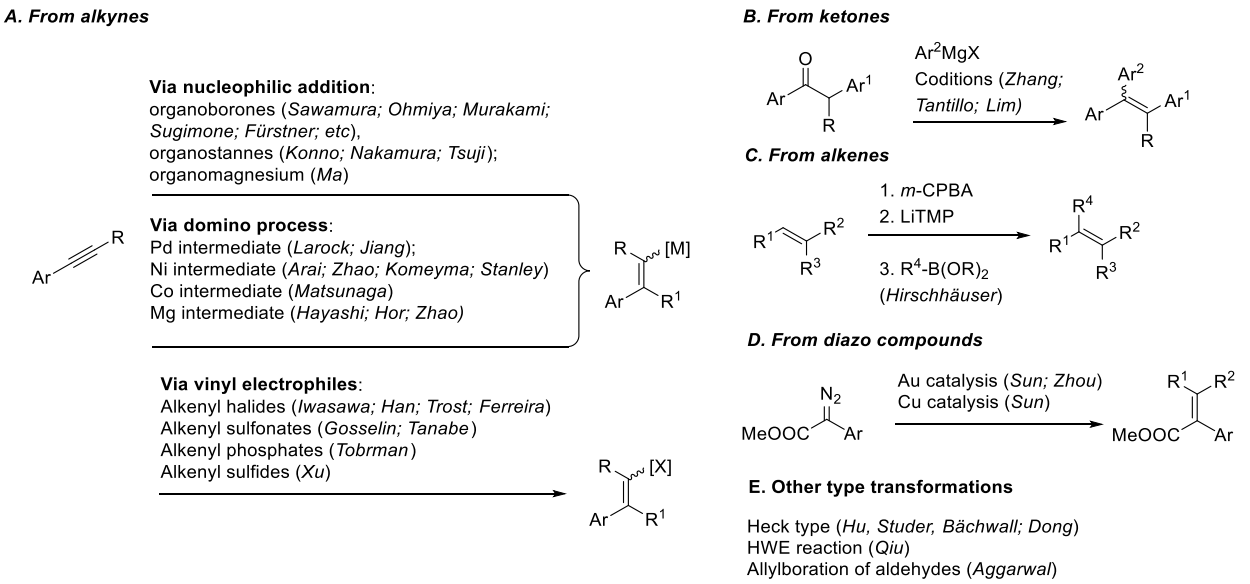


Figure 8. Bioactive compounds containing tetrasubstituted olefine moiety

Different synthetic approaches are available to access them. McMurry reaction, a 1,2-addition-elimination sequence, cross-coupling reactions through carbometalation and bis-metalation of alkynes, Heck and Wittig reactions, are often used. However, most of them suffer from low regio- and

[250] Flynn, A.B.; Ogilvie, W.W. *Chem Rev.* **2007**, *107*, 4698 – 4745.
[251] Polak, P.; Vanova, H.; Dvorak, D.; Tobrman, T. *Tetrahedron Lett.* **2016**, *57*, 3684 – 3693.
[252] Buttard, F.; Sharma, J.; Champagne, P.A. *Chem. Commun.* **2021**, *57*, 4071 – 4088.
[253] Heijen, D.; van Zuijlen, M.; Tosi, F.; Feringa, B.L. *Org. Biomol. Chem.* **2019**, *17*, 2315 – 2320.

stereoselectivity. At the same time, high eclipsing interactions in the transition state and in the final products should not be underestimated. Despite the fact that the stereoselective synthesis of acyclic olefins stays challenging, some efficient ways for the synthesis of tetrasubstituted olefins are presented in Scheme 81. Most of them are based on nucleophilic addition or formation of vinyl halides starting from alkynes.[254]

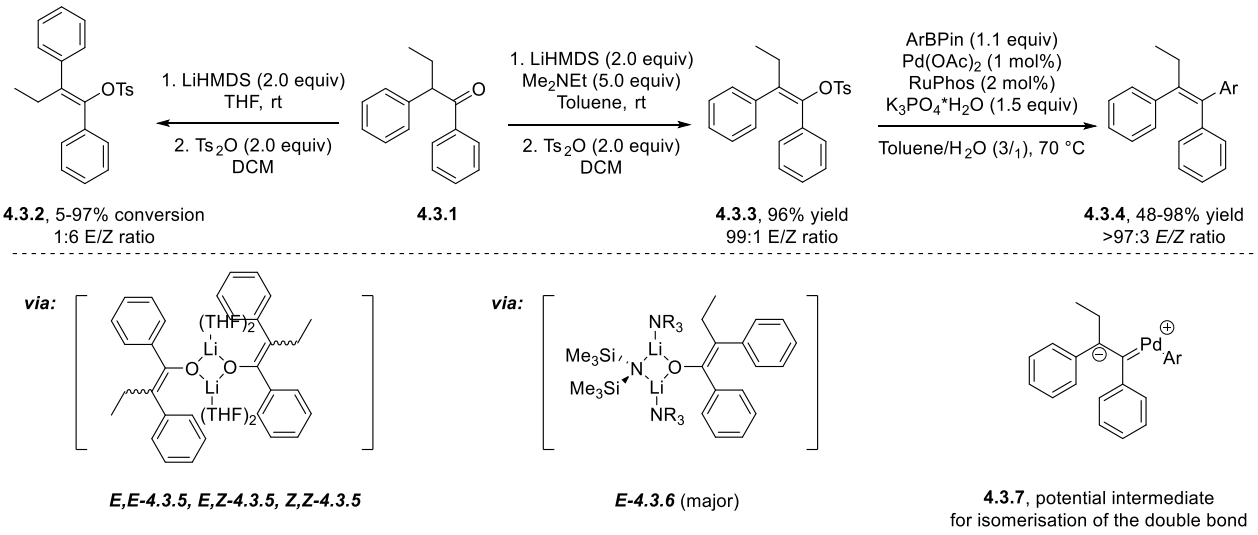


Scheme 81. Stereoselective synthesis of tetrasubstituted olefins

In 2017 Gosselin showed that the *E*-selective enolization of ketones **4.3.1** could be applied to the synthesis of trisubstituted *E*-enol tosylates **4.3.3**, which can then be used in the stereospecific Suzuki-Miyaura cross-coupling with aryl boronates (Scheme 82).[255,256] The stereoselectivity of the tosylation step highly depends on the nature of the solvent, its concentration and the presence of additives. Based on spectroscopic studies and DFT calculations, the authors could explain this observation by the formation of different aggregates, leading to different reaction outcomes.[257] For the LiHMDS/THF system – mixed dimeric aggregates **4.3.5** were suggested. In the case where the reaction is run in toluene in combination with amines (as a poorly coordinating additives) – mixed aggregates **4.3.6** were proposed, where the *E*-isomer was dominating. It is to mention that the formed enolate aggregates can be slow to equilibrate. Nevertheless, the obtained tosylates can be efficiently transformed into tetrasubstituted olefins **4.3.4** through highly stereospecific Suzuki-Miyaura cross-coupling. With non-optimized conditions, an olefin isomerization was observed, which was explained by the formation of a zwitterionic palladium carbenoid specie **4.3.7**. Later on, the authors showed that after a high throughput optimization of the reaction

[254] [(a)] Nagao, K.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 10605 – 10608; [(b)] *Org. Lett.* **2015**, *17*, 1304 – 1307; [(c)] Ishida, N.; Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 4381 – 4383; [(d)] Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003,** *125*, 6358 – 6359; [(e)] *Angew. Chem. Int. Ed.* **2005**, *44*, 2380 – 2382.
[255] Li, B.X.; Le, D.N.; Mack, K.A.; McClory, A.; Lim, N.-K. ; Cravillion, T.; Savage, S. ; Han, C.; Collum, D.B.; Zhamg, H.; Gosselin, F. *J. Am. Chem. Soc.* **2017**, *139*, 10777 – 10783.
[256] Zell, D.; Kingston, C.; Jermaks, J.; Smith, S.R.; Seeger, N.; Wassmer, J.; Sirois, L.E.; Han, C.; Zhang, H.; Sigman, M.S.; Gosselin, F. *J. Am. Chem. Soc.* **2021**, *143*, 19078 – 19090.
[257] Mack, K.A.; McClory, A.; Zhang, H.; Gosselin, F.; Collum, D.B. *J. Am. Chem. Soc.* **2017**, *139*, 12182 – 12189.

conditions, they could perform a diastereodivergent and diastereoconvergent synthesis of tetrasubstituted alkenes through Ni-catalyzed cross-coupling reaction.[258]



Scheme 82. Synthesis of tetrasubstituted olefins via stereospecific Suzuki-Miyaura cross-coupling

In the case of our starting material **4.3.1** (Figure 9), the *o*-nitro-group creates a more significant steric hindrance around the double bond and could provoke a number of potential side reactions, e.g., the single-electron transfer induced transformations. Nevertheless, inspired by Gosselin's work on the synthesis of tetrasubstituted alkenes and some promising entries depicted in his reaction scope, we decided to exploit this chemistry for our purpose. Two disconnections based on a late-stage Suzuki-Miyaura cross-coupling are depicted in Scheme 83. For the first synthetic pathway, we proposed that alkene **4.3.10** would be formed by the Suzuki-Miyaura cross-coupling between enol triflate **4.3.11** and 2-nitrophenylboronic acid **4.3.12**. This triflate, in its turn, would be synthesized in two steps starting from the ketone **4.3.14** by alkylation and triflate formation. However, electron-poor organoboron reagents such as 2-nitrophenylboronic acid **4.3.12** are known to react less efficiently in the transmetalation step. Besides, steric repulsion can further reduce the reactivity and drop the yield for this transformation. To overcome this potential problem, a second synthetic sequence was developed in parallel, in which alkene **4.3.10** would be prepared by the Suzuki-Miyaura cross-coupling reaction between enol triflate **4.3.16** and phenylboronic acid **4.3.17**, which already contains the 2-nitroaryl substituent. Triflate **4.3.16** would be readily obtained from ketone **4.3.19** *via* alkylation and triflate formation. Ketone **4.3.19**, being not commercially available, would be synthesized *via* the Liebeskind-Srogl reaction between thioester **4.3.20** and arylstannane **4.3.21**.

[258] Woltornist, R.A.; Collum, D.B. *J. Am. Chem. Soc.* **2021**, *143*, 17452 – 17464.

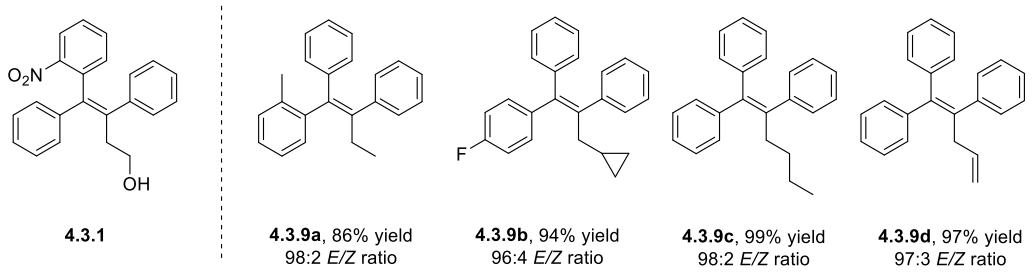
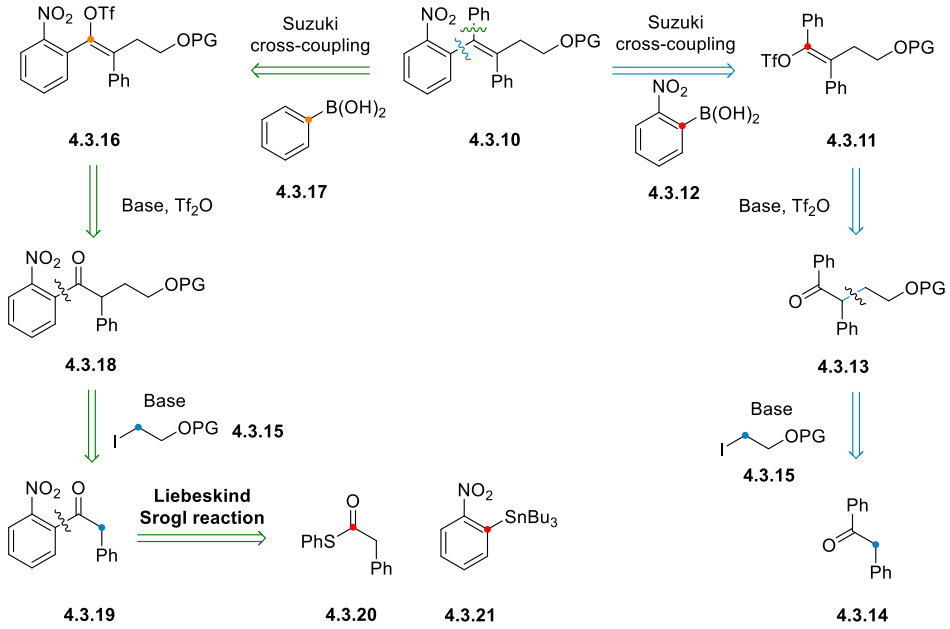


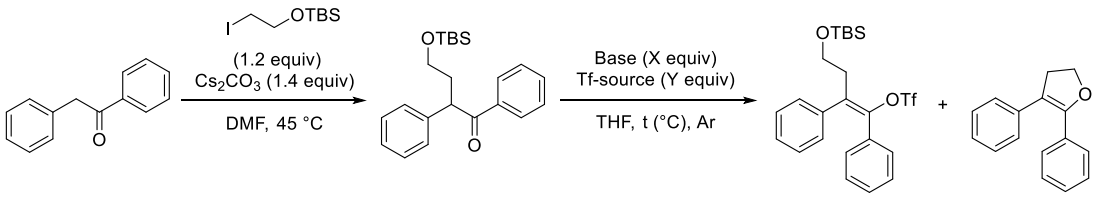
Figure 9. Examples of tetrasubstituted olefins from the work of Gosselin et al.



*Scheme 83. Proposed retrosynthesis for tetrasubstituted alkene **4.3.10** bearing a 2-nitroaryl substituent*

1st synthetic pathway

This first pathway was initiated by the synthesis of ketone **4.3.22** in 60% yield starting from commercially available 2-phenylacetophenone **4.3.14** and TBS-protected 2-iodoethanol. The TBS-protecting group was chosen for its good stability and easiness of deprotection. The formation of the vinyl pseudohalide was next investigated (Table 23). Initially, enol triflate **4.3.23** was chosen as the desired target due to its known efficiency in cross-coupling reactions. Unfortunately, despite the number of reaction conditions tested, the desired transformation could not be accomplished. The source of triflate, the base and the temperature were varied, however, in all cases, only starting material **4.3.22** and dihydrofuran **4.3.24** were observed. High reactivity and instability of the desired enol triflate may be part of the problem.



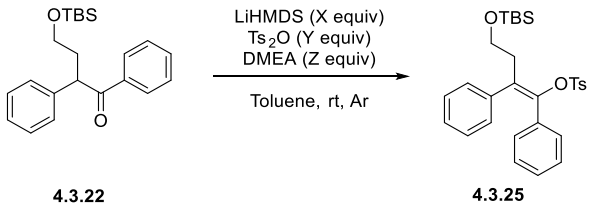
4.3.14 **4.3.22**, 60% yield **4.3.23** **4.3.24**

Entry	Base (X equiv)	Tf-source (Y equiv)	T °C	Results
1.	LiHMDS (2.0 equiv)	Tf_2O[a] (1.5 equiv)	1. -78°C – 0 °C (1 h) 2. 0 °C – rt (1h)	**4.3.22 + 4.3.24**
2.	LiHMDS (2.0 equiv)	Tf_2O (2.0 equiv)	1. -78°C – 0 °C (1 h) 2. 0 °C – rt (overnight)	**4.3.24**
3.	LiHMDS (3.0 equiv)	Tf_2O (4.0 equiv)	1. -78°C – 0 °C (1 h) 2. 0 °C – rt (overnight)	Decomposition
4.	LiHMDS (2.0 equiv)	$PhNTf_2$ (1.5 equiv)	1. -78°C – 0 °C (1 h) 2. 0 °C – rt (1 h)	**4.3.22 +** Decomposition
5.	LiHMDS (2.0 equiv)	$PhNTf_2$ (2.0 equiv)	1. -78°C – 0 °C (1 h) 2. 0 °C – rt (overnight)	**4.3.22 +** Decomposition
6.	LiHMDS (1.1 equiv)	Comin's reagent (1.1 equiv)	1. -78°C – 0 °C (1h) 2. 0 °C – rt (overnight)	**4.3.22 +** Decomposition
7.	LiHMDS (2.0 equiv)	Comin's reagent (2.0 equiv)	1. -78°C – 0 °C (1h) 2. 0 °C – rt (overnight)	**4.3.22 +** Decomposition
8.	NaH (2.0 equiv)	$PhNTf_2$ (1.5 equiv)	1. 0 °C - rt (1h) 2. 0 °C – rt (overnight)	**4.3.22 +** Decomposition

[a]Tf_2O – freshly distilled

*Table 23. Attempted synthesis of enol triflate **4.3.23** form ketone **4.3.22***

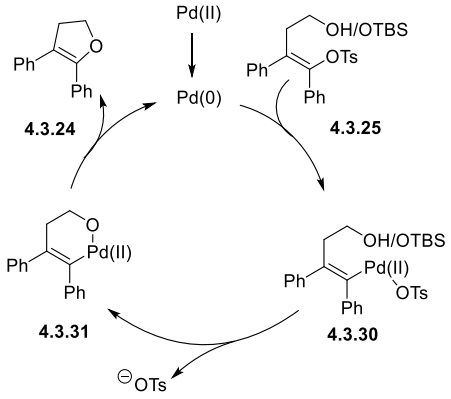
Assuming that tosylate can be more stable on the basis of Gosselin's work, we decided to prepare enol tosylate **4.3.25**. Applying the conditions described in their paper produced the desired product **4.3.25**, albeit in only 20% isolated yield. The starting material was remaining in the reaction mixture (Table 24). Quick optimization of the reaction conditions was performed. Increasing the amount of base and co-base to 3 equiv gave compound **4.3.25** in 56% yield. When the amount of Ts_2O was increased to 3.0 equiv, enol tosylate **4.3.25** was isolated in 60% yield. It is interesting to note that by applying these optimized conditions to the synthesis of enol triflate **4.3.23**, the desired product was isolated in 34% yield accompanied by an equal amount of dihydrofuran **4.3.24**.



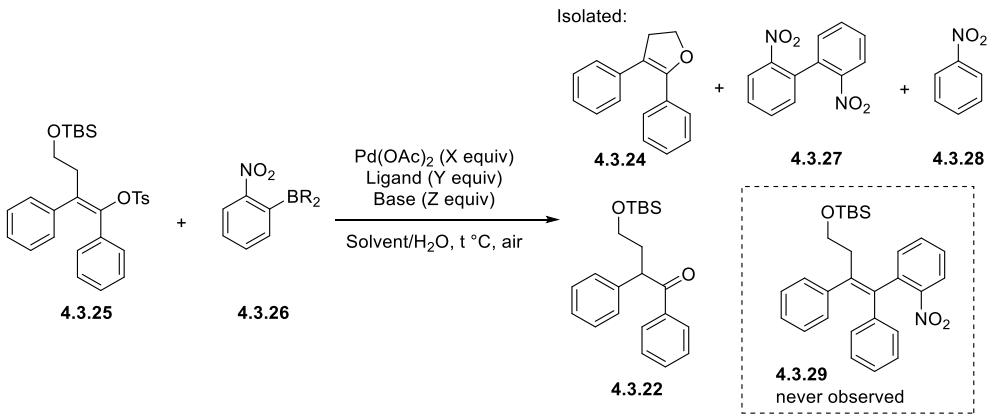
Entry	LiHMDS (1.0M in toluene)	DMEA	Ts_2O	Results
1.	2.0 equiv	2.0 equiv	2.0 equiv	**4.3.25** 20%
2.	3.0 equiv	3.0 equiv	2.0 equiv	**4.3.25** 56%
3.	3.0 equiv	3.0 equiv	3.0 equiv	**4.3.25** 60%
4.	3.0 equiv	3.0 equiv	Tf_2O (3.0 equiv)	**4.3.23** 34%

*Table 24. Optimization of the tosylation of ketone **4.3.22***

Having enol tosylate **4.3.25** in hands, the Suzuki-Miyaura cross-coupling with 2-nitrophenylboronic ester was undertaken (Table 25). Firstly, the conditions described in Gosselin's paper were tested. Unfortunately, only starting material **4.3.25** was recovered along with its decomposition products: ketone **4.3.22** and dihydrofuran **4.3.24**. The formation of side-product **4.3.24** could be potentially explained through the oxidative addition of the enol tosylate **4.3.25** to the Pd(0) catalyst, followed by an intramolecular ligand exchange between the tosylate anion and the alcohol (Scheme 84). Finally, a reductive elimination would afford the dihydrofuran **4.3.24** with the concurrent generation of Pd(0) catalyst, closing, therefore, the catalytic cycle. Alternatively, **4.3.24** could be formed under basic conditions from **4.3.22**. However, though no desired product **4.3.29** was obtained, the organoboron coupling partner **4.3.26** was totally consumed under all tested conditions leading to the formation of 2,2'-dinitro-1,1'-biphenyl **4.3.27** and nitrobenzene **4.3.28** (Table 25, entry 1). Increasing the amount of catalyst and ligand, as well as base and temperature, gave similar results (entries 2-5). Replacing the 2-nitrophenylboronic acid pinacol ester by 2-nitrophenylboronic acid did not change the outcome of the reaction. No change was observed when the reaction was carried out in the presence of Cs_2CO_3 (entry 6). Exchanging RuPhos with other ligands (XantPhos, XPhos and PPh_3), which worked well in the work of Gosselin, gave similar results (entries 7-13). The same outcome was observed when toluene was replaced by dioxane (entries 10-13). Finally, in an attempt to identify the origin of the problem, enol tosylate **4.3.25** was reacted with phenylboronic acid. However, the desired cross-coupling product was not isolated either in this case (entry 14).



*Scheme 84. Mechanism of formation of side-product **4.3.24***



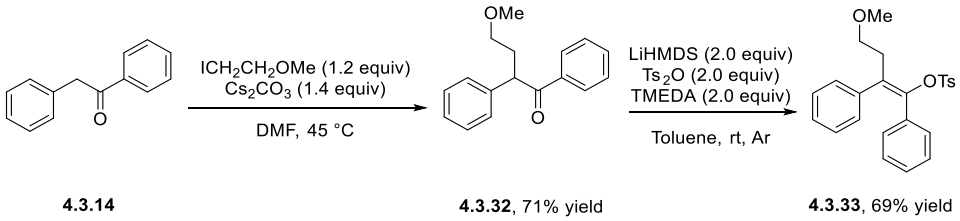
	-BR_2	[Pd]	Ligand	Base	T °C	Solvent	Results
1.	BPin	$Pd(OAc)_2$	RuPhos	K_3PO_4	70 °C	Toluene/H_2O	
2.	BPin	$Pd(OAc)_2$	RuPhos	K_3PO_4	90 °C	Toluene/H_2O	
3.	BPin	$Pd(OAc)_2$ (10 mol%)	RuPhos (15 mol%)	K_3PO_4	90 °C	Toluene/H_2O	
4.	BPin	$Pd(OAc)_2$ (10 mol%)	RuPhos (15 mol%)	K_3PO_4 (2.0 equiv)	90 °C	Toluene/H_2O	
5.	$B(OH)_2$ (1.1 equiv)	$Pd(OAc)_2$	RuPhos	K_3PO_4	90 °C	Toluene/H_2O	
6.	BPin (2.0 equiv)	$Pd(OAc)_2$ (10 mol%)	RuPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Toluene/H_2O	**4.3.25** **4.3.22** **4.3.24** **4.3.27** **4.3.28**
7.			XantPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Toluene/H_2O	
8.			XPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Toluene/H_2O	
9.			PPh_3 (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Toluene/H_2O	
10.			RuPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Dioxane/H_2O	
11.			XantPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Dioxane/H_2O	
12.			XPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Dioxane/H_2O	
13.			PPh_3 (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Dioxane/H_2O	
14.	$PhB(OH)_2$ (1.1 equiv)	$Pd(OAc)_2$	RuPhos	K_3PO_4	90 °C	Toluene/H_2O	

Conditions: enol tosylate **4.3.25** (0.1 mmol), Ar-BPin (1.1 or 2.0 equiv), palladium (2 or 10 mol%), ligand (4 or 15 mol%), base (1.5 or 3.0 mmol), toluene or dioxane / water (0.06 M). RuPhos - 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; XantPhos - 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene; XPhos - 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

*Table 25. Attempted Suzuki-Miyaura cross-coupling with enol tosylate **4.3.25***

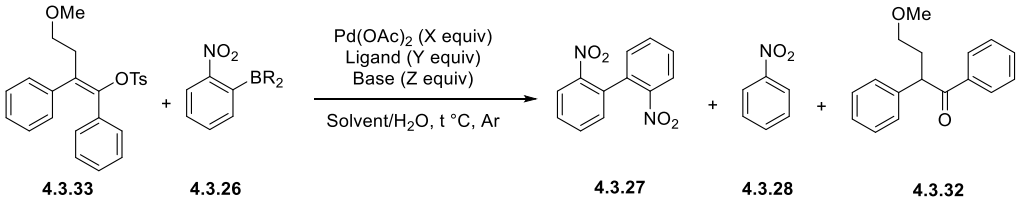
The formation of dihydrofuran product **4.3.24** suggested that the TBS-protecting group was labile under our conditions. To test this hypothesis, this protecting group was replaced by a methyl ether (Scheme

85). The modified enol tosylate **4.3.33** was synthesized similarly in 49% yield over 2 steps starting from 2-phenylacetophenone **4.3.14**.



*Scheme 85. Synthesis of enol tosylate **4.3.33***

The obtained pseudohalide **4.3.33** was submitted to the Suzuki-Miyaura reaction. As mentioned before, similar conditions were tested, but again the key reaction was not observed (Table 26, entries 1-10). At the same time, to prevent the formation of 2,2'-dinitro-1,1'-biphenyl **4.3.27** *via* homocoupling of the organoboron coupling partner **4.3.26**, all reactions were performed under strictly inert atmosphere using a Freeze-Pump-Thaw Cycling technique. Indeed, no more traces of this side product were observed in the following experiments. Solvents, ligands and bases were varied, but no conditions were found to form the desired product. Delightfully, a test reaction with phenylboronic acid gave the desired coupling product.



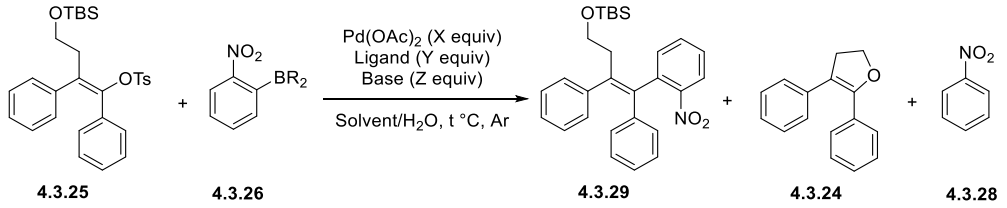
	-BR_2	[Pd]	Ligand	Base	T °C	Solvent	Result
1.	BPin (1.1 equiv)	$Pd(OAc)_2$ (5 mol%)	RuPhos (10 mol%)	K_3PO_4 (1.5 equiv)	70 °C	Toluene/H_2O	
2.	$B(OH)_2$ (1.1 equiv)		RuPhos (10 mol%)		70 °C	Toluene/H_2O	
3.	BPin (2.0 equiv)	$Pd(OAc)_2$ (10 mol%)	RuPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Toluene/H_2O	
4.			XantPhos (15 mol%)		90 °C	Toluene/H_2O	**4.3.33**
5.			XPhos (15 mol%)		90 °C	Toluene/H_2O	**4.3.28**
6.			PPh_3 (15 mol%)		90 °C	Toluene/H_2O	**4.3.32**
7.	BPin (2.0 equiv)	$Pd(OAc)_2$ (10 mol%)	RuPhos (15 mol%)	Cs_2CO_3 (3.0 equiv)	90 °C	Dioxane/H_2O	
8.			XantPhos (15 mol%)		90 °C	Dioxane/H_2O	
9.			XPhos (15 mol%)		90 °C	Dioxane/H_2O	
10.			PPh_3 (15 mol%)		90 °C	Dioxane/H_2O	
11.	$PhB(OH)_2$ (1.1 equiv)	$Pd(OAc)_2$ (5 mol%)	RuPhos (10 mol%)	K_3PO_4 (1.5 equiv)	70 °C	Toluene/H_2O	DP

Conditions: enol tosylate **4.3.33** (0.1 mmol), Ar-BPin (1.1 or 2.0 equiv), $Pd(OAc)_2$ (5 or 10 mol%), ligand (10 or 15 mol%), base (1.5 or 3.0 mmol), toluene or dioxane / water (0.06 M).

*Table 26. Attempted Suzuki-Miyaura cross-coupling with enol tosylate **4.3.33***

The use of methyl ether as a protecting group for alcohol is inconvenient due to the difficulties with the liberation of alcohol and we decided to continue working on substrate with TBS-group. More reaction conditions were screened with enol tosylate **4.3.25** as a starting material (Table 27). Firstly, reactions with

different bases (K_2CO_3, Na_2CO_3, NaOH, KO*t*-Bu) were examined (Table 27, entries 1-4). Only in the presence of KO*t*-Bu, the desired product **4.3.29** was obtained in about 10% NMR yield. Boronic acid was tested as a coupling partner, but no reaction was observed (entries 5-6, 8 and 10). Decreasing the temperature to 80 °C reduced the yield of side product **4.3.24** without increasing the yield of the desired product **4.3.29**.

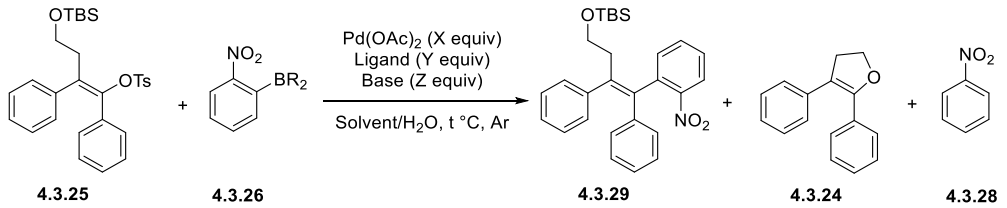


	-BR_2 (2.0 equiv)	[Pd] (10 mol%)	Ligand (15 mol%)	Base (3.0 equiv)	T °C	Solvent (3/1) (0.06 M)	Results[a]
1.	BPin	$Pd(OAc)_2$	RuPhos	**K_2CO_3**	100	Dioxane/H_2O	**4.3.24-5, 4.3.28-9**
2.	BPin	$Pd(OAc)_2$	RuPhos	**Na_2CO_3**	100	Dioxane/H_2O	
3.	BPin	$Pd(OAc)_2$	RuPhos	**NaOH**	100	Dioxane/H_2O	
4.	BPin	$Pd(OAc)_2$	RuPhos	**KO*t*-Bu**	100	Dioxane/H_2O	**4.3.29** 10 %
5.	**$B(OH)_2$**	$Pd(OAc)_2$	RuPhos	K_2CO_3	100	Dioxane/H_2O	
6.	**$B(OH)_2$**	$Pd(OAc)_2$	RuPhos	Na_2CO_3	100	Dioxane/H_2O	**4.3.24,**
7.	BPin	$Pd(OAc)_2$	RuPhos	K_2CO_3	**80**	Dioxane/H_2O	**4.3.25,**
8.	$B(OH)_2$	$Pd(OAc)_2$	RuPhos	K_2CO_3	**80**	Dioxane/H_2O	**4.3.28,**
9.	BPin	$Pd(OAc)_2$	RuPhos	NaOH	**80**	Dioxane/H_2O	**4.3.29**
10.	$B(OH)_2$	$Pd(OAc)_2$	RuPhos	NaOH	**80**	Dioxane/H_2O	

Conditions: enol tosylate **4.3.25** (0.1 mmol), Ar-BR_2 (2.0 equiv), palladium (10 mol%), ligand (15 mol%), base (3.0 mmol), toluene or dioxane / water (0.06 M). [a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 27. Optimization of the Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.3.25***

Using KO*t*-Bu as a base, the conditions were further fine-tuned by systematically varying the organoboron partner, the temperature, the bases, the ligands and the Pd-sources. When pinacol borane **4.3.26** was replaced by boronic acid or organotrifluoroborate salt (Table 28, entries 1-3), the coupling product was formed in reduced yields. Increasing the reaction temperature led to a higher conversion of tosylate **4.3.25** to side-products **4.3.24**. In contrast, decreasing the temperature to 80 °C showed better results, forming product **4.3.29** in 18% yields (entry 4). Further reducing the temperature below 80 °C was detrimental to the reaction (entry 6). The beneficial effect of using KO*t*-Bu as the base was confirmed as replacing it with Na_2CO_3, K_2CO_3, and LiO*t*-Bu delivered the desired product with diminished yields (entries 7-9). When XPhos, XantPhos and PPh_3 were used as ligands, low conversion of the starting material was observed (entries 10-12). The Pd-source played an important role in the reaction. Indeed, the reaction did not take place when $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(dppf)Cl_2$ were used as pre-catalysts (entries 13-15).

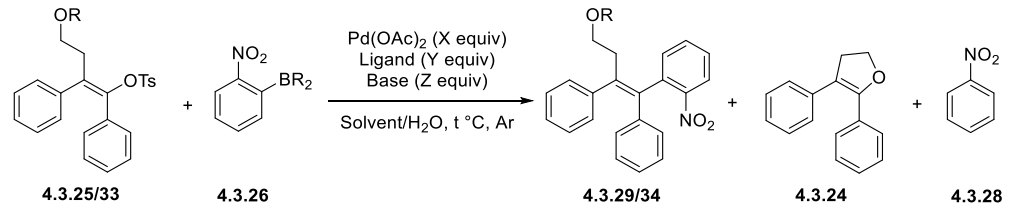


	-BR_2	[Pd]	Ligand	Base	T °C	Solvent (3/1)	**[29]**[a]	**[24]**[a]	**[25]**[a]
1.	**BPin**	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	100	Dioxane/H_2O	10	27	-
2.	**$B(OH)_2$**	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	100	Dioxane/H_2O	9	32	-
3.	**BF_3K**	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	100	Dioxane/H_2O	-	41	-
4.	BPin	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	**80**	Dioxane/H_2O	18	26	-
5.	$B(OH)_2$	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	**80**	Dioxane/H_2O	-	38	-
6.	BPin	$Pd(OAc)_2$	RuPhos	KO*t*-Bu	**70**	Dioxane/H_2O	4	27	-
7.	BPin	$Pd(OAc)_2$	RuPhos	**Na_2CO_3**	100	Dioxane/H_2O	4	13	26
8.	BPin	$Pd(OAc)_2$	RuPhos	**K_2CO_3**	100	Dioxane/H_2O	-	30	-
9.	BPin	$Pd(OAc)_2$	RuPhos	**LiO*t*-Bu**	100	Dioxane/H_2O	4	32	-
10.	BPin	$Pd(OAc)_2$	**XPhos**	KO*t*-Bu	100	Dioxane/H_2O	-	75	-
11.	BPin	$Pd(OAc)_2$	**XantPhos**	KO*t*-Bu	100	Dioxane/H_2O	-	32	46
12.	BPin	$Pd(OAc)_2$	**PPh_3**	KO*t*-Bu	100	Dioxane/H_2O	-	22	71
13.	BPin	**$Pd(PPh_3)_4$**	RuPhos	KO*t*-Bu	80	Dioxane/H_2O	-	-	75
14.	BPin	**$Pd_2(dba)_3$**	RuPhos	KO*t*-Bu	80	Dioxane/H_2O	-	15	15
15.	BPin	**$Pd(dppf)Cl_2$**	RuPhos	KO*t*-Bu	80	Dioxane/H_2O	-	-	70

Conditions: enol tosylate **4.3.25** (0.1 mmol), Ar-BR_2 (2.0 equiv), palladium (10 mol%), ligand (15 mol%), base (3.0 mmol), toluene or dioxane / water (0.06 M). [a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 28. Optimization of the Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.3.25***

Due to the low productive conversion of enol tosylate **4.3.25**, a few more parameters were varied (Table 29). A problem of reproducibility was observed for the reactions with KO*t*-Bu, probably due to the difficulties with weighting this highly hygroscopic reagent. As an alternative solution, KOH was found to promote similar reactivity without reproducibility issues (entry 1). Reducing the amount of base did not improve the outcome (entries 2 and 7). No improvement was noticed when solvents were evaluated. In the absence of water, starting material was only converted to dihydrofuran **4.3.24** (entry 3). Mixture of toluene/water gave no conversion of enol tosylate, which was recovered in 98% yield (entry 4). Performing the reaction in THF/water, the desired product was obtained with similar yields as in dioxane/water, along with a higher formation of side-product **4.3.24** (entry 5). Applying similar conditions to enol tosylate **4.3.33** – afforded desired product in slightly higher 29% yields (entry 6).

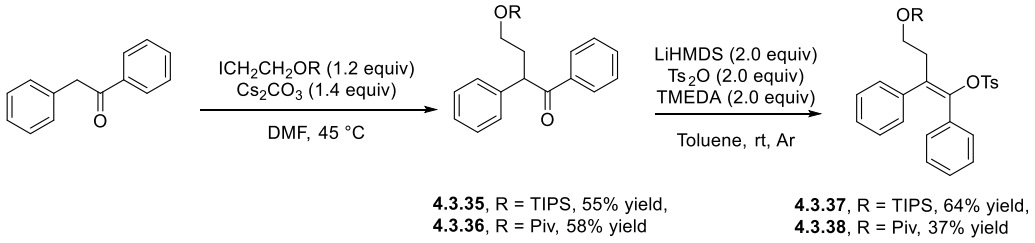


	OR	Base (3.0 equiv)	Solvent (0.06 M)	**[29/32]**[a]	**[24]**[a]	**[25/31]**[a]
1.	-OTBS	KOH	Dioxane/H_2O (3/1)	13	24	-
2.	-OTBS	KOH (2 equiv)	Dioxane/H_2O (3/1)	13	18	-
3.	-OTBS	KO*t*-Bu	Dioxane	-	69	-
4.	-OTBS	KOH	Toluene/H_2O (3/1)	-	-	98
5.	-OTBS	KOH	THF/H_2O (3/1)	12	65	-
6.	-OMe	KOH	Dioxane/H_2O	29	-	46
7.	-OMe	KOH (2 equiv)	Dioxane/H_2O	18	-	67

Conditions: enol tosylate **4.3.25/33** (0.1 mmol), Ar-BR_2 (2.0 equiv), palladium (10 mol%), ligand (15 mol%), base (3.0 mmol), toluene or dioxane / water (0.06 M). [a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

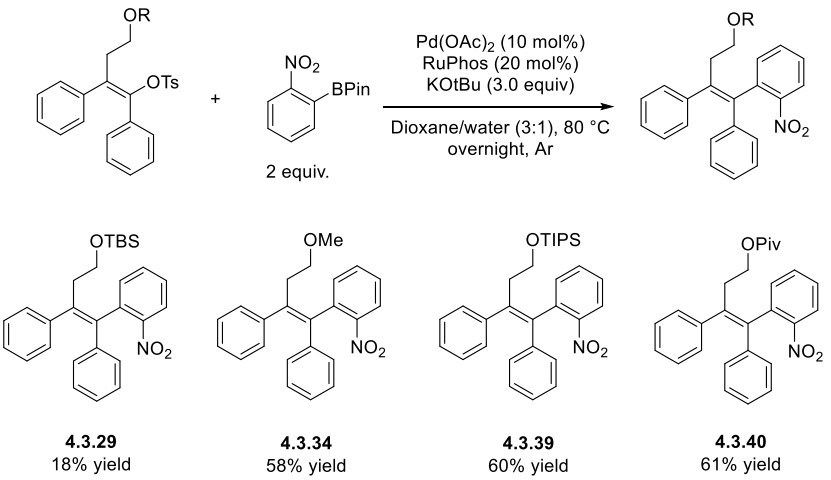
*Table 29. Optimization of the Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.3.25/33** - KOH as a base*

Our efforts to improve the desired transformation were so far ineffective. Our substrate **4.3.25** appeared to be unstable under the majority of the conditions, as the mass-balance at the end of the reaction rarely exceeded 50%. To evaluate the importance of O-protecting group on the reaction outcome, two other substrates in which the primary alcohol was protected as triisopropylsilyl ether (TIPS) **4.3.37** and pivalate (Piv) **4.3.38**, were synthesized in two conventional steps as summarized in Scheme 86.



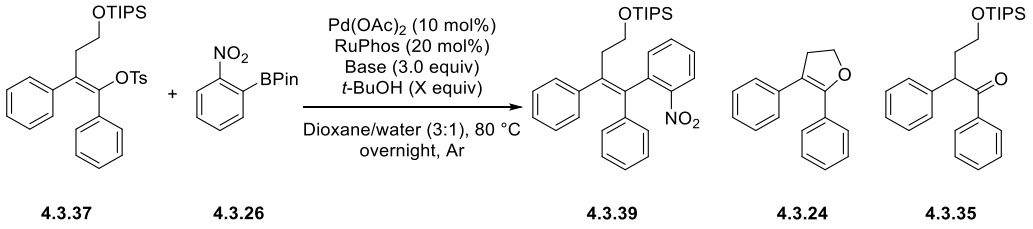
*Scheme 86. Synthesis of enol tosylates **4.3.37** and **4.3.38***

Indeed, by replacing the labile TBS-protecting group with methyl ether, TIPS- and Piv-protecting groups, the yields of the Suzuki-Miyaura coupling increased dramatically (Scheme 87). Performing the reaction in degassed solvent (dioxane/water, v/v= 3:1, *c* 0.06 M) at 80 °C in the presence of $Pd(OAc)_2$ (10 mol%), RuPhos (20 mol%) and KO*t*-Bu (3 equiv) afforded **4.3.34**, **4.3.39** and **4.3.40** in yields of 58%, 60% and 61%, respectively. As the TIPS-derivative showed similar results as others and can be easily deprotected after the Suzuki-Miyaura cross-coupling step, we decided to restrict ourselves to this protecting group.



*Scheme 87. Suzuki-Miyaura cross-coupling reaction with enol tosylates **4.3.25, 4.3.33, 4.3.37-38***

Finally yet importantly, the solvent mixture was examined to further optimize the process. Reducing the relative amount of water in the reaction mixture lead to diminished yields (Table 30, entries 1-3). Knowing that under our conditions, KO*t*-Bu should be hydrolyzed into KOH and *t*-BuOH, we decided to repeat the reaction with the addition of *t*-BuOH. When a solution of dioxane and *t*-BuOH was used, only side products **4.3.24** and **4.3.35** were formed (entry 4). Similar results were obtained when *t*-BuOH was used alone as a solvent (entry 5). However, combination of an equal amounts of KOH and *t*-BuOH let to a good result, desired product was formed in 65% yield (entry 6). The alkene **4.3.39** could be isolated in 60% yield when the reaction was performed on 1 mmol scale highlightig the reproducibility of our conditions.



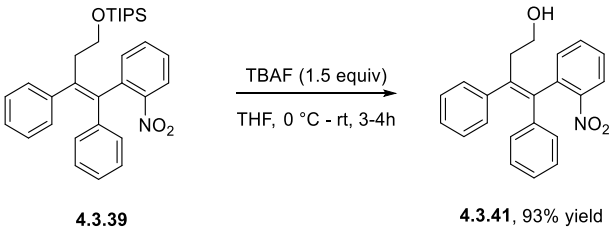
	Base (3.0 equiv)	*t*-BuOH (X equiv)	Solvent (0.06 M)	**4.3.39**[a]	**4.3.24**[a]	**4.3.35**[a]
1.	KO*t*-Bu	-	Dioxane/H_2O (3/1)	67	7	24
2.	KO*t*-Bu	-	Dioxane/H_2O (4/1)	55	16	25
3.	KO*t*-Bu	-	Dioxane/H_2O (6/1)	41	21	22
4.	KO*t*-Bu	-	Dioxane/ *t*-BuOH (3/1)	-	17	22
5.	KO*t*-Bu	-	*t*-BuOH	-	38	28
6.	KOH	3 equiv	Dioxane/H_2O (3/1)	65	12	20
7.	KOH	3 equiv	Dioxane/H_2O (4/1)	34	15	24
8.*	KOH	3 equiv	Dioxane/H_2O (3/1)	60	-	-

*1 mmol of enol tosylate **4.3.37.** Conditions: enol tosylate **4.3.37** (0.1 mmol), Ar-BR_2 (2.0 equiv), palladium (10 mol%), ligand (15 mol%), base (3.0 mmol), toluene or dioxane / water (0.06 M). [a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 30. Optimization of the Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.3.37** - solvents and additives*

In conclusion, the optimum conditions consisted of performing the reaction of **4.3.37** in the mixture dioxane/H_2O (c 0.06 M) in the presence of KOH (3 equiv) and *t*-BuOH (3 equiv), a catalytic amount of

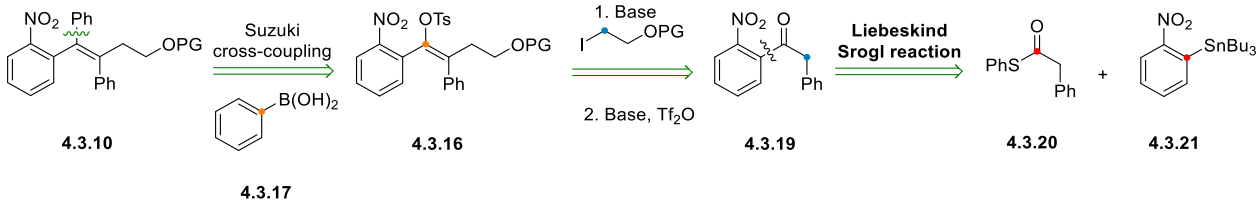
$Pd(OAc)_2$ (10 mol%) and RuPhos (20 mol%) at 80 °C under argon atmosphere. The final deprotection of the alcohol was straightforward. The silyl ether **4.3.41** was cleaved with TBAF solution in THF at room temerature to give the desired product in 83% yield on small scale and 93% yield on 0.9 mmol scale (Scheme 88).



*Scheme 88. Deprotection of alcohol **4.3.39***

2nd synthetic pathway

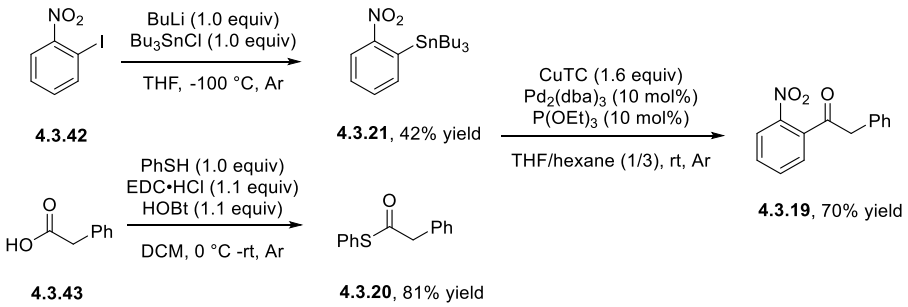
Due to the apparent complexity of the Suzuki-Miyaura cross-coupling reaction, we worked in parallel on another strategy, based on the coupling of enol tosylate **4.3.16**, containing an (*ortho*-nitroaryl) substituent, and phenylboronic acid **4.3.17** (Scheme 89). In this case, we expected a matched reactivity, as our organoboron reagent would be electron-neutral and vinyl pseudohalide **4.3.16** would be electron-poor, thanks to the *ortho*-nitroaryl group. The latter was disconnected to the ketone **4.3.19** through a similar sequence of steps: alkylation and tosylation. Having experience with the Liebeskind-Srogl reaction, we imagined that the desired ketone could be synthesized starting with thioester **4.3.20** and tributyl(2-nitrophenyl)stannane **4.3.21**.



*Scheme 89. 2nd synthetic pathway torwards the synthesis of tetrasubstitute olefine **4.3.10***

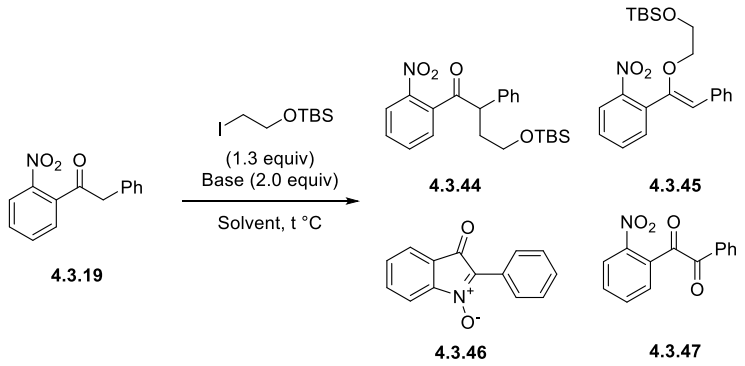
The first precursor for the Liebeskind Srogl reaction – organostannane **4.3.21** was synthesized based on a literature report.[259] The treatment of 1-iodo-2-nitrobenzene **4.3.42** at -100 °C in THF with BuLi followed by quenching with tributyltin chloride afforded compound **4.3.21** in 42% yield (Scheme 90). At the same time, the thioesterification of phenylacetic acid **4.3.43** with thiophenol using EDC*HCl as activating agent gave the thioester **4.3.20** in 81% yield. We then turned our attention toward the Liebeskind-Srogl reaction. Applying conditions optimized for the total synthesis of trigonoliimine C, we could obtain the desired ketone **4.3.19** in 70% yield. Knowing that CuDPP can sometimes give better results than CuTC, the reaction with CuDPP was tested in parallel, however, a lower yield was obtained.

[259] Izgu, E.C.; Hoye, T.R. *Tetrahedron Lett.* **2012**, *53*, 4938 – 4941.



*Scheme 90. Liebeskind-Srogl reaction with thioester **4.3.20***

The next step was to perform the alkylation with TBS-protected 2-iodoethanol, however, the starting material was found to be unstable under basic conditions. Different bases were tested: Cs_2CO_3, Li_2CO_3, K_2CO_3, LiHMDS and NaH (Table 31). Weak bases such as Cs_2CO_3, Li_2CO_3, K_2CO_3, K_3PO_4 led to poor conversion at room temperature. Upon increase of the temperature to 45 °C, several side-products were isolated. In the case of Cs_2CO_3, along with the desired ketone **4.3.44**, O-alkylation (**4.3.45**), cyclization (**4.3.46**) and oxidation product (**4.3.47**) were isolated (Table 31, entry 1). With Li_2CO_3 or K_2CO_3 only side-products **4.3.46** and **43.47** were isolated (DMF - entry 2-3, THF - entry 5-6). When the reaction was performed in THF, the temperature was increased to 60 °C to improve conversion. No traces of ketone **4.3.44** were observed, when K_3PO_4 was used (entry 4). The use of strong bases did not change the outcome. LiHMDS gave only products **4.3.46** and **4.3.47** (entry 7), while the instantaneous decomposition of starting material was observed when NaH was used as a base in THF (entry 8).

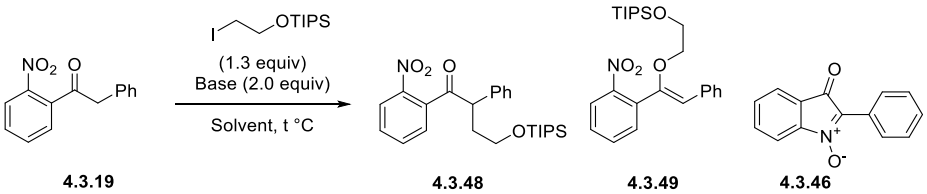


	Base	Solvent	T °C	Results
1.[a]	Cs_2CO_3	DMF	rt – > 45°C	**4.3.44** (35 %), **4.3.45** (17%), **4.3.46** and **4.3.47**
2.	Li_2CO_3	DMF	rt – > 45°C	**4.3.46** and **4.3.47**
3.	K_2CO_3	DMF	rt – > 45°C	**4.3.46** and **4.3.47**
4.	K_3PO_4	DMF	rt – > 45°C	**4.3.45** (17%), **4.3.46** and **4.3.47**
5.	Li_2CO_3	THF	rt – > 45°C -> 60 °C	**4.3.46** and **4.3.47**
6.	K_2CO_3	THF	rt – > 45°C -> 60 °C	**4.3.46** and **4.3.47**
7.	LiHMDS	THF	-78 °C – 0 °C – rt	**4.3.46** and **4.3.47**
8.	NaH	THF	0 °C - rt	Decomposition

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 31. Attempted alkylation of ketone **4.3.19***

The fast formation of diketone **4.3.47** revealed the instability of our starting material towards oxygen and required the use of degassed solvents using Freeze-Pump-Thaw Cycling technique. Cs_2CO_3 showing promising results was selected as a base for the reaction with the more stable TIPS-protected 2-iodoethanol (Table 32). Performing the reaction with 1.3 equiv of Cs_2CO_3 and 1.5 equiv of the alkylating agent at 40 °C in DMF yielded desired ketone **4.3.48** in 25% yield (entry 1) along with products of O-alkylation **4.3.49** (11%), cyclization **4.3.46** (7%) and decomposition. Increasing the amount of alkylating partner to 2.5 equivalents improved the yield to 35% (entry 2). The temperature was found to play an important role. Indeed, when the reaction temperature was decreased to room temperature, **4.3.48** was accessed in 45% yield (entry 3). However, only 30% of product **4.3.48** was obtained at 0 °C (entry 4). Changing the base amount did not influence the result (entries 5-6), nor did the reaction mixture dilution (entry 7). Noteworthy, in all cases apart at 0 °C (entry 4), no more starting material was observed after a few hours. The starting material was slowly decomposing under the applied conditions leading to a low mass-balance. For entry 4, the prolongation of the reaction did not increase the conversion of the starting material.

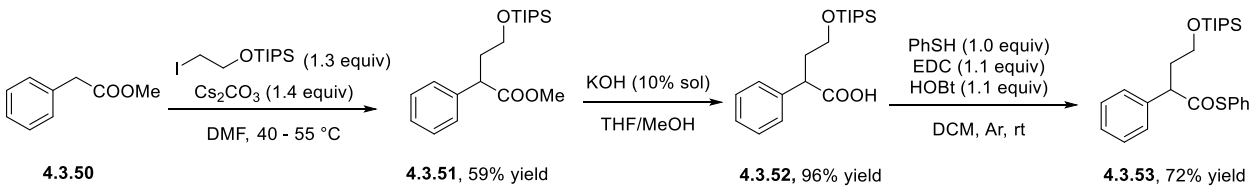


	Base	Alk-I	Solvent[b]	T °C	**4.3.48**[a]	**4.3.49**[a]	**4.3.46**[a]
1.	Cs_2CO_3 (1.3 equiv)	1.5 equiv	DMF	40 °C	25%	11%	7%
2.	Cs_2CO_3 (1.3 equiv)	**2.5** equiv	DMF	40 °C	35%	16%	-
3.	Cs_2CO_3 (1.3 equiv)	2.5 equiv	DMF	**rt**	45%	13%	-
4.	Cs_2CO_3 (1.3 equiv)	2.5 equiv	DMF	**0 °C**	30%	9	-
5.	Cs_2CO_3 (**1.0** equiv)	2.5 equiv	DMF	rt	33%	11%	-
6.	Cs_2CO_3 (**2.0** equiv)	2.5 equiv	DMF	rt	30%	9%	-
7.	Cs_2CO_3 (1.3 equiv)	2.5 equiv	DMF **(diluted)**	rt	42%	16%	-

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard. [b] Freeze-Pump-Thaw Cycling technique

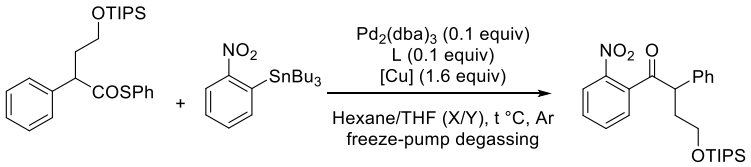
*Table 32. Optimization of alkylation of ketone **4.3.19***

As both ketone **4.3.19** and possibly the product of alkylation **4.3.48** were not stable under basic conditions, we decided to change the order of reactions in which the desired product was synthesized. The idea was to perform the alkylation step before the Liebeskind-Srogl reaction to prevent stability issues. To do so, we started with the alkylation of methyl ester **4.3.50**. Under the optimized conditions, the reaction worked in 59% yield (Scheme 91). Saponification of the ester **4.3.51** afforded acid **4.3.52** in quantitative yield. The latter was then transformed into thioester **4.3.53** in 72% yield under the same conditions mentioned above.



*Scheme 91. Conversion of methyl ester **4.3.50** into thioester **4.3.53***

Thioester **4.3.53** was next subjected to the Liebeskind-Srogl coupling at room temperature. Under these conditions, only a limited amount of the thioester was converted into product **4.3.54**, the rest remaining untouched (Table 33, entry 1). The reaction was performed overnight and stopped when no more conversion was detected. Increasing the temperature to 40 °C and 50 °C improved the yields to 50% and 57% (entries 2-3). The polarity of the solvent played a crucial role to the success of the reaction. In general, the use of apolar solvent mixture is preferred, as it reduces the speed of protodestannation. However in the present case, increasing the amount of hexane (v/v THF/hexane = 1/6) reduced the reaction efficiency affording product in 49% yield (entry 5), while reducing the THF/hexane ratio from 1/3 to 1/1 gave product **4.3.54** in an excellent 73% yield (entry 4). The reaction with 1/1 ratio of solvents was repeated and the desired product was isolated in 71% yield (entry 6). Changing the Cu source to CuDPP at room temperature increased the yield from 25% to 52% yield under otherwise identical conditions (entry 7). The source of Pd and ligand did not improve the reaction outcome (entries 8-9). Comparing the two approaches, the second pathway towards ketone **4.3.54** wins in terms of overall yield and simplicity of procedures.



4.3.53 **4.3.21** 2 equiv **4.3.54** 71% yield

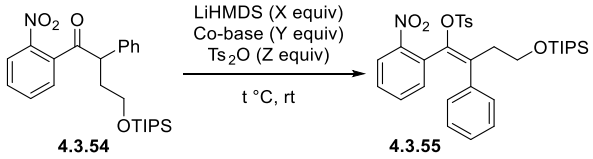
	[Pd]	L	[Cu]	THF/hexane[b]	T °C	**4.3.54**[a]	**4.3.53**[a]
1.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	1/3	rt	25%	65%
2.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	1/3	**40 °C**	50%	14%
3.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	1/3	**50 °C**	57%	-
4.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	**1/6**	rt	49%	46%
5.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	**1/1**	rt	73%	20%
6.	$Pd_2(dba)_3$	$P(OEt)_3$	CuTC	**1/1**	rt	71%	15%
7.	$Pd_2(dba)_3$	$P(OEt)_3$	**CuDPP**	1/3	rt	52%	19%
8.	$Pd_2(dba)_3$ **(different source)**	$P(OEt)_3$	CuTC	1/3	rt	43%	30%
9.	$Pd_2(dba)_3$	**$AsPh_3$**	CuTC	1/3	rt	33%	49%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard. [b]Freeze-Pump-Thaw Cycling technique

*Table 33. Optimization of Liebeskind-Srogl reaction with thioester **4.3.53***

From ketone **4.3.54**, enol tosylate **4.3.55** should be synthesized. Remembering that our starting material is potentially not stable under basic conditions and oxygen, we started the optimization of the next step directly under an inert atmosphere. Applying conditions, which worked efficiently for substrate **4.3.22**, produced the desired product **4.3.55** with only 12% yield along with significant decomposition of precursor (Table 34, entry 1). Gosselin's conditions did not improve the situation (entry 2-3). Replacing the co-base with any other amine (e.g. Et_3N), and removing the co-base from the reaction, led to the complete decomposition of the starting material (entries 4-5). Shorting the time of premixing of ketone and bases gave similar results (entries 6-7). Decreasing the temperature to 0 °C and to -12 °C, had a positive impact on the reaction, the desired product was formed in 40% yield with 3.0 equiv of base and 50% when 2.0 equiv of the base were used (entries 10 and 12). To maintain the reaction, the premixing time was increased to 1.5 h at low temperatures. Further decrease of temperatures to -40 °C and -78 °C led to the recovery of

starting material. Unfortunately, enol tosylate **4.3.55** was not stable on silica gel, even with basified chromatography column used, the final product was isolated in 25% yield instead of 50%.

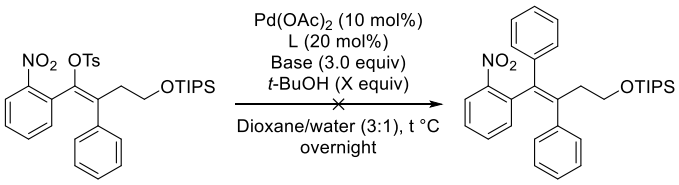


	LiHMDS	Co-base	Ts_2O	T °C	Premixing **XX+bases**	**4.3.55**[a]
1.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	rt	30 min	12%
2.	2.0 equiv	TMEDA (**2.0** equiv)	**2.0** equiv	rt	30 min.	20%
3.	2.0 equiv	TMEDA (**5.0** equiv)	**2.0** equiv	rt	30 min.	16%
4.	3.0 equiv	**Et_3N** (3.0 equiv)	3.0 equiv	rt	30 min.	Decomposition
5.	3.0 equiv	-	3.0 equiv	rt	30 min.	Decomposition
6.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	rt	**10 min.**	17%
7.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	rt	**20 min.**	<10%
8.	**2.0** equiv	TMEDA (**5.0** equiv)	**3.0** equiv	0 °C	30 min.	25%
9.	**2.0** equiv	TMEDA (**5.0** equiv)	-	0 °C		Stable
10.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	0 °C	1h	40%
11.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	-12 °C	1.5h	23%
12.	**2.0** equiv	TMEDA (**5.0** equiv)	**3.0** equiv	-12 °C	1.5h	50%
13.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	-40 °C	1.5h	No reaction
14.	3.0 equiv	TMEDA (3.0 equiv)	3.0 equiv	-78 °C	1.5h	No reaction

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard. [b]Freeze-Pump-Thaw Cycling technique

*Table 34. Optimization of tosylation of ketone **4.3.54***

With enol tosylate **4.3.55** in hands, we moved to the optimization of the Suzuki-Miyaura cross-coupling with phenylboronic acid. The reaction was firstly set-up under an inert atmosphere with a catalytic amount of $Pd(OAc)_2$ (10 mol%), RuPhos (20 mol%), KOH (3 equiv) and *t*-BuOH (3 equiv) as an additive in a mixture of solvent (dioxane/water, v/v = 3:1, *c* 0.06 M) at 80 °C. However, no conversion to the desired product **4.3.39** was observed (Table 35, entry 1). Increasing the temperature to 90, 100 and 110 °C leads to slow decomposition. Unfortunately, no reaction was observed with different ligands and bases (entries 5-11). At this time, the first strategy to synthesize desired tetrasubstituted alkene bearing a *o*-nitrophenyl substituent **4.3.39** was accomplished and we moved to the optimization of the key step.



4.3.55 **4.3.39**

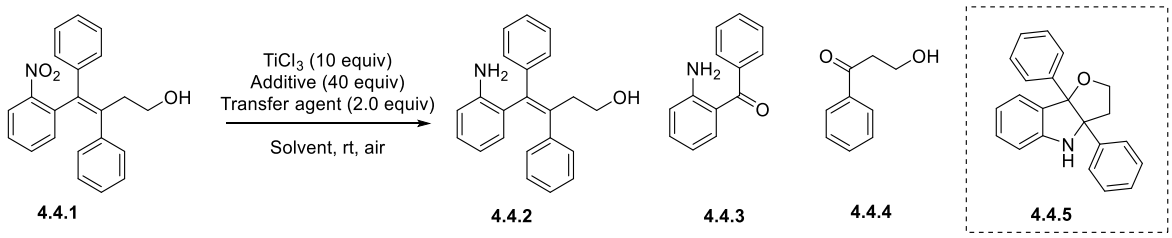
	L	Base	*t*-BuOH	T °C	Results
1.	RuPhos	KOH	3 equiv	80 °C	
2.	RuPhos	KOH	3 equiv	**90** °C	
3.	RuPhos	KOH	3 equiv	**100** °C	
4.	RuPhos	KOH	3 equiv	**110** °C	
5.	**XPhos**	KOH	3 equiv	80 °C	No reaction, slow decomposition
6.	**PPh_3**	KOH	3 equiv	80 °C	
7.	**TFP**	KOH	3 equiv	80 °C	
8.	RuPhos	**Cs_2CO_3**	-	80 °C	
9.	RuPhos	**KOH**	-	80 °C	
10	RuPhos	**K_3PO_4**	-	80 °C	
11.	RuPhos	**CsF**	-	80 °C	

*Table 35. Optimization of the Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.3.55***

4.4. **Optimization of the key reaction**

With precursor **4.4.1** in hand, we turned our attention towards the optimization of the key-transformation, various conditions were tested to affect the reductive cyclization of *o*-nitrostyrenes. Unfortunately, under a variety of conditions, varying solvents (Table 36, entries 1-12), concentrations (entries 1-4), phase transfer agents (entries 5-6) and additives (entries 7-12), the desired tricyclic compound **4.4.5** was not formed. Instead, aniline **4.4.2** and products of oxidative cleavage of the double bond were identified. The isolation of compounds **4.4.3** and **4.4.4** was interesting, as our conditions are not oxidative. The observed process is opposite to the known McMurry reaction.[260,261]

[260] Furstner, A.; Bogdanovic, B. *Angew Chem. Int. Ed.* **1996**, *35*, 2442 – 2469.
[261] Banwell, M.G. *Encyclopedia of Reagents for Organic Synthesis* **2001**, 1 – 2.



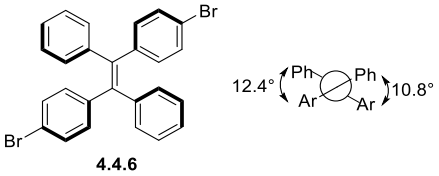
4.4.1 4.4.2 4.4.3 4.4.4 4.4.5

	Additive	Transfer agent	Solvent	**4.4.2**[a]	**4.4.3**[a]	**4.4.4**[a]
1.	-	-	MeCN (0.1 M)	20%	-	-
2.	-	-	MeCN (0.05 M)	27%	-	-
3.	-	-	Acetone (0.1 M)	30%	-	-
4.	-	-	Acetone (0.05 M)	36%	20%	18%
5.	-	SDS (2 equiv)	MeCN (0.1 M)	40%	14%	22%
6.	-	SDS (2 equiv)	Acetone (0.1 M)	60%	-	-
7.	HCOONa	-	MeCN (0.1 M)	-	56%	34%
8.	HCOONa	-	Acetone (0.1 M)	32%	30%	32%
9.	NH_4OAc	-	MeCN (0.1 M)	30%	22%	30%
10	NH_4OAc	-	Acetone (0.1 M)	32%	27%	31%
11.	NH_4OAc	SDS (2 equiv)	MeCN (0.1 M)	30%	28%	23%
12.	NH_4OAc	SDS (2 equiv)	Acetone (0.1 M)	75%	-	-

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 36. Attempted reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1***

The overcrowded surrounding of the tetrasubstituted double bond makes it more destabilized due to the steric hindrance and eclipsing interactions of the orbitals in the double bond. For example, the tetraaryl-substituted alkene **4.4.6** has an 11-12° deviation from planarity (confirmed by X-ray, Figure 10).[262]



4.4.6

*Figure 10. The structure of a tertasubstituted alkene **4.4.6***

It is well known in the literature that different transition metals can oxidize double bonds in combination with co-oxidants. Wacker process,[263] Ru- catalyzed oxidation,[264,265,266] Os-catalyzed oxidation

[262] Daik, R.; Feast, W. J.; Batsanov, A. S.; Howard, J. A. K. *New J. Chem*. **1998**, 1047.
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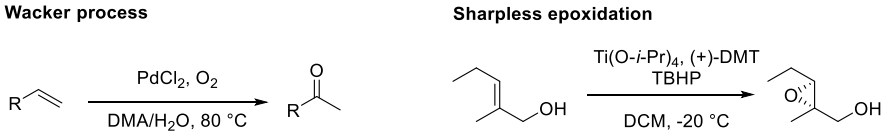
(e.g. Sharpless and Upjohn dihydroxylation),[267,268] Ti-catalyzed Sharpless epoxidation,[269] or Mn-catalyzed Jacobsen epoxidation,[270] are largely used reactions (Scheme 92).[271]



Scheme 92. Metal-catalyzed oxidation of double bonds

Different research groups worked on the development of efficient and active catalytic systems for the oxidative cleavage of double bonds. Unfortunately, in most cases expensive and "nongreen" oxidants are required. The use of molecular oxygen for the oxidation of carbon-carbon double bonds to the corresponding carbonyl compounds is a highly desirable alternative.[272] During the last decades different reports were published concerning the use of oxygen together with transition metals[273] (e.g. Fe,[274] Ru,[275] Pd,[276] Co,[277,278,279,280,281] Cu,[282] Mn[283,284]) in oxidative transformations of alkenes.

Titanium complexes are considered as effective catalysts for the oxidation of olefins, as exemplify by the Sharpless epoxidation with Ti^{IV}-complexes, where tert-butyl hydroperoxide or Ti-silicates (titanosilsesquioxanes and titanosiloxanes) are used as co-oxidant.[285] Hydroperoxo and alkyl peroxo complexes of Ti^{IV} are considered as reactive species, while $Ti^{IV}\eta^2$-peroxo complexes are considered inactive in the oxidative process (Scheme 93).[286] The precise structure of the active site remains unclear in most cases.[287] Once an active Ti-complex is formed, the alkene accepts an oxygen atom from this intermediate.[288,289,290] The energy barrier of oxidation decreases in the order: acyclic double bond > cyclic double bond, along with the increase of the HOMO of alkene. Computational studies showed that the α-

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[284] Chen, H.; Ji, H.; Zhou, X.; Xu, J.; Wang, L. *Catal. Commun.* **2009**, *10*, 828.
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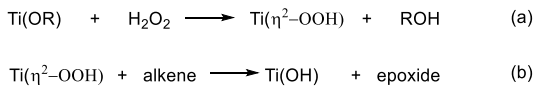
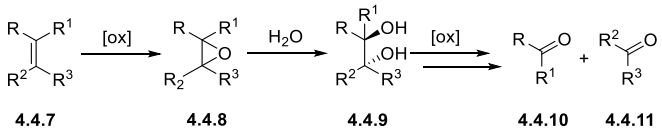
oxygen atom in alkyl peroxo complexes of Ti^{IV} is responsible for the attack on the double bond over the β-oxygen center.



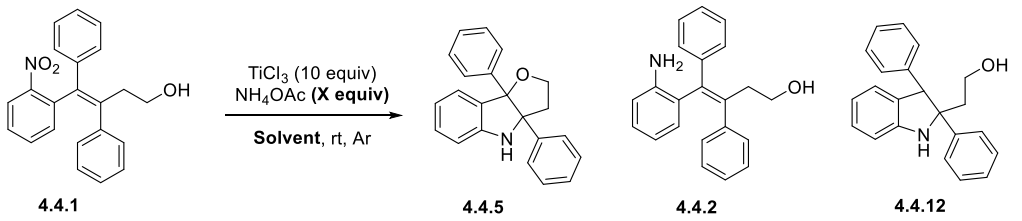
Scheme 93. Oxidation of alkenes with Ti(IV)

In our case, we believe that the oxidation of compound **4.4.7** could proceed with a tandem use of Ti^{IV} and oxygen. Ti^{III} is known to be unstable under aerobic conditions and can be slowly oxidized in the presence of molecular oxygen to Ti^{IV}. It is possible that under our acidic conditions (2.0 N HCl), the molecular oxygen could either directly react with the alkene catalyzed by the Ti^{IV} (coordination and activation of a double bond), or could be reduced to a peroxide and oxidize the double bond in the form of a hydroperoxy complexe of Ti. Most probably, the process begins with the formation of an epoxide **4.4.8**, which would be then transformed into a diol **4.4.9** by nucleophilic opening with a molecule of water (Scheme 94). A subsequent oxidation would deliver **4.4.10** and **4.4.11**.



*Scheme 94. Plausible mechanism of the Ti-mediated oxidation of olefin **4.4.7***

To avoid the oxidative cleavage of the double bond, we decided to degas the $TiCl_3$ solution and solvents with the Freeze-Pump-Thaw Cycling technique. Indeed resubmitting the starting material **4.4.1** to inert conditions fully inhibited the formation of side-products **4.4.3** and **4.4.4** (Table 37). Performing the reaction in acetonitrile or acetone resulted only in the formation of aniline **4.4.2** (entries 1-2). Slight modifications were then applied to these standard conditions. Keeping acetonitrile as a solvent, ammonium acetate was added to the reaction mixture in different amounts. Encouraging results were obtained with 1 to 6 and 1 to 8 ratio between $TiCl_3$ and additive at 0.1 M concentration. The desired product **4.4.5** was finally obtained in 10% and 15% NMR yield, respectively (entries 6-7). The dilution of the reaction mixture to 0.05 M concentration in acetonitrile led to similar results with the indoline **4.4.5** formed in 15% yield. An interesting side-product **4.4.12** was isolated in some cases (entries 6-8), resulting from the reductive opening of the tetrahydrofuran ring.



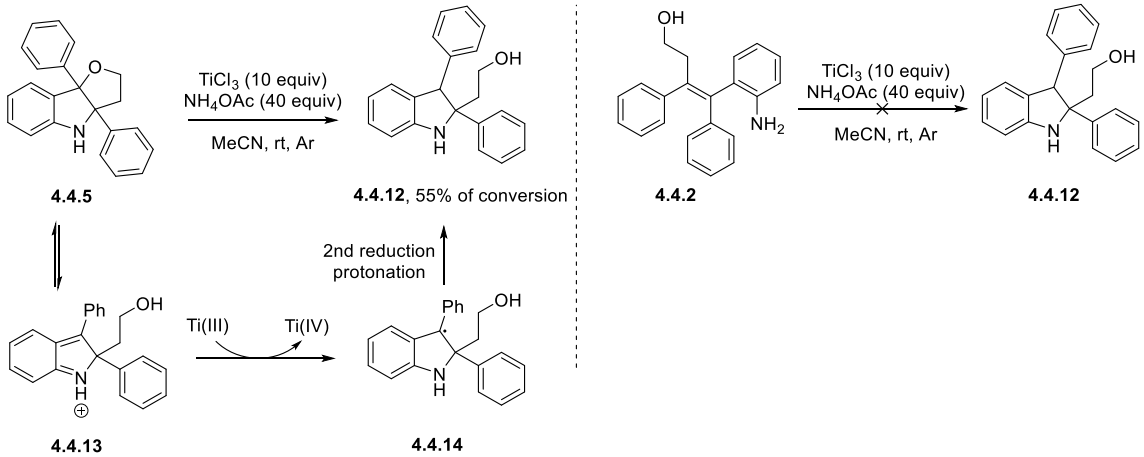
4.4.1 4.4.5 4.4.2 4.4.12

	Ti	Additive	Solvent	**4.4.5**[a]	**4.4.2**[a]	**4.4.12**[a]
1.	10 equiv	-	MeCN (0.1 M)		29%	
2.	10 equiv	-	Acetone (0.1 M)		17%	
3.	10 equiv	NH_4OAc (10 equiv)	MeCN (0.1 M)			
4.	10 equiv	NH_4OAc (20 equiv)	MeCN (0.1 M)		25%	
5.	10 equiv	NH_4OAc (40 equiv)	MeCN (0.1 M)		31%	
6.	10 equiv	NH_4OAc (60 equiv)	MeCN (0.1 M)	10%	58%	30%
7.	10 equiv	NH_4OAc (80 equiv)	MeCN (0.1 M)	15%	57%	30%
8.	10 equiv	NH_4OAc (40 equiv)	MeCN (0.05 M)	15%	20%	10%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 37. Optimization of the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1***

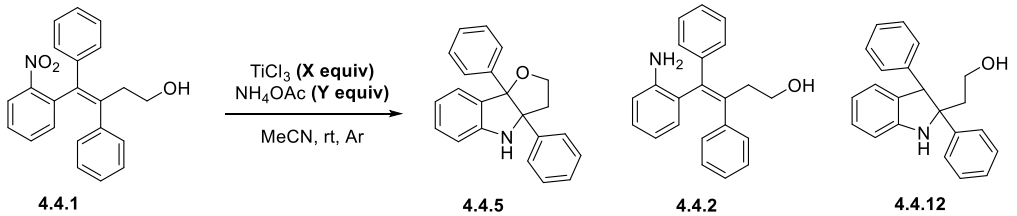
To understand the nature of compound **4.4.12**, we decided to submit our desired product **4.4.5** and aniline **4.4.2** to the same reductive conditions and see if one of them will be transformed into this side-product **4.4.12** (Scheme 95). We observed that the 3*H*-indoline **4.4.12** is formed from our desired product **4.4.5**. Therefore, for the following optimization, the yields of compounds **4.4.5** and **4.4.12** will be counted together. We believe that furo[3,2-*b*]indoline **4.4.5** is in equilibrium with the open form **4.4.13**. It is possible that Ti(III) can reduce this protonated intermediate to its radical form **4.4.14** and later to the carboanion, which can trap a proton from the reaction media to give 3*H*-indoline **4.4.12.**



Scheme 95. Reductive opening of the tetrahydrofuran ring

Testing different amounts of Ti, it was found that with 20 equiv of reducing agent, the mixture of desired product **4.4.5** and side-product **4.4.12** could be obtained in slightly higher yields 51% (Table 38,

entry 2). However, further increase of the $TiCl_3$ amount indeed improved the results but only to 58% yield (entry 3). Therefore, since the difference was not significant, we decided to continue with 20 equiv.



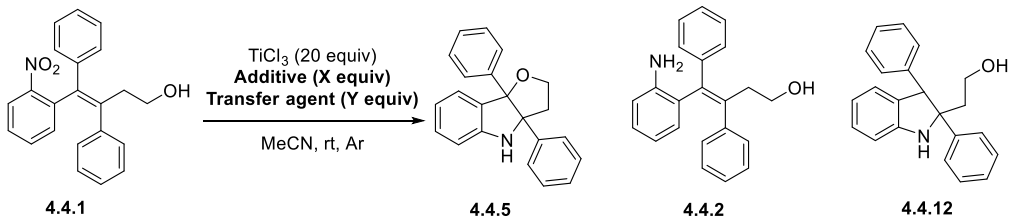
4.4.1 4.4.5 4.4.2 4.4.12

	Ti	Additive	Solvent	**4.4.5**[a]	**4.4.2**[a]	**4.4.12**[a]	**4.4.5 + 4.4.12**[a]
1.	10 equiv	NH_4OAc (40 equiv)	MeCN (0.05 M)	15%	20%	10%	25%
2.	20 equiv	NH_4OAc (80 equiv)	MeCN (0.05 M)	21%	30%	30%	51%
3.	50 equiv	NH_4OAc (200 equiv)	MeCN (0.01 M)	16%	38%	42%	58%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 38. Optimization of $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1** – $TiCl_3$ amount*

Regarding the amount of additive, no improvement was observed when the amount of ammonium acetate was increased. On the contrary, the yield for the desired product **4.4.5** slowly decreased (Table 39, entry 1-4). The dilution of the reaction mixture could not help this time. With 160 equiv of NH_4OAc, the mixture of desired products was formed in a similar 59% yield (entry 6). To improve the yield, a variety of additives were tested. The replacement of NH_4OAc by NH_4OOCH, NH_4Cl, NaI or NaOAc led to the decomposition of the starting material (entry 7-10). The addition of a phase transfer agent, i.e. SDS, gave similar results as before (entries 11-12).



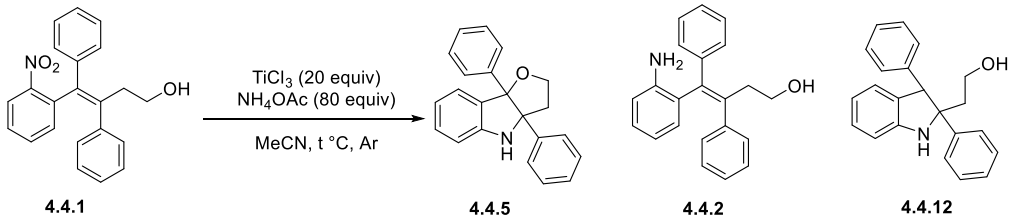
4.4.1 4.4.5 4.4.2 4.4.12

	Additive	Transfer agent	Solvent	**4.4.5**[a]	**4.4.2**[a]	**4.4.12**[a]	**5+12**[a]
1.	NH_4OAc (80 equiv)	-	MeCN (0.05 M)	21%	30%	30%	51%
2.	NH_4OAc (100 equiv)	-	MeCN (0.05 M)	12%	45%	28%	40%
3.	NH_4OAc (120 equiv)	-	MeCN (0.05 M)	8%	50%	25%	33%
4.	NH_4OAc (160 equiv)	-	MeCN (0.05 M)	-	50%	37%	37%
5.	NH_4OAc (80 equiv)	-	MeCN (0.01 M)	-	14%	4%	4%
6.	NH_4OAc (160 equiv)	-	MeCN (0.01 M)	24%	33%	35%	59%
7.	NH_4OOCH (80 equiv)	-	MeCN (0.05 M)	-	24%	-	-
8.	NH_4Cl (80 equiv)	-	MeCN (0.05 M)	-	50%	-	-
9.	NaI (80 equiv)	-	MeCN (0.05 M)	-	98%	-	-
10.	NaOAc (80 equiv)	-	MeCN (0.05 M)	15%	65%	13%	28%
11.	-	SDS (2 equiv)	MeCN (0.05 M)	-	45%	-	-
12.	NH_4OAc (80 equiv)	SDS (2 equiv)	MeCN (0.05 M)	22%	30%	25%	47%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 39. Optimization of the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1** - additives*

The temperature played an essential role in our reaction. Indeed, when the reaction temperature was decreased to 0 °C and -10 °C, the reaction yield increased respectively to 43% and 52% (Table 40, entries 1-2). However, lower temperature (-20 °C) leads to only 36% yield. Gratifyingly, under the presented conditions, further reduction of the desired tricyclic furoindoline into indoline side-product **4.4.12** was inhibited.



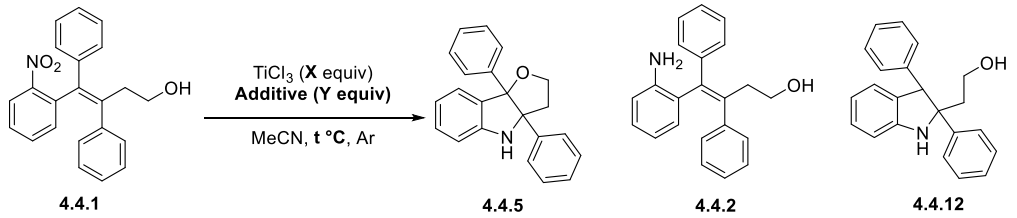
4.4.1 4.4.5 4.4.2 4.4.12

	Additive	Transfer agent	T °C	**4.4.5**[a]	**4.4.2**[a]	**4.4.12**[a]	**5+12**[a]
1	20 equiv	NH_4OAc (80 equiv)	rt	21%	30%	30%	50%
2	20 equiv	NH_4OAc (80 equiv)	0 °C	43%	20%	5%	43%
3	20 equiv	NH_4OAc (80 equiv)	-10 °C	52%	40%		52%
4	20 equiv	NH_4OAc (80 equiv)	-20 °C	36%	31%		36%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 40. Optimization of the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene **4.4.1** - temperature*

To decrease the amount of reducing agent, a reaction with 15 equiv of $TiCl_3$ was tested. At room temperature, similar results were observed as with 20 equiv and products **4.4.5** and **4.4.12** were formed in 47% yield (Table 41, entry 1). As before, by performing the reaction at -10 °C, we could increase the yield to 63% yield (entry 2). However, at the same temperature, with only 10 equiv of $TiCl_3$, furo[3,2-*b*]indoline **4.4.45** was obtained in only 55% yield (entry 4). With the main parameters of the reaction being optimized, we decided to try a few special conditions. As shown in Table 41, for the presented transformation, it is necessary to use additive to increase the yield. To improve our results, we wanted to see if adding any external base (amine) and basifying the reaction mixture could enhance the yield of the desired product. Unfortunately, the addition of Bu_4NOAc or Et_3N only increased the formation of aniline (entries 5-7). Our general reaction set-up requires that a 1.3 M solution of $TiCl_3$ in 2.0 M HCl is slowly added to the solution of starting material and additive in acetonitrile at 0 °C. Notably, NH_4OAc is not very soluble in acetonitrile. Attempt to add water to the reaction mixture to solubilize the additive before the addition of the $TiCl_3$ proved to be inefficient.



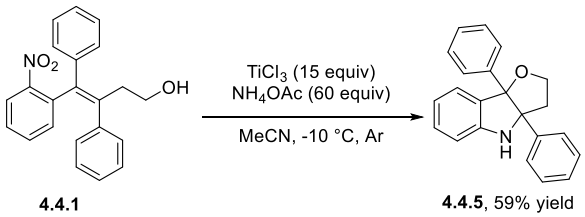
4.4.1 4.4.5 4.4.2 4.4.12

	Ti	Additive	T °C	**5**[a]	**2**[a]	**12**[a]	**5+12**[a]
1.	15 equiv	NH_4OAc (60 equiv)	rt	22%	30%	25%	47%
2.	15 equiv	NH_4OAc (60 equiv)	-10 °C	63%	25%	-	63%
3.	15 equiv	NH_4OAc (60 equiv)	-20 °C	50%	39%	-	50%
4.	10 equiv	NH_4OAc (40 equiv)	-10° C	55%	27%	-	55%
5.	15 equiv	Bu_4NOAc (60 equiv)	-10 °C	-	98%	-	-
6.	15 equiv	NH_4OAc (60 equiv) Et_3N (10 equiv)	-10 °C	15%	75%	-	15%
7.	15 equiv	Et_3N (60 equiv)	-10 °C	-	91%	-	-
8.	15 equiv	NH_4OAc (60 equiv), H_2O	-10 °C	48%	50%	-	48%

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

*Table 41. Optimization of the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1** - temperature and bases*

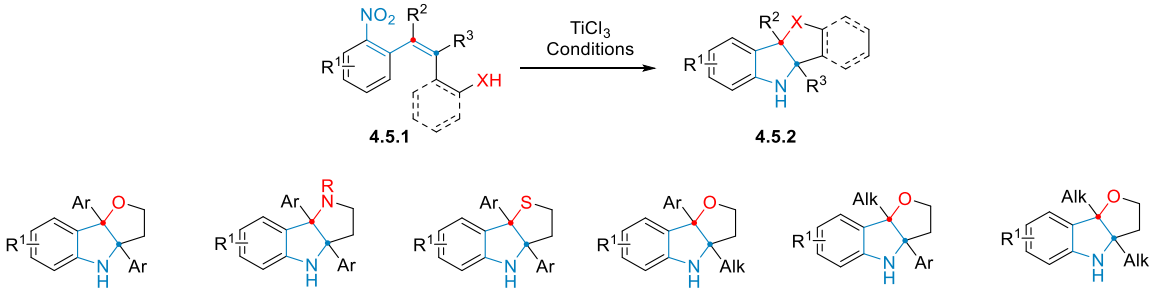
Finally, the optimal conditions consisted of the slow addition of 15 equiv of $TiCl_3$ solution to the reaction mixture containing the starting material **4.4.1** and NH_4OAc (60 equiv) in freshly degassed acetonitrile (0.05 M) at -10 °C (Scheme 96). The reaction was stirred at -10 °C for 3h. Under these conditions 3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole **4.4.5** was obtained in 59% isolated yield.



*Scheme 96. $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.4.1** under optimized conditions*

4.5. **Scope of the furo[3,2-*b*]indolenines**

With the optimized conditions in hand, the generality of this novel reductive cyclization was examined. For the scope of this methodology, different parameters can be varied: the source of nucleophile (alcohol, thiol, amine), as well as substituents on the nitroaryl ring and different combinations of substituents on the double bond (alkyl vs aryl) (Scheme 97).

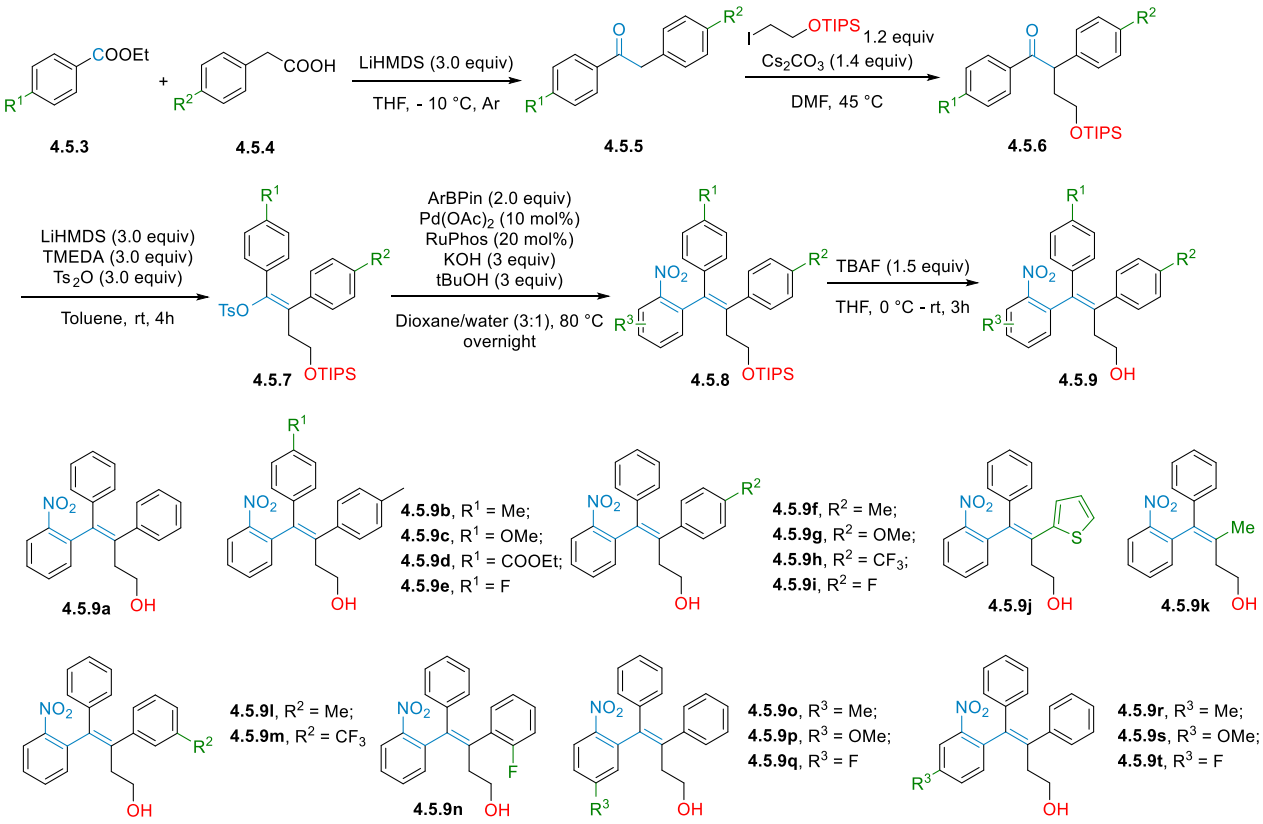


*Scheme 97. Proposed scope for the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.1***

4.5.1. **Starting material synthesis**

Most of the *o*-nitrostyrene derivatives were synthesized using the same synthetic route (Scheme 98) through the synthesis of the ketone, alkylation, tosylate formation, the Suzuki-Miyaura cross-coupling reaction and deprotection. The yields for each step and substrate are presented in the Supporting information. For the starting materials with different substituents on the nitroaryl ring, a divergent synthesis was performed from 2-phenylacetophenone, where the Suzuki-Miyaura cross-coupling with advanced intermediate (enol tosylate **4.5.7**) was done with different *ortho*-nitro substituted arylboronic esters. All non-commercially available starting ketones **4.5.5** were synthesized following Huang's procedure through a Claisen–decarboxylation cascade reaction starting from the corresponding ethyl benzoate and arylacetic acid.[291]

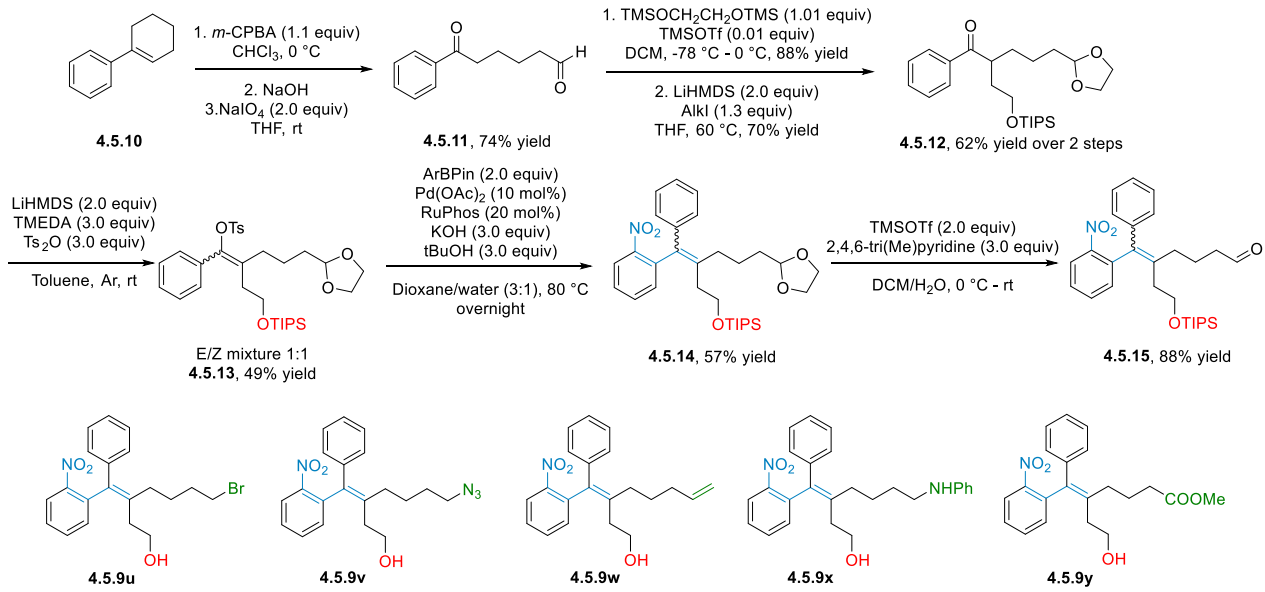
[291] Wu, G.; Yin, W., Shen, H.C.; Huang, Y. *Green Chem.* **2012**, *41*, 580 – 585.



*Scheme 98. Synthesis of starting materials **4.5.9***

We then moved to the scope of the *o*-nitrostyrene derivatives containing alkyl chains in α- and β-position of the nitroaryl ring. Compounds **4.5.9u-y** were synthesized starting from 1-phenylcyclohexene **4.5.10**, as shown in Scheme 99. Ketoaldehyde **4.5.11** was accessed following the procedure developed by Du in a 3-step sequence. The oxidative cleavage of the double bond delivered keto-aldehyde **4.5.11** through the formation of an epoxide, followed by epoxide-opening and periodiate-mediated cleavage of the resulting diol.[292] Chemoselective protection of the aldehyde with 2,2,7,7-tetramethyl-3,6-dioxa-2,7-disilaoctane was done with the conditions described by Qiu.[293] The first assay to perform alkylation of protected ketone failed. However, after a quick screening of the reaction conditions, the desired product **4.5.12** could be isolated in 70% yields. With the previously optimized conditions for the tosylate formation, ketone **4.5.12** was transformed into enol **4.5.13** in 49% yield as a mixture of *E*- and *Z*- isomers (1/1 ratio). The Suzuki-Miyaura cross-coupling reaction of **4.5.13** with 2-nitrophenylboronic ester afforded tetrasubstituted alkene **4.5.14** in 57% yield. The selective deprotection of aldehyde function under mild conditions delivered aldehyde **4.5.5** in 88% yield. Aldehyde **4.5.15** served as a platform for the divergent synthesis of several substrates.

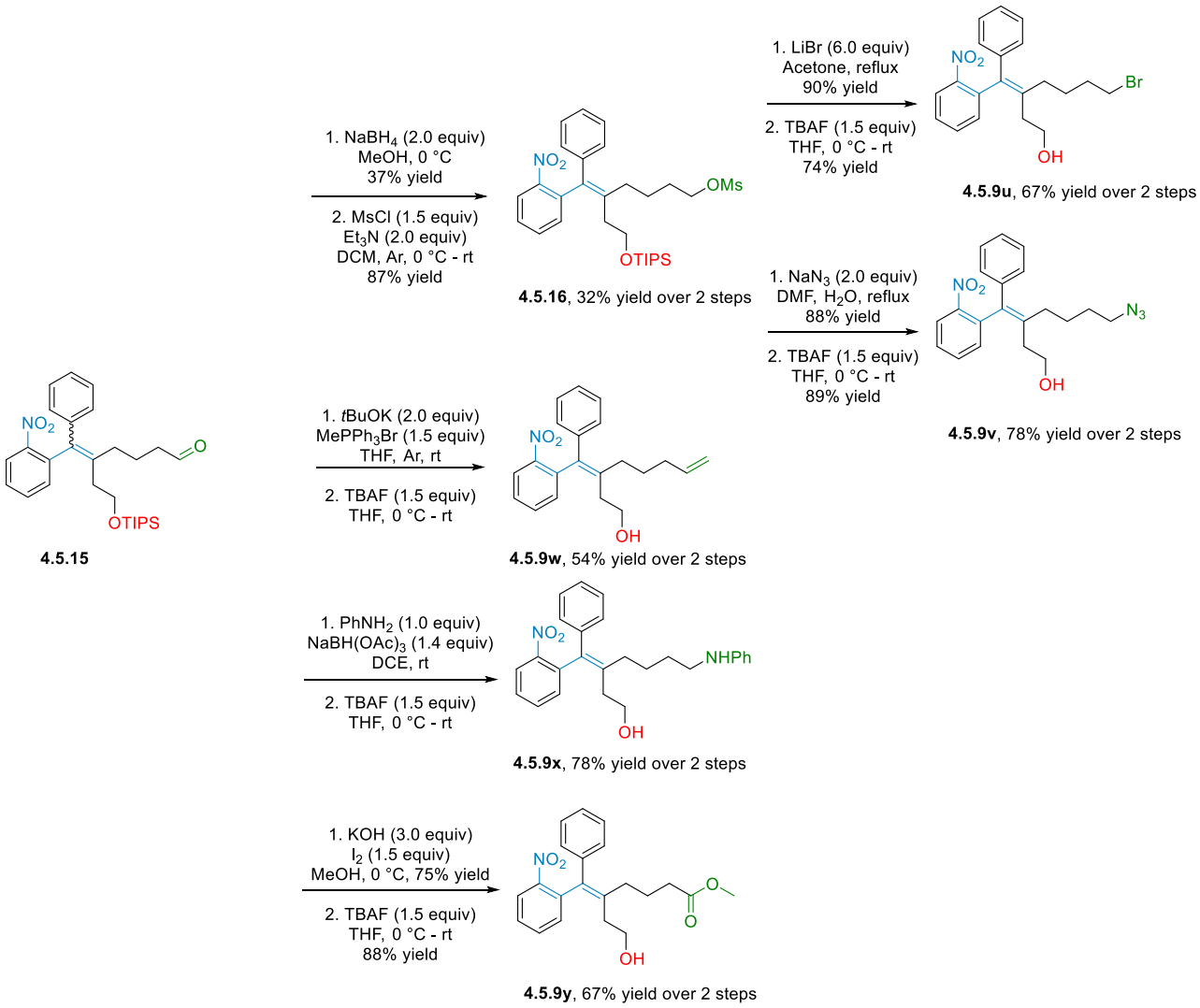
[292] Wang, Y. ; Du, H. *J. Org. Chem.* **2010**, *75*, 3503 – 3506.
[293] Xu, B.; Wang, B.; Xun, W.; Qiu, F.G. *Angew. Chem. Int. Ed*, **2019**, *58*, 5754 – 5757.



*Scheme 99. Synthesis of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9u-y***

In order to access bromide and azide substituted derivatives, aldehyde **4.5.15** was reduced and the resulting alcohol was converted to mesylate **4.5.16** (Scheme 100). Simple S_N2-substitution with either LiBr or NaN_3 followed by deprotection of the TIPS-protecting group delivered desired products **4.5.9u** and **4.5.9v** in yields of 67% and 78%, respectively, over 2 steps from mesylate **4.5.16**. The Wittig reaction of aldehyde **4.5.15** with methyltriphenylphosphonium bromide followed by removal of TIPS protecting group afforded 1,6-diene **4.5.9w** in 54% yield over 2 steps. Amine derivative **4.5.9x** was synthesized through a reductive amination/deprotection sequence in 78% yield over 2 steps. The mild oxidation of aldehyde **4.5.15** using Yamamoto's conditions followed by O-deprotection gave desired ester **4.5.9y** in 67% yield over 2 steps.[294]

[294] Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329 – 4332.



*Scheme 100. Synthesis of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9u-y** - post-modifications*

Having in hand 2-nitrophenylstyrene derivatives containing an alkyl chain at β-position, we turned our attention towards α-alkyl substituted counterparts. We imagined to synthesize four different substrates **4.5.9z-ac** (Figure 11). Firstly, Sonogashira cross-coupling between 2-nitrophenyliodide **4.5.17** and but-3-yn-1-ol **4.5.18** followed by TIPS-protection of the resulting 4-(2-nitrophenyl)but-3-yn-1-ol delivered alkyne **4.5.19** in 74% yield over 2 steps (Scheme 101). The triple bond was then hydrolyzed under basic conditions using the procedure described by Fukuyama.[295] Alkylation of formed ketone with MeI worked efficiently to afford **4.5.20** in 83% yield. However, the same alkylation reaction with 1-(2-bromoethyl)-1,3-dioxolane turned out to be more challenging. After optimization of the reaction conditions the desired product **4.5.21** was obtained in only 33% yields.

[295] Tokuyama, H; Makido, T.; Han-ya, Y.; Fukuyama, T. *Hetetocycles* **2007**, *72*, 191 – 197.

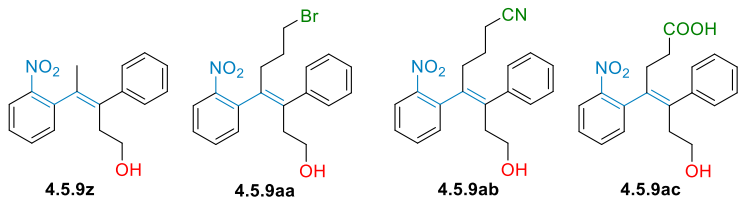
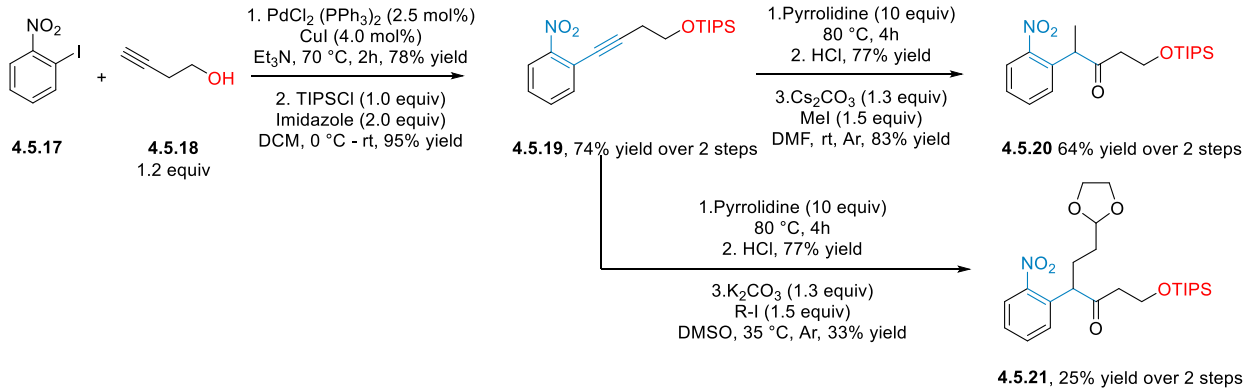
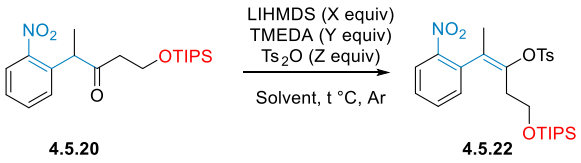


*Figure 11. Tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9z-ac***



*Scheme 101. Synthesis of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9z-ac***

The tosylation of ketones **4.5.20** and **4.5.21** turned out to be more complicated than expected. Selected examples for the optimization of the reaction conditions with substrate **4.5.20** are presented in Table 42. Firstly, we found that the reaction in toluene led only to the decomposition of starting material **4.5.20** (entries 1-2). Replacing toluene with THF enol tosylate **4.5.22** was formed in 17 % yields at -40 °C. At lower temperature the reaction took more time and had lower conversion (entries 3-4). Varying the amount of tosyl anhydride (entry 5), base (entry 6) and additive (TMEDA, entry 7) enabled to access the desired product **4.5.22** with a maximum 43% yield (entry 8). Unfortunately for compound **4.5.21**, the reaction never worked with yields higher than 9%.

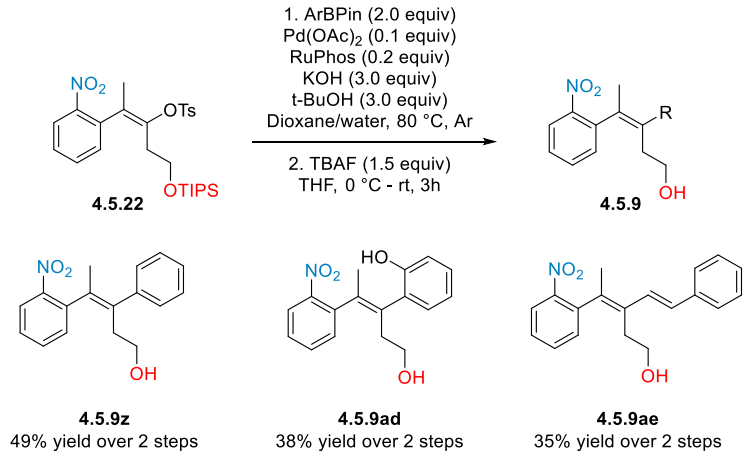


	LiHMDS (equiv)	TMEDA (equiv)	Ts_2O (equiv)	Solvent	T °C	**4.5.22**[a]	**4.5.20**[a]
1.	1.2	-	1.4	Toluene	-40 °C	-	50%
2.	1.2	-	1.4	Toluene	-78 °C	-	17%
3.	1.2	-	1.4	THF	-40 °C	17%	46%
4.	1.2	-	1.4	THF	-78 °C	10%	58%
5.	1.2	-	2.0	THF	-40 °C	10%	32%
6.	2.0	-	1.4	THF	-40 °C	38%	-
7.	1.2	2.0	1.4	THF	-40 °C	28%	41%
8.	1.8	3.0	1.4	THF	-40 °	43%	-

[a] NMR yields with 1,3,5-trimethoxybenzene as a standard.

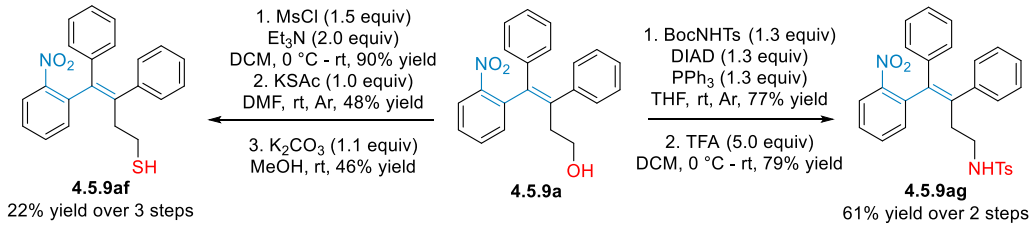
*Table 42. Optimization of tosylation of ketone **4.5.20***

The Suzuki-Miyaura cross-coupling with 3 different oganoboronic esters and TIPS-deprotection delivered three new tetrasubstituted alkenes for the key-transformation (Scheme 102).



*Scheme 102. Synthesis of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.z, 4.5.9ad-ae** via the Suzuki-Miyaura cross-coupling*

Alcohol **4.5.9a** was a precursor for substrates **4.5.9af** and **4.5.9ag**. Amine-derivative **4.5.9ag** was prepared through a Mitsunobu reaction using the conditions described by Falck, followed by a Boc-deprotection (Scheme 103).[296] For the thiol-derivative a S_N2 reaction with potassium thioacetate followed by deprotection of thiol afforded alkene **4.5.9af** in 22% yield over 3 steps. [297]



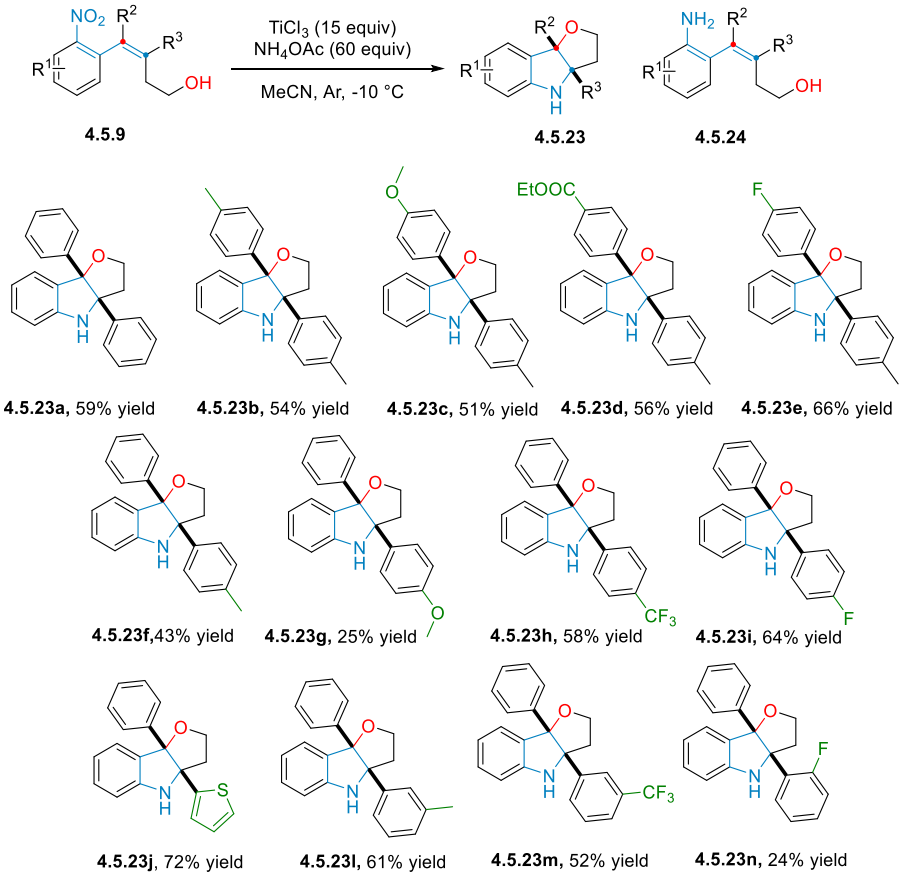
*Scheme 103. Synthesis of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9af** and **4.5.9ag***

4.5.2. Scope of the Ti-mediated reductive cyclization of tetrasubstituted alkenes 4.5.9 bearing a 2-nitrophenyl substituent

The variation of substituents on both aromatic rings (R^2 and R^3, α- and β-position of the *o*-nitrophenyl ring) on the double bond did not drastically influence the yield (Scheme 104). Electron-donating, as well as electron-withdrawing group, were well tolerated. In all presented reactions, a complete conversion of the starting material **4.5.9** was observed, though the formation of side-product – aniline **4.5.24** could not be avoided. Apart from substrates **4.5.23f**, **4.5.23g** and **4.5.23n**, all compounds could be accessed in yields

[296] Munnuri, S.; Adebesin, A.M.; Paudyal, M.P.; Yousufuddin, M.; Dalipe, A.; Falck, J.R. *J. Am. Chem. Soc.* **2017**, *139*, 18288 – 18294.
[297] Carta, P.; Puljic, N.; Robert, C.; Djimane, A.-L.; Ollivier, C.; Fensterbank, L.; Lacote, E.; Malacria, M. *Tetrahedron* **2008**, *64*, 11865 – 11875.

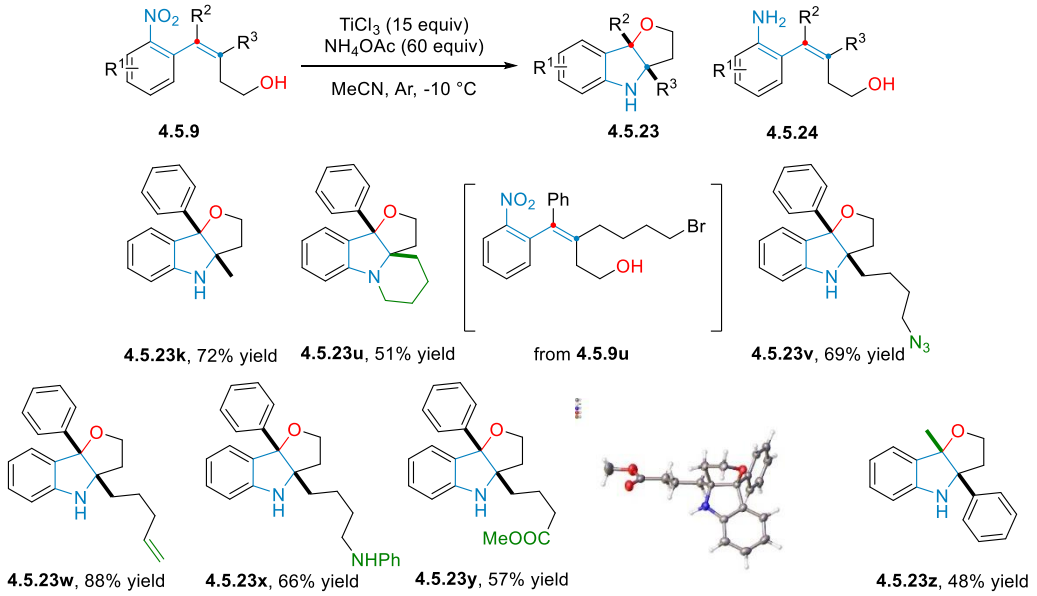
higher than 50%. The slight decrease in the yield for substrate **4.5.23g** was attributed to the relative increase of electron density on the double bond, as slightly better yields were obtained in the case of substrates with the electron-withdrawing group on both sides of the double bond (**4.5.23d-e, 4.5.23h-i**). This observation can be as well applied to compound **4.5.23f**. The high yields for furo[3,2-*b*]indoline **4.5.23j** can be potentially explained by the smaller ring size of the thiophene substituent. The key step of this transformation is an intramolecular 6π-electrocyclization of a nitrosoarene intermediate with the alkene part. The size of the substituents on the double bond can likely influence the ease of rotation of the nitrosoarene ring around the double bond. It is to note that the reaction could be performed on a 2.4 mmol scale delivering the same compound **4.5.23h** in a similar 70% yield. Meta-substituents on the arene ring are well tolerated, substrates **4.5.23l** and **4.5.23m** with methyl and a trifluoromethyl groups were obtained in good yields. However, *ortho*-substituents on the aryl ring R^3 were poorly tolerated. Indeed, even the incorporation of a fluorine atom led to a dramatic loss of the yield for **4.5.23n**.



*Scheme 104. Scope of $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9a-n***

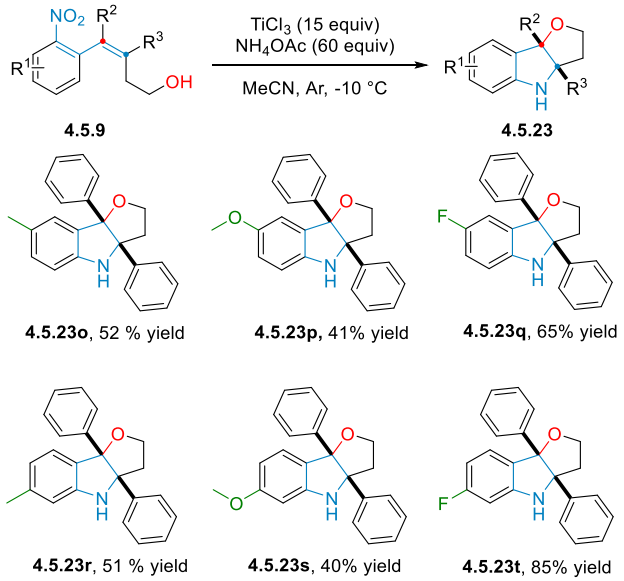
Finished the investigation of the scope of modified aromatic rings, we turned our attention to alkyl-substituted substrates (Scheme 105). The incorporation of a methyl group at the β-positon of *o*-nitrostyrene derivatives lead to a dramatic increase of the yields to 72%, confirming our idea about the influence of steric hindrance. Easily reduced functional groups (-N_3, -COOMe), as well as polar groups (NHPh), were well tolerated, and the reactions worked with very good yields. It is to note that when starting compound **4.5.9u** was used, the tetracyclic product **4.5.23u** was isolated in 51% yield. The desired Br-derivative was detected at the end of the reaction, but was completely transformed into furo[3,2-*b*]indoline **4.5.23u** during the

purification. Finally, X-Ray crystallographic analysis of **4.5.23y** confirmed the structure of the furo[3,2-*b*]indolines. Interestingly, when the aryl ring was replaced with a methyl group at the α-position of *o*-nitrostyrene derivatives **4.5.9z**, product **4.5.23z** was isolated with slightly lower yields.

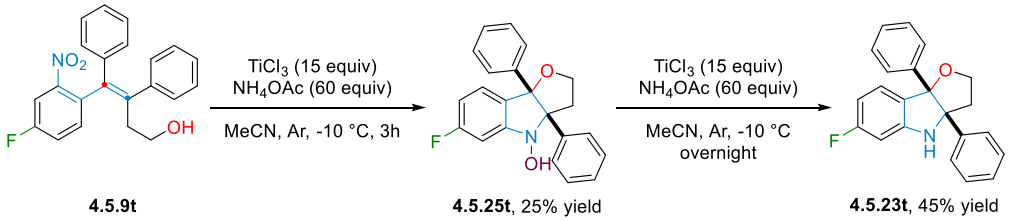


*Scheme 105. Scope of $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9k** and **4.5.9u-z***

Finally, while varying substituents on the nitroarene ring, it was found that starting materials with electron-neutral (**4.5.23a, o** and **r**), electron-rich (**4.5.23s**) and electron-poor (**4.5.23p**, **q** and **t**) substituents all reacted comparably well under our optimized conditions (Scheme 106). However, a noticeable preference in favor of the electron-withdrawing group should be mentioned. It is to note that a prolonged reaction time was necessary for substrates **4.5.23q** and **4.5.23t**. Interestingly, in the case of compound **4.5.23t**, one of the intermediates of the reaction (*N*-hydroxyindoline **4.5.25t**) could be isolated and characterized (Scheme 107). Resubmitting this intermediate to the reaction conditions enabled the formation of the desired product **4.5.23t** in 45% yield.

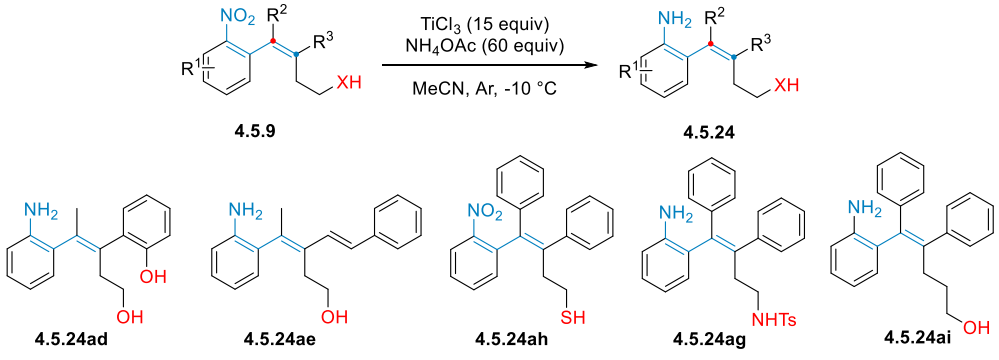


*Scheme 106. Scope of the $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.5.9o-t***



*Scheme 107. Formation of N-hydroxy indoline **4.5.25t***

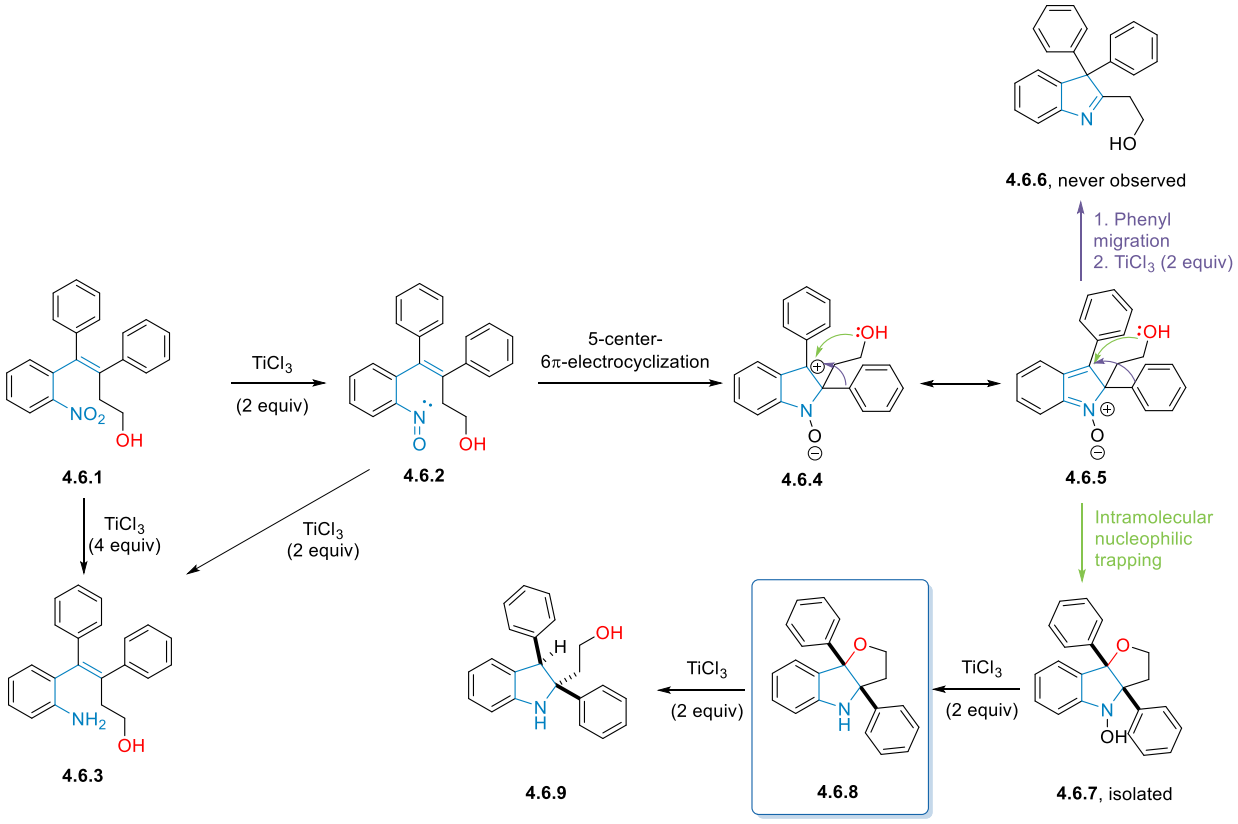
Unfortunately, some substrates did not work in our transformation, instead, products of over-reduction, i.e. anilines **4.5.24ad-ai** were isolated (Scheme 108). For substrates **4.5.9ad** and **4.5.9ag**, the difference in the polarity of the starting material could play a role. The fact that thiol-derivative **4.5.9ah** did not work under our conditions can probably be explained by the poisoning of the reaction mixture with thiol.



Scheme 108. Unsuccessful examples

4.6. **Mechanism**

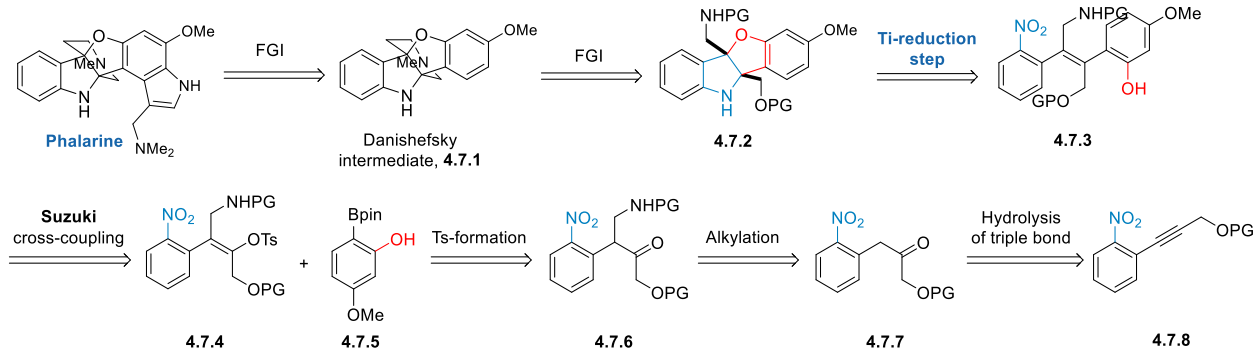
In view of our observations, a tentative mechanism for the $TiCl_3$-mediated reductive cyclization of *o*-nitrostyrene derivatives is shown in Scheme 109. The reaction begins with the partial reduction of the nitroarene **4.6.1** to nitroso intermediate **4.6.2**, as previously described in our work. This intermediate is very reactive and can be easily reduced to aniline **4.6.3**, which was isolated in every case. At the same time, nitroso intermediate **4.6.2** can proceed in a 5-atom-6π-electrocyclization to form zwitterion **4.6.4**. This intermediate has another resonance structure – nitrone **4.6.5**. At this step, two processes are possible: a migration of the phenyl ring (purple arrow, as phenyl ring has a higher migratory aptitude compared to alkyl group) or an intramolecular trapping of the carbocation by hydroxyl (green arrow). Compound **4.6.6** has never been observed under our conditions. This could imply that the cyclization proceeds much faster. The product of cyclization **4.6.7** is then reduced with two molecules of $TiCl_3$ to the desired furo[3,2-*b*]indoline **4.6.8**. Performing the reaction under ambient temperature or higher with prolonged reaction time led to the partial transformation of desired product into indoline **4.6.9**.



*Scheme 109. Proposed mechanism for the reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.6.1***

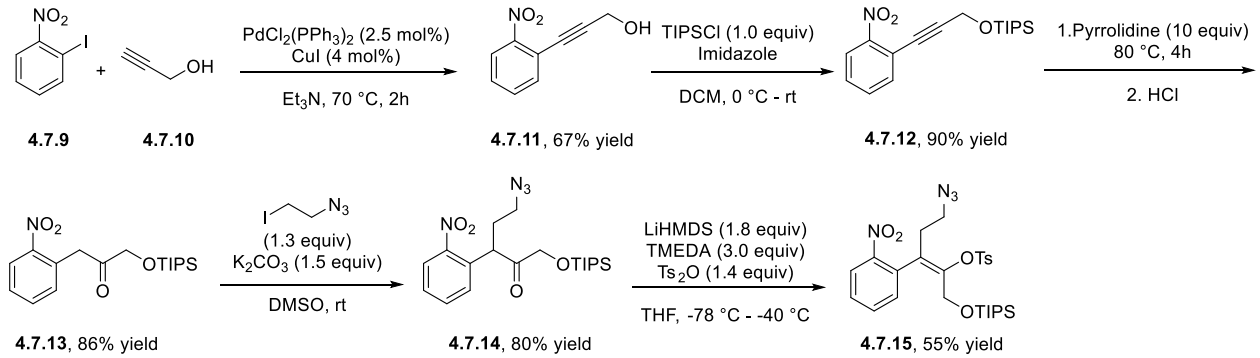
4.7. **Synthetic studies towards phalarine**

The proposed retrosynthesis is depicted in Scheme 110. We decided to perform a formal total synthesis of phalarine by accessing intermediate **4.7.1** reported in Danishefsky's total synthesis. The *N*-methyl piperidine cycle can be synthesized either by Mitsunobu reaction or reductive amination from indoline **4.7.2**. Benzofuroindoline moiety **4.7.2** would be formed by applying our reductive cyclization conditions to *o*-nitrostyrene **4.7.3**. Tetrasubstituted alkene **4.7.3** would be readily obtained from enol tosylate **4.7.4** by a Suzuki-Miyaura cross-coupling reaction. Finally, *o*-nitroaryl substituted enol tosylate **4.7.4** should be accessed in a couple of steps (i.e. hydrolysis of the triple bond, alkylation, Ts-formation) from alkyne **4.7.8**.



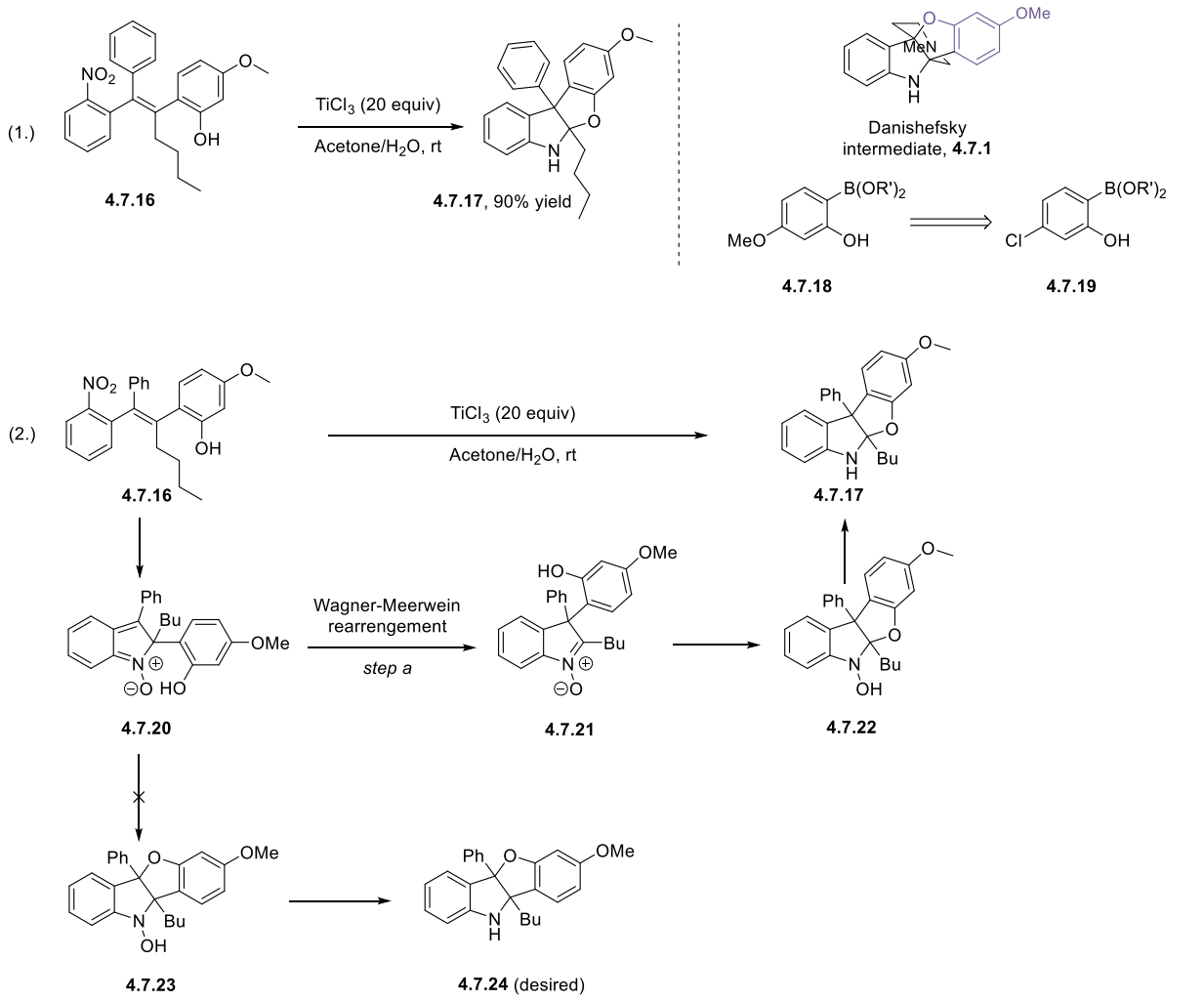
Scheme 110. Retrosynthetic scheme for the racemic total synthesis of phalarine

The synthesis of tosyl enol ester **4.7.15** bearing appropriate functional group for the late stage elaboration of piperidine ring is depicted in Scheme 111. The choice of substituents (azido and TIPS ether) can be explained by the fact that azido group is well tolerated under our reductive cyclization conditions and the TIPS-protecting group was stable during the Suzuki-Miyaura reaction. The Sonogashira reaction between 1-iodo-2-nitrobenzene **4.7.9** and propargylic alcohol **4.7.10** followed by a TIPS-protection delivered alkyne **4.7.12** in 60% yield over 2 steps (Scheme 111). Hydrolysis of the triple bond with pyrrolidine/HCl worked efficiently to afford ketone **4.7.13** in 86% yield. The alkylation of compound **4.7.13** with 1-azido-2-iodoethane and K_2CO_3 as base in DMSO gave product **4.7.14** in 80% yield. Ketone **4.7.14** was then transformed into enol tosylate **4.7.15** with 1.8 equiv LiHMDS, 3.0 equiv of TMEDA and 1.4 equiv of Ts_2O in THF at lower temperatures in 55% yield.



*Scheme 111. Synthesis of enol tosylate **4.7.15***

The Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.7.15** was tested with different arylboronic esters. The optimal coupling partner would be 4-methoxy-2-hydroxyphenylboronic acid **4.7.18**. However, previous results obtained in the group showed that $TiCl_3$-promoted reductive cyclization of compound **4.7.16** and provided benzofuro[2,3-*b*]indoline **4.7.17** (in 90% yield) instead of the desired furo[3,2-*b*]indoline **4.7.23** (Scheme 112). The result can be explained by the fact that the migration of aryl ring in the intermediate **4.7.20** (*step a*) is faster than the cyclization (*step b*) due to the electron-rich nature of the aromatic ring. Cyclization of the rearranged nitrone **4.7.21** would afford tetracyclic compound **4.7.22** which, upon further reduction of the N-O bond, was converted to the product **4.7.17**.

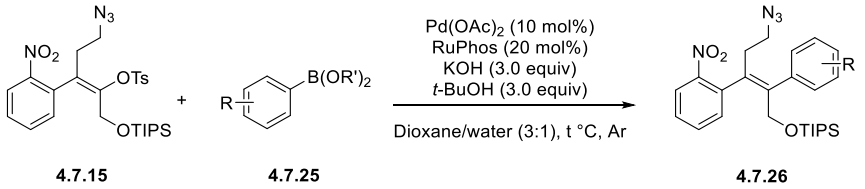


*Scheme 112. $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent **4.7.16***

To bypass the aforementioned competitive reaction process, we thought to use chorine atom as a surrogate of the methoxy group and have synthesized 3-chloro-2-hydroxyphenylboronic acid **4.7.19** as a coupling partner of the tosyl enolate **4.7.15**. Firstly, the reaction with boronic acid **4.7.25a** was attempted at 2 different temperatures: 60 and 80 °C (

Table 43). Unfortunately, no traces of desired product were obtained; under applied conditions starting material was slowly decomposing and boronic acid proceeded in protodeborylation (entries 1-2).

The free alcohol in the ortho-position of boronic acid **4.7.25s** could be a potential problem. However, replacing it by a methoxy- group led only to a full decomposition of the starting material with prolonged reaction time (entries 3-4). The removal of the chlorine atom avoiding the homocoupling of the boron-partner did not affect the outcome. With both organoboron substrates **4.7.25c** and **4.7.25d**, only products of decomposition were isolated (entries 5-8). Finally, no reaction was observed with simple phenyl boronic ester **4.7.25e**.



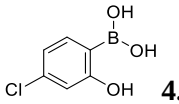
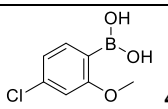
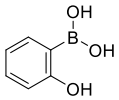
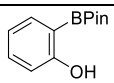
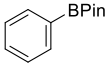
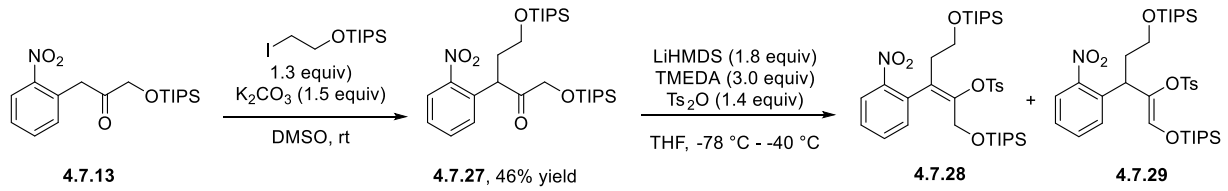
	Ar-B(OR`)$_2$ (2 equiv)	T °C	Results
1.	 **4.7.25a**	80	55% **4.7.15** + protodeborylation
2.		60	42% **4.7.15** + protodeborylation
3.	 **4.7.25b**	80	Decomposition + protodeborylation
4.		60	Decomposition + protodeborylation
5.	 **4.7.25c**	80	Decomposition + protodeborylation
6.		60	28% **4.7.15** + protodeborylation
7.	 **4.7.25d**	80	32% **4.7.15** + protodeborylation
8.		60	35% **4.7.15** + protodeborylation
9.	 **4.7.25e**	80	Decomposition + protodeborylation
10.		60	Decomposition + protodeborylation

*Table 43. Suzuki-Miyaura cross-coupling reaction with enol tosylate **4.7.15***

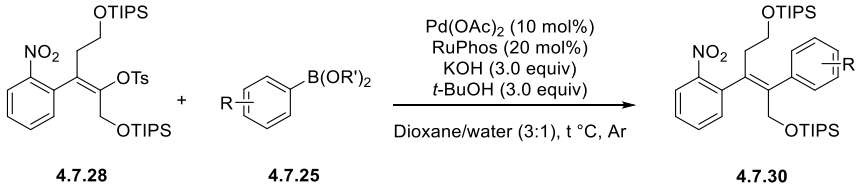
The presence of the azido group may be part of the problem. We decided then to replace azide with another TIPS-protected alcohol. In this way, for the post-modifications of benzofuro[3,2-*b*]indoline both alcohols would be easily deprotected under the same conditions. The synthesis of precursor **4.7.28** started similarly (Table 44). However, low yields were obtained for the alkylation of ketone **4.7.13**. It is possible that the high steric hindrance of the two TIPS-protecting groups was responsible for this observation. Unexpectedly, the tosylation of compound **4.7.27** delivered desired product **4.7.28** in only 15% yields along with substrate **4.7.29** (21% yield). As for the alkylation, our substrate **4.7.27** is probably too sterically hindered and orbitals eclipsing interactions on the way to enol tosylate **4.7.28** prevent its formation. A short optimization did not improve the outcome of the reaction (Table 44).



	LiHMDS	TMEDA	Ts_2O	Solvent	T °C	**4.7.28**	**4.7.29**	**4.7.27**
1.	1.8 equiv	3.0 equiv	1.4 equiv	THF	-78 °C	15%	21%	15%
2.	1.8 equiv	3.0 equiv	1.4 equiv	THF	-40 °C	15%	13%	59%
3.	2.0 equiv	3.0 equiv	1.4 equiv	THF	-78 °C	23%	25%	20%
4.	1.8 equiv	3.0 equiv	2.0 equiv	THF	-78 °C	20%	20%	30%
5.	1.8 equiv	3.0 equiv	-	THF	-78 °C	-	-	66%
6.	NaH	3.0 equiv	1.4 equiv	THF	-78 °C	Decomposition		
7.	LDA	3.0 equiv	1.4 equiv	THF	-78 °C			

*Table 44. Optimization of the enol tosylate formation from ketone **4.7.27***

Unfortunately, the Suzuki-Miyaura coupling of **4.7.28** with different phenylboronic esters **4.7.25a-e** failed to afford the coupling product **4.7.30**. While the phenylboronic acid underwent the protodeborylation, the enol ester was recoved from all the experiments (Table 45).



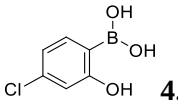
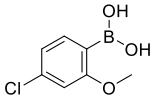
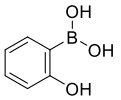
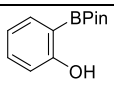
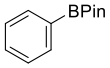
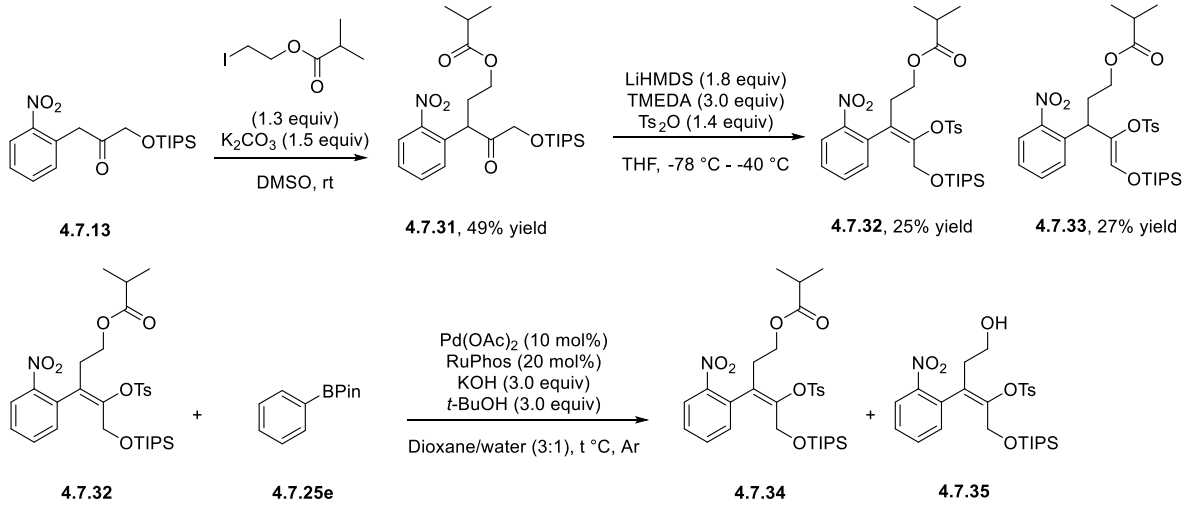
	Ar-B(OR`)$_2$ (2 equiv)	T °C	Results
1.	 **4.7.25a**	80	SM – recovered, protodeborylation
2.		60	
3.	 **4.7.25b**	80	
4.		60	
5.	 **4.7.25c**	80	
6.		60	
7.	 **4.7.25d**	80	
8.		60	
9.	 **4.7.25e**	80	
10.		60	

*Table 45. Suzuki-Miyaura cross-coupling with enol-tosylate **4.7.28***

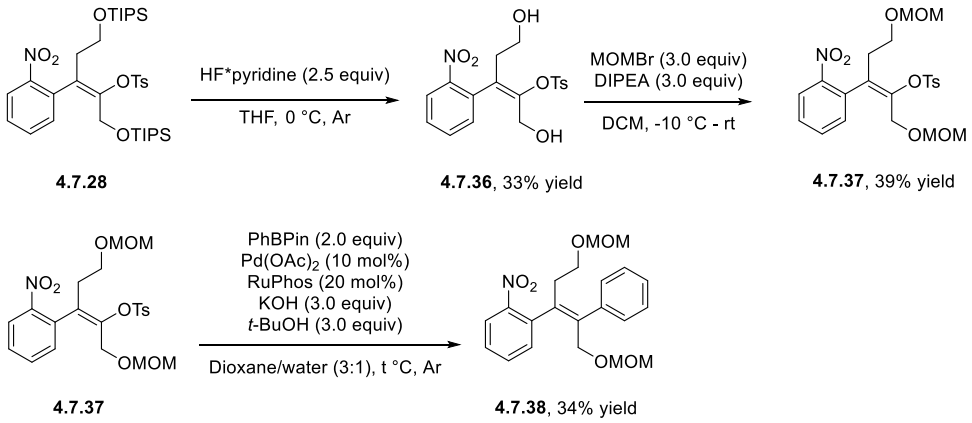
The absence of conversion in the case of enol tosylate **4.7.28** is likely due to the steric hindrance. In these conditions, the Pd catalyst cannot approach the vinyl tosylate and the oxidative addition does not occur. To understand which TIPS protecting group was critical, we firstly synthesized ester-derivative

4.7.32. Both reactions: alkylation and tosylate- formation worked with slightly higher yield compare to TIPS-derivative **4.7.28** (Scheme 113). The desired tosyl enol ester **4.7.32** was isolated in 25% yield together with the regioisomeric tosyl enol ester **4.7.33** (27%). Unfortunately, the Suzuki-Miyaura coupling between **4.7.32** and phenylboronate **4.7.25e** failed again. Changing the base (K_2CO_3 and K_3PO_4) did not change the reaction outcome.



*Scheme 113. Synthesis of enol tosylate **4.7.34***

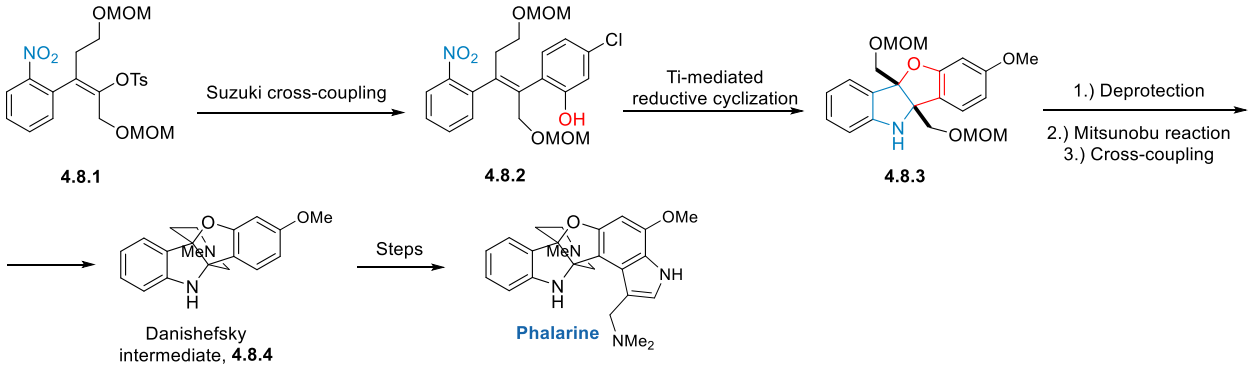
Then the second TIPS-protecting group was replaced by a MOM-protecting group. Deprotection of **4.7.28** with HF.pyridine afforded diol **4.7.36** in 33% yield together with mono-deprotected product (Scheme 114). MOM protection of **4.7.36** (MOMBr and DIPEA in DCM) gave product **4.7.37** in 39% yields. Gratefully, the Suzuki-Miyaura cross-coupling between MOM-protected enol tosylate **4.7.37** and phenylboronic acid pinacol ester gave desired product **4.7.38** in 34% yields.



*Scheme 114. Synthesis of tetrasubstituted olefin **4.7.38***

4.8. Outlook. Completion of the total synthesis of phalarine

To complete the total synthesis of the natural product phalarine, the Suzuki-Miyaura reaction of tosyl enol ester **4.8.1** with an appropriately functionalized arylboronic acid would have to be futher optimized (Scheme 115). We are confident that the $TiCl_3$-mediated reductive cyclization of **4.8.2** would afford the desired benzofuro[3,2-*b*]indoline **4.8.3**. MOM-deprotection of the latter followed by double Mitsunobu reaction would then form the piperidine ring. The Cu-mediated coupling of aryl chloride with methanol would give the tetracyclic compound **4.8.4** which has previously been converted to phalarine by Danishefsky.



Scheme 115. Planned sequence of steps for the completion of phalarine

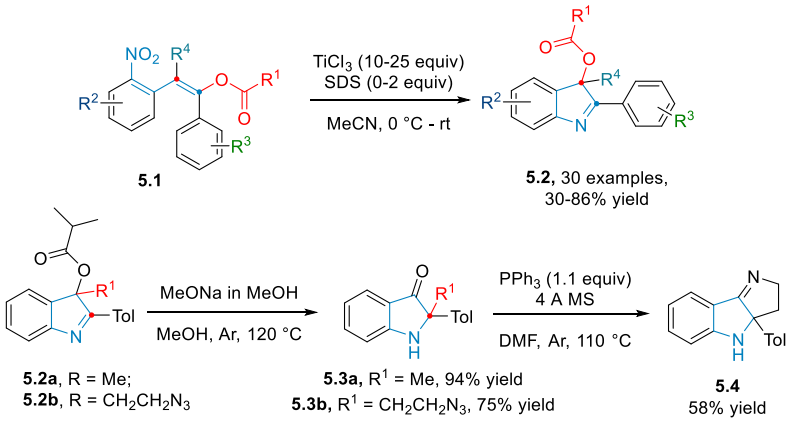
4.9. Conclusion

A new method for the synthesis of furo[3,2-*b*]indoline **4.5.23** by a Ti(III)-mediated reductive cyclization of *o*-nitrostyrene derivatives **4.5.9** has been developed. Access to this type of scaffolds under reductive conditions is unprecedented. The reaction displays good functional group compatibility and excellent regioselectivity. A 5-step synthesis of sterically hindered tetrasubstituted olefins containing *o*-nitroaryl substitutent is developed based on the work of Gosselin and is characterized by Suzuki-Miyaura cross couling of tosyl enol esters with arylboronic acids. Total synthesis of phalarine featuring this novel reductive cyclization methodology was exploited. Though the synthesis is not completed, a reliable synthetic pathway to reach the intermediate for the key-step is developed.

Chapter 5. General conclusion

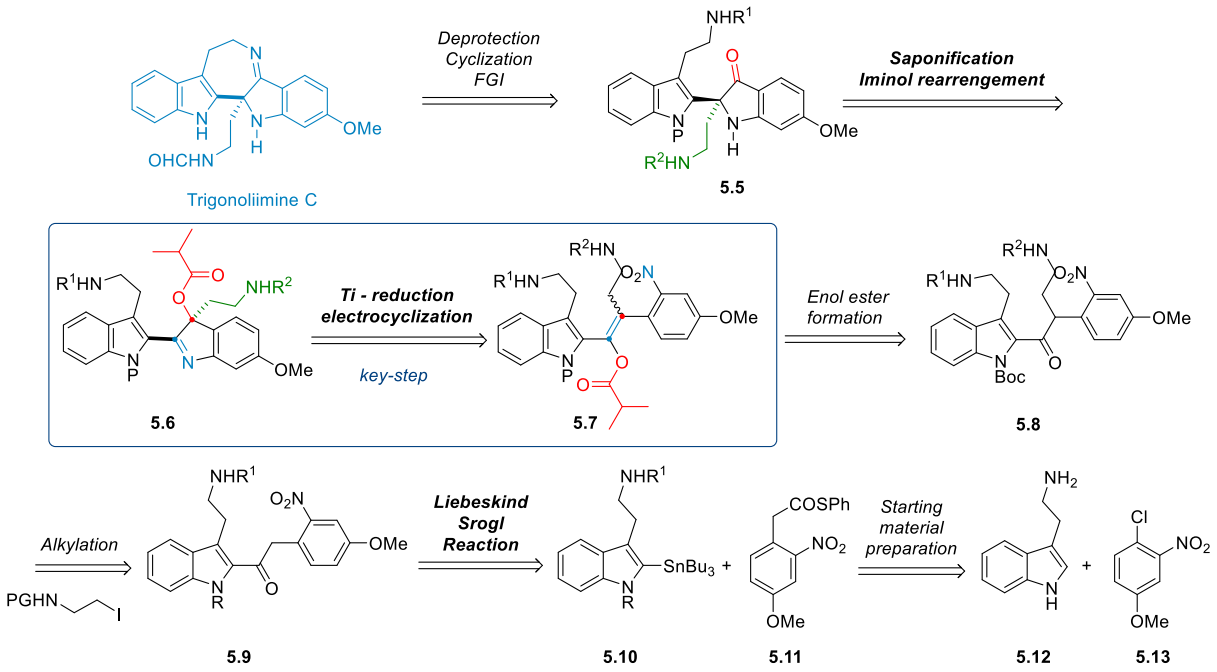
This thesis describes the development of $TiCl_3$-mediated Cadogan-Sundberg reductive cyclization of previously unexploited 2-nitrostyrene derivatives for the synthesis of two important heterocycles: 3-acyloxy-2,3-disubstituted indolenines and (benzo)furo[3,2-*b*]indolines. Approaches towards the total synthesis of trigonoiimine C and phalarine featuring these reactions as key steps were also explored.

In spite of extensive investigations on the reductive cyclization of 2-nitrostyrene derivatives, the related enol esters have never been examined as substrates for the Cadogan-Sundberg reaction. We described in Chapter 2 that simply stirring an acetonitrile solution of trisubstituted enol esters bearing a 2-nitrostyrene substituent **5.1** with aqueous solution of $TiCl_3$ afforded the 3-acyloxy-2,3-disubstituted indolenines **5.2** in good to excellent yields (Scheme 116). Mechanistically, a domino process involving a partial reduction of nitro to nitroso group followed by a 5-center-6π-electrocyclization, 1,2-acyloxy migration and further reduction of the resulting nitrone intermediate accounts for the reaction outcome. The higher migratory aptitude of acyl group related to aryl/alkyl group is observed and is accounted for by the participation of the carbonyl oxygen in the 1,2-shift process. The 3-acyloxy-2,3-disubstituted indolenines **5.2** can be transformed into 2,2-disubstituted 3-oxindole **5.3** *via* α-iminol rearrangement and more elaborated tricyclic compound, such as tetrahydropyrroloindole **5.4** *via* a sequence of 1,2-rearrangement and intramolecular Staudinger (aza-Wittig) reaction.

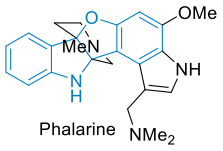


*Scheme 116. $TiCl_3$-mediated reductive cyclization of trisubstituted enol esters **5.1***

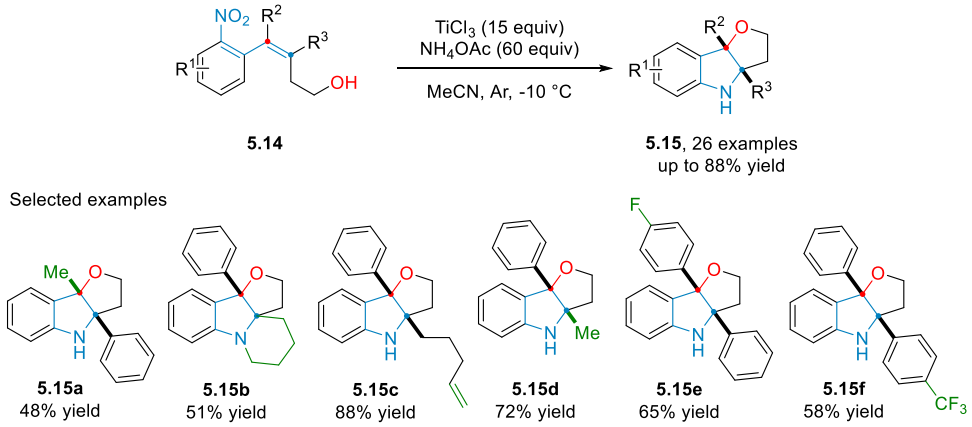
A retro-synthetic analysis of trigonoliimine C featuring the reductive cyclization of the enol ester **5.7** is depicted in Scheme 117. A domino sequence involving saponification followed by α-iminol rearrangement was expected to convert 3-acetoxy indolenine **5.6** to oxindole **5.5** whose conversion to natural product is known. Compound **5.7** was synthesized *via* Pd-catalyzed Liebeskind-Srogl cross-coupling between an organostannane derivative of tryptamine **5.10** and thioester **5.11** followed by alkylation and enol ester formation. Unfortunately, $TiCl_3$ promoted reductive cyclization of the enol ester **5.7** failed to produce the desired indolenine **5.6**. In most of the conditions examined, aniline resulting from the reduction of the nitro group was the major isolated product.



Scheme 117. Retrosynthetic analysis of trigonoliimine C



Benzofuro[3,2-*b*]indoline is a key structural motif found in (–)-phalarine. It is synthetically much more difficult to access than its isomer, the benzofuro[2,3-*b*]indoline. The few existing methods suffer from the low regioselectivity in the oxidative coupling of two selected building blocks. We developed a $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkenes bearing a 2-nitrophenyl substituent and a properly tethered nucleophile. The starting materials were prepared *via* a key Suzuki-Miyaura cross couping of tosyl enol ester with aryl boronic acid based on Gosselin's report. Treatment of a MeCN solution of tetrasubstituted alkenes with aqueous $TiCl_3$ and NH_4OAc afforded the desired (benzo)furo[3,2-*b*]indolines in good to high yield with excellent regioselectivities (Scheme 118). Total synthesis of phalarine featuring this novel reductive cyclization methodology was exploited and is being pursued in our laboratory.



Scheme 118. $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkene bearing a 2-nitrophenyl substituent ***5.14***

Chapter 6. Experimental section

6.1. General information

Reagents and solvents were purchased from commercial sources and preserved under argon. More sensitive compounds were stored in a desiccator or in the glove-box if required. Reagents were used without further purification unless otherwise noted. All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted. When needed, glassware was dried at least overnight in an oven (170 °C) or under vacuum with a heat gun (650 °C).

Solvents indicated as dry were either purchased as such, distilled prior to use or dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubbs' design. Flash column chromatography was performed using Silicycle SiliaFlash® P60 230-400 mesh. Reactions were monitored using Merck Kieselgel 60F254 aluminum or glass backed plates. TLC's were revealed by UV fluorescence (254 nm) then one of the following: $KMnO_4$, phosphomolybdic acid, ninhydrin, pancaldi, p-anisaldehyde, vanillin.

NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 Brüker DPX-400 spectrometer at room temperature, ^{1}H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: $CHCl_3$ [^{1}H: 7.26, ^{13}C: 77.2] and CD_2HOD [^{1}H: 3.34, ^{13}C: 49.9]). Coupling constants (*J*) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), hept (heptet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. COSY, HSQC, HMBC and NOESY experiments were used when needed to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacle™ ATR accessory as neat films compressed onto a Zinc Selenide window or a Perkin Elmer Spectrum BX FT-IR. The spectra are reported in cm^{-1}. Abbreviations used are: w (weak), m (medium), s (strong) and br (broad).

Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionization (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were done by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters.

Melting points were determined using a Stuart SMP30 or Büchi B-540.

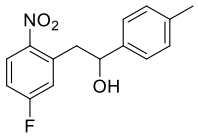
X-ray structures were determined with a SuperNova, Dual, Cu at home/near, Atlas diffractometer operating at T = 140.00(10) K or XtaLAB Synergy R, DW system, HyPix-Arc 150 diffractometer operating at T = 139.99(10) K. Data were measured using ω scans using Cu or Mo K_α radiation. The diffraction pattern was indexed and the total number of runs and images was based on the strategy calculation from the program CrysAlisPro. The unit cell was refined using CrysAlisPro. Data reduction, scaling and absorption corrections were performed using CrysAlisPro. A gaussian absorption correction was performed using CrysAlisPro. The numerical absorption correction was based on gaussian integration over a multifaceted crystal model. The empirical absorption correction was carried out using spherical harmonics, implemented

in SCALE3 ABSPACK scaling algorithm. The structure was solved and the space group determined by the ShelXT structure solution program using dual methods and refined by full matrix least squares minimisation on F^2 using ShelXL. All non-hydrogen atoms were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model.

6.2. $TiCl_3$-Mediated Reductive Cyclization of 2-(*ortho*-nitro)aryl Substituted Enol Esters

6.2.1. General procedure A for the synthesis of the alcohols

Following a reported procedure,[1] to a solution of 4-methoxy-2-methyl-1-nitrobenzene (**2.3.5g**) (4.9 g, 29 mmol, 1.0 equiv) in DMSO (10 mL, 3.0 M) was added 4-methylbenzaldehyde (**2.3.6**) (3.4 mL, 29 mmol, 1.0 equiv) and DBU (4.4 mL, 29 mmol, 1.0 equiv). The reaction mixture was stirred for 3 days, then water was added, followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to silica gel column chromatography to afford the desired alcohol **2.3.7g.**



2.3.7f, 2-(5-fluoro-2-nitrophenyl)-1-(p-tolyl)ethan-1-ol

This compound was prepared following the general procedure **A** using 4-fluoro-2-methyl-1-nitrobenzene (8.0 g, 52 mmol) as starting material. Yield: 49% (7.0 g), isolated as yellow solid. Purification: Flash chromatography (PE/Et_2O, 85:15), R_f = 0.23 (PE/Et_2O 80:20).

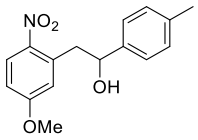
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 9.9, 5.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.03 (m, 2H), 5.00 (dt, *J* = 8.9, 3.8 Hz, 1H), 3.37 (dd, *J* = 13.6, 3.8 Hz, 1H), 3.22 (dd, *J* = 13.6, 8.9 Hz, 1H), 2.36 (s, 3H), 2.03 (d, *J* = 3.5 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4 (d, *J* = 256.4 Hz), 146.0 (d, *J* = 3.0 Hz), 140.7, 137.9, 137.6 (d, *J* = 9.3 Hz), 129.5, 127.7 (d, *J* = 10.0 Hz), 125.7, 120.4 (d, *J* = 23.2 Hz), 114.8 (d, *J* = 23.3 Hz), 74.0, 43.0 (d, *J* = 1.0 Hz), 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -107.73.

HRMS (APPI/LTQ-Orbitrap) m/z: $[M\text{-}OH]^+$ Calcd for $C_{15}H_{13}FNO_2^+$ 258.0925; Found 258.0921.

IR (ν_{max}, cm^{-1}) 2930 (w), 2856 (w), 1608 (s), 1587 (s), 1521 (s), 1481 (m), 1346 (s), 1301 (s), 1268 (s), 1246 (s), 1070 (m), 818 (s), 756 (s).



2.3.7g, 2-(5-methoxy-2-nitrophenyl)-1-(p-tolyl)ethan-1-ol

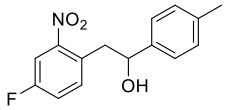
This compound was prepared following the general procedure **A** using 4-methoxy-2-methyl-1-nitrobenzene (4.9 g, 29 mmol) as starting material. Yield: 33% (2.8 g), isolated as white solid (mp = 62 – 63 °C). Purification: Flash chromatography (PE/EtOAc, 50:10), R_f = 0.21 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.84 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.74 (d, *J* = 2.8 Hz, 1H), 5.02 (dt, *J* = 8.8, 3.8 Hz, 1H), 3.83 (s, 3H), 3.44 (dd, *J* = 13.3, 3.8 Hz, 1H), 3.21 (dd, *J* = 13.3, 8.8 Hz, 1H), 2.36 (s, 3H), 2.12 (d, *J* = 3.6 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9, 142.7, 141.1, 137.6, 137.1, 129.3, 127.9, 125.8, 118.3, 113.0, 74.1, 55.9, 44.0, 21.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{17}NNaO_4^+$ 310.1050; Found 310.1050.

IR (ν_{max}, cm^{-1}) 3384 (w), 1606 (m), 1588 (m), 1578 (m), 1519 (m), 1337 (m), 1328 (m), 1291 (m), 1258 (m), 1073 (m), 816 (m).



2.3.7i, 2-(4-fluoro-2-nitrophenyl)-1-(p-tolyl)ethan-1-ol

This compound was prepared following the general procedure **A** using 4-fluoro-1-methyl-2-nitrobenzene (10.0 g, 65 mmol) as starting material. Yield: 52% (9.3 g), isolated as white solid (mp = 72 – 73 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 80:20).

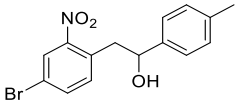
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 8.4, 2.6 Hz, 1H), 7.31 (dd, *J* = 8.6, 5.6 Hz, 1H), 7.28 – 7.20 (m, 3H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.96 (dt, *J* = 8.6, 3.7 Hz, 1H), 3.32 (dd, *J* = 13.7, 4.2 Hz, 1H), 3.21 (dd, *J* = 13.7, 8.6 Hz, 1H), 2.36 (s, 3H), 1.99 (m, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.9 (d, *J* = 250.1 Hz), 150.1 (d, *J* = 8.4 Hz), 140.7, 137.8, 135.2 (d, *J* = 7.8 Hz), 129.6 (d, *J* = 3.8 Hz), 129.4, 125.7, 120.2 (d, *J* = 20.8 Hz), 112.3 (d, *J* = 26.3 Hz), 74.2 (d, *J* = 1.3 Hz), 42.2, 21.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.63 (td, *J* = 7.9, 5.6 Hz).

HRMS (APPI/LTQ-Orbitrap) m/z: $[M\text{-}OH]^+$ Calcd for $C_{15}H_{13}FNO_2^+$ 258.0925; Found 258.0923.

IR (ν_{max}, cm^{-1}) 3369 (w), 2916 (w), 1533 (s), 1496 (m), 1363 (m), 1344 (m), 1236 (m), 1041 (m), 1022 (m), 816 (m), 795 (m).



2.3.7j, 2-(4-bromo-2-nitrophenyl)-1-(p-tolyl)ethan-1-ol

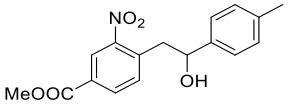
This compound was prepared following the general procedure **A** using 4-bromo-1-methyl-2-nitrobenzene (10.0 g, 46 mmol) as starting material. Yield: 51% (8.0 g), isolated as brown solid (mp = 102 – 103 °C). Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.23 (PE/EtOAc 90:10).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, *J* = 2.1 Hz, 1H), 7.62 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.27 – 7.24 (m, 2H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 4.96 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.29 (dd, *J* = 13.7, 4.1 Hz, 1H), 3.20 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.35 (s, 3H), 1.98 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 140.7, 137.9, 135.8, 135.1, 132.6, 129.5, 127.7, 125.7, 120.7, 74.1, 42.3, 21.3.

HRMS (APPI/LTQ-Orbitrap) m/z: $[M - OH]^+$ Calcd for $C_{15}H_{13}BrNO_2^+$ 318.0124; Found 318.0125.

IR (ν_{max}, cm^{-1}) 2921 (w), 2867 (w), 1525 (s), 1344 (s), 1039 (m), 881 (m), 823 (m), 802 (m), 737 (w).



2.3.7k, methyl 4-(2-hydroxy-2-(p-tolyl)ethyl)-3-nitrobenzoate

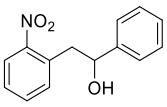
This compound was prepared following the general procedure **A** using methyl 4-methyl-3-nitrobenzoate (5.0 g, 26 mmol) as starting material. Yield: 56% (4.5 g), isolated as white solid (mp = 109 – 110 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.45 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.8 Hz, 1H), 8.13 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 5.00 (dt, *J* = 7.9, 3.5 Hz, 1H), 3.96 (s, 3H), 3.38 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.31 (dd, *J* = 13.5, 8.4 Hz, 1H), 2.35 (s, 3H), 2.02 (d, *J* = 3.5 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.2, 150.0, 140.6, 138.4, 138.0, 134.1, 133.1, 130.1, 129.5, 126.0, 125.7, 74.1, 52.8, 42.8, 21.3.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_5^+$ 338.0999; Found 338.1002.

IR (ν_{max}, cm^{-1}) 2950 (w), 2921 (w), 2860 (w), 1728 (s), 1620 (m), 1533 (s), 1437 (m), 1348 (m), 1292 (s), 1263 (s), 1198 (m), 1119 (s), 1041 (m), 974 (m), 822 (m), 771 (m), 744 (m), 710 (m).



2.3.7l, 2-(2-nitrophenyl)-1-phenylethan-1-ol

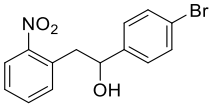
This compound was prepared following the general procedure **A** using 1-methyl-2-nitrobenzene (12.9 g, 94 mmol) as starting material. Yield: 34% (7.7 g), isolated as white solid (mp = 69 – 70 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.13 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.25 (m, 7H), 5.03 (dt, *J* = 8.8, 4.4 Hz, 1H), 3.37 (dd, *J* = 13.6, 4.1 Hz, 1H), 3.23 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.17 (d, *J* = 3.5 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 143.9, 133.7, 133.5, 132.9, 128.7, 127.9, 127.8, 125.8, 124.9, 74.4, 42.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{13}NNaO_3^+$ 266.0788; Found 266.0790.

IR (ν_{max}, cm^{-1}) 2925 (w), 2852 (w), 1610 (s), 1522 (s), 1452 (m), 1422 (m), 1346 (s), 1311 (m), 1199 (m), 1053 (m), 704 (s).



2.3.7n, 1-(4-bromophenyl)-2-(2-nitrophenyl)ethan-1-ol

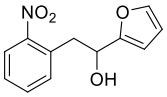
This compound was prepared following the general procedure **A** using 1-methyl-2-nitrobenzene (12.9 g, 94 mmol) as starting material. Yield: 34% (10.3 g), isolated as a light yellow solid (mp = 68 – 69 °C). Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.31 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.52 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41 (td, *J* = 7.9, 1.5 Hz, 1H), 7.30 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 5.00 (dd, *J* = 8.8, 3.9 Hz, 1H), 3.34 (dd, *J* = 13.6, 4.0 Hz, 1H), 3.17 (dd, *J* = 13.6, 8.7 Hz, 1H), 2.29 (br s, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 142.9, 133.7, 133.1, 133.0, 131.7, 128.0, 127.5, 125.0, 121.7, 73.7, 43.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{12}BrNNaO_3^+$ 343.9893; Found 343.9897.

IR (ν_{max}, cm^{-1}) 2933 (w), 2867 (w), 1520 (s), 1485 (m), 1342 (s), 1070 (m), 1038 (m), 1009 (m), 822 (m), 787 (m), 739 (m), 702 (m).



2.3.7p, 1-(furan-2-yl)-2-(2-nitrophenyl)ethan-1-ol

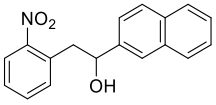
This compound was prepared following the general procedure **A** using 1-methyl-2-nitrobenzene (8.3 g, 60 mmol) as starting material. Yield: 57% (8.0 g), isolated as light orange solid (mp = 41 – 43 °C). Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.25 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.32 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.24 (dt, *J* = 3.2, 0.7 Hz, 1H), 5.04 (dt, *J* = 7.7, 4.8 Hz, 1H), 3.48 (dd, *J* = 13.6, 5.1 Hz, 1H), 3.43 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.25 (d, *J* = 5.2 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 155.4, 150.0, 142.4, 133.4, 133.0, 132.8, 128.0, 124.9, 110.4, 106.8, 68.1, 39.2.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{11}NNaO_4^+$ 256.0580; Found 256.0582.

IR (ν_{max}, cm^{-1}) 2875 (w), 1522 (s), 1344 (s), 1147 (m), 1041 (m), 1009 (m), 869 (m), 813 (m), 784 (m), 721 (s).



2.3.7q, 1-(naphthalen-2-yl)-2-(2-nitrophenyl)ethan-1-ol

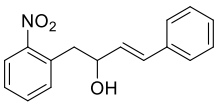
This compound was prepared following the general procedure **A** using 1-methyl-2-nitrobenzene (5.0 g, 36.5 mmol) as starting material. Yield: 66% (7.0 g), isolated as orange solid (mp = 70 – 71 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.32 (PE/EtOAc 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.90 – 7.80 (m, 4H), 7.56 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.53 – 7.46 (m, 3H), 7.43 – 7.37 (m, 1H), 7.34 (dd, *J* = 7.6, 1.6 Hz, 1H), 5.21 (dt, *J* = 8.8, 4.0 Hz, 1H), 3.47 (dd, *J* = 13.6, 4.0 Hz, 1H), 3.30 (dd, *J* = 13.6, 8.8 Hz, 1H), 2.22 (d, *J* = 3.5 Hz, 1H, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 141.3, 133.8, 133.5, 133.4, 133.2, 133.0, 128.6, 128.2, 127.9, 127.86, 126.4, 126.1, 125.0, 124.5, 123.9, 74.5, 43.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{15}NNaO_3^+$ 316.0944; Found 316.0943.

IR (ν_{max}, cm^{-1}) 3060 (w), 2929 (w), 1608 (m), 1522 (s), 1440 (m), 1348 (s), 1049 (m), 862 (m), 759 (m), 730 (m).



2.3.7ak, (E)-1-(2-nitrophenyl)-4-phenylbut-3-en-2-ol

This compound was prepared following the general procedure **A** using 1-methyl-2-nitrobenzene (8.3 g, 61 mmol) as starting material. Yield: 39% (6.3 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.2 (PE/EtOAc 8:2).

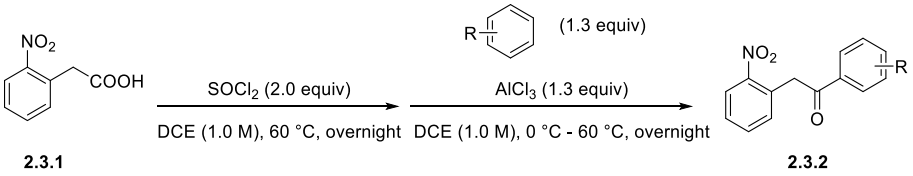
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.49 – 7.20 (m, 9H), 6.62 (dd, *J* = 15.9, 1.2 Hz, 1H), 6.32 (dd, *J* = 15.9, 6.5 Hz, 1H), 4.71 – 4.56 (m, 1H), 3.35 (dd, *J* = 13.6, 4.5 Hz, 1H), 3.18 (dd, *J* = 13.6, 8.2 Hz, 1H), 1.99 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.1, 136.5, 133.6, 133.2, 132.9, 131.2, 130.9, 128.7, 128.0, 127.8, 126.7, 125.0, 73.0, 40.8.

HRMS (APPI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_3^+$ 292.0944; Found 292.0941.

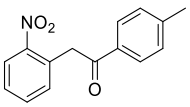
6.2.2. Synthesis of the ketones

General procedure B for the synthesis of the ketones By Friedel Crafts reaction



2.3.1 **2.3.2**

To a solution of 2-nitrophenylacetic acid **2.3.1** (6.0 g, 33 mmol, 1.0 equiv) in DCE (10 mL, 3.0 M) was added thionyl chloride (4.8 mL, 66 mmol, 2.0 equiv). The reaction mixture was heated at 60 °C in the oil bath overnight. The excess of thionyl chloride was evaporated under reduced pressure. The crude acyl chloride was dissolved in DCE (10 mL, 3.0 M) followed by addition of the substituted toluene (1.3 equiv). Then $AlCl_3$ (1.3 equiv) was added portion-wise to the reaction mixture upon 10 min at 0 °C. The reaction mixture was heated at 60 °C (oil bath) overnight. After completion of the reaction, aq. NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with DCM. The combined organic layers were washed with brine, dried, filtered and evaporated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2**.



2.3.2a, 2-(2-nitrophenyl)-1-(p-tolyl)ethan-1-one

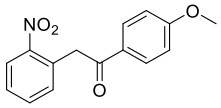
This compound was prepared following the general procedure **B** using 2-nitrophenyl acetic acid (6.0 g, 33 mmol) as starting material. Yield: 83% (6.2 g), isolated as brown solid (mp = 73 – 74 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.36 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 2H), 7.61 (td, *J* = 7.5, 1.4 Hz, 1H), 7.48 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.71 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.0, 149.2, 144.4, 134.1, 133.7, 133.5, 130.9, 129.5, 128.4, 128.39, 125.3, 44.1, 21.8.

HRMS (ESI) calcd for $C_{15}H_{13}NNaO_3^+$ $[M+Na]^+$ 278.0788; found 278.0790.

IR (ν_{max}, cm^{-1}) 2908 (w), 2863 (w), 1676 (s), 1519 (s), 1408 (m), 694 (s).



2.3.2m, 1-(4-methoxyphenyl)-2-(2-nitrophenyl)ethan-1-one

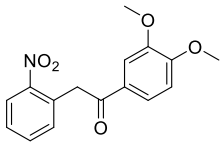
This compound was prepared following the general procedure **B** using 2-nitrophenyl acetic acid (2.2 g, 11 mmol) as starting material. Yield: 77% (2.3 g), isolated as brown solid (mp = 115 – 116 °C). Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.25 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.5 Hz, 1H), 7.33 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.68 (s, 2H), 3.87 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.9, 163.9, 149.2, 133.7, 133.5, 131.0, 130.6, 129.6, 128.3, 125.2, 114.0, 55.6, 43.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{13}NNaO_4^+$ 294.0737; Found 294.0745.

IR (ν_{max}, cm^{-1}) 2937 (w), 2839 (w), 1678 (m),1599 (s),1574 (s), 1522 (s), 1419 (m), 1342 (s), 1309 (m), 1261 (s),1223 (s), 1201(m), 1169 (s), 1028 (m), 991 (m), 829 (m),810 (m), 789 (m), 727 (s).



2.3.2o, 1-(3,4-dimethoxyphenyl)-2-(2-nitrophenyl)ethan-1-one

This compound was prepared following the general procedure **B** using 2-nitrophenyl acetic acid (4.0 g, 22 mmol) as starting material. Yield: 45% (3.0 g), isolated as brown solid (mp = 131 – 132 °C). Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.23 (DCM).

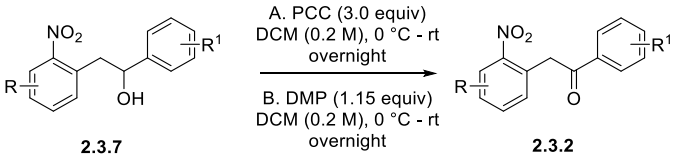
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.54 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.18 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.10 (d, *J* = 1.5 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 4.53 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.0, 153.7, 149.32, 149.26, 133.7, 133.5, 131.0, 129.8, 128.4, 125.3, 123.0, 110.5, 110.2, 56.3, 56.1, 43.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_5^+$ 324.0842; Found 324.0858.

IR (ν_{max}, cm^{-1}) 2933(w), 2840 (w), 1676 (m), 1583 (m), 1514 (s), 1464 (m), 1415 (m), 1344 (s), 1261 (s), 1242 (s), 1200 (m), 1151 (s), 1130 (m), 1020 (s), 808 (m), 789 (m), 762 (m), 723 (s).

General procedures C and D for the synthesis of the ketones By oxidation of the alcohol

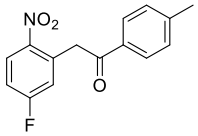


Procedure **C**

To a solution of the alcohol **2.3.7g** (1.1 g, 4.1 mmol, 1.0 equiv) in DCM (20 mL, 0.2 M) was added PCC (2.6 g, 12 mmol, 3.0 equiv) portion-wise at 0 °C. The reaction mixture was stirred at rt overnight, then filtered through silica gel, concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2g**.

Procedure **D**

To a solution of the alcohol **2.3.7f** (2.6 g, 10 mmol, 1.0 equiv) in DCM (50 mL, 0.2 M) was added DMP (5.0 g, 12 mmol, 1.15 equiv) portion-wise at 0 °C under Ar atmosphere. The reaction mixture was stirred at rt overnight. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water and extracted with diethyl ether. The combined ether extracts were concentrated in vacuo. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2f**.



2.3.2f, 2-(5-fluoro-2-nitrophenyl)-1-(p-tolyl)ethan-1-one

This compound was prepared following general procedure **D** using compound **2.3.7f** (7.0 g, 25.4 mmol) as starting material. Yield: 90% (6.2 g), isolated as bright yellow solid (mp = 82 – 83 °C). Purification: Flash chromatography (PE/Et_2O, 80:20), R_f = 0.32 (PE/Et_2O 80:20).

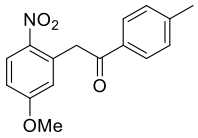
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, J = 9.1, 5.2 Hz, 1H), 7.92 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.15 (ddd, J = 9.1, 7.2, 2.8 Hz, 1H), 7.05 (dd, J = 8.6, 2.8 Hz, 1H), 4.70 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.4, 164.9 (d, J = 257.2 Hz), 145.3 (br s), 144.7, 134.6 (d, J = 9.5 Hz), 133.9, 129.6, 128.5, 128.2 (d, J = 10.0 Hz), 120.7 (d, J = 23.5 Hz), 115.4 (d, J = 23.1 Hz), 44.3 (d, J = 1.0 Hz), 21.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ -107.06.

HRMS (APPI/LTQ-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}FNO_3^+$ 274.0874; Found 274.0883.

IR (ν_{max}, cm^{-1}) 2925 (w), 2875 (w), 1682 (s), 1622 (m), 1606 (m), 1589 (m), 1523 (s), 1483 (m), 1406 (m), 1344 (s), 1327 (s), 1309 (m), 1277 (m), 1250 (s), 1223 (m), 1207 (m), 1182 (m), 1005 (m), 841 (m), 810 (s), 752 (m).



2.3.2g, 2-(5-methoxy-2-nitrophenyl)-1-(p-tolyl)ethan-1-one

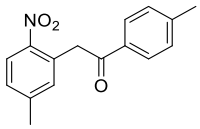
This compound was prepared following general procedure **D** using compound **2.3.7g** (2.6 g, 10.1 mmol) as starting material. Yield: 88% (2.3 g), isolated as white solid (mp = 120 – 121 °C). Purification: Flash chromatography (PE/EtOAc, 50:10), R_f = 0.23 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.23 (d, *J* = 9.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.28 (m, 2H), 6.92 (dd, *J* = 9.2, 2.8 Hz, 1H), 6.79 (d, *J* = 2.8 Hz, 1H), 4.69 (s, 2H), 3.89 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 195.2, 163.5, 144.4, 142.1, 134.3, 134.1, 129.5, 128.5, 128.2, 119.0, 113.0, 56.0, 44.9, 21.8.

HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}NNaO_4^+$ 308.0893; Found 308.0900.

IR (ν_{max}, cm^{-1}) 2940 (w), 1682 (m), 1608 (m), 1508 (m), 1502 (m), 1337 (m), 1264 (s), 1085 (w), 815 (m).



2.3.2h, 2-(5-methyl-2-nitrophenyl)-1-(p-tolyl)ethan-1-one

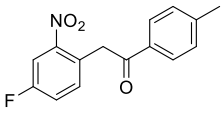
This compound was prepared following general procedure **C** using compound **2.3.7h** (1.1 g, 4.1 mmol) as starting material. Yield: 92% (1.0 g), isolated as yellow solid (mp = 96 – 97 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.27 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.08 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.13 (br s, 1H), 4.67 (s, 2H), 2.43 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 195.4, 146.9, 144.9, 144.4, 134.4, 134.3, 131.1, 129.5, 129.0, 128.5, 125.6, 44.2, 21.8, 21.5.

HRMS (ESI/QTOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{15}NaNO_3^+$ 292.0944; Found 292.0951.

IR (ν_{max}, cm^{-1}) 2921 (w), 2852 (w), 1684 (m), 1608 (m), 1589 (m), 1514 (s), 1338 (s), 1309 (m), 1223 (m), 1205 (m), 1180 (m), 985 (m), 837 (m), 808 (s), 746 (m), 731 (m).



2.3.2i, 2-(4-fluoro-2-nitrophenyl)-1-(p-tolyl)ethan-1-one

This compound was prepared following general procedure **D** using compound **2.3.7i** (9.0 g, 35 mmol) as starting material. Yield: 80% (7.2 g), isolated as white solid (mp = 89 – 90 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.33 (PE/EtOAc 80:20).

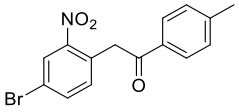
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.3 Hz, 2H), 7.91 – 7.86 (m, 1H), 7.35 – 7.32 (m, 2H), 7.31 (d, J = 8.1 Hz, 2H), 4.69 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.8, 161.5 (d, J = 250.7 Hz), 149.6 (d, J = 8.7 Hz), 144.7, 135.1 (d, J = 7.7 Hz), 134.0, 129.6, 128.5, 126.9 (d, J = 3.8 Hz), 120.8 (d, J = 20.9 Hz), 113.1 (d, J = 26.6 Hz), 43.5, 21.9.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.66 (dt, J = 8.5, 6.6 Hz).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{13}FNO_3^+$ 274.0874; Found 274.0874.

IR (ν_{max}, cm^{-1}) 3076 (w), 1685 (m), 1606 (m), 1553 (s), 1352 (m), 1333 (m), 1238 (m), 1223 (m), 1184 (m), 816 (m).



2.3.2j, 2-(4-bromo-2-nitrophenyl)-1-(p-tolyl)ethan-1-one

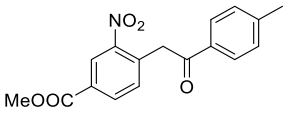
This compound was prepared following general procedure **D** using compound **2.3.7j** (7.6 g, 22.6 mmol) as starting material. Yield: 87% (6.6 g), isolated as light yellow solid (mp = 115 – 116 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.42 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.1 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.72 (dd, J = 8.2, 2.1 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.2 Hz, 1H), 4.67 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.5, 149.6, 144.7, 136.5, 135.0, 133.9, 129.9, 129.6, 128.5, 128.3, 121.5, 43.7, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}NBrNaO_3^+$ 355.9893; Found 355.9902.

IR (ν_{max}, cm^{-1}) 2917 (w), 2859 (w), 1682 (m), 1604 (m), 1525 (s), 1344 (s), 1327 (m), 1225 (m), 1180 (m), 999 (m),883 (m), 812 (m),779 (m), 748 (m), 702 (w).



2.3.2k, methyl 3-nitro-4-(2-oxo-2-(p-tolyl)ethyl)benzoate

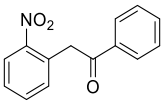
This compound was prepared following general procedure **D** using compound **2.3.7k** (2.1 g, 6.7 mmol) as starting material. Yield: 82% (1.7 g), isolated as light yellow solid (mp = 73 – 74 °C). Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.27 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.7 Hz, 1H), 8.25 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.77 (s, 2H), 3.98 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.3, 165.1, 149.3, 144.8, 135.6, 134.1, 134.0, 133.9, 130.9, 129.6, 128.5, 126.5, 52.9, 44.2, 21.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}NNaO_5^+$ 336.0842; Found 336.0844.

IR (ν_{max}, cm^{-1}) 2954 (w), 2917 (w), 1724 (s), 1684 (s), 1606 (m), 1533 (s), 1435 (m), 1350 (m), 1292 (s), 1265 (s), 1223 (s), 1180 (s), 1119 (m), 1001 (m), 810 (m), 773 (m), 739 (m).



2.3.2l, 2-(2-nitrophenyl)-1-phenylethan-1-one

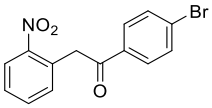
This compound was prepared following general procedure **C** using compound **2.3.7l** (3.0 g, 12.3 mmol) as starting material. Yield: 96% (2.8 g), isolated as brown solid (mp = 74 – 75 °C). Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.57 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.62 (td, *J* = 7.4, 1.4 Hz, 2H), 7.55 – 7.45 (m, 3H), 7.35 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.74 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.5, 149.2, 136.6, 133.8, 133.63, 133.62, 130.8, 128.9, 128.5, 128.4, 125.4, 44.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{12}NO_3^+$ 242.0812; Found 242.0815.

IR (ν_{max}, cm^{-1}) 3060 (w), 2925 (w), 2848 (w), 1685 (s), 1448 (m), 1412 (m), 1342 (s), 1309 (m), 1217 (s), 993 (s), 862 (m), 789 (m), 756 (s), 731 (s), 690 (s).



2.3.2n, 1-(4-bromophenyl)-2-(2-nitrophenyl)ethan-1-one

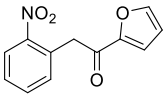
This compound was prepared following general procedure **C** using compound **2.3.7n** (4.0 g, 12.5 mmol) as starting material. Yield: 94% (3.7 g), isolated as light brown solid (mp = 85 – 86 °C). Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.5 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.61 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.50 (td, *J* = 7.8, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.5 Hz, 1H), 4.68 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.6, 149.0, 135.3, 133.8, 133.7, 132.2, 130.5, 129.9, 128.8, 128.7, 125.5, 44.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{11}BrNO_3^+$ 319.9917; Found 319.9910.

IR (ν_{max}, cm^{-1}) 2917 (w), 1687 (s), 1583 (m), 1522 (s), 1342 (s), 1215 (m), 1070 (m), 991 (s), 816 (m), 789 (m), 735 (m), 708 (m).



2.3.2p, 1-(furan-2-yl)-2-(2-nitrophenyl)ethan-1-one

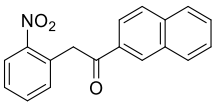
This compound was prepared following general procedure **D** using compound **2.3.7p** (2.0 g, 8.6 mmol) as starting material. Yield: 56% (1.1 g), isolated as light brown solid (mp = 70 -71 °C). Purification: Flash chromatography (PE/DCM, 1:1), R_f = 0.25 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.63 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.60 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.49 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.29 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.59 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 184.5, 152.4, 149.2, 146.7, 133.9, 133.6, 129.8, 128.6, 125.4, 117.6, 112.7, 43.7.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_9NNaO_4^+$ 254.0424; Found 254.0430.

IR (ν_{max}, cm^{-1}) 2917 (w), 2848 (w), 1759 (m), 1707 (m), 1678 (m), 1523 (s), 1466 (m), 1344 (s), 1146 (m), 1084 (m), 997 (m), 914 (m),887 (m), 827 (m), 789 (m), 725 (m), 704 (m).



2.3.2q, 1-(naphthalen-2-yl)-2-(2-nitrophenyl)ethan-1-one

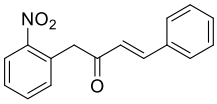
This compound was prepared following general procedure **C** using compound **2.3.7q** (7.0 g, 24 mmol) as starting material. Yield: quant. (7.0 g), isolated as brown solid (mp = 126 – 127 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.36 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.70 – 7.54 (m, 3H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 4.88 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.4, 149.2, 135.9, 134.0, 133.8, 133.7, 132.7, 130.9, 130.1, 129.8, 128.79, 128.78, 128.6, 128.0, 127.0, 125.5, 124.0, 44.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{13}NNaO_3^+$ 314.0788; Found 314.0788.

IR (ν_{max}, cm^{-1}) 3068 (w), 2925 (w), 1681 (s), 1520 (s), 1469 (m), 1346 (s), 1184 (m), 1124 (m), 998 (m), 943 (m), 862 (m), 821 (m), 723 (s).



2.3.2ak, (E)-1-(2-nitrophenyl)-4-phenylbut-3-en-2-one

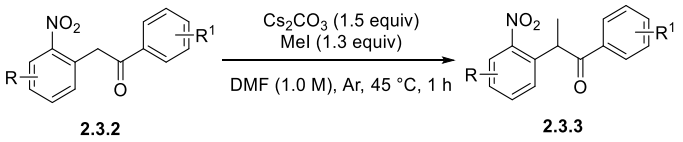
This compound was prepared following general procedure **C** using compound **2.3.7ak** (6.3 g, 23 mmol) as starting material. Yield: 82% (5.1 g), isolated as colorless oil. Purification: Flash chromatography (PE/DCM, 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.68 (d, *J* = 16.1 Hz, 1H), 7.64 – 7.54 (m, 3H), 7.52 – 7.45 (m, 1H), 7.44 – 7.38 (m, 3H), 7.35 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.87 (d, *J* = 16.1 Hz, 1H), 4.40 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.0, 149.2, 143.8, 134.4, 133.7, 133.6, 130.9, 130.6, 129.1, 128.6, 128.5, 125.5, 125.4, 46.2.

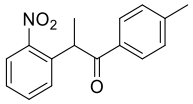
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}NO_3^+$ 268.0969; Found 268.0979.

6.2.3. **General procedure E for the alkylation of the ketones**



2.3.2 **2.3.3**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **2.3.2a** (2.4 g, 9.4 mmol, 1.0 equiv) in DMF (9.4 mL, 1.0 M), Cs_2CO_3 (6.0 g, 14.1 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of MeI (0.96 mL, 14.4 mmol, 1.3 equiv). The reaction mixture was heated at 45 °C in the oil bath for 1 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.3a**.



2.3.3a, 2-(2-nitrophenyl)-1-(p-tolyl)propan-1-one

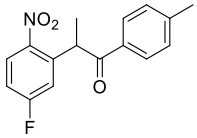
This compound was prepared following general procedure **E** using compound **2.3.2a** (2.1 g, 9.5 mmol) as starting material. Yield: 76% (1.9 g), isolated as light brown solid (mp = 65 – 66 °C). Purification: Flash chromatography (PE/EtOAc, 50:10), R_f = 0.4 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.3, 7.3, 1.4 Hz, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.34 (q, *J* = 6.9 Hz, 1H), 2.37 (s, 3H), 1.58 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.2, 148.8, 144.2, 136.0, 133.5, 133.4, 129.9, 129.6, 128.9, 127.9, 125.0, 42.4, 21.8, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_3^+$ 292.0944; Found 292.0946.

IR (ν_{max}, cm^{-1}) 2988 (w), 2918 (w), 2854 (w), 1674 (s), 1518 (s), 1339 (s), 1182 (s), 965 (s), 719 (s).



2.3.3f, 2-(5-fluoro-2-nitrophenyl)-1-(p-tolyl)propan-1-one

This compound was prepared following general procedure **E** using compound **2.3.2f** (1.3 g, 4.8 mmol) as starting material. Yield: 77% (1.05 g), isolated as yellow solid (mp = 58 – 59 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.21 (PE/EtOAc 98:2).

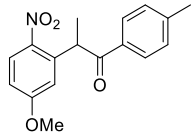
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 9.1, 5.2 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.17 (dd, *J* = 9.5, 2.8 Hz, 1H), 7.06 (ddd, *J* = 9.4, 7.0, 2.8 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 2.39 (s, 3H), 1.58 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 165.1 (d, *J* = 256.9 Hz), 144.8 (br), 144.6, 139.9 (d, *J* = 9.0 Hz), 133.2, 129.7, 128.9, 128.0 (d, *J* = 10.0 Hz), 117.2 (d, *J* = 24.3 Hz), 115.1 (d, *J* = 23.4 Hz), 42.5, 21.8, 18.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ -105.89.

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}FNO_3^+$ 288.1030; Found 288.1031.

IR (ν_{max}, cm^{-1}) 3064 (w), 2981 (w),2940 (w), 1680 (m), 1587 (m), 1523 (s), 1346 (m),1265 (m), 1227 (m), 1203 (m), 1184 (m), 964 (m), 829 (m), 735 (s), 719 (s), 702 (m).



2.3.3g, 2-(5-methoxy-2-nitrophenyl)-1-(p-tolyl)propan-1-one

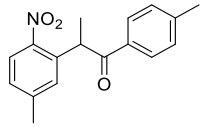
This compound was prepared following general procedure **E** using compound **2.3.2g** (2.2 g, 7.6 mmol) as starting material. Yield: 53% (1.2 g), isolated as light brown solid (mp = 112 – 113 °C). Purification: Flash chromatography (PE/EtOAc, 50:10), R_f = 0.36 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.9 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.86 – 6.78 (m, 2H), 5.55 (q, *J* = 6.9 Hz, 1H), 3.82 (s, 3H), 2.37 (s, 3H), 1.57 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.4, 163.6, 144.2, 141.5, 139.5, 133.6, 129.6, 128.9, 128.2, 115.0, 112.6, 56.0, 42.8, 21.8, 18.5.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_4^+$ 322.1050; Found 322.1052.

IR (ν_{max}, cm^{-1}) 2973 (w), 2937 (w), 2877 (w), 1680 (s), 1606 (s), 1578 (s), 1508 (s), 1338 (s), 1292 (s), 1281 (s), 1246 (s), 1180 (m),964 (m), 829 (m).



2.3.3h, 2-(5-methyl-2-nitrophenyl)-1-(p-tolyl)propan-1-one

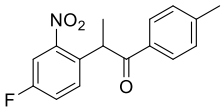
This compound was prepared following general procedure **E** using compound **2.3.2h** (0.9 g, 3.3 mmol) as starting material. Yield: 72% (0.68 g), isolated as colorless crystals (mp = 88 – 89 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.5 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18 – 7.12 (m, 2H), 5.40 (q, *J* = 7.0 Hz, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.4, 146.4, 144.8, 144.2, 136.2, 133.5, 130.2, 129.5, 128.9, 128.6, 125.3, 42.3, 21.7, 21.67, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_3^+$ 306.1101; Found 306.1105.

IR (ν_{max}, cm^{-1}) 2987 (w), 2925 (w), 1680 (m), 1606 (m), 1516 (s), 1342 (s), 1265 (m), 1234 (m), 1182 (m), 962 (m), 843 (m), 829 (m), 735 (s), 704 (m).



2.3.3i, 2-(4-fluoro-2-nitrophenyl)-1-(p-tolyl)propan-1-one

This compound was prepared following general procedure **E** using compound **2.3.2i** (6.0 g, 22 mmol) as starting material. Yield: 85% (5.4 g), isolated as yellow solid (mp = 83 – 85 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.46 (PE/EtOAc 90:10).

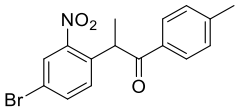
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.65 (dd, J = 8.2, 2.7 Hz, 1H), 7.44 (dd, J = 8.8, 5.4 Hz, 1H), 7.30 – 7.20 (m, 3H), 5.33 (q, J = 7.0 Hz, 1H), 2.38 (s, 3H), 1.57 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.1, 161.0 (d, J = 251.2 Hz), 149.1 (d, J = 8.1 Hz), 144.5, 133.3, 132.0 (d, J = 3.9 Hz), 131.7 (d, J = 8.0 Hz), 129.7, 128.8, 120.9 (d, J = 20.9 Hz), 112.5 (d, J = 26.4 Hz), 41.8, 21.8, 18.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.00 (td, J = 7.7, 5.4 Hz).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}FNaNO_3^+$ 310.0850; Found 310.0850.

IR (ν_{max}, cm^{-1}) 2948 (w), 1682 (m), 1608 (m), 1533 (s), 1500 (w), 1352 (m), 1234 (m), 964 (m), 935 (w), 832 (w).



2.3.3j, 2-(4-bromo-2-nitrophenyl)-1-(p-tolyl)propan-1-one

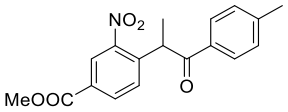
This compound was prepared following general procedure **E** using compound **2.3.2j** (3.0 g, 9.0 mmol) as starting material. Yield: 67% (2.1 g), isolated as yellow solid (mp = 80 – 81 °C). Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.65 (dd, J = 8.5, 2.1 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 5.29 (q, J = 7.0 Hz, 1H), 2.38 (s, 3H), 1.56 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 149.2, 144.5, 136.4, 134.9, 133.2, 131.4, 129.7, 128.8, 127.8, 121.1, 42.0, 21.8, 18.6.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}BrNNaO_3^+$ 370.0049; Found 370.0058.

IR (ν_{max}, cm^{-1}) 2981 (w), 2933 (w), 2867 (w), 1680 (s), 1606 (m), 1525 (s), 1477 (m), 1450 (m), 1375 (m), 1346 (s), 1281 (m), 1263 (m), 1246 (m), 1225 (m), 1203 (m), 1103 (m), 1005 (m), 964 (m), 874 (m), 829 (m), 791 (m), 771 (m), 758 (m), 735 (s), 700 (m).



2.3.3k, methyl 3-nitro-4-(1-oxo-1-(p-tolyl)propan-2-yl)benzoate

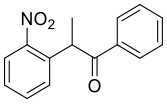
This compound was prepared following general procedure **E** using compound **2.3.2k** (1.6 g, 5.1 mmol) as starting material. Yield: 84% (1.4 g), isolated as colorless crystals (mp = 59 – 60 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.38 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.37 (q, *J* = 7.0 Hz, 1H), 3.94 (s, 3H), 2.38 (s, 3H), 1.60 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 164.9, 148.9, 144.6, 140.5, 134.2, 133.2, 130.4, 130.3, 129.7, 128.9, 126.1, 52.9, 42.6, 21.8, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}NNaO_5^+$ 350.0999; Found 350.0995.

IR (ν_{max}, cm^{-1}) 2948 (w), 1726 (s), 1680 (m), 1606 (m), 1533 (s), 1437 (m), 1350 (m), 1294 (m), 1265 (s), 1180 (m), 1122 (m), 966 (m), 823 (m), 735 (s), 719 (s).



2.3.3l, 2-(2-nitrophenyl)-1-phenylpropan-1-one

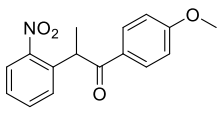
This compound was prepared following general procedure **E** using compound **2.3.2l** (1.0 g, 4.2 mmol) as starting material. Yield: 55% (0.58 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.27 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.91 (m, 3H), 7.57 – 7.49 (m, 2H), 7.45 – 7.36 (m, 4H), 5.38 (q, *J* = 7.0 Hz, 1H), 1.59 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6, 148.8, 136.0, 135.8, 133.5, 133.4, 129.9, 129.89, 128.8, 128.0, 125.1, 42.6, 18.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}NO_3^+$ 256.0968; Found 256.0966.

IR (ν_{max}, cm^{-1}) 3050 (w), 2994 (w), 2921 (w), 1685 (s), 1523 (s), 1450 (m), 1346 (s), 1209 (m), 968 (m), 855 (m), 784 (m), 727 (m), 703 (s).



2.3.3m, 1-(4-methoxyphenyl)-2-(2-nitrophenyl)propan-1-one

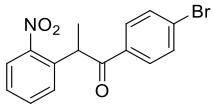
This compound was prepared following general procedure **E** using compound **2.3.2m** (1.0 g, 3.7 mmol) as starting material. Yield: 83% (0.87 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.88 (m, 3H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.32 (q, *J* = 7.0 Hz, 1H), 3.80 (s, 3H), 1.56 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 163.6, 148.7, 136.0, 133.3, 130.9, 129.7, 128.7, 127.8, 124.7, 113.9, 55.4, 41.9, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_4^+$ 308.0893; Found 308.0899.

IR (ν_{max}, cm^{-1}) 2937 (w), 2839 (w), 2676 (m), 1599 (s), 1512 (s), 1460 (m), 1344 (s), 1248 (s), 1228 (s), 1169 (s), 1028 (m), 966 (m), 856 (m), 841 (s), 787(m), 752 (m).



2.3.3n, 1-(4-bromophenyl)-2-(2-nitrophenyl)propan-1-one

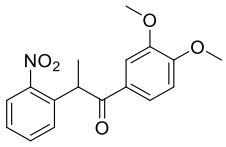
This compound was prepared following general procedure **E** using compound **2.3.2n** (1.2 g, 3.8 mmol) as starting material. Yield: 70% (1.1 g), isolated as yellow solid (mp = 67 – 68 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.27 (PE/EtOAc 95:5).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.59 – 7.51 (m, 3H), 7.44 – 7.35 (m, 2H), 5.31 (q, *J* = 6.9 Hz, 1H), 1.57 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 148.7, 135.4, 134.7, 133.6, 132.2, 130.3, 129.8, 128.6, 128.2, 125.1, 42.6, 18.5.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{12}BrNNaO_3^+$ 355.9893; Found 355.9898.

IR (ν_{max}, cm^{-1}) 2981 (w), 2929 (w), 2871 (w), 1684 (s), 1583 (m), 1522 (s), 1481 (m), 1396 (m), 1344 (s), 1306 (m), 1286 (m), 1221 (m), 1203 (m), 1176 (m), 1070 (m), 1009 (m), 966 (s), 947 (m), 856 (m), 841 (m), 783 (s), 744 (s), 733 (s), 706 (m).



2.3.3o, 1-(3,4-dimethoxyphenyl)-2-(2-nitrophenyl)propan-1-one

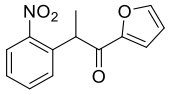
This compound was prepared following general procedure **E** using compound **2.3.2o** (1.3 g, 4.3 mmol) as starting material. Yield: 55% (0.75 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.22 (PE/EtOAc 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.55 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.39 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.38 – 7.33 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 5.30 (q, *J* = 6.9 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 1.56 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 153.4, 149.1, 148.8, 136.1, 133.4, 129.7, 129.0, 127.9, 124.8, 123.3, 110.9, 110.3, 56.1, 56.0, 41.9, 19.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}BrNO_2^+$ 316.1180; Found 316.0335.

IR (ν_{max}, cm^{-1}) 2933 (w), 2834 (w), 1674 (m), 1581 (m), 1514 (s), 1464 (m), 1444 (m), 1415 (m), 1344 (m), 1261 (s), 1242 (s), 1205 (s), 1167 (m), 1151 (s), 1132 (m), 1020 (s), 791 (m), 766 (m), 744 (m), 729 (m), 715 (m).



2.3.3p, 1-(furan-2-yl)-2-(2-nitrophenyl)propan-1-one

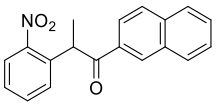
This compound was prepared following general procedure **E** using compound **2.3.2p** (1.2 g, 5.2 mmol) as starting material. Yield: 88% (1.12 g), isolated as colorless oil. Purification: Flash chromatography (PE/Et_2O, 93:7), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.4 Hz, 1H), 7.50 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 (ddd, *J* = 8.6, 7.2, 1.6 Hz, 1H), 7.19 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.47 (dd, *J* = 3.6, 1.7 Hz, 1H), 5.11 (q, *J* = 6.9 Hz, 1H), 1.60 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 188.2, 152.0, 149.4, 146.8, 135.1, 133.3, 129.7, 128.1, 124.8, 118.2, 112.5, 42.5, 17.9.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{11}NNaO_4^+$ 268.0580; Found 268.0578.

IR (ν_{max}, cm^{-1}) 3037 (w), 2942 (w), 1674 (s), 1524 (s), 1465 (m), 1348 (m), 1257 (w), 1095 (w), 10118 (w), 756 (s).



2.3.3q, 1-(naphthalen-2-yl)-2-(2-nitrophenyl)propan-1-one

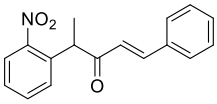
This compound was prepared following general procedure **E** using compound **2.3.2q** (1.5 g, 5.2 mmol) as starting material. Yield: 75% (1.2 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.4 (PE/Et_2O 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.00 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.93-7.90 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 8.2, 1.5 Hz, 1H), 7.55-7.50 (m, 2H), 7.45 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.37 (td, *J* = 8.5, 1.5 Hz, 1H), 5.52 (q, *J* = 6.9 Hz, 1H), 1.65 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.5, 149.0, 135.8, 135.7, 133.5, 133.2, 132.6, 130.6, 129.9, 129.8, 128.8, 128.75, 128.1, 127.8, 126.9, 125.0, 124.4, 42.6, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{15}NNaO_3^+$ 328.0944; Found 328.0939.

IR (ν_{max}, cm^{-1}) 2976 (m), 2935 (w), 2867 (w), 1745 (s), 1525 (s), 1352 (s), 1167 (m), 1130 (s), 1103 (s), 1066 (m), 787 (m), 748 (s), 706 (m).



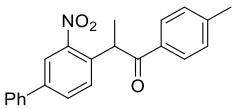
2.3.3ak, (E)-4-(2-nitrophenyl)-1-phenylpent-1-en-3-one

This compound was prepared following general procedure **E** using compound **2.3.2ak** (1.3 g, 5.1 mmol) as starting material. Yield: 66% (0.9 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.18 (PE/Et_2O 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.64 (d, *J* = 16.0 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.52 – 7.47 (m, 2H), 7.46 – 7.32 (m, 6H), 6.76 (d, *J* = 15.9 Hz, 1H), 4.70 (q, *J* = 6.9 Hz, 1H), 1.55 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.3, 149.6, 143.8, 135.2, 134.4, 133.4, 130.8, 130.0, 129.0, 128.6, 128.2, 124.8, 124.6, 45.9, 17.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}NNaO_3^+$ 304.0944; Found 304.0944.



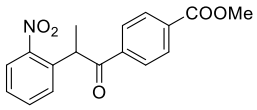
2.3.3al, 2-(3-nitro-[1,1'-biphenyl]-4-yl)-1-(p-tolyl)propan-1-one

This compound was prepared following general procedure **E** using compound **2.3.2al** (1.2 g, 3.6 mmol) as starting material. Yield: 73% (0.9 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.32 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.74 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.51 – 7.37 (m, 4H), 7.25 – 7.20 (m, 2H), 5.38 (q, *J* = 6.9 Hz, 1H), 2.38 (s, 3H), 1.62 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.3, 149.2, 144.3, 141.3, 138.3, 134.6, 133.5, 131.8, 130.3, 129.6, 129.3, 128.9, 128.6, 127.1, 123.3, 42.2, 21.8, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{19}NNaO_3^+$ 368.1258; Found 368.1267.



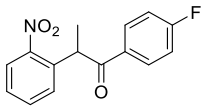
2.3.3ap, methyl 4-(2-(2-nitrophenyl)propanoyl)benzoate

This compound was prepared following general procedure **E** using compound **2.3.2ap** (160 mg, 0.5 mmol) as starting material. Yield: 62% (0.1 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.08 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.5 Hz, 2H), 8.02 – 7.92 (m, 3H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 – 7.33 (m, 2H), 5.38 (q, *J* = 7.0 Hz, 1H), 3.93 (s, 3H), 1.60 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.2, 166.2, 148.7, 139.3, 135.3, 134.0, 133.6, 130.0, 129.8, 128.6, 128.2, 125.2, 52.6, 43.1, 18.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{16}NO_5^+$ 314.1023; Found 314.1026.



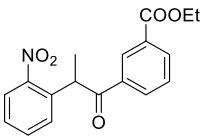
2.3.3aq, 1-(4-fluorophenyl)-2-(2-nitrophenyl)propan-1-one

This compound was prepared following general procedure **E** using compound **2.3.2aq** (150 mg, 0.6 mmol) as starting material. Yield: 68% (0.11 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.12 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.85 (m, 3H), 7.61 – 7.51 (m, 1H), 7.45 – 7.35 (m, 2H), 7.14 – 7.03 (m, 2H), 5.33 (q, *J* = 6.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 165.80 (d, *J* = 255.3 Hz), 148.7, 135.5, 133.5, 132.30 (d, *J* = 3.1 Hz), 131.37 (d, *J* = 9.5 Hz), 129.8, 128.1, 125.0, 115.98 (d, *J* = 21.8 Hz), 42.5, 18.6.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{15}NNaO_3^+$ 304.0944; Found 304.0944.



2.3.3ar, ethyl 3-(2-(2-nitrophenyl)propanoyl)benzoate

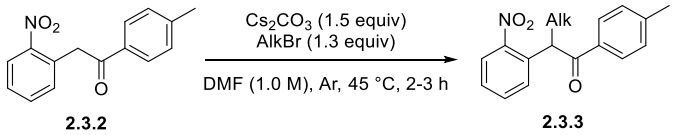
This compound was prepared following general procedure **E** using compound **2.3.2ar** (1.0 g, 3.2 mmol) as starting material. Yield: 56% (0.59 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.22 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (t, *J* = 1.8 Hz, 1H), 8.20 (dt, *J* = 7.7, 1.4 Hz, 1H), 8.16 – 8.08 (m, 1H), 7.95 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.65 – 7.47 (m, 2H), 7.44 – 7.34 (m, 2H), 5.41 (q, *J* = 6.9 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 1.61 (d, *J* = 6.9 Hz, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 165.8, 148.5, 136.2, 135.5, 134.1, 133.7, 132.7, 131.4, 129.8, 129.1, 128.2, 125.2, 61.6, 42.9, 18.5, 14.4.

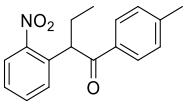
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{17}NNaO_5^+$ 350.0999; Found 350.1005.

Procedure F



2.3.2 **2.3.3**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask was charged ketone **2.3.2a** (1.5 g, 5.9 mmol, 1.0 equiv) in DMF (6.0 mL, 1.0 M), Cs_2CO_3 (2.9 g, 8.8 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of ethyl iodide (0.6 mL, 7.6 mmol, 1.3 equiv). The reaction mixture was heated at 45 °C in the oil bath for 2-3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the desired ketone **2.3.3r**.



2.3.3r, 2-(2-nitrophenyl)-1-(p-tolyl)butan-1-one

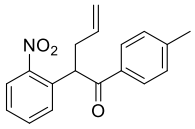
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.5 g, 5.9 mmol) as starting material. Yield: 72% (1.1 g), isolated as colorless oil. Purification: Flash chromatography (PE/DCM, 85:15), R_f = 0.28 (PE/DCM 7:3).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 2H), 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.35 (ddd, *J* = 8.1, 7.1, 1.7 Hz, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 5.20 (t, *J* = 7.3 Hz, 1H), 2.37 (s, 3H), 2.27-2.17 (m, 1H), 1.92-1.82 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 149.7, 144.4, 134.1, 134.1, 133.2, 130.0, 129.6, 128.9, 127.9, 124.8, 48.6, 27.4, 21.8, 12.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_3^+$ 306.1101; Found 306.1108.

IR (ν_{max}, cm^{-1}) 2969 (w), 2932 (w), 2875 (w), 1678 (s), 1604 (m), 1524 (s), 1454 (m), 1349 (s), 1265 (m), 1228 (m), 1180 (m), 858 (m), 784 (m), 738 (s).



2.3.3s, 2-(2-nitrophenyl)-1-(p-tolyl)pent-4-en-1-one

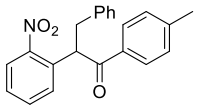
This compound was prepared following general procedure **F** using compound **2.3.2a** (0.6 g, 2.4 mmol) as starting material. Yield: 77% (0.5 g), isolated as colorless crystals (mp = 64 – 65 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.54 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 2H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.35 (ddd, *J* = 8.5, 7.2, 1.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.80 – 5.68 (m, 1H), 5.42 (t, *J* = 7.2 Hz, 1H), 5.03 – 4.95 (m, 2H), 2.98 – 2.89 (m, 1H), 2.61 – 2.50 (m, 1H), 2.36 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.1, 149.4, 144.5, 134.8, 133.8, 133.7, 133.3, 130.0, 129.6, 128.9, 128.1, 125.0, 117.9, 47.2, 38.0, 21.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_3^+$ 296.1281; Found 296.1283.

IR (ν_{max}, cm^{-1}) 3064 (w), 1678 (s), 1606 (m), 1523 (s), 1348 (s), 1263 (m), 1246 (m), 1203 (m), 1180 (m), 997 (m), 918 (m), 854 (m), 814 (m), 785 (m), 739 (s), 721 (s).



2.3.3u, 2-(2-nitrophenyl)-3-phenyl-1-(p-tolyl)propan-1-one

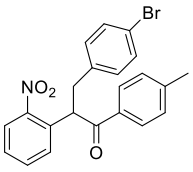
This compound was prepared following general procedure **F** using compound **2.3.2a** (2.0 g, 7.8 mmol) as starting material. Yield: 81% (2.2 g), isolated as brown solid (mp = 71 – 72 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.80 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.37 – 7.30 (m, 1H), 7.24 – 7.11 (m, 7H), 5.71 (dd, *J* = 7.8, 6.7 Hz, 1H), 3.57 (dd, *J* = 13.6, 7.8 Hz, 1H), 3.08 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 149.3, 144.4, 138.7, 133.8, 133.82, 133.4, 129.9, 129.6, 129.3, 128.9, 128.6, 128.1, 126.6, 125.0, 49.3, 40.0, 21.7.

HRMS (ESI) calcd for $C_{22}H_{19}NNaO_3^+$ $[M+Na]^+$ 368.1257; found 368.1256.

IR (ν_{max}, cm^{-1}) 3062 (w), 3027 (w), 2946 (w), 1667 (s), 1524 (s), 1354 (m), 1295 (m), 784 (m), 739 (m), 700 (s).



2.3.3v, 3-(4-bromophenyl)-2-(2-nitrophenyl)-1-(p-tolyl)propan-1-one

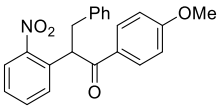
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 60% (0.96 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.29 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.50 (td, *J* = 7.4, 1.4 Hz, 1H), 7.44 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.35 (td, *J* = 7.4, 1.5 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 5.61 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.50 (dd, *J* = 13.6, 8.3 Hz, 1H), 3.02 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.32 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 149.1, 144.6, 137.8, 133.7, 133.5, 133.5, 131.6, 131.1, 129.7, 129.6, 128.8, 128.3, 125.2, 120.6, 49.2, 39.2, 21.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}BrNNaO_3^+$ 446.0362; Found 446.0365.

IR (ν_{max}, cm^{-1}) 3064 (w), 2922 (w), 1678 (s), 1606 (m), 1523 (s), 1487 (m), 1441 (m), 1348 (s), 1294 (m), 1238 (m), 1221 (m), 1180 (m), 1072 (m), 1011 (m), 930 (m), 854 (m), 831 (m), 785 (m), 737 (s), 717 (s).



2.3.3w, 1-(4-methoxyphenyl)-2-(2-nitrophenyl)-3-phenylpropan-1-one

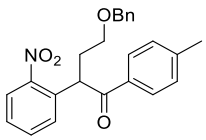
This compound was prepared following general procedure **F** using compound **2.3.2m** (1.0 g, 3.7 mmol) as starting material. Yield: 80% (1.1 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 2H), 7.78 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.54 – 7.48 (m, 2H), 7.38 – 7.31 (m, 1H), 7.23 – 7.07 (m, 5H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.66 (dd, *J* = 7.7, 6.7 Hz, 1H), 3.79 (s, 3H), 3.53 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.05 (dd, *J* = 13.6, 6.7 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.8, 163.8, 149.2, 138.7, 134.0, 133.4, 131.2, 129.9, 129.3, 128.5, 128.1, 126.6, 124.9, 114.0, 55.6, 49.0, 40.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}NO_4^+$ 362.1387; Found 362.1370.

IR (ν_{max}, cm^{-1}) 2937 (w), 2839 (w), 1672 (m), 1599 (s), 1523 (s), 1493 (m), 1346 (s), 1244 (s), 1169 (s), 1026 (m), 941 (m), 852 (m), 752 (s),



2.3.3x, 4-(benzyloxy)-2-(2-nitrophenyl)-1-(p-tolyl)butan-1-one

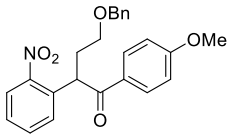
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 64% (0.98 g), isolated as brown solid (mp = 52 – 53 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.51 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.35 (ddd, *J* = 8.4, 6.2, 2.3 Hz, 1H), 7.32 – 7.23 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.56 (t, *J* = 7.1 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 3.49 (ddd, *J* = 9.6, 6.2, 5.4 Hz, 1H), 3.38 (ddd, *J* = 9.6, 7.4, 5.2 Hz, 1H), 2.54 (dtd, *J* = 14.1, 7.1, 5.4 Hz, 1H), 2.36 (s, 3H), 2.12 (dddd, *J* = 14.1, 7.1, 6.2, 5.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 149.8, 144.4, 138.3, 133.9, 133.8, 133.2, 130.2, 129.6, 129.0, 128.4, 128.0, 127.7, 127.6, 124.9, 73.0, 67.7, 43.8, 34.1, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_4^+$ 412.1519; Found 412.1522.

IR (ν_{max}, cm^{-1}) 2933 (w), 2868 (w),1678 (m), 1606 (m), 1523 (s), 1452 (m), 1350 (s), 1273 (s), 1250 (m), 1238 (m), 1203 (m), 1103 (s), 1072 (m), 1001 (m), 970 (m), 856 (m), 839 (m), 820 (m), 785 (s), 737 (s), 717 (s).



2.3.3y, 4-(benzyloxy)-1-(4-methoxyphenyl)-2-(2-nitrophenyl)butan-1-one

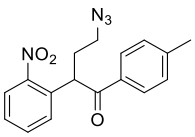
This compound was prepared following general procedure **F** using compound **2.3.2m** (0.6 g, 2.2 mmol) as starting material. Yield: 60% (0.54 g), isolated as orange crystals (mp = 106 – 107 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.37 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 2H), 7.83 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.39 – 7.33 (m, 1H), 7.32 – 7.21 (m, 5H), 6.88 (d, *J* = 9.0 Hz, 2H), 5.54 (t, *J* = 7.1 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 4.36 (d, *J* = 11.9 Hz, 1H), 3.83 (s, 3H), 3.49 (ddd, *J* = 9.6, 6.3, 5.3 Hz, 1H), 3.38 (ddd, *J* = 9.6, 7.3, 5.1 Hz, 1H), 2.52 (dtd, *J* = 14.3, 7.2, 5.3 Hz, 1H), 2.11 (dddd, *J* = 12.3, 7.1, 6.3, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 163.8, 149.7, 138.3, 133.9, 133.1, 131.2, 130.2, 129.3, 128.4, 127.9, 127.7, 127.6, 124.8, 114.0, 73.0, 67.6, 55.6, 43.4, 34.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_5^+$ 428.1468; Found 428.1465.

IR (ν_{max}, cm^{-1}) 2929 (w), 2873 (w), 2839 (w), 1674 (m), 1500 (s), 1574 (m), 1523 (s), 1510 (s), 1454 (m), 1348 (s), 1309 (m), 1257 (s), 1211 (m), 1171 (s), 1111 (s), 1086 (m), 1072 (m), 1028 (s), 985 (m), 858 (m), 785 (m), 758 (m), 733 (s).



2.3.3z, 4-azido-2-(2-nitrophenyl)-1-(p-tolyl)butan-1-one

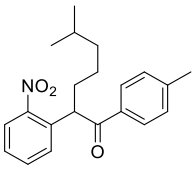
This compound was prepared following general procedure **F** using compound **2.3.2a** (5.0 g, 20.7 mmol) as starting material. Yield: 75% (4.8 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.37 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.48 (m, 1H), 7.41 – 7.36 (m, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.41 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.42 – 3.27 (m, 2H), 2.57 – 2.45 (m, 1H), 2.36 (s, 3H), 2.14 – 2.04 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.6, 149.3, 144.8, 133.5, 133.47, 133.2, 129.8, 129.7, 128.9, 128.4, 125.2, 49.5, 44.3, 32.9, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}N_4NaO_3^+$ 347.1115; Found 347.1114.

IR (ν_{max}, cm^{-1}) 3058 (w), 2921 (w), 2092 (s), 1680 (s), 1608 (m), 1523 (s),1348 (s),1263 (m), 1183 (m), 972 (w),785 (m), 741 (m).



2.3.3aa, 6-methyl-2-(2-nitrophenyl)-1-(p-tolyl)heptan-1-one

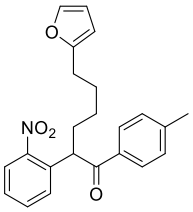
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.5 g, 5.9 mmol) as starting material. Yield: 74% (1.5 g), isolated as colorless. Purification: Flash chromatography (PE/Et_2O, 97:3), R_f = 0.38 (PE/Et_2O 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.82 (m, 3H), 7.55 – 7.45 (m, 2H), 7.38 – 7.32 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.28 (t, *J* = 7.4 Hz, 1H), 2.37 (s, 3H), 2.22 – 2.11 (m, 1H), 1.84 – 1.72 (m, 1H), 1.53-1.43 (m, 1H), 1.38 – 1.10 (m, 4H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 149.6, 144.4, 134.3, 134.1, 133.2, 130.0, 129.6, 128.9, 127.9, 124.8, 47.0, 38.8, 34.4, 27.9, 25.7, 22.7, 22.6, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{25}NNaO_3^+$ 362.1727; Found 362.1727.

IR (ν_{max}, cm^{-1}) 2950 (m), 2925 (m), 2867 (w), 1680 (s), 1608 (m), 1522 (s), 1465 (m), 1348 (s), 1274 (m), 1180 (m), 785 (m), 740 (m).



2.3.3ab, 6-(furan-2-yl)-2-(2-nitrophenyl)-1-(p-tolyl)hexan-1-one

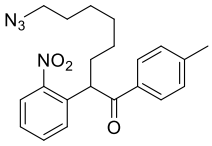
This compound was prepared following general procedure **F** using compound **2.3.2a** (0.94 g, 3.7 mmol) as starting material. Yield: 41% (0.57 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.44 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 3H), 7.53 – 7.48 (m, 1H), 7.45 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.35 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.21 (d, *J* = 7.7 Hz, 2H), 6.24 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.93 (dd, *J* = 3.1, 0.9 Hz, 1H), 5.28 (t, *J* = 7.0 Hz, 1H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 2.29 – 2.17 (m, 1H), 1.90 – 1.79 (m, 1H), 1.73 – 1.59 (m, 2H), 1.48 – 1.35 (m, 1H), 1.35 – 1.24 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.6, 156.1, 149.5, 144.4, 140.9, 134.2, 134.0, 133.3, 130.0, 129.6, 128.8, 127.9, 124.9, 110.2, 104.9, 47.0, 33.8, 28.1, 27.8, 27.4, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{23}NaNO_4^+$ 400.1519; Found 400.1527.

IR (ν_{max}, cm^{-1}) 2930 (w), 2863 (m), 1678 (m), 1606 (m), 1523 (s), 1348 (m), 1300 (m), 1265 (m), 1232 (m), 1205 (m), 1180 (m), 1146 (m), 1117 (m), 1020 (m), 1003 (m), 978 (m), 958 (m), 930 (m), 854 (m), 827 (m), 808 (m), 785 (m), 735 (s), 719 (s), 700 (m).



2.3.3ac, 8-azido-2-(2-nitrophenyl)-1-(p-tolyl)octan-1-one

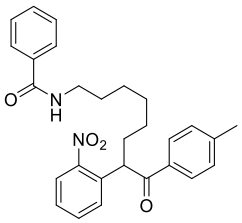
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 40% (0.6 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 3H), 7.50 (td, *J* = 7.6, 1.4 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 5.27 (t, *J* = 7.1 Hz, 1H), 3.22 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 2.25 – 2.16 (m, 1H), 1.83 – 1.77 (m, 1H), 1.57-1.52 (m, 2H), 1.37 – 1.29 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 149.4, 144.5, 134.2, 133.9, 133.3, 129.9, 129.6, 128.8, 127.9, 124.9, 51.5, 46.9, 34.0, 29.1, 28.8, 27.7, 26.5, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{24}N_4NaO_3^+$ 403.1741; Found 403.1745.

IR (ν_{max}, cm^{-1}) 2929 (w), 2859 (w), 2362 (w), 2337 (w), 2094 (s), 1680 (s), 1604 (m), 1525 (s), 1350 (s), 1253 (m), 1180 (m), 784 (m), 740 (m), 723 (m).



2.3.3ad, N-(7-(2-nitrophenyl)-8-oxo-8-(p-tolyl)octyl)benzamide

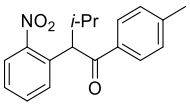
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 67% (1.2 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 70:20), R_f = 0.4 (PE/EtOAc 20:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.81 (m, 3H), 7.78 – 7.72 (m, 2H), 7.53 – 7.38 (m, 5H), 7.34 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.16 (br t, *J* = 6.3 Hz, 1H), 5.27 (t, *J* = 7.0 Hz, 1H), 3.42 (apparent q, *J* = 5.6 Hz, 2H), 2.36 (s, 3H), 2.26 – 2.14 (m, 1H), 1.84 – 1.74 (m, 1H), 1.71 – 1.52 (m, 3H), 1.41 – 1.23 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 167.6, 149.5, 144.4, 135.0, 134.2, 134.0, 133.3, 131.4, 129.9, 129.6, 128.8, 128.7, 127.9, 127.0, 124.9, 46.9, 40.1, 34.0, 29.6, 29.2, 27.7, 26.8, 21.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{31}N_2O_4^+$ 459.2278; Found 459.2290.

IR (ν_{max}, cm^{-1}) 2927 (w), 2854 (w), 1680 (m), 1637 (m), 1604 (m), 1552 (m), 1489 (m), 1348 (m), 1308 (m), 1263 (m), 1250 (m), 1180 (m), 785 (m), 733 (s), 710 (s).



2.3.3ae, 3-methyl-2-(2-nitrophenyl)-1-(p-tolyl)butan-1-one

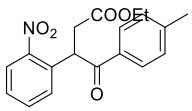
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 66% (0.77 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.84 (m, 2H), 7.75 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 1.4 Hz, 1H), 7.32 (ddd, *J* = 8.6, 7.4, 1.4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.10 (d, *J* = 10.0 Hz, 1H), 2.56 (dp, *J* = 10.0, 6.7 Hz, 1H), 2.37 (s, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.6, 150.7, 144.5, 134.8, 133.0, 132.9, 130.2, 129.6, 128.9, 127.8, 124.5, 52.7, 33.6, 22.0, 21.7, 20.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}NNaO_3^+$ 320.1258; Found 320.1266.

IR (ν_{max}, cm^{-1}) 2927 (w), 2854 (w), 1680 (m), 1637 (m), 1604 (m), 1552 (m), 1489 (m), 1348 (m), 1308 (m), 1263 (m), 1250 (m), 1180 (m), 785 (m), 733 (s), 710 (s).



2.3.3af, ethyl 3-(2-nitrophenyl)-4-oxo-4-(p-tolyl)butanoate

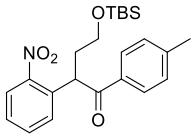
This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 42% (0.56 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 92:8), R_f = 0.54 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.21 – 7.15 (m, 2H), 5.70 (dd, *J* = 9.4, 5.1 Hz, 1H), 4.10 (q, *J* = 7.3 Hz, 2H), 3.27 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.83 (dd, *J* = 16.9, 5.1 Hz, 1H), 2.34 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.5, 171.2, 149.2, 144.6, 133.5, 133.3, 132.7, 129.9, 129.6, 129.0, 128.6, 125.3, 61.1, 43.8, 38.2, 21.8, 14.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NNaO_5^+$ 364.1156; Found 364.1167.

IR (ν_{max}, cm^{-1}) 2945 (w), 2840 (w), 1665 (m), 1610 (m), 1554 (m), 1493 (m), 1323 (m), 1270 (m), 1186 (m), 785 (m), 710 (s).



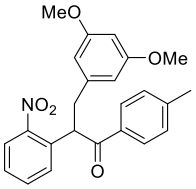
2.3.3ag, 4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)-1-(p-tolyl)butan-1-one

This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 68% (1.1 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.15 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.40 – 7.31 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.56 (t, *J* = 7.0 Hz, 1H), 3.68 – 3.43 (m, 2H), 2.51 – 2.35 (m, 4H), 2.01 (dq, *J* = 12.9, 5.9 Hz, 1H), 0.85 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.8, 149.8, 144.3, 133.9, 133.9, 133.0, 130.4, 130.0, 129.0, 127.9, 124.8, 60.6, 43.3, 36.8, 26.0, 21.8, 18.3, -5.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{31}NNaO_4Si^+$ 436.1915; Found 436.1917.



2.3.3ah, 3-(3,5-dimethoxyphenyl)-2-(2-nitrophenyl)-1-(p-tolyl)propan-1-one

This compound was prepared following general procedure **F** using compound **2.3.2a** (1.0 g, 3.9 mmol) as starting material. Yield: 60% (0.9 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 70:20), R_f = 0.2 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.80 (dd, J = 8.1, 1.3 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.38 – 7.30 (m, 1H), 7.20 – 7.12 (m, 2H), 5.68 (t, J = 7.2 Hz, 1H), 3.48 (dd, J = 13.6, 7.6 Hz, 1H), 2.99 (dd, J = 13.6, 6.8 Hz, 1H), 2.33 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.0, 160.8, 149.9, 144.4, 140.9, 133.9, 133.8, 133.4, 129.9, 129.6, 129.0, 128.1, 125.0, 107.3, 98.9, 55.4, 49.0, 40.2, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_5^+$ 428.1468; Found 428.1474.

Following a reported procedure,[2] to a solution of deoxybenzoin **2.3.22** (1.85 g, 9.4 mmol, 1.0 equiv) in DMSO (9.4 mL, 1.0 M) was added KOH (1.1 g, 18.8 mmol, 2 equiv) and the reaction mixture was stirred for 5-10 min. Then a solution of the 1-fluoro-2-nitrobenzene **2.3.19** (1.3 g, 9.4 mmol, 1.0 equiv) in 30 mL of DMSO was added dropwise to the stirred mixture. The reaction was carried out at 45-50 °C in the oil bath for 1-1.5 h and then the mixture was poured into water. The precipitate was filtered off. Purification: Crystallization from EtOH, R_f = 0.28 (PE/EtOAc 90:10). Yield: 77% (2.3 g), isolated as yellow solid (mp = 120 – 121 °C).

2.3.23, 2-(2-nitrophenyl)-1,2-diphenylethan-1-one

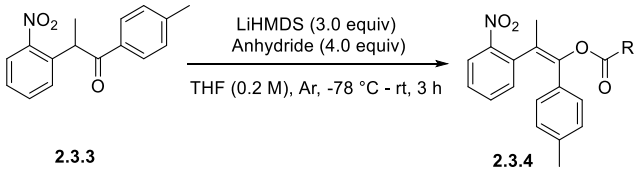
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.1, 1.5 Hz, 1H), 8.00 – 7.96 (m, 2H), 7.52 – 7.46 (m, 2H), 7.44 – 7.30 (m, 6H), 7.30 – 7.26 (m, 2H), 7.03 (dd, J = 7.9, 1.5 Hz, 1H), 6.74 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.9, 148.5, 136.5, 136.49, 135.4, 133.4, 133.3, 132.6, 130.0, 129.6, 129.1, 128.8, 128.2, 128.1, 125.1, 55.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{15}NNaO_3^+$ 340.0944; Found 340.0952.

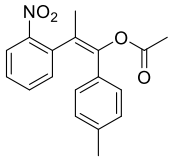
IR (ν_{max}, cm^{-1}) 3061 (w), 3024 (w), 1682 (s), 1597 (m), 1579 (m), 1522 (s), 1448 (m), 1346 (s), 1298 (m), 1268 (m), 1213 (m), 1180 (m), 998 (m), 730 (s), 694 (s).

6.2.4. **General procedure G for the synthesis of the enol esters**



2.3.3 **2.3.4**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged with ketone **2.3.3a** (1.9 g, 7.1 mmol, 1.0 equiv) in THF (36 mL, 0.2 M). Then a solution of LiHMDS (22 mL, 21.4 mmol, 1.0 M in THF, 3.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 5 min before warming to 0 °C. Then the anhydride (4.7 mL, 29.0 mmol, 4.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **2.3.4b**.



2.3.4a, (E)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl acetate

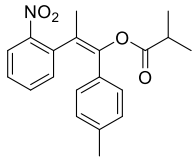
This compound was prepared following general procedure **G** using compound **2.3.3a** (0.5 g, 2.0 mmol) as starting material. Yield: 94% (0.57 g), isolated as yellow solid (mp = 62 – 63 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.38 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.30 (m, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 2.24 (s, 3H), 2.21 (s, 3H), 2.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 148.6, 144.0, 138.2, 136.5, 133.3, 132.7, 132.0, 128.8, 128.4, 128.2, 124.7, 123.6, 21.4, 21.0, 18.8.

HRMS (ESI) calcd for $C_{18}H_{17}NNaO_4^+$ $[M+Na]^+$ 334.1050; found 334.1051.

IR (ν_{max}, cm^{-1}) 2985 (w), 2918 (w), 2856 (w), 1756 (s), 1519 (s), 1344 (m), 1205 (s), 1079 (m), 822 (m).



2.3.4b, (E)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

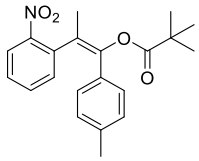
This compound was prepared following general procedure **G** using compound **2.3.3a** (1.9 g, 7.1 mmol) as starting material. Yield: 62% (1.5 g), isolated as yellow solid (mp = 59 – 60 °C). Purification: Crystallization from PE and Et_2O, R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 – 7.30 (m, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 2.76 (hept, *J* = 7.0 Hz, 1H), 2.21 (s, 3H), 2.03 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 148.7, 144.0, 138.0, 136.6, 133.2, 132.7, 132.1, 128.8, 128.3, 128.2, 124.6, 123.3, 34.2, 21.3, 19.0, 18.7.

HRMS (ESI) calcd for $C_{20}H_{21}NNaO_4^+$ $[M+Na]^+$ 362.1363; found 362.1368.

IR (ν_{max}, cm^{-1}) 3033 (w), 2975 (w), 2874 (w), 1745 (s), 1568 (s), 1383 (s), 832 (s).



2.3.4c, (E)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl pivalate

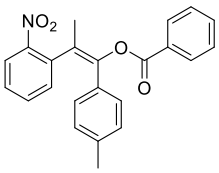
This compound was prepared following general procedure **G** using compound **2.3.3a** (0.5 g, 2.0 mmol) as starting material. Yield: 80% (0.53 g), isolated as yellow solid (mp = 69 – 70 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.49 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 – 7.29 (m, 2H), 6.91 – 6.86 (m, 4H), 2.21 (s, 3H), 2.03 (s, 3H), 1.33 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 148.6, 144.0, 137.8, 136.5, 133.1, 132.6, 132.0, 128.6, 128.1, 128.0, 124.1, 123.0, 39.1, 27.5, 21.2, 18.5.

HRMS (ESI) calcd for $C_{21}H_{23}NNaO_4^+$ $[M+Na]^+$ 376.1519; found 376.1519.

IR (ν_{max}, cm^{-1}) 2975 (w), 2933 (w), 2872 (w), 1743 (s), 1524 (s), 1106 (s), 722 (m).



2.3.4d, (E)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl benzoate

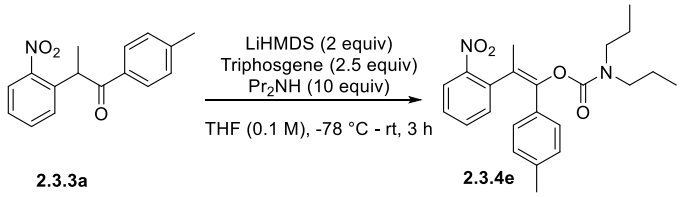
This compound was prepared following general procedure **G** using compound **2.3.3a** (0.5 g, 2.0 mmol) as starting material. Yield: 32% (0.22 g), isolated as yellow oil as a mixture of *E* and *Z* isomers in a ratio of around 3/1. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.30 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 2H, major), 7.91 (d, *J* = 8.1 Hz, 1/3H, minor), 7.90 (d, *J* = 8.1 Hz, 1H, major), 7.75 (d, *J* = 8.3 Hz, 2/3H, minor), 7.63 (t, *J* = 7.5 Hz, 1H, major), 7.51 (t, *J* = 7.7 Hz, 2H, major), 7.53-7.46 (m, 1H, major + 2/3H, minor), 7.45 (d, *J* = 7.7 Hz, 2/3H + 1/3H, minor), 7.39 (d, *J* = 7.6 Hz, 1H, major), 7.37 (t, *J* = 7.7 Hz, 1H, major), 7.31 (t, *J* = 7.7 Hz, 2/3H + 1/3H, minor), 7.19 (d, *J* = 7.7 Hz, 2/3H, minor), 7.00 (d, *J* = 8.2 Hz, 2H, major), 6.89 (d, *J* = 8.2 Hz, 2H, major), 2.36 (s, 1H, minor), 2.23 (s, 1H, minor), 2.20 (s, 3H, major), 2.09 (s, 3H, major).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7, 164.69, 148.7, 148.4, 144.2, 142.9, 138.8, 138.2, 136.6, 135.6, 133.7, 133.4, 133.2, 132.8, 131.9, 131.7, 130.5, 130.3, 129.9, 129.6, 129.2, 129.1, 128.9, 128.87, 128.7, 128.42, 128.4, 128.3, 128.2, 124.8, 124.3, 123.9, 122.9, 21.5, 21.4, 20.0, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{19}NNaO_4^+$ 396.1206; Found 396.1209.

IR (ν_{max}, cm^{-1}) 3060 (w), 2917 (w), 1734 (s), 1604 (w), 1523 (s), 1452 (w), 1349 (m), 1261 (s), 1089 (s), 1062 (m), 1024 (m), 817 (m), 755 (m), 707 (s).



Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged the ketone **2.3.3a** (250 mg, 0.93 mmol, 1.0 equiv) in THF (10 mL, 0.1 M). Then a solution of LiHMDS (2.1 mL, 1.9 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 5 min before warming to 0 °C. Then triphosgene (690 mg, 2.3 mmol, 2.5 equiv) was added portion-wise. After stirring for another 5 min dipropylamine (1.3 mL, 9.3 mmol, 10 equiv) was added. The reaction mixture was warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol carbamate **2.3.4e**.

2.3.4e, (E)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl dipropylcarbamate

Yield: 82% (300 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.25 (PE/EtOAc 90:10).

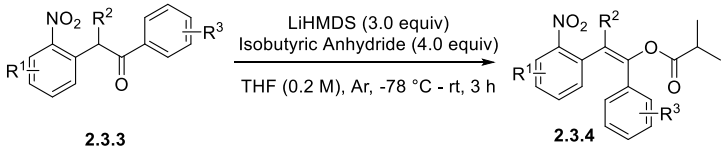
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.1, 1.3 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.37 – 7.29 (m, 2H), 6.93 (d, J = 8.3 Hz, 2H), 6.89 – 6.86 (d, J = 8.1 Hz, 2H), 3.35 (t, J = 7.6 Hz, 2H), 3.29-3.17 (m, 2H), 2.21 (s, 3H), 2.05 (s, 3H), 1.71-1.64 (m, 2H), 1.62-1.55 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.2, 148.7, 144.4, 137.7, 137.0, 133.2, 133.0, 132.6, 128.7, 128.4, 128.0, 124.5, 123.1, 49.4, 49.2, 22.2, 21.4, 21.3, 18.8, 11.5, 11.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{28}N_2NaO_4^+$ 419.1941; Found 419.1942.

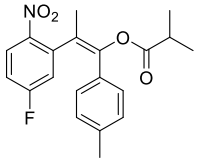
IR (ν_{max}, cm^{-1}) 2964 (w),2933 (w), 2871 (w), 1712 (s), 1523 (s), 1468 (m), 1441 (m), 1415 (s), 1381 (m), 1344 (s), 1286 (m), 1232 (s), 1209 (m), 1153 (s), 1120 (m), 1105 (s), 1090 (s), 1057 (m), 1039 (m), 860 (m), 818 (m), 756 (s).

General procedure H



2.3.3 2.3.4

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged a solution of ketone **2.3.3g** (1.0 g, 3.5 mmol, 1.0 equiv) in THF (17 mL, 0.2 M). Then a solution of LiHMDS (1.2 mL, 10.5 mmol, 1.0 M in THF, 3.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 5 min before warming to 0 °C. Then isobutyric anhydride (2.3 mL, 14 mmol, 4.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted from the aqueous phase with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **2.3.4g**.



2.3.4f, (E)-2-(5-fluoro-2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4f** (1.05 g, 3.7 mmol) as starting material. Yield: 80% (1.04 g), isolated as yellow solid (mp = 74 – 75 °C). Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.26 (PE/EtOAc 96:4).

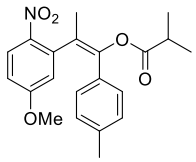
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.91 (m, 1H), 7.04 – 6.97 (m, 2H), 6.92 (m, 4H), 2.76 (hept, *J* = 7.0 Hz, 1H), 2.23 (s, 3H), 2.02 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 164.6 (d, *J* = 257.8 Hz), 144.8, 144.5, 140.0 (d, *J* = 9.7 Hz), 138.4, 131.8, 129.0, 128.3, 127.5 (d, *J* = 10.1 Hz), 122.7, 119.5 (d, *J* = 23.2 Hz), 115.3 (d, *J* = 23.2 Hz), 34.2, 21.4, 19.0, 18.5.

^{19}F NMR (377 MHz, $CDCl_3$) δ -106.90.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{20}FNaNO_4^+$ 380.1269; Found 380.1270.

IR (ν_{max}, cm^{-1}) 2973 (w), 2925 (w), 2871 (w), 1751 (s), 1579 (m), 1525 (s), 1510 (m), 1471 (m), 1344 (s), 1261 (m), 1232 (m), 1182 (m), 1134 (m), 1113 (s), 1090 (s), 1047 (m), 926 (m), 879 (m), 841 (m), 818 (s).



2.3.4g, (E)-2-(5-methoxy-2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

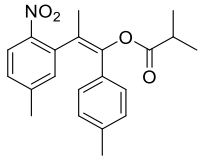
This compound was prepared following general procedure **H** using compound **2.3.4g** (1.0 g, 3.5 mmol) as starting material. Yield: 53% (0.69 g), isolated as yellow solid (mp = 136 – 137 °C). Purification: Crystallization from hot EtOAc, R_f = 0.26 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.1 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.78 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.72 (d, *J* = 2.8 Hz, 1H), 3.75 (s, 3H), 2.77 (hept, *J* = 7.0 Hz, 1H), 2.21 (s, 3H), 2.01 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 163.2, 143.5, 141.6, 139.5, 138.0, 132.3, 128.8, 128.2, 127.4, 124.2, 116.9, 113.6, 56.0, 34.2, 21.4, 19.1, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_5^+$ 392.1468; Found 392.1486.

IR (ν_{max}, cm^{-1}) 2978 (w), 2940 (w), 2879 (w), 1751 (m), 1608 (m), 1578 (m), 1513 (s), 1465 (m), 1338 (s), 1305 (s), 1241 (s), 1224 (m), 1180 (m), 1110 (s), 1095 (s), 1045 (s), 817 (s).



2.3.4h, (E)-2-(5-methyl-2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

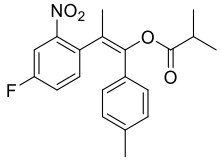
This compound was prepared following general procedure **H** using compound **2.3.4h** (0.6 g, 2.1 mmol) as starting material. Yield: 72% (0.54 g), isolated as yellow solid (mp = 136 – 137 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.32 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.8 Hz, 1H), 7.15 – 7.09 (m, 2H), 6.92-6.87 (m, 4H), 2.77 (hept, J = 7.0 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.02 (s, 3H), 1.29 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 146.3, 144.5, 143.5, 137.9, 136.6, 133.0, 132.1, 128.8, 128.75, 128.2, 124.8, 123.6, 34.2, 21.5, 21.3, 19.1, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_4^+$ 376.1519; Found 376.1530.

IR (ν_{max}, cm^{-1}) 2972 (w), 2925 (w), 2879 (w), 1751 (s), 1518 (s), 1342 (s), 1232 (m), 1182 (m), 1134 (s), 1115 (s), 1090 (s), 1053 (s), 839 (m), 820 (m).



2.3.4i, (E)-2-(4-fluoro-2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4i** (1.5 g, 5.2 mmol) as starting material. Yield: 45% (1.0 g), isolated as yellow solid (mp = 65 – 66 °C). Purification: Flash chromatography (PE/DCM, 80:20), R_f = 0.50 (PE/EtOAc 90:10).

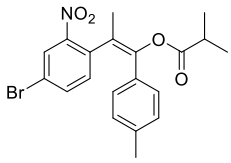
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.58 (m, 1H), 7.33 – 7.25 (m, 1H), 7.23 – 7.15 (m, 1H), 6.91 (s, 4H), 2.77 (hept, J = 7.0 Hz, 1H), 2.23 (s, 3H), 2.01 (s, 3H) 1.28 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 161.1 (d, J = 251.6 Hz), 148.9 (d, J = 8.4 Hz), 144.5, 138.2, 134.3 (d, J = 7.6 Hz), 132.7 (d, J = 3.9 Hz), 131.9, 128.9, 128.3, 122.5, 120.7 (d, J = 21.0 Hz), 112.3 (d, J = 26.4 Hz), 34.2, 21.3, 19.0, 18.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -114.22 (td, J = 7.7, 5.5 Hz).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{20}FNNaO_4^+$ 380.1269; Found 380.1270.

IR (ν_{max}, cm^{-1}) 2954 (w), 2929 (w), 2852 (w), 1739 (s), 1531 (s), 1355 (m), 1243 (m), 1103 (m), 837 (s), 775 (m).



2.3.4j, (E)-2-(4-bromo-2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

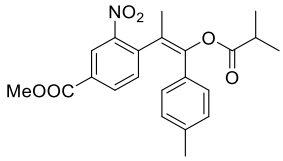
This compound was prepared following general procedure **H** using compound **2.3.4j** (1.5 g, 4.3 mmol) as starting material. Yield: 48% (0.86 g), isolated as yellow solid (mp = 92 – 93 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 2.0 Hz, 1H), 7.56 (dd, J = 8.2, 2.0 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 6.92 (s, 4H), 2.75 (hept, J = 7.0 Hz, 1H), 2.23 (s, 3H), 1.99 (s, 3H), 1.27 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 149.0, 144.6, 138.4, 136.3, 135.6, 134.1, 131.8, 129.0, 128.4, 127.7, 122.4, 121.2, 34.2, 21.4, 19.0, 18.5.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{20}NBrNaO_4^+$ 440.0468; Found 440.0479.

IR (ν_{max}, cm^{-1}) 2974 (w), 2921 (w), 2875 (w), 1751 (s),1527 (s), 1508 (m), 1469 (m), 1344 (s), 1230 (m), 1182 (m), 1134 (m), 1111 (s), 1088 (s), 1074 (s), 1047 (s), 877 (m), 835 (m), 818 (s), 735 (m).



2.3.4k, methyl (E)-4-(1-(isobutyryloxy)-1-(p-tolyl)prop-1-en-2-yl)-3-nitrobenzoate

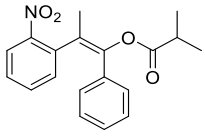
This compound was prepared following general procedure **H** using compound **2.3.4k** (0.7 g, 2.1 mmol) as starting material. Yield: 71% (0.6 g), isolated as yellow crystals (mp = 101 – 102 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.33 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 1.7 Hz, 1H), 8.08 (dd, J = 8.0, 1.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 6.90 (s, 4H), 3.93 (s, 3H), 2.76 (hept, J = 7.0 Hz, 1H), 2.21 (s, 3H), 2.02 (s, 3H), 1.28 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 165.0, 148.7, 144.8, 141.0, 138.5, 133.7, 133.2, 131.8, 130.3, 129.0, 128.4, 125.9, 122.7, 52.8, 34.2, 21.4, 19.0, 18.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NNaO_6^+$ 420.1418; Found 420.1430.

IR (ν_{max}, cm^{-1}) 2974 (w), 2933 (w), 2875 (w), 1753 (m), 1728 (s), 1533 (s), 1437 (m), 1348 (m), 1302 (m), 1284 (s), 1230 (m), 1184 (m), 1151 (m), 1111 (s), 1078 (s), 1047 (m), 982 (m), 818 (m), 766 (m), 733 (m), 704 (m).



2.3.4l, (E)-2-(2-nitrophenyl)-1-phenylprop-1-en-1-yl isobutyrate

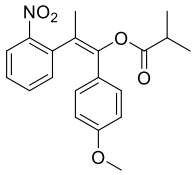
This compound was prepared following general procedure **H** using compound **2.3.4l** (0.56 g, 2.2 mmol) as starting material. Yield: 94% (0.67 g), isolated as yellow solid (mp = 86 – 87 °C). Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.0, 1.1 Hz, 1H), 7.38 (td, J = 7.6, 1.3 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.06 – 6.98 (m, 3H), 6.98 – 6.93 (m, 2H), 2.70 (hept, J = 7.0 Hz, 1H), 1.97 (s, 3H), 1.21 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 148.7, 143.9, 136.4, 135.0, 133.2, 132.6, 128.4, 128.3, 128.2, 128.0, 124.7, 124.0, 34.2, 19.0, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NNaO_4^+$ 348.1206; Found 348.1205.

IR (ν_{max}, cm^{-1}) 2978 (w), 29225 (w), 2875 (w), 1749 (s), 1524 (s), 1348 (s), 1232 (m), 1180 (m), 1111 (s), 1095 (s), 1053 (m), 858 (m), 752 (s), 698 (s).



2.3.4m, (E)-1-(4-methoxyphenyl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

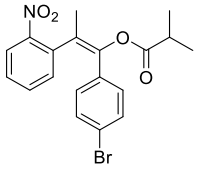
This compound was prepared following general procedure **H** using compound **2.3.4m** (0.57 g, 2.0 mmol) as starting material. Yield: 90% (0.64 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.38 – 7.32 (m, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.63 (d, J = 8.7 Hz, 2H), 3.72 (s, 3H), 2.79 (hept, J = 7.0 Hz, 1H), 2.04 (s, 3H), 1.30 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 159.3, 148.7, 143.8, 136.7, 133.2, 132.7, 129.9, 128.1, 127.5, 124.7, 122.9, 113.5, 55.2, 34.2, 19.1, 18.6.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{21}NNaO_5^+$ 378.1312; Found 378.1322.

IR (ν_{max}, cm^{-1}) 2976 (w), 2937 (w), 1749 (m), 1604 (m), 1525 (s), 1510 (s), 1466 (m), 1441 (m), 1344 (s), 1250 (s), 1230 (s),1174 (s), 1134(s), 1113 (s), 1030 (s), 858 (m), 831 (s), 752 (s), 735 (m), 704 (m).



2.3.4n, (E)-1-(4-bromophenyl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

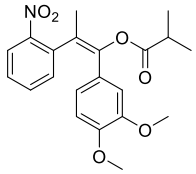
This compound was prepared following general procedure **H** using compound **2.3.4n** (0.44 g, 1.3 mmol) as starting material. Yield: 85% (0.45 g), isolated as yellow solid (mp = 57 – 58 °C). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.3 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 8.1, 1.3 Hz, 1H), 7.47 (td, J = 7.5, 1.3 Hz, 1H), 7.37 (ddd, J = 8.1, 7.4, 1.5 Hz, 1H), 7.28 (dd, J = 7.7, 1.5 Hz, 1H), 7.22 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.6 Hz, 2H), 2.76 (hept, J = 7.0 Hz, 1H), 2.02 (s, 3H), 1.28 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 148.6, 142.9, 136.0, 134.1, 133.4, 132.5, 131.3, 130.1, 128.5, 124.9, 124.8, 122.4, 34.2, 19.0, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}BrNNaO_4^+$ 426.0311; Found 426.0313.

IR (ν_{max}, cm^{-1}) 2976 (w), 2932 (w), 2875 (w), 1751 (s), 1523 (s), 1487 (m), 1468 (m), 1344 (s), 1230 (m), 1182 (m), 1132 (m), 1113 (s), 1092 (s), 1070 (m), 1053 (m), 1038 (m), 1011 (m), 858 (m), 825 (s), 787 (m),754 (s), 731 (m), 708 (m).



2.3.4o, (E)-1-(3,4-dimethoxyphenyl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

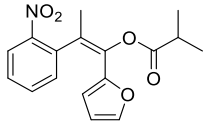
This compound was prepared following general procedure **H** using compound **2.3.4o** (0.7 g, 2.2 mmol) as starting material. Yield: 57% (0.48 g), isolated as yellow solid (mp = 63 – 64 °C). Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.27 (PE/EtOAc 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, J = 8.5, 1.4 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.36-7.32 (m, 2H), 6.66 (dd, J = 8.4, 2.0 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 6.48 (d, J = 2.0 Hz, 1H), 3.78 (s, 3H), 3.53 (s, 3H), 2.78 (hept, J = 7.0 Hz, 1H), 2.04 (s, 3H), 1.29 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 148.9, 148.8, 148.2, 143.8, 136.7, 133.2, 132.6, 128.2, 127.6, 124.6, 122.9, 121.0, 111.7, 110.6, 55.8, 55.6, 34.2, 19.1, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_6^+$ 408.1418; Found 408.1415.

IR (ν_{max}, cm^{-1}) 2974 (m), 2933(w), 2871 (w), 2842 (w), 1749 (m), 1514 (s),1466 (m), 1441 (m), 1350 (m), 1325 (m), 1263 (s), 1240 (s), 1207 (m), 1186 (m), 1169 (m), 1140 (s), 1113 (s), 1090 (s), 1024 (s), 852 (m), 810 (m), 787 (m), 754 (m), 717 (m), 702 (m).



2.3.4p, (E)-1-(furan-2-yl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

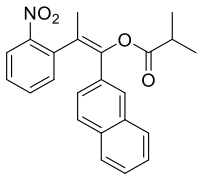
This compound was prepared following general procedure **H** using compound **2.3.4p** (1.0 g, 4.3 mmol) as starting material. Yield: 83% (1.12 g), isolated as yellow oil. Purification: Flash chromatography (PE/Et_2O, 95:5), R_f = 0.33 (PE/EtOAc 90:10).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.15 (dd, J = 3.5, 1.8 Hz, 1H), 5.67 (d, J = 3.5 Hz, 1H), 2.86 (hept, J = 7.0 Hz, 1H), 2.05 (s, 3H), 1.36 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 148.2, 148.1, 142.3, 136.0, 134.8, 133.8, 132.0, 128.7, 124.7, 123.5, 111.1, 109.0, 34.2, 19.2, 19.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_5^+$ 316.1179; Found 316.1178.

IR (ν_{max}, cm^{-1}) 2973 (w), 2937 (w), 2871 (w), 1755 (s), 1523 (s), 1346 (s), 1159 (m), 1115 (s), 1092 (s), 1057 (m), 1039 (m), 1020 (m), 789 (m), 739 (s), 704 (m).



2.3.4q, (E)-1-(naphthalen-2-yl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

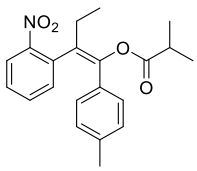
This compound was prepared following general procedure **H** using compound **2.3.4q** (1.0 g, 3.4 mmol) as starting material. Yield: 77% (1.0 g), isolated as yellow solid (mp = 89 – 90 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.63 – 7.57 (m, 1H), 7.56-7.54 (m, 2H), 7.45 – 7.36 (m, 3H), 7.36 – 7.28 (m, 2H), 7.13 (dd, *J* = 8.7, 1.7 Hz, 1H), 2.81 (hept, *J* = 7.0 Hz, 1H), 2.09 (s, 3H), 1.31 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 148.7, 144.0, 136.5, 133.3, 132.9, 132.87, 132.86, 132.6, 128.4, 128.3, 128.2, 127.7, 127.6, 126.6, 126.2, 125.9, 124.7, 124.6, 34.3, 19.1, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_4^+$ 398.1363; Found 398.1367.

IR (ν_{max}, cm^{-1}) 2970 (w), 2937 (w), 2871 (w), 1749 (s), 1523 (s), 1344 (s), 1182 (m), 1126 (s), 1109 (s), 1090 (s), 1055 (m), 1038 (m), 852 (m), 820 (m), 787 (m), 750 (s), 735 (s), 715 (m).



2.3.4r, (E)-2-(2-nitrophenyl)-1-(p-tolyl)but-1-en-1-yl isobutyrate

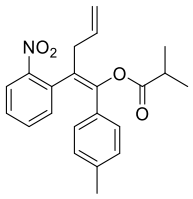
This compound was prepared following general procedure **H** using compound **2.3.4r** (1.15 g, 4.0 mmol) as starting material. Yield: 42% (0.6 g), isolated as orange solid (mp = 61 – 62 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.48 (PE/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.46 (td, *J* = 7.6, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 2.75 (hept, *J* = 7.0 Hz, 1H), 2.67-2.56 (m, 1H), 2.35-2.25 (m, 1H), 2.20 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 149.1, 143.8, 138.0, 135.0, 133.3, 132.9, 132.4, 128.8, 128.7, 128.4, 128.1, 124.5, 34.2, 25.5, 21.4, 19.0, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_4^+$ 376.1519; Found 376.1523.

IR (ν_{max}, cm^{-1}) 2970 (m), 2937 (w), 2875 (w), 1751 (s), 1525 (s), 1348 (s), 1130 (s), 1117 (s), 1093 (s), 821 (m), 748 (m).



2.3.4s, (E)-2-(2-nitrophenyl)-1-(p-tolyl)penta-1,4-dien-1-yl isobutyrate

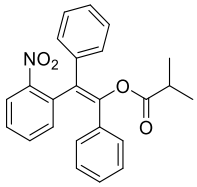
This compound was prepared following general procedure **H** using compound **2.3.4s** (0.45 g, 1.5 mmol) as starting material. Yield: 84% (0.47 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.37 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.26 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 5.82 – 5.69 (m, 1H), 5.01 – 4.92 (m, 2H), 3.42 (dd, *J* = 15.2, 6.2 Hz, 1H), 2.99 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.74 (hept, *J* = 7.0 Hz, 1H), 2.21 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 148.9, 144.7, 138.2, 134.8, 134.3, 133.5, 132.9, 132.2, 128.8, 128.3, 128.2, 125.4, 124.7, 117.2, 37.0, 34.2, 21.4, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NNaO_4^+$ 388.1519; Found 388.1530.

IR (ν_{max}, cm^{-1}) 5-012975 (w), 2925 (w), 2879 (w), 1751 (s), 1523 (s), 1465 (m), 1346 (s), 1232 (m), 1185 (m), 1110 (s), 1093 (s), 1045 (m), 989 (m), 914 (m), 818 (m), 788 (m), 756 (m), 719 (m).



2.3.4t, (E)-2-(2-nitrophenyl)-1,2-diphenylvinyl isobutyrate

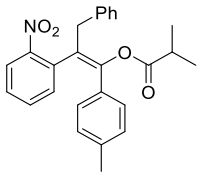
This compound was prepared following general procedure **H** using compound **2.3.23** (0.4 g, 1.3 mmol) as starting material. Yield: 77% (0.38 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.33 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.40 – 7.33 (m, 2H), 7.30 – 7.12 (m, 10H), 2.53 (hept, *J* = 7.0 Hz, 1H), 1.05 (br s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.5, 149.6, 144.9, 137.3, 135.5, 135.3, 134.4, 133.0, 129.4, 128.8, 128.6, 128.5, 128.47, 128.3, 128.2, 128.0, 124.8, 34.2, 18.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{21}NNaO_4^+$ 410.1363; Found 410.1367.

IR (ν_{max}, cm^{-1}) 3064 (w), 2969 (w), 2938 (w), 1751 (s), 1523 (s), 1491 (m), 1465 (m), 1444 (m), 1348 (s), 1224 (m), 1176 (m), 1106 (s), 1062 (s), 1026 (m), 854 (m), 764 (s), 696 (s).



2.3.4u, (E)-2-(2-nitrophenyl)-3-phenyl-1-(p-tolyl)prop-1-en-1-yl isobutyrate

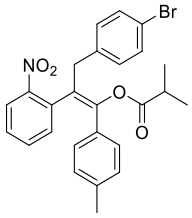
This compound was prepared following general procedure **H** using compound **2.3.4u** (0.5 g, 1.5 mmol) as starting material. Yield: 68% (0.41 g), isolated as yellow solid (mp = 84 – 85 °C). Purification: Flash chromatography (PE/DCM, 1:1), R_f = 0.45 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.79 (m, 1H), 7.24-7.15 (m, 5H), 7.12-7.10 (m, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.84-6.82 (m, 1H), 4.16 (d, *J* = 14.9 Hz, 1H), 3.46 (d, *J* = 14.9 Hz, 1H), 2.75 (hept, *J* = 7.0 Hz, 1H), 2.20 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 149.0, 144.7, 138.2, 138.0, 134.2, 133.7, 132.5, 132.2, 129.5, 128.8, 128.5, 128.4, 128.2, 126.5, 126.4, 124.5, 38.2, 34.2, 21.4, 19.0, 18.96.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{25}NNaO_4^+$ 438.1676; Found 438.1688.

IR (ν_{max}, cm^{-1}) 3026 (w), 2976 (w), 2935 (w), 2922 (w), 1751 (s), 1523 (s), 1452 (m), 1346 (s), 12332 (m), 1180 (m), 1095 (s), 1045 (m), 993 (m), 821 (m), 784 (m), 741 (m), 704 (s).



2.3.4v, (E)-3-(4-bromophenyl)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

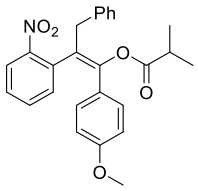
This compound was prepared following general procedure **H** using compound **2.3.4v** (0.2 g, 0.5 mmol) as starting material. Yield: 52% (0.12 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.43 (PE/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82-7.80 (m, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.27-7.25 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.85-6.83 (m, 1H), 4.08 (d, *J* = 15.0 Hz, 1H), 3.42 (d, *J* = 15.0 Hz, 1H), 2.74 (hept, *J* = 7.0 Hz, 1H), 2.20 (s, 3H), 1.25 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 148.9, 145.1, 138.4, 137.0, 133.9, 133.6, 132.7, 131.9, 131.6, 131.2, 128.8, 128.4, 128.36, 125.7, 124.7, 120.4, 37.6, 34.2, 21.4, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{24}BrNNaO_4^+$ 516.0781; Found 516.0797.

IR (ν_{max}, cm^{-1}) 2976 (w), 2929 (w), 2871 (w), 1753 (m), 1525 (s), 1510 (m), 1476 (m), 1468 (m), 1344 (s), 1228 (m), 1182 (m), 1111 (s), 1093 (s), 1070 (m), 1012 (m), 858 (m), 818 (s), 783 (m), 756 (m), 727 (m).



2.3.4w, (E)-1-(4-methoxyphenyl)-2-(2-nitrophenyl)-3-phenylprop-1-en-1-yl isobutyrate

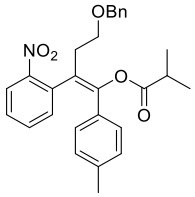
This compound was prepared following general procedure **H** using compound **2.3.4w** (1.0 g, 3.0 mmol) as starting material. Yield: 51% (0.64 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.59 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.77 (m, 1H), 7.25 – 7.08 (m, 7H), 7.03 (d, *J* = 8.9 Hz, 2H), 6.86 – 6.81 (m, 1H), 6.61 (d, *J* = 8.9 Hz, 2H), 4.14 (d, *J* = 14.9 Hz, 1H), 3.69 (s, 3H), 3.45 (d, *J* = 14.9 Hz, 1H), 2.75 (hept, *J* = 7.0 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 159.3, 149.0, 144.5, 138.0, 134.3, 133.7, 132.5, 130.0, 129.5, 128.5, 128.1, 127.5, 126.5, 126.0, 124.5, 113.5, 55.2, 38.1, 34.2, 19.0, 18.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{25}NNaO_5^+$ 454.1625; Found 454.1630.

IR (ν_{max}, cm^{-1}) 2973 (w), 2937 (w), 1751 (m), 1606 9M), 1525 (s), 1510 (s), 1468 (m), 1454 (m), 1346 (m), 1298 (m), 1250 (s), 1228 (m), 1176 (m), 1132 (m), 1113 (s), 1093 (s), 1074 (m), 1049 (m), 1030 (m), 991 (m), 856 (m), 831 (m), 787 (m), 764 (m), 733 (s), 700 (s).



2.3.4x, (*E*)-4-(benzyloxy)-2-(2-nitrophenyl)-1-(p-tolyl)but-1-en-1-yl isobutyrate

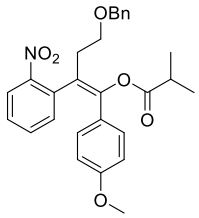
This compound was prepared following general procedure **H** using compound **2.3.4x** (0.5 g, 1.3 mmol) as starting material. Yield: 96% (0.57 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.20 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 3.66 – 3.49 (m, 2H), 2.95 (dt, *J* = 14.6, 7.4 Hz, 1H), 2.71 (hept, *J* = 7.0 Hz, 1H), 2.68 – 2.61 (m, 1H), 2.20 (s, 3H), 1.242 (d, *J* = 7.0 Hz, 3H), 1.236 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 149.1, 145.6, 138.4, 138.2, 134.9, 133.3, 132.9, 132.1, 128.8, 128.4, 128.37, 128.2, 127.7, 127.6, 124.7, 124.2, 72.9, 68.1, 34.2, 32.9, 21.4, 18.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{29}NNaO_5^+$ 482.1938; Found 482.1942.

IR (ν_{max}, cm^{-1}) 2978 (w), 2931 (w), 2860 (w), 1753 (m), 1525 (s), 1344 (m), 1230 (m), 1182 (m), 1132 (m), 1113 (s), 1092 (s), 1068 (s), 1045 (s), 1045 (m), 1028 (m), 820 (m), 787 (m), 735 (m).



2.3.4y, (E)-4-(benzyloxy)-1-(4-methoxyphenyl)-2-(2-nitrophenyl)but-1-en-1-yl isobutyrate

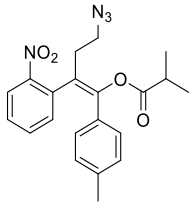
This compound was prepared following general procedure **H** using compound **2.3.4y** (0.36 g, 0.9 mmol) as starting material. Yield: 74% (0.3 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.45 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.81 (m, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 – 7.22 (m, 7H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 3.70 (s, 3H), 3.65 – 3.50 (m, 2H), 2.94 (ddd, *J* = 14.6, 8.2, 6.6 Hz, 1H), 2.72 (hept, *J* = 7.0 Hz, 1H), 2.68 – 2.60 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 159.3, 149.1, 145.4, 138.4, 135.0, 133.3, 132.9, 129.9, 128.4, 128.2, 127.7, 127.6, 127.4, 124.7, 123.7, 113.5, 72.9, 68.1, 55.2, 34.2, 32.8, 18.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{29}NNaO_6^+$ 498.1887; Found 498.1892.

IR (ν_{max}, cm^{-1}) 2970 (w), 2925 (w),2863 (w), 1751 (m), 1606 (m), 1525 (s), 1510 (s), 1456 (m), 1439 (m), 1346 (m), 1296 (m), 1252 (s), 1230 (m), 1205 (m), 1176 (m), 1132 (s), 1115 (s), 1092 (s), 1068 (s), 1032 (s), 1003 (m), 850 (m), 831 (m),787 (m), 754 (m), 739 (m), 719 (m), 700 (m).



2.3.4z, (E)-4-azido-2-(2-nitrophenyl)-1-(p-tolyl)but-1-en-1-yl isobutyrate

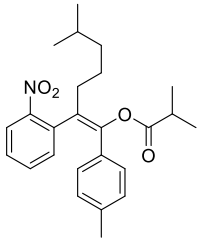
This compound was prepared following general procedure **H** using compound **2.3.4z** (3.0 g, 9.3 mmol) as starting material. Yield: 46% (1.7 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 95: 5), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.50 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 (td, *J* = 7.7, 1.5 Hz, 1H), 7.32 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.94 – 6.87 (m, 4H), 3.49 – 3.38 (m, 1H), 3.37 – 3.26 (m, 1H), 2.94 – 2.82 (m, 1H), 2.76 (hept, *J* = 7.0 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.21 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 149.1, 146.4, 138.5, 134.1, 133.2, 133.1, 131.7, 128.9, 128.7, 128.3, 125.0, 123.1, 49.1, 34.2, 32.1, 21.4, 18.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{22}N_4NaO_4^+$ 417.1533; Found 417.1535.

IR (ν_{max}, cm^{-1}) 2933 (w), 2102 (m), 1751 (m), 1522 (s), 1346 (m), 1132 (m), 818 (m), 760 (m), 712 (m).



2.3.4aa, (E)-6-methyl-2-(2-nitrophenyl)-1-(p-tolyl)hept-1-en-1-yl isobutyrate

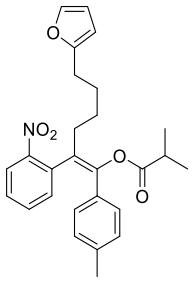
This compound was prepared following general procedure **H** using compound **2.3.4aa** (1.4 g, 4.1 mmol) as starting material. Yield: 83% (1.4 g), isolated as yellow oil. Purification: Flash chromatography (PE/Et_2O, 95:5), R_f = 0.43 (PE/Acetone 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.1, 1.4 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.34 (td, J = 8.5, 1.5 Hz, 1H), 7.27 (dd, J = 7.6, 1.5 Hz, 1H), 6.94 (d, J = 8.2 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 2.73 (hept, J = 7.0 Hz, 1H), 2.59-2.51 (m, 1H), 2.25-2.13 (m, 1H), 2.20 (s, 3H), 1.49 (dt, J = 13.3, 6.6 Hz, 1H), 1.40 – 1.30 (m, 2H), 1.27 (d, J = 7.0 Hz, 3H), 1.26 (d, J = 7.0 Hz, 3H), 1.20 – 1.12 (m, 2H), 0.824 (d, J = 6.7 Hz, 3H), 0.816 (d, J = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 149.0, 144.2, 137.9, 135.3, 133.3, 132.9, 132.4, 128.7, 128.4, 128.1, 127.7, 124.8, 39.2, 34.2, 32.7, 27.9, 25.3, 22.8, 22.6, 21.4, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{31}NNaO_4^+$ 432.2145; Found 432.2151.

IR (ν_{max}, cm^{-1}) 2956 (m), 2929 (w), 2871 (w),1751 (m), 1525 (s), 1510 (m), 1468 (m), 1346 (s), 1230 (m), 1182 (m), 1134 (s), 1115 (s), 1095 (s), 1047 (m), 852 (s), 820 (m), 785 (m), 739 (m), 704 (m).



2.3.4ab, (E)-6-(furan-2-yl)-2-(2-nitrophenyl)-1-(p-tolyl)hex-1-en-1-yl isobutyrate

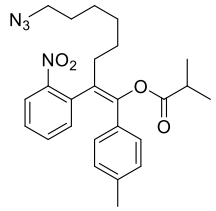
This compound was prepared following general procedure **H** using compound **2.3.4ab** (0.5 g, 1.3 mmol) as starting material. Yield: 85% (0.5 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.44 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 (td, *J* = 8.0, 1.6 Hz, 1H), 7.27-7.22 (m, 2H), 6.96 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.27 (t, *J* = 2.5 Hz, 1H), 5.95 (d, *J* = 3.1 Hz, 1H), 2.75 (hept, *J* = 7.0 Hz, 1H), 2.67 – 2.56 (m, 3H), 2.34 – 2.25 (m, 1H), 2.23 (s, 3H), 1.69-1.61 (m, 2H), 1.45 (p, *J* = 7.8 Hz, 2H), 1.26 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 156.2, 149.0, 144.4, 140.8, 138.0, 135.1, 133.3, 132.9, 132.3, 128.8, 128.4, 128.2, 127.2, 124.8, 110.2, 104.9, 34.2, 32.2, 28.2, 27.8, 27.0, 21.7, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{29}NNaO_5^+$ 470.1938; Found 470.1945.

IR (ν_{max}, cm^{-1}) 2965 (w), 2940 (w), 2871 (w), 1751 (m), 1525 (s), 1344 (m), 1111 (s), 1088 (m), 820 (m), 787 (m), 750 (m), 735 (s), 717 (s), 700 (m).



2.3.4ac, (E)-8-azido-2-(2-nitrophenyl)-1-(p-tolyl)oct-1-en-1-yl isobutyrate

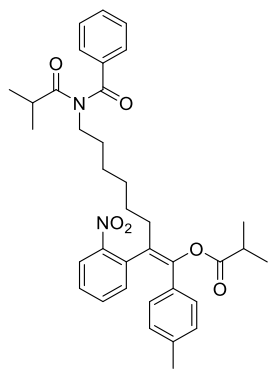
This compound was prepared following general procedure **H** using compound **2.3.4ac** (0.55 g, 1.4 mmol) as starting material. Yield: 62% (0.4 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.54 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.34 (td, *J* = 7.8, 1.6 Hz, 1H), 7.26 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.94 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 3.23 (t, *J* = 6.9 Hz, 2H), 2.74 (hept, *J* = 7.0 Hz, 1H), 2.63 – 2.52 (m, 1H), 2.29 – 2.20 (m, 1H), 2.20 (s, 3H), 1.60 – 1.50 (m, 2H), 1.44 – 1.22 (m, 6H), 1.27 (d, *J* = 7.2 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 149.1, 144.3, 138.0, 135.2, 133.2, 132.9, 132.3, 128.8, 128.4, 128.2, 127.3, 124.8, 51.5, 34.2, 32.4, 29.4, 28.9, 27.3, 26.6, 21.3, 19.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{30}N_4NaO_4^-$ 473.2170; Found 473.2180.

IR (ν_{max}, cm^{-1}) 2931 (w), 2860 (w), 2090 (s), 1751 (s), 1525 (s), 1468 (m), 1346 (s), 1290 (m), 1257 (m), 1230 (m), 1182 (m), 1132 (s), 1115 (s), 1093 (s), 1047 (m), 820 (m), 787 (m), 750 (m).



2.3.4ad, (E)-8-(N-isobutyrylbenzamido)-2-(2-nitrophenyl)-1-(p-tolyl)oct-1-en-1-yl isobutyrate

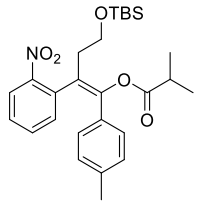
This compound was prepared following general procedure **H** using compound **2.3.4ad** (1.2 g, 2.6 mmol) as starting material. Yield: 56% (0.77 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.22 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.47-7.42 (m, 3H), 7.33 (td, *J* = 7.8, 1.5 Hz, 1H), 7.24 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.92 (d, *J* = 8.1 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 3.73 – 3.66 (m, 2H), 2.76 – 2.65 (m, 2H), 2.58 – 2.48 (m, 1H), 2.25 – 2.13 (m, 1H), 2.20 (s, 3H), 1.58 – 1.49 (m, 2H), 1.37 – 1.18 (m, 12H), 1.04 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 182.0, 175.0, 174.6, 149.0, 144.3, 138.0, 136.3, 135.2, 133.2, 132.9, 132.6, 132.4, 129.0, 128.8, 128.6, 128.4, 128.1, 127.4, 124.8, 47.0, 36.4, 34.2, 32.4, 29.5, 29.2, 27.4, 26.9, 21.4, 19.8, 19.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{43}N_2O_6^+$ 599.3116; Found 599.3127.

IR (ν_{max}, cm^{-1}) 2973 (m), 2931 (m), 2863 (w), 1751 (m), 1711 (m), 1684 (m), 1657 (s), 1525 (s), 1510 (m), 1468 (m), 1448 (m), 1387 (m), 1346 (s), 1298 (m), 1228 (m), 1184 (m), 1165 (m), 1130 (s), 1111 (s), 1090 (s), 1072 (s), 1047 (m), 1024 (m), 999 (m), 852 (m), 820 (m), 789 (m), 750 (m), 733 (s), 713 (s), 702 (s).



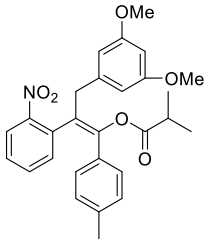
2.3.4ag, (E)-4-((tert-butyldimethylsilyl)oxy)-2-(2-nitrophenyl)-1-(p-tolyl)but-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4ag** (1.1 g, 2.7 mmol) as starting material. Yield: 46% (600 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 40:60).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.36 – 7.28 (m, 2H), 6.92 (d, J = 7.9 Hz, 2H), 6.87 (d, J = 8.0 Hz, 2H), 3.80 – 3.59 (m, 2H), 2.91 – 2.79 (m, 1H), 2.73 (hept, *J* = 7.0 Hz, 1H), 2.58 – 2.46 (m, 1H), 2.20 (s, 3H), 1.26 (d, *J* = 7.0 Hz, 6H), 0.84 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 149.0, 145.5, 138.1, 135.2, 133.4, 132.9, 132.2, 128.8, 128.4, 128.2, 124.7, 124.4, 120.3, 61.0, 36.1, 34.2, 26.0, 25.9, 21.4, 18.9, 18.3, -5.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{37}NNaO_5Si^+$ 506.2334; Found 506.2340.



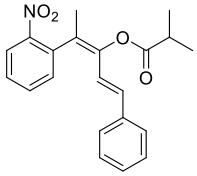
2.3.4ah, (E)-3-(3,5-dimethoxyphenyl)-2-(2-nitrophenyl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4ah** (0.2 g, 0.5 mmol) as starting material. Yield: 83% (190 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 60:40), R_f = 0.15 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 1H), 7.29 – 7.22 (m, 2H), 6.97 (d, J = 8.2 Hz, 2H), 6.94 – 6.84 (m, 3H), 6.34 – 6.24 (m, 3H), 4.13 (d, J = 14.9 Hz, 1H), 3.71 (s, 6H), 3.37 (d, J = 14.9 Hz, 1H), 2.75 (hept, J = 7.0 Hz, 1H), 2.20 (s, 3H), 1.26 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 160.8, 148.9, 145.0, 140.3, 138.2, 134.1, 133.6, 132.5, 132.1, 128.7, 128.4, 128.2, 125.9, 124.5, 107.3, 98.9, 55.4, 38.3, 34.2, 21.3, 18.94, 18.92.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{29}NNaO_6^+$ 498.1887; Found 498.1892.



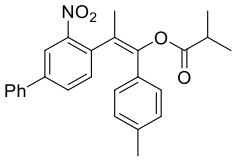
2.3.4ak, (1E,3E)-4-(2-nitrophenyl)-1-phenylpenta-1,3-dien-3-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4ak** (0.9 g, 3.0 mmol) as starting material. Yield: 80% (0.86 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.35 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (ddd, *J* = 8.2, 7.5, 1.5 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.25 – 7.11 (m, 5H), 6.46 (d, *J* = 15.8 Hz, 1H), 6.26 (d, *J* = 15.8 Hz, 1H), 2.92 (hept, *J* = 7.0 Hz, 1H), 1.99 (s, 3H), 1.41 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 148.4, 143.2, 136.4, 135.5, 132.6, 129.0, 128.6, 128.1, 126.9, 126.2, 124.9, 120.1, 34.4, 19.4, 18.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NNaO_4^+$ 374.1363; Found 374.1358.

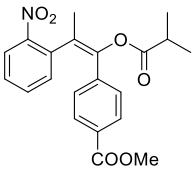


2.3.4al, (E)-2-(3-nitro-[1,1'-biphenyl]-4-yl)-1-(p-tolyl)prop-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4al** (0.9 g, 2.6 mmol) as starting material. Yield: 62% (0.67 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.24 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.9 Hz, 1H), 7.68 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.50 – 7.32 (m, 4H), 7.01 – 6.95 (m, 2H), 6.91 (d, *J* = 8.1 Hz, 2H), 2.78 (p, *J* = 7.0 Hz, 1H), 2.22 (s, 3H), 2.05 (s, 3H), 1.30 (d, *J* = 7.0 Hz, 6H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{25}NNaO_4^+$ 438.1676; Found 438.1681.



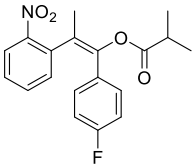
2.3.4ap, methyl (E)-4-(1-(isobutyryloxy)-2-(2-nitrophenyl)prop-1-en-1-yl)benzoate

This compound was prepared following general procedure **H** using compound **2.3.4ap** (0.1 g, 0.3 mmol) as starting material. Yield: 88% (0.11 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.17 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.79 – 7.66 (m, 2H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.28 (dd, J = 7.6, 1.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 3.83 (s, 3H), 2.78 (hept, J = 7.0 Hz, 1H), 2.05 (s, 3H), 1.28 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 166.6, 148.6, 142.9, 139.5, 135.8, 133.4, 132.4, 129.5, 129.3, 128.6, 128.3, 125.8, 124.8, 52.2, 34.1, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{21}NNaO_6^+$ 406.1261; Found 406.1245.

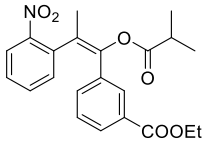


2.3.4aq, (E)-1-(4-fluorophenyl)-2-(2-nitrophenyl)prop-1-en-1-yl isobutyrate

This compound was prepared following general procedure **H** using compound **2.3.4aq** (0.1 g, 0.6 mmol) as starting material. Yield: 60% (70 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 70:30), R_f = 0.69 (PE/EtOAc 40:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.47 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 – 7.32 (m, 1H), 7.30 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.06 – 6.97 (m, 2H), 6.82 – 6.71 (m, 2H), 2.76 (p, *J* = 7.0 Hz, 1H), 2.03 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 7H).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}NFO_4^+$ 344.1293; Found 344.1297.



2.3.4ar, ethyl (E)-3-(1-(isobutyryloxy)-2-(2-nitrophenyl)prop-1-en-1-yl)benzoate

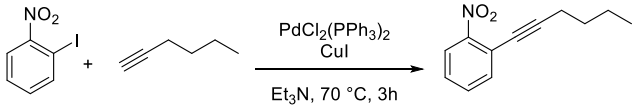
This compound was prepared following general procedure **H** using compound **2.3.4ar** (0.24 g, 0.73 mmol) as starting material. Yield: 79% (240 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.41 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.79 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.71 (t, *J* = 1.8 Hz, 1H), 7.48 (td, *J* = 7.5, 1.3 Hz, 1H), 7.40 – 7.29 (m, 2H), 7.22 – 7.10 (m, 2H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.79 (hept, *J* = 7.0 Hz, 1H), 2.07 (s, 3H), 1.34 – 1.28 (m, 9H).

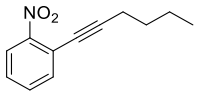
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 166.1, 148.6, 142.9, 136.0, 135.2, 133.4, 132.5, 132.5, 130.4, 129.4, 129.2, 128.6, 128.2, 125.1, 124.8, 61.1, 34.2, 19.0, 18.9, 14.4.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NNaO_6^+$ 420.1418; Found 420.1418.

6.2.5. **Synthsis of enol esters 2.3.4am-ao**



To a solution of 1-iodo-2-nitrobenzene **2.3.8** (3.0 g, 12.0 mmol, 1.0 equiv) in Et_3N (30 mL, 0.5 M) was added hex-1-yne **2.3.9am** (1.68 mL, 14.4 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (210 g, 0.3 mmol, 2.5 mol%) and CuI (92 mg, 0.48 mmol, 4 mol%). The reaction mixture was heated at 70 °C for 3 h, then water was added, the reaction crude was filtered through celite followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step without purification.



2.3.10am, 1-(hex-1-yn-1-yl)-2-nitrobenzene

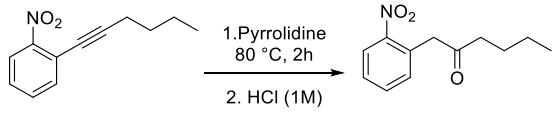
Yield: 89% (2.2 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 92:8), R_f = 0.67 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 8.2, 1.3 Hz, 1H), 7.57 (dd, J = 7.8, 1.6 Hz, 1H), 7.51 (td, J = 7.5, 1.3 Hz, 1H), 7.42 – 7.36 (m, 1H), 2.48 (t, J = 7.0 Hz, 2H), 1.70 – 1.42 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2, 134.9, 132.6, 127.9, 124.5, 119.5, 99.6, 76.0, 30.5, 22.1, 19.6, 13.8.

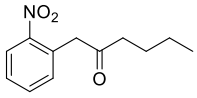
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{14}O_2^+$ 204.1020; Found 204.1026.

IR (ν_{max}, cm^{-1}) 2958 (w), 2936 (w), 2868 (w), 2228 (w), 1608 (w), 1568 (w), 1525 (s), 1342 (s), 850 (m), 782 (m), 742 (s).



2.3.10am **2.3.2am**

A solution of 1-(hex-1-yn-1-yl)-2-nitrobenzene **2.3.10am** (8.0 g, 24 mmol, 1.0 equiv) in pyrrolidine (20 mL, 0.4 M) was heated at 80 °C for 3 h. Upon completion of the reaction, the excess of pyrrolidine was evaporated. The reaction mixture was then acidified with 1N HCl and stirred for 30 min. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2am**.



2.3.2am, 1-(2-nitrophenyl)hexan-2-one

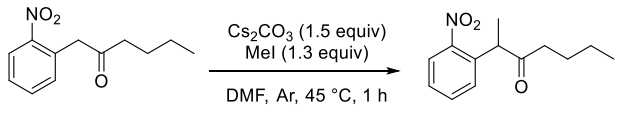
Yield: 77% (1.9 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.18 (PE/EtOAc 96:4).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.1, 1.3 Hz, 1H), 7.58 (td, J = 7.5, 1.4 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.31 – 7.21 (m, 1H), 4.10 (s, 2H), 2.60 (t, J = 7.4 Hz, 2H), 1.70 – 1.58 (m, 2H), 1.43 – 1.26 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.0, 148.9, 133.7, 133.6, 130.6, 128.4, 125.4, 48.0, 42.7, 25.9, 22.4, 14.0.

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_3^+$ 222.1125; Found 222.1122.

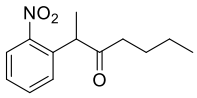
IR (ν_{max}, cm^{-1}) 2929 (w), 1714 (m), 1522 (m), 1342 (m), 1268 (s), 1106 (s), 752 (s).



2.3.2am **2.3.3am**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone

2.3.2am (0.5 g, 2.3 mmol, 1.0 equiv) in DMF (3 mL, 0.75 M), Cs_2CO_3 (1.1 g, 3.4 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of MeI (0.17 mL, 2.7 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.3am**.



2.3.3am, 2-(2-nitrophenyl)heptan-3-one

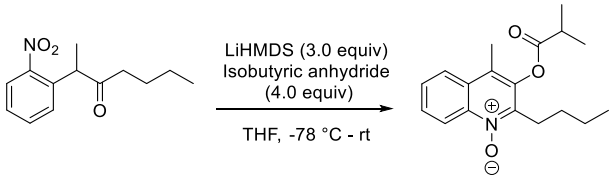
Yield: 78% (410 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.64 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, CD_3OD) δ 7.90 (dd, J = 8.1, 1.4 Hz, 1H), 7.64 (td, J = 7.6, 1.4 Hz, 1H), 7.52 – 7.35 (m, 2H), 4.28 (q, J = 7.1 Hz, 1H), 2.59 – 2.32 (m, 2H), 1.56 – 1.41 (m, 5H), 1.30 – 1.13 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ 211.3, 150.8, 136.2, 134.3, 131.2, 129.3, 125.6, 49.1, 41.6, 26.8, 23.2, 17.2, 14.2.

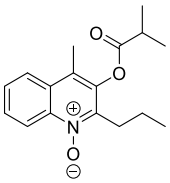
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{13}H_{18}NO_3^+$ 236.1281; Found 236.1276.

IR (ν_{max}, cm^{-1}) 2971 (w), 1678 (m), 1600 (s), 1522 (s), 1448 (m), 1350 (s), 1255 (s), 1170 (s), 842 (m).



2.3.3am **2.3.11a**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged with ketone **2.3.3am** (400 mg, 1.7 mmol, 1.0 equiv) in THF (9.0 mL, 0.2 M). Then a solution of LiHMDS (5.1 mL, 5.1 mmol, 1.0 M in THF, 3.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 5 min before warming to 0 °C. Then the anhydride (1.1 mL, 6.8 mmol, 4.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol 3-acyloxyquinoline *N*-oxides **2.3.11a**.



2.3.11a, 3-(isobutyryloxy)-4-methyl-2-propylquinoline 1-oxide

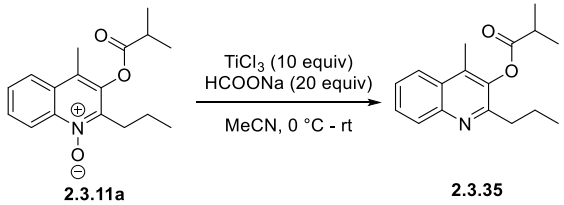
Yield: 41% (210 mg), isolated as orange solid. Purification: Flash chromatography (PE/EtOAc, 60:40), R_f = 0.09 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 – 8.65 (m, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.67 – 7.61 (m, 1H), 3.22 – 2.78 (m, 3H), 2.41 (s, 3H), 1.82 – 1.68 (m, 2H), 1.43 (d, *J* = 7.0 Hz, 6H), 1.05 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.6, 145.1, 141.9, 140.1, 129.7, 128.4, 127.6, 125.1, 124.6, 120.5, 34.4, 28.7, 19.14, 19.09, 14.6, 11.8.

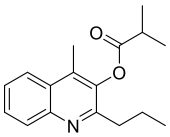
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_3^+$ 288.1595; Found 288.1585.

IR (ν_{max}, cm^{-1}) 2876 (m), 2886 (m), 2358 (w), 1758 (m), 1464 (m), 1383 (m), 1338 (m), 1230 (m), 1116 (s), 1083 (s), 760 (m).



2.3.11a **2.3.35**

In a 10 mL pressure resistant round bottomed flask was charged the 3-acyloxyquinoline *N*-oxides **2.3.11a** (30 mg, 0.1 mmol, 1.0 equiv) and HCOONa (134 mg, 2.0 mmol, 20 equiv) in MeCN (0.5 mL, 0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 0.76 mL, 1.0 mmol, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired 3-acyloxyquinoline **2.3.35**.



2.3.35, 4-methyl-2-propylquinolin-3-yl isobutyrate

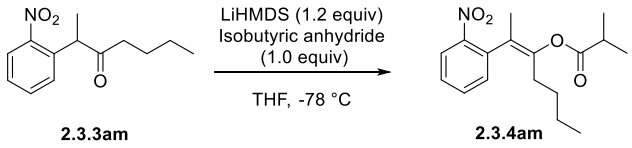
Yield: quant, isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.58 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 1H), 7.92 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.69 – 7.62 (m, 1H), 7.56 – 7.48 (m, 1H), 2.96 (p, *J* = 7.0 Hz, 1H), 2.86 – 2.71 (m, 2H), 2.44 (s, 3H), 1.79 (q, *J* = 7.6 Hz, 2H), 1.43 (d, *J* = 7.0 Hz, 6H), 1.02 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.0, 156.7, 145.7, 141.7, 134.5, 129.4, 128.7, 127.7, 126.2, 123.9, 36.4, 34.4, 22.2, 19.2, 14.3, 11.7.

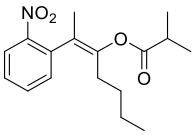
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_2^+$ 272.1646; Found 272.1655.

IR (ν_{max}, cm^{-1}) 2972 (m), 2875 (m), 1754 (s), 1468 (m), 1381 (m), 1223 (m), 1112 (s), 1091 (s), 1038 (m), 757 (s).



2.3.3am **2.3.4am**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged with ketone **2.3.3am** (100 mg, 0.4 mmol, 1.0 equiv) in THF (2.0 mL, 0.2 M). Then a solution of LiHMDS (0.48 mL, 0.48 mmol, 1.0 M in THF, 1.2 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 30 min. Then the anhydride (0.1 mL, 0.4 mmol, 1.0 equiv) was added to the reaction mixture. The reaction mixture was stirred for 4 h at -78 °C. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **2.3.4am**.



2.3.4am, (E)-2-(2-nitrophenyl)hept-2-en-3-yl isobutyrate

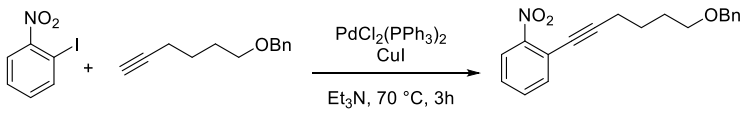
Yield: 52% (67 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.28 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.59 (td, *J* = 7.5, 1.3 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.37 (dd, *J* = 7.6, 1.5 Hz, 1H), 2.73 (p, *J* = 7.0 Hz, 1H), 1.98 – 1.87 (m, 2H), 1.85 (s, 3H), 1.29 (d, *J* = 7.0 Hz, 6H), 1.22 – 1.08 (m, 4H), 0.74 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 148.5, 146.0, 136.3, 133.3, 132.1, 128.4, 124.6, 121.7, 34.3, 30.7, 28.8, 22.2, 19.2, 17.9, 13.9.

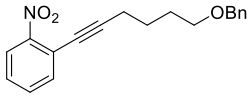
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{23}NNaO_4^+$ 328.1519; Found 328.1515.

IR (ν_{max}, cm^{-1}) 2968 (s), 2882 (s), 2365 (m), 1748 (s), 1525 (s), 1464 (m), 1349 (s), 1134 (s), 1058 (s), 853 (m), 786 (m).



2.3.8 **2.3.9an** **2.3.10an**

To a solution of 1-iodo-2-nitrobenzene (1.7 g, 6.6 mmol, 1.0 equiv) in Et_3N (13 mL, 0.5 M) was added ((hex-5-yn-1-yloxy)methyl)benzene (1.5 g, 8.0 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (120 g, 0.17 mmol, 2.5 mol%) and CuI (50 mg, 0.27 mmol, 4 mol%). The reaction mixture was heated at 70 °C for 3 h, then water was added, the reaction crude was filtered through celite followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step without purification.



2.3.10an, 1-(6-(benzyloxy)hex-1-yn-1-yl)-2-nitrobenzene

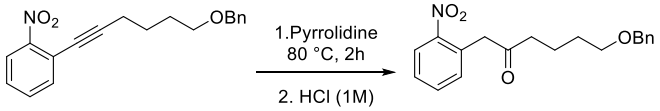
Yield: 98% (2.0 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.3, 1.3 Hz, 1H), 7.60 – 7.46 (m, 2H), 7.43 – 7.27 (m, 6H), 4.52 (s, 2H), 3.55 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 1.88 – 1.67 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.2, 138.7, 134.9, 132.7, 128.5, 128.0, 127.8, 127.76, 127.66, 124.5, 119.4, 99.1, 73.0, 69.9, 29.0, 25.3, 19.8.

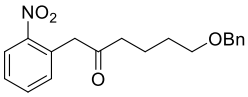
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{19}NNaO_3^+$ 332.1257; Found 332.1260

IR (ν_{max}, cm^{-1}) 2970 (s), 2894 (s), 1749 (s), 1520 (s), 1444 (m), 1350 (s), 1235 (s), 1080 (s), 746 (s).



2.3.10 an **2.3.2an**

A solution of 1-(6-(benzyloxy)hex-1-yn-1-yl)-2-nitrobenzene (2.0 g, 6.5 mmol, 1.0 equiv) in pyrrolidine (11 mL, 0.4 M) was heated at 80 °C for 3 h. Upon completion of the reaction, the excess of pyrrolidine was evaporated. The reaction mixture was then acidified with 1N HCl and stirred for 30 min. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2an**.



2.3.2an, 6-(benzyloxy)-1-(2-nitrophenyl)hexan-2-one

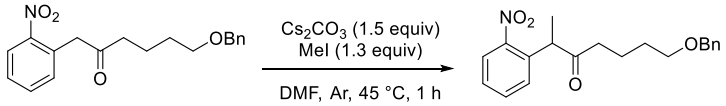
Yield: 76% (1.6 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 86:14), R_f = 0.5 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 8.2, 1.4 Hz, 1H), 7.50 (td, J = 7.5, 1.4 Hz, 1H), 7.37 (ddd, J = 8.9, 7.5, 1.5 Hz, 1H), 7.30 – 7.24 (m, 4H), 7.24 – 7.12 (m, 2H), 4.42 (s, 2H), 4.00 (s, 2H), 3.42 (t, J = 6.2 Hz, 2H), 2.56 (t, J = 7.2 Hz, 2H), 1.75 – 1.52 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.7, 148.8, 138.7, 130.7, 133.65, 130.6, 128.5, 128.46, 127.8, 127.7, 125.4, 73.1, 70.1, 48.0, 42.6, 29.4, 20.6.

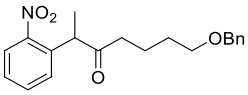
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}NNaO_4^+$ 350.1363; Found 350.1360.

IR (ν_{max}, cm^{-1}) 2964 (m), 2904 (m), 1720 (s), 1526 (s), 1354 (s), 1193 (m), 1057 (s), 740 (m).



2.3.2an **2.3.3an**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **2.3.2an** (200 mg, 0.6 mmol, 1.0 equiv) in DMF (2.4 mL, 0.25 M), Cs_2CO_3 (0.3 g, 0.9 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of MeI (0.05 mL, 0.7 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.3an**.



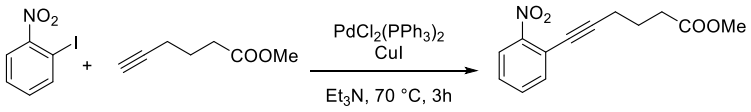
XX, 7-(benzyloxy)-2-(2-nitrophenyl)heptan-3-one

Yield: 72% (150 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.23 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.1, 1.4 Hz, 1H), 7.59 (td, J = 7.6, 1.4 Hz, 1H), 7.46 – 7.20 (m, 7H), 4.48 (s, 2H), 4.35 (q, J = 7.0 Hz, 1H), 3.44 (t, J = 6.2 Hz, 2H), 2.64 – 2.41 (m, 2H), 1.73 – 1.51 (m, 4H), 1.48 (d, J = 7.0 Hz, 3H).

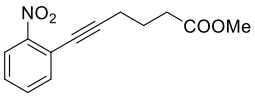
^{13}C NMR (101 MHz, $CDCl_3$): δ 209.2, 149.4, 138.6, 135.2, 133.3, 129.8, 128.4, 128.0, 127.7, 127.6, 124.8, 72.9, 70.0, 47.4, 41.1, 29.1, 20.5, 17.4.

IR (ν_{max}, cm^{-1}) 2953 (w), 1740 (s), 1554 (s), 1436 (m), 1335 (s), 1200 (m), 749 (m).



2.3.8 **2.3.9ao** **2.3.10ao**

To a solution of 1-iodo-2-nitrobenzene **2.3.8** (4.0 g, 16.0 mmol, 1.0 equiv) in Et_3N (32 mL, 0.5 M) was added methyl hex-5-ynoate **2.3.9ao** (2.12 mL, 19 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (280 g, 0.4 mmol, 2.5 mol%) and CuI (120 mg, 0.64 mmol, 4 mol%). The reaction mixture was heated at 70 °C for 3 h, then water was added, the reaction crude was filtered through celite followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step without purification.



2.3.10ao, methyl 6-(2-nitrophenyl)hex-5-ynoate

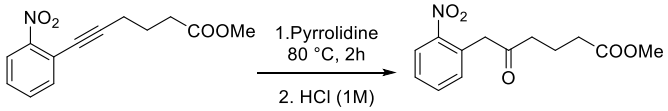
Yield: 82% (2.9 g), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.47 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.94 (m, 1H), 7.62 – 7.49 (m, 2H), 7.44 – 7.38 (m, 1H), 3.69 (s, 3H), 2.61 – 2.53 (m, 4H), 2.04 – 1.89 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.7, 135.0, 132.8, 128.2, 124.6, 119.2, 97.9, 51.8, 32.8, 23.7, 19.4.

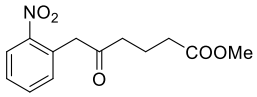
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{13}NNaO_4^+$ 270.0737; Found 270.0739.

IR (ν_{max}, cm^{-1}) 2968 (s), 2900 (s), 2340 (w), 1734 (s), 1525 (s), 1439 (m), 1346 (s), 1227 (s), 1072 (s), 786 (m), 746 (s).



2.3.10ao **2.3.2ao**

A solution of methyl 6-(2-nitrophenyl)hex-5-ynoate **2.3.10ao** (1.7 g, 7.2 mmol, 1.0 equiv) in pyrrolidine (18 mL, 0.4 M) was heated at 80 °C for 3 h. Upon completion of the reaction, the excess of pyrrolidine was evaporated. The reaction mixture was then acidified with 1N HCl and stirred for 30 min. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.2ao**.



2.3.2ao, methyl 6-(2-nitrophenyl)-5-oxohexanoate

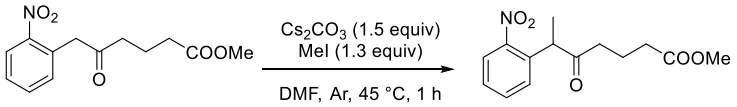
Yield: 46% (820 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.11 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dt, *J* = 8.2, 1.2 Hz, 1H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 (td, *J* = 7.8, 1.5 Hz, 1H), 7.33 – 7.21 (m, 1H), 4.09 (s, 2H), 3.67 (s, 3H), 2.69 (t, *J* = 7.1 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.96 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.0, 173.8, 148.7, 133.7, 133.73, 130.4, 128.6, 125.4, 51.7, 48.0, 41.6, 33.0, 18.9.

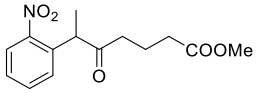
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{15}NNaO_5^+$ 288.0843; Found 288.0851.

IR (ν_{max}, cm^{-1}) 2968 (m), 2896 (m), 2340 (w), 1719 (s), 1522 (s), 1345 (s), 1187 (m), 1062 (s), 789 (m), 732 (m).



2.3.2ao **2.3.3ao**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was prepared a solution of ketone **2.3.2ao** (250 mg, 1.0 mmol, 1.0 equiv) in DMF (4 mL, 0.25 M), Cs_2CO_3 (0.48 g, 1.5 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of MeI (0.07 mL, 1.2 mmol, 1.2 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **2.3.3ao**.



2.3.3ao, methyl 6-(2-nitrophenyl)-5-oxoheptanoate

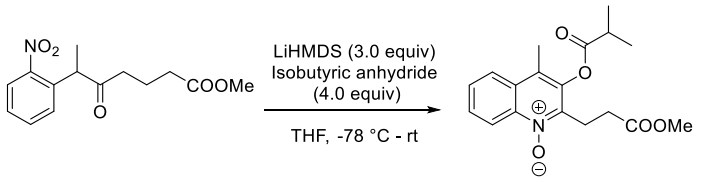
Yield: 91% (240 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.31 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.60 (td, *J* = 7.7, 1.5 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.38 (dd, *J* = 7.9, 1.4 Hz, 1H), 4.33 (q, *J* = 7.0 Hz, 1H), 3.64 (s, 3H), 2.66 – 2.46 (m, 2H), 2.37 – 2.22 (m, 2H), 1.95 – 1.85 (m, 2H), 1.48 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.6, 173.7, 135.1, 133.4, 129.9, 128.2, 124.9, 51.7, 47.6, 40.2, 33.0, 19.0, 17.3.

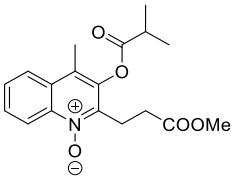
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{17}NNaO_5^+$ 302.0999; Found 302.1003.

IR (ν_{max}, cm^{-1}) 2947 (w), 1737 (s), 1525 (s), 1439 (m), 1349 (s), 1199 (m), 1166 (m), 749 (m).



2.3.3ao **2.3.11c**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged with ketone **2.3.3ao** (200 mg, 0.9 mmol, 1.0 equiv) in THF (4.5 mL, 0.2 M). Then a solution of LiHMDS (1.2 mL, 1.1 mmol, 1.0 M in THF, 1.2 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 5 min before warming to 0 °C. Then the anhydride (0.16 mL, 1.0 mmol, 1.1 equiv) was added to the reaction mixture. The reaction mixture was warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol 3-acyloxyquinoline *N*-oxides **2.3.11c**.



2.3.11c, 3-(isobutyryloxy)-2-(3-methoxy-3-oxopropyl)-4-methylquinoline 1-oxide

Yield: 20% (52 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 10:10), R_f = 0.18 (PE/EtOAc 10:10).

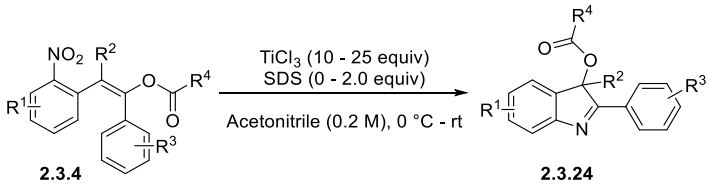
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, J = 8.6, 1.3 Hz, 1H), 7.97 (dd, J = 8.3, 1.3 Hz, 1H), 7.76 – 7.69 (m, 1H), 7.68 – 7.61 (m, 1H), 3.67 (s, 3H), 3.31 (br s, 2H), 2.98 (p, J = 7.0 Hz, 1H), 2.89 – 2.63 (m, 2H), 2.41 (s, 3H), 1.41 (d, J = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.9, 173.3, 143.1, 141.6, 140.0, 129.8, 128.7, 127.8, 125.3, 124.6, 120.3, 51.9, 34.3, 29.1, 22.5, 19.1, 11.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{22}NO_5^+$ 332.1493; Found 332.1482.

IR (ν_{max}, cm^{-1}) 2972 (s), 2896 (s), 2632 (m), 1734 (s), 1525 (s), 1349 (s), 1227 (s), 1058 (s), 754 (m).

6.2.6. **General procedures for the synthesis of the 3-acyloxyindolenines**



Procedure I

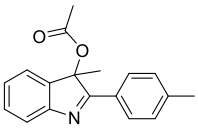
In a 10 mL pressure resistant round bottomed flask was charged the enol ester **2.3.4a** (1.0 equiv) in MeCN (0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired 3-acyloxyindolenines **2.3.24a**.

Procedure J

Into a 10 mL pressure resistant round bottomed flask was charged the enol ester **2.3.4c** (63 mg, 0.17 mmol, 1.0 equiv) in MeCN (0.9 mL, 0.2 M). Then $TiCl_3$ (1.3 mL, 1.7 mmol, 1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. Due to incomplete reaction another 5 equiv of $TiCl_3$ (0.65 mL) was added dropwise at 0 °C. The process was repeated 2 more times every 12 h (25 equiv of $TiCl_3$ totally), then the reaction mixture was stirred for 2 days. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired 3-acyloxyindolenines **2.3.24c**.

Procedure K

Into a 10 mL pressure resistant round bottomed flask were charged the enol ester **2.3.4e** (50 mg, 0.19 mmol, 1.0 equiv) and SDS (sodium dodecyl sulfate, 110 mg, 0.38 mmol, 2.0 equiv) in MeCN (1.0 mL, 0.2 M). Then $TiCl_3$ (1.46 mL, 1.9 mmol, 1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. Due to incomplete reaction another 5 equiv of $TiCl_3$ was added dropwise at 0 °C. The process was repeated 2 more times every 12 h (25 equiv of $TiCl_3$), then the reaction mixture was stirred for 2 days. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired 3-acyloxyindolenines **2.3.24e**.



2.3.24a, 3-methyl-2-(p-tolyl)-3H-indol-3-yl acetate

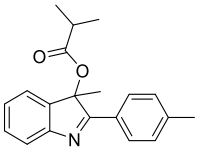
This compound was prepared following general procedure **I** using compound **2.3.4a** (40 mg, 0.13 mmol) as starting material. Yield: 55% (20 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.40 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 2H), 7.63 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.39 (td, *J* = 7.6, 1.3 Hz, 1H), 7.35 – 7.28 (m, 3H), 7.23 (td, *J* = 7.4, 1.0 Hz, 1H), 2.42 (s, 3H), 2.03 (s, 3H), 1.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 168.4, 152.9, 141.9, 140.0, 129.7, 128.7, 128.0, 126.3, 121.4, 120.6, 87.3, 25.0, 21.8, 21.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{18}NO_2^+$ 280.1332; Found 280.1332.

IR (ν_{max}, cm^{-1}) 3046 (w), 2994 (w), 2929 (w), 2856 (w), 1751 (s), 1535 (m), 1442 (m), 1367 (m), 1228 (s), 1081 (s), 1012 (m), 825 (m), 760 (m).



2.3.24b, 3-methyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

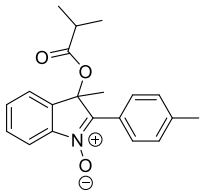
This compound was prepared following general procedure **I** using compound **2.3.4a** (100 mg, 0.3 mmol) as starting material. Yield: 70% (64 mg), isolated as white solid (mp = 97 – 98 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.38 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.39 (td, *J* = 7.6, 1.4 Hz, 1H), 7.32 – 7.27 (m, 3H), 7.22 (td, *J* = 7.4, 1.0 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.42 (s, 3H), 1.74 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.1, 174.3, 153.0, 141.9, 140.1, 129.7, 129.6, 128.7, 128.1, 126.3, 121.4, 120.4, 87.0, 34.0, 25.1, 21.8, 18.9, 18.8.

HRMS (ESI) calcd for $C_{20}H_{22}NO_2^+$ $[M+H]^+$ 308.1645; found 308.1646.

IR (ν_{max}, cm^{-1}) 2966 (w), 2929 (w), 2872 (w), 1738 (s), 1148 (s), 1079 (s), 1055 (s), 752 (s).



2.3.27b, 3-(isobutyryloxy)-3-methyl-2-(p-tolyl)-3H-indole 1-oxide

In a 10 mL pressure resistant round bottomed flask was charged the enol ester **2.3.4b** (34 mg, 0.1 mmol, 1.0 equiv) and $HCOONH_4$ (380 mg, 6.0 mmol, 60 equiv) in MeCN (0.5 mL, 0.2 M). Then $TiCl_3$ (0.78 mL, 1.0 mmol, 1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired 3-(isobutyryloxy)-3-methyl-2-(p-tolyl)-3H-indole 1-oxide **2.3.27b**.

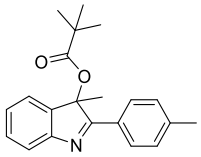
Yield: 71% (23 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 7.8 Hz, 1H), 7.53 (br t, J = 7.3 Hz, 1H), 7.44 (br t, J = 7.3, 1.0 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.32 (d, J = 8.5 Hz, 2H), 2.55 (hept, J = 7.0 Hz, 1H), 2.42 (s, 3H), 1.88 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 146.4, 143.8, 141.2, 135.8, 130.1, 129.5, 129.4, 127.2, 124.8, 120.3, 115.3, 82.4, 34.2, 25.1, 21.9, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_3^+$ 324.1594; Found 324.1590.

IR (ν_{max}, cm^{-1}) 2975.6 (w), 2882.6 (w), 2250.5 (w), 1747.7 (m), 1500.4 (w), 1371.1 (m), 1072.6 (s), 1066.0 (s), 915.1 (m).



2.3.24c, 3-methyl-2-(p-tolyl)-3H-indol-3-yl pivalate

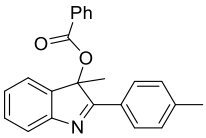
This compound was prepared following general procedure **I** using compound **2.3.4c** (50 mg, 0.14 mmol) as starting material. Yield: 65% (30 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.52 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.7 Hz, 1H), 7.38 (td, J = 7.5, 1.5 Hz, 1H), 7.31 – 7.25 (m, 3H), 7.21 (td, J = 7.3, 1.0 Hz, 1H), 2.41 (s, 3H), 1.73 (s, 3H), 1.18 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.3, 175.6, 153.0, 141.9, 140.2, 129.7, 129.5, 128.7, 128.1, 126.3, 121.4, 120.2, 86.9, 38.7, 27.1, 25.0, 21.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_2^+$ 322.1802; Found 322.1801.

IR (ν_{max}, cm^{-1}) 2974 (w), 2933 (w), 2871 (w), 1743 (s), 1608 (m), 1535 (m), 1457 (m), 1282 (m), 1143 (s), 1078 (s), 825 (m), 752 (s), 731 (m).



2.3.24d, 3-methyl-2-(p-tolyl)-3H-indol-3-yl benzoate

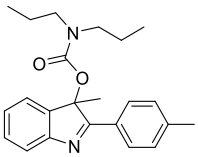
This compound was prepared following general procedure **J** using compound **2.3.4d** (63 mg, 0.17 mmol) as starting material. Yield: 62% (36 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.41 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 8.07 – 8.01 (m, 2H), 7.68 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.47 – 7.35 (m, 4H), 7.26 – 7.19 (m, 3H), 2.37 (s, 3H), 1.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.0, 164.0, 153.1, 141.9, 139.9, 133.5, 130.0, 129.8, 129.7, 128.7, 128.6, 128.1, 126.4, 121.5, 120.9, 87.6, 25.1, 21.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{20}NO_2^+$ 342.1489; Found 342.1483.

IR (ν_{max}, cm^{-1}) 3058 (w), 2987 (w), 2925 (w), 1729 (s), 1535 (m), 1452 (m), 1274 (s), 1245 (m), 1103 (s), 1074 (s), 756 (m), 711 (s).



2.3.24e, 3-methyl-2-(p-tolyl)-3H-indol-3-yl dipropylcarbamate

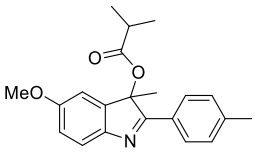
This compound was prepared following general procedure **K** using compound **2.3.4e** (120 mg, 0.3 mmol) as starting material. Yield: 45% (50 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.46 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.3 Hz, 2H), 7.60 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.36 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 – 7.24 (m, 3H), 7.20 (td, *J* = 7.4, 1.0 Hz, 1H), 3.42 (dt, *J* = 14.6, 7.5 Hz, 1H), 3.25 (dt, *J* = 14.6, 7.5 Hz, 1H), 3.10 (dt, *J* = 14.7, 7.6 Hz, 1H), 2.92 (dt, *J* = 14.1, 7.6 Hz, 1H), 2.41 (s, 3H), 1.70 (s, 3H), 1.69 – 1.62 (m, 2H), 1.35 (sext, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.66 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2, 153.4, 152.8, 141.5, 140.8, 129.4, 129.2, 128.1, 126.0, 121.4, 120.5, 87.2, 49.0, 25.3, 22.3, 21.7, 21.1, 11.6, 11.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{29}N_2O_2^+$ 365.2224; Found 365.2217.

IR (ν_{max}, cm^{-1}) 2964 (w), 2931 (w), 1709 (s), 1535 (s), 1468 (m), 1444 (m), 1419 (m), 1375 (m), 1267 (m), 1240 (s), 1203 (m), 1165 (m), 1088 (s), 1059 (m), 823 (m), 756 (s), 731 (s).



2.3.24g, 5-methoxy-3-methyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

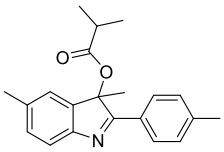
This compound was prepared following general procedure **J** using compound **2.3.4g** (100 mg, 0.3 mmol) as starting material. Yield: 53% (49 mg), isolated as yellow solid (mp = 84 – 85 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.38 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.89 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 3.83 (s, 3H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 1.72 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 174.3, 158.8, 146.6, 141.9, 141.4, 129.5, 128.8, 127.7, 121.8, 113.4, 107.7, 86.9, 55.8, 34.0, 25.2, 21.7, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_3^+$ 338.1751; Found 338.1750.

IR (ν_{max}, cm^{-1}) 2925 (w), 2856 (w), 1747 (s), 1473 (s), 1290 (m), 1261 (m), 1209 (s), 1184 (m), 1151 (s), 1101 (m), 1063 (s), 1003 (m), 822 (s), 796 (s), 723 (s).



2.3.24h, 3,5-dimethyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

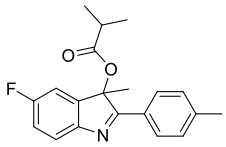
This compound was prepared following general procedure **K** using compound **2.3.4h** (50 mg, 0.14 mmol) as starting material. Yield: 77% (35 mg), isolated as red solid (mp = 116 – 117 °C). Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.42 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.09 (s, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 2.39 (s, 3H), 1.72 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1, 174.3, 150.8, 141.6, 140.3, 136.3, 130.2, 129.5, 128.8, 127.9, 121.2, 121.0, 86.9, 34.0, 25.1, 21.7, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_2^+$ 322.1802; Found 322.1802.

IR (ν_{max}, cm^{-1}) 2977 (w), 2924 (w), 2967 (w), 1747 (s), 1535 (m), 1510 (m), 1473 (m), 1452 (m), 1184 (s), 1151 (s), 1078 (s), 821 (s).



2.3.24f, 5-fluoro-3-methyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

This compound was prepared following general procedure **I** using compound **2.3.4f** (100 mg, 0.28 mmol) as starting material. Yield: 75% (68 mg), isolated as colorless crystals (mp = 148 – 150 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.72 (PE/EtOAc 80:20).

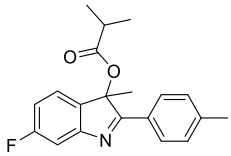
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.55 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.06 (ddd, *J* = 9.3, 8.4, 2.6 Hz, 1H), 6.99 (dd, *J* = 7.5, 2.6 Hz, 1H), 2.57 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 1.72 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.1 (d, *J* = 4.0 Hz), 174.3, 161.8 (d, *J* = 245.9 Hz), 148.9 (d, *J* = 2.2 Hz), 142.1 (d, *J* = 8.6 Hz), 142.0, 129.6, 128.5, 127.9, 122.2 (d, *J* = 8.7 Hz), 116.0 (d, *J* = 23.5 Hz), 108.5 (d, *J* = 25.2 Hz), 86.9 (d, *J* = 2.0 Hz), 34.0, 25.0, 21.7, 18.9, 18.8.

^{19}F NMR (377 MHz, $CDCl_3$) δ -118.82.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}FNO_2^+$ 326.1551; Found 326.1552.

IR (ν_{max}, cm^{-1}) 2977 (w), 2933 (w), 2875 (w), 1745 (s), 1535 (m), 1464 (s), 1444 (m), 1344 (m), 1267 (m), 1201 (m), 1180 (s), 1147 (s), 1119 (m), 1101 (m), 1080 (s), 1055 (m), 868 (m), 852 (m), 825 (s), 773 (m), 754 (m), 733 (m), 719 (m).



2.3.24i, 6-fluoro-3-methyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

This compound was prepared following general procedure **J** using compound **2.3.4i** (50 mg, 0.14 mmol) as starting material. Yield: 50% (23 mg), isolated as brown solid (mp = 126 – 127 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.44 (PE/EtOAc 90:10).

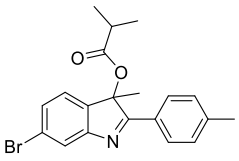
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.2 Hz, 2H), 7.32 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.22 (dd, *J* = 8.1, 5.2 Hz, 1H), 6.90 (ddd, *J* = 9.4, 8.1, 2.3 Hz, 1H), 2.55 (hept, *J* = 7.0 Hz, 1H), 2.42 (s, 3H), 1.72 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 179.1, 174.4, 164.0 (d, *J* = 245.4 Hz), 154.6 (d, *J* = 11.4 Hz), 142.4, 135.7 (d, *J* = 2.9 Hz), 129.7, 128.4, 128.2, 121.0 (d, *J* = 9.9 Hz), 112.7 (d, *J* = 23.4 Hz), 109.2 (d, *J* = 24.2 Hz), 86.4, 34.0, 25.1, 21.8, 18.9, 18.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ -115.56 (td, *J* = 8.9, 5.2 Hz).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}FNO_2^+$ 326.1551; Found 326.1549.

IR (ν_{max}, cm^{-1}) 2994 (w), 2929 (w), 1747 (s), 1612 (m), 1531 (m), 1473 (s), 1338 (m), 1257 (m), 1187 (m), 1151 (s), 1132 (s), 814 (m).



2.3.24j, 6-bromo-3-methyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

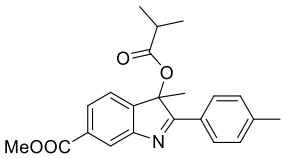
This compound was prepared following general procedure **J** using compound **2.3.4j** (50 mg, 0.12 mmol) as starting material. Yield: 42% (19 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.25 (PE/EtOAc 95:5).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.35 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.42 (s, 3H), 1.71 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.6, 174.4, 154.4, 142.5, 139.1, 129.7, 129.1, 128.3, 128.2, 124.8, 123.1, 121.5, 86.6, 33.9, 24.9, 21.8, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{21}BrNO_2^+$ 386.0750; Found 386.0746.

IR (ν_{max}, cm^{-1}) 2962 (w), 2925 (w), 2848 (w),1705 (m), 1689 (m), 1595 (s), 1469 (m), 1452 (s), 1427 (m), 1385 (m), 1290 (s), 1265 (s), 1203 (s), 1155 (s), 1128 (m), 1109 (m), 1066 (m), 1049 (s), 928 (m), 849 (m), 827 (m), 750 (m).



2.3.24k, methyl 3-(isobutyryloxy)-3-methyl-2-(p-tolyl)-3H-indole-6-carboxylate

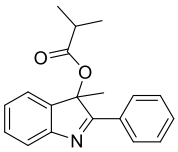
This compound was prepared following general procedure **I** using compound **2.3.4k** (66 mg, 0.17 mmol) as starting material. Yield: 64% (39 mg), isolated as white solid (mp = 124 – 125 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.45 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 1.4 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.96 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 3.93 (s, 3H), 2.57 (hept, *J* = 7.0 Hz, 1H), 2.42 (s, 3H), 1.74 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.0, 174.4, 166.9, 153.1, 145.1, 142.4, 131.8, 129.7, 128.4, 128.2, 128.17, 122.4, 120.1, 86.7, 52.4, 33.9, 24.8, 21.8, 18.9, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NNaO_4^+$ 388.1519; Found 388.1517.

IR (ν_{max}, cm^{-1}) 2981 (w), 2933 (w), 2879 (w), 1745 (m), 1720 (s), 1532 (m), 1510 (m), 1432 (m), 1281 (s), 1230 (m), 1200 (m), 1188 (m), 1147 (m), 1082 (s), 906 (m), 825 (m), 768 (m), 727 (m).



2.3.24l, 3-methyl-2-phenyl-3H-indol-3-yl isobutyrate

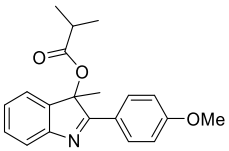
This compound was prepared following general procedure **I** using compound **2.3.4l** (50 mg, 0.15 mmol) as starting material. Yield: 71% (32 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.15 (m, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.40 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.23 (td, *J* = 7.4, 1.0 Hz, 1H), 2.57 (hept, *J* = 7.0 Hz, 1H), 1.74 (s, 3H), 1.58 (s, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.1, 174.4, 152.9, 140.2, 131.4, 131.37, 129.7, 128.8, 128.1, 126.6, 121.6, 120.4, 87.0, 34.0, 24.9, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_2^+$ 294.1489; Found 294.1487.

IR (ν_{max}, cm^{-1}) 2977 (w), 2932 (w), 1747 (s), 1536 (m), 1469 (m), 1445 (m), 1189 (s), 1145 (s), 1079 (s), 756 (s), 694 (m).



2.3.24m, 2-(4-methoxyphenyl)-3-methyl-3H-indol-3-yl isobutyrate

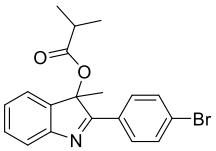
This compound was prepared following general procedure **I** using compound **2.3.4m** (50 mg, 0.14 mmol) as starting material. Yield: 72% (33 mg), isolated as red oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.41 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.9 Hz, 2H), 7.60 (dt, *J* = 7.8, 0.8 Hz, 1H), 7.37 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29-7.26 (m, 1H), 7.20 (td, *J* = 7.4, 1.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.88 (s, 3H), 2.55 (hept, *J* = 7.0 Hz, 1H), 1.73 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 174.3, 162.2, 153.1, 140.0, 129.9, 129.7, 126.0, 124.2, 121.2, 120.3, 114.2, 87.0, 55.5, 34.0, 25.2, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_3^+$ 324.1594; Found 324.1588.

IR (ν_{max}, cm^{-1}) 2974 (w), 2933 (w), 1745 (m), 1604 (m), 1510 (s), 1466 (m), 1441 (m), 1419 (m), 1309 (m), 1255 (s), 1205 (m), 1176 (s), 1147 (s), 1119 (m), 1078 (s), 1030 (s), 1011 (m), 839 (m), 756 (s), 735 (s), 719 (s), 700 (m).



2.3.24n, 2-(4-bromophenyl)-3-methyl-3H-indol-3-yl isobutyrate

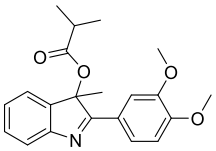
This compound was prepared following general procedure **J** using compound **2.3.4n** (50 mg, 0.12 mmol) as starting material. Yield: 45% (21 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.61 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 7.9 Hz, 1H), 7.61 (d, J = 8.7 Hz, 2H), 7.40 (td, J = 7.5, 1.5 Hz, 1H), 7.32 – 7.20 (m, 2H), 2.56 (hept, J = 7.0 Hz, 1H), 1.72 (s, 3H), 1.12 (d, J = 7.0 Hz, 7H), 1.10 (d, J = 7.0 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.2, 174.4, 152.7, 140.1, 132.1, 130.3, 129.8, 129.5, 126.8, 126.1, 121.8, 120.5, 86.8, 34.0, 24.8, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{19}BrNO_2^+$ 372.0594; Found 372.0588.

IR (ν_{max}, cm^{-1}) 2969 (m), 2924 (m), 2856 (w), 1706 (s), 1488 (m), 1452 (s), 1388 (m), 1359 (m), 1268 (s), 1195 (m), 1130 (m), 1060 (m), 1008 (m), 850 (m), 748 (s).



2.3.24o, 2-(3,4-dimethoxyphenyl)-3-methyl-3H-indol-3-yl isobutyrate

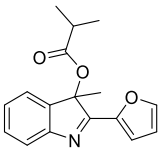
This compound was prepared following general procedure **I** using compound **2.3.4o** (50 mg, 0.13 mmol) as starting material. Yield: 79% (36 mg), isolated as red solid (mp = 120 – 121 °C). Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.53 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 2.0 Hz, 1H), 7.64 – 7.59 (m, 2H), 7.38 (td, J = 7.6, 1.4 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.20 (td, J = 7.4, 1.0 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.55 (hept, J = 7.0 Hz, 1H), 1.74 (s, 3H), 1.12 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 174.2, 153.0, 152.1, 149.4, 140.1, 129.6, 126.1, 124.5, 121.7, 121.2, 120.3, 110.5, 110.4, 86.9, 56.2, 56.1, 34.0, 25.5, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_4^+$ 354.1700; Found 354.1689.

IR (ν_{max}, cm^{-1}) 2969 (m), 2937 (w), 2834 (m), 1743 (m), 1506 (s), 1464 (m), 1444 (m), 1421 (m), 1269 (s), 1248 (s), 1227 (s), 1203 (m), 1178 (m), 1138 (s), 1099 (m), 1078 (s),1022 (s), 758 (s), 733 (m).



2.3.24p, 2-(furan-2-yl)-3-methyl-3H-indol-3-yl isobutyrate

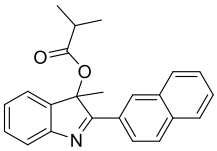
This compound was prepared following general procedure **J** using compound **2.3.4p** (50 mg, 0.16 mmol) as starting material. Yield: 50% (23 mg), isolated as brown oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.35 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 1.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 6.58 (dd, *J* = 3.6, 1.8 Hz, 1H), 2.54 (hept, *J* = 7.0 Hz, 1H), 1.72 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 168.5, 153.3, 147.5, 145.8, 138.7, 129.9, 126.5, 121.8, 120.6, 114.7, 112.3, 86.4, 34.0, 24.9, 18.9, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_3^+$ 284.1281; Found 284.1280.

IR (ν_{max}, cm^{-1}) 2973 (w), 2920 (w), 2867 (w), 1739 (m), 1700 (s), 1579 (m), 1531 (m), 1454 (m), 1375 (m), 1334 (m), 1236 (m), 1195 (m), 1155 (m), 1081 (m), 755 (s).



2.3.24q, 3-methyl-2-(naphthalen-2-yl)-3H-indol-3-yl isobutyrate

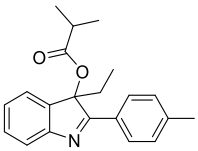
This compound was prepared following general procedure **J** using compound **2.3.4q** (50 mg, 0.13 mmol) as starting material. Yield: 63% (29 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 94:6), R_f = 0.18 (PE/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.43 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.60-7.53 (m, 2H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 1H), 2.62 (hept, *J* = 7.0 Hz, 1H), 1.84 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.1, 174.3, 152.9, 140.3, 134.8, 133.1, 129.7, 129.1, 128.9, 128.6, 128.5, 128.0, 127.8, 126.7, 126.6, 124.9, 121.7, 120.4, 87.1, 34.1, 25.3, 18.9, 18.86.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_2^+$ 366.1464; Found 366.1459.

IR (ν_{max}, cm^{-1}) 2976 (w), 2933 (w), 1743 (s), 1535 (m), 1468 (m), 1186 (m), 1147 (s), 1124 (m), 1099 (m), 1078 (s), 1059 (m), 864 (m), 823 (m), 756 (s), 731 (s), 702 (m).



2.3.24r, 3-ethyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

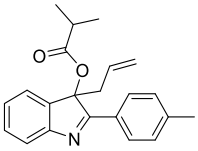
This compound was prepared following general procedure **J** using compound **2.3.4r** (50 mg, 0.14 mmol) as starting material. Yield: 71% (32 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 95: 5), R_f = 0.39 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.38 (td, *J* = 7.4, 1.6 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 2H), 7.27 – 7.24 (m, 1H), 7.21 (td, *J* = 7.3, 1.0 Hz, 1H), 2.57 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 2.36 (dq, *J* = 13.3, 7.5 Hz, 1H), 2.04 (dq, *J* = 13.3, 7.5 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.57 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 174.2, 153.8, 141.9, 138.1, 129.7, 129.5, 129.1, 127.9, 126.0, 121.2, 120.9, 90.6, 34.1, 30.9, 21.7, 19.0, 18.8, 6.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_2^+$ 322.1802; Found 322.1805.

IR (ν_{max}, cm^{-1}) 2972 (m), 2924 (w), 2881 (w), 1747 (s), 1535 (m), 1512 (m), 1456 (m), 1442 (m), 1254 (m), 1201 (m), 1184 (s), 1147 (s), 1115 (m), 1090 (m), 1063 (s), 883 (m), 825 (m), 748 (s).



2.3.24s, 3-allyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

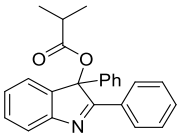
This compound was prepared following general procedure **J** using compound **2.3.4s** (50 mg, 0.14 mmol) as starting material. Yield: 48% (22 mg), isolated as red solid (mp = 76 – 77 °C). Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.35 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.3 Hz, 2H), 7.60 (dt, *J* = 7.7, 0.8 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 – 7.24 (m, 3H), 7.20 (td, *J* = 7.4, 1.0 Hz, 1H), 5.37 (dddd, *J* = 16.8, 10.2, 7.8, 6.6 Hz, 1H), 4.93 (ddt, *J* = 10.2, 1.4, 0.9 Hz, 1H), 4.82 (dq, *J* = 16.8, 1.4 Hz, 1H), 3.11 (ddt, *J* = 13.5, 6.6, 1.3 Hz, 1H), 2.66 – 2.54 (m, 2H), 2.42 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.9, 174.1, 153.6, 141.9, 137.9, 129.7, 129.6, 129.5, 129.1, 127.9, 125.9, 121.3, 120.3, 89.1, 42.0, 34.1, 21.8, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{23}NNaO_2^+$ 356.1621; Found 356.1610.

IR (ν_{max}, cm^{-1}) 2972 (m), 2932 (w), 2874 (w), 2021 (m), 1747 (s), 1535 (m), 1510 (m), 1456 (m), 1437 (m), 1265 (m), 1248 (m), 1184 (s), 1146 (s), 1117 (m), 1097 (m), 1055 (s), 1014 (m), 991 (m), 924 (m), 904 (m), 847 (m), 760 (s), 733 (s), 708 (m).



2.3.24t, 2,3-diphenyl-3H-indol-3-yl isobutyrate

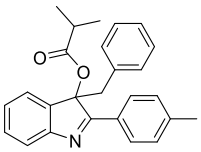
This compound was prepared following general procedure **J** using compound **2.3.4t** (40 mg, 0.1 mmol) as starting material. Yield: 31% (11 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 92:8), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.27 (m, 9H), 7.13 (td, *J* = 7.4, 1.0 Hz, 1H), 7.07 (dd, *J* = 7.4, 1.4 Hz, 1H), 2.65 (hept, *J* = 7.0 Hz, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 177.2, 173.7, 153.5, 141.3, 137.5, 131.3, 131.1, 129.8, 129.3, 128.8, 128.6, 128.3, 126.9, 124.1, 121.8, 121.4, 90.1, 34.4, 18.94, 18.92.

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{22}NO_2^+$ 356.1645; Found 356.1635.

IR (ν_{max}, cm^{-1}) 3058 (w), 2975 (w), 2919 (w), 2875 (w), 1753 (s), 1600 (m), 1578 (m), 1536 (m), 1494 (m), 1446 (s), 1263 (m), 1140 (s), 1119 (m), 767 (s), 744 (s), 698 (s).



2.3.24u, 3-benzyl-2-(p-tolyl)-3H-indol-3-yl isobutyrate

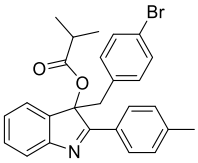
This compound was prepared following general procedure **J** using compound **2.3.4u** (50 mg, 0.12 mmol) as starting material. Yield: 47% (22 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.3 Hz, 2H), 7.47 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.36 – 7.29 (m, 3H), 7.19 – 7.13 (m, 1H), 7.12 – 7.05 (m, 3H), 6.81 – 6.76 (m, 2H), 6.74 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 3.68 (d, *J* = 13.4 Hz, 1H), 2.96 (d, *J* = 13.4 Hz, 1H), 2.60 (hept, *J* = 7.0 Hz, 1H), 2.44 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.1, 174.0, 153.5, 141.9, 137.4, 133.5, 130.9, 129.7, 129.66, 129.4, 128.0, 127.7, 127.3, 125.5, 122.0, 121.2, 89.7, 43.8, 34.2, 21.8, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}NO_2^+$ 384.1958; Found 384.1949.

IR (ν_{max}, cm^{-1}) 3032 (w), 2974 (w), 2922 (w), 2875 (w), 1750 (s), 1610 (m), 1535 (m), 1510 (m), 1452 (s), 1241 (m), 1188 (s), 1140 (s), 1053 (s), 822 (m), 764 (s), 698 (s).



2.3.24v, 3-(4-bromobenzyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

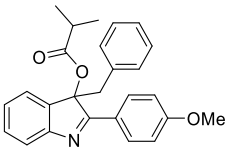
This compound was prepared following general procedure **J** using compound **2.3.4v** (50 mg, 0.1 mmol) as starting material. Yield: 32% (15 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 85:15), R_f = 0.27 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.34 (td, *J* = 7.6, 1.2 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 6.8 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 2H), 3.61 (d, *J* = 13.3 Hz, 1H), 2.97 (d, *J* = 13.3 Hz, 1H), 2.60 (hept, *J* = 7.0 Hz, 1H), 2.44 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 173.9, 153.4, 142.1, 137.1, 132.4, 132.3, 130.8, 129.9, 129.7, 129.2, 128.0, 125.7, 121.7, 121.5, 121.4, 89.4, 43.2, 34.2, 21.8, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}BrNO_2^+$ 462.1063; Found 462.1068.

IR (ν_{max}, cm^{-1}) 2968 (w), 2927 (w), 2869 (w), 1749 (s0, 1535 (m), 1487 (s), 1450 (s), 1203 (m), 1188 (s), 1144 (s), 1115 (s), 1097 (s), 1070 (s), 1053 (s), 1012 (s), 827 (s), 814 (s), 783 (s), 769 (s), 748 (s).



2.3.24w, 3-benzyl-2-(4-methoxyphenyl)-3H-indol-3-yl isobutyrate

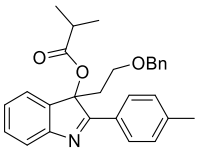
This compound was prepared following general procedure **J** using compound **2.3.4w** (50 mg, 1.2 mmol) as starting material. Yield: 52% (24 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.32 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.0 Hz, 2H), 7.45 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.31 (td, *J* = 7.6, 1.2 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.12 – 7.05 (m, 3H), 7.01 (d, *J* = 9.0 Hz, 2H), 6.80 – 6.76 (m, 2H), 6.75 (d, *J* = 7.4 Hz, 1H), 3.90 (s, 3H), 3.66 (d, *J* = 13.4 Hz, 1H), 2.97 (d, *J* = 13.4 Hz, 1H), 2.61 (hept, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 174.0, 162.2, 153.6, 137.3, 133.5, 130.9, 129.9, 129.7, 127.7, 127.3, 125.3, 124.9, 121.9, 120.9, 114.3, 89.7, 55.5, 44.0, 34.2, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}NO_3^+$ 400.1907; Found 400.1915.

IR (ν_{max}, cm^{-1}) 2974 (w), 2927 (w), 1747 (m), 1604 (s), 1509 (s), 1454 (m), 1308 (m), 1253 (s), 1176 (s), 1147 (m), 1029 (m), 837 (m), 764 (m), 738 (m), 702 (m).



2.3.24x, 3-(2-(benzyloxy)ethyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

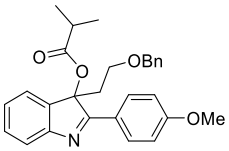
This compound was prepared following general procedure **J** using compound **2.3.4x** (50 mg, 0.11 mmol) as starting material. Yield: 50% (23 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.5 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 6.8 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.29 – 7.17 (m, 7H), 7.12 – 7.06 (m, 2H), 4.23 (d, *J* = 11.7 Hz, 1H), 4.19 (d, *J* = 11.7 Hz, 1H), 3.25 – 3.18 (m, 2H), 2.70 (ddd, *J* = 13.6, 7.8, 6.0 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.45 – 2.36 (m, 1H), 2.41 (s, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 174.1, 153.7, 141.9, 138.0, 137.99, 129.9, 129.6, 129.0, 128.4, 128.0, 127.6, 126.2, 121.4, 121.2, 88.5, 73.1, 64.6, 37.5, 34.1, 21.8, 19.0, 18.7.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}NO_3^+$ 428.2220; Found 428.2230.

IR (ν_{max}, cm^{-1}) 2969 (w), 2923 (w), 2865 (w), 1747 (m), 1608 (m), 1535 (m), 1452 (s), 1269 (m), 1184 (m), 1147 (s), 1115 (s), 1095 (s), 1072 (s), 1059 (s), 1016 (m), 985 (m), 825 (m), 766 (s), 748 (s), 735 (s), 717 (s).



2.3.24y, 3-(2-(benzyloxy)ethyl)-2-(4-methoxyphenyl)-3H-indol-3-yl isobutyrate

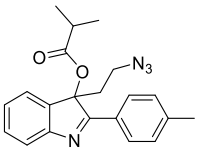
This compound was prepared following general procedure **J** using compound **2.3.4y** (60 mg, 0.13 mmol) as starting material. Yield: 68% (38 mg), isolated as brown oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.33 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.0 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28 – 7.16 (m, 5H), 7.12 – 7.08 (m, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.24 (d, *J* = 11.7 Hz, 1H), 4.20 (d, *J* = 11.7 Hz, 1H), 3.88 (s, 3H), 3.25 – 3.19 (m, 2H), 2.70 (ddd, *J* = 13.6, 7.9, 6.0 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.44 – 2.35 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.0, 174.0, 162.2, 153.8, 138.0, 137.8, 129.9, 129.8, 128.4, 127.6, 127.59, 125.9, 124.5, 121.1, 121.09, 114.2, 88.5, 73.1, 65.0, 55.5, 37.7, 34.1, 19.0, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}NO_4^+$ 444.2169; Found 444.2179.

IR (ν_{max}, cm^{-1}) 2965 (w), 2934 (w), 2863 (w), 2834 (w), 1743 (m), 1722 (m), 1604 (s), 1510 (s), 1452 (m), 1254 (s), 1176 (s), 1107 (m), 1030 (m), 837 (m), 760 (m), 710 (m).



2.3.24z, 3-(2-azidoethyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

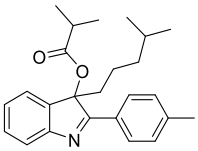
This compound was prepared following general procedure **J** using compound **2.3.4z** (0.7 g, 1.8 mmol) as starting material. Yield: 40% (260 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 10:90), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.18 (m, 4H), 3.09 – 2.92 (m, 2H), 2.66 – 2.53 (m, 2H), 2.41 (s, 3H), 2.27 – 2.17 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H), 1.11 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 173.9, 153.5, 142.3, 137.2, 130.3, 129.7, 128.6, 127.8, 126.4, 121.7, 121.0, 88.2, 45.7, 36.6, 34.0, 21.8, 19.0, 18.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{23}N_4O_2^+$ 363.1816; Found 363.1813.

IR (ν_{max}, cm^{-1}) 2974 (m), 2926 (w), 2871 (w), 2350 (m), 2094 (s), 1751 (s),1535 (m), 1458 (m), 1261 (m),1188 (m), 1078 (m), 760 (s), 723 (m).



2.3.24aa, 3-(4-methylpentyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

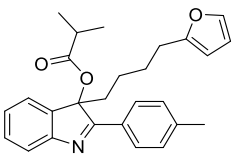
This compound was prepared following general procedure **K** using compound **2.3.4aa** (48 mg, 0.12 mmol) as starting material. Yield: 63% (28 mg), isolated as brown oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.33 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.5 Hz, 1H), 7.29 – 7.24 (m, 3H), 7.20 (td, *J* = 7.4, 1.0 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 2.32 – 2.22 (m, 1H), 1.99 – 1.89 (m, 1H), 1.35 (hept, *J* = 6.4 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 1.07 – 0.87 (m, 4H), 0.69 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.7, 174.2, 153.7, 141.8, 138.5, 129.6, 129.5, 129.1, 127.9, 126.0, 121.2, 120.9, 90.1, 38.7, 37.8, 34.1, 27.5, 22.5, 22.4, 21.8, 20.0, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{32}NO_2^+$ 378.2428; Found 378.2425.

IR (ν_{max}, cm^{-1}) 2951 (m), 2925 (m), 2870 (w), 1749 (s), 1535 (m), 1512 (m), 1456 (s), 1263 (m), 1246 (m), 1201 (m), 1184 (s), 1147 (s), 1099 (s), 1034 (m), 1020 (m), 825 (m), 768 (s), 750 (s).



2.3.24ab, 3-(4-(furan-2-yl)butyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

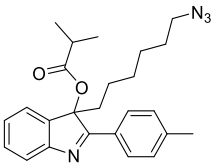
This compound was prepared following general procedure **K** using compound **2.3.4ab** (50 mg, 0.11 mmol) as starting material. Yield: 30% (14 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 2H), 7.60 (dt, *J* = 7.6, 0.8 Hz, 1H), 7.38 (td, *J* = 7.4, 1.6 Hz, 1H), 7.28-7.26 (m, 2H), 7.25 – 7.16 (m, 3H), 6.18 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.78 (dd, *J* = 3.1,1.9 Hz, 1H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.44-2.40 (m, 2H), 2.42 (s, 3H), 2.32 (td, *J* = 12.5, 4.6 Hz, 1H), 2.00 (td, *J* = 12.4, 4.8 Hz, 1H), 1.51 – 1.41 (m, 2H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.15-1.03 (m, 1H), 1.02-0.91 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.5, 174.2, 155.8, 153.7, 141.9, 140.8, 138.4, 129.7, 129.6, 129.0, 127.9, 126.1, 121.3, 121.0, 110.1, 104.8, 90.0, 37.4, 34.1, 28.0, 27.6, 21.8, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{30}NO_3^+$ 416.2220; Found 416.2223.

IR (ν_{max}, cm^{-1}) 2919 (w), 2852 (w), 1747 (s), 1604 (m), 1540 (m), 1510 (m), 1465 (s), 1249 (m), 1187 (s), 1143 (s), 1060 (s), 1008 (m), 825 (m), 760 (s), 744 (s), 727 (s).



2.3.24ac, 3-(6-azidohexyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

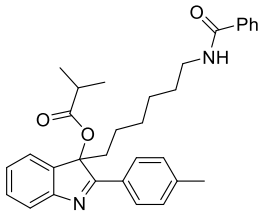
This compound was prepared following general procedure **J** using compound **2.3.4ac** (60 mg, 0.13 mmol) as starting material. Yield: 46% (26 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95: 5), R_f = 0.39 (PE/EtOAc 90:10).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.38 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 3.12 (t, *J* = 6.9 Hz, 2H), 2.55 (hept, *J* = 7.0 Hz, 1H), 2.41 (s, 3H), 2.29 (td, *J* = 12.6, 4.4 Hz, 1H), 1.99 (td, *J* = 12.7, 4.7 Hz, 1H), 1.39 (p, *J* = 6.9 Hz, 2H), 1.19 – 1.07 (m, 4H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05 – 0.96 (m, 1H), 0.91 – 0.82 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.5, 174.2, 153.7, 141.9, 138.4, 129.7, 129.6, 129.0, 127.9, 126.1, 121.3, 120.9, 90.0, 51.4, 37.6, 34.1, 29.0, 28.7, 26.3, 22.0, 21.8, 19.0, 18.8.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}N_4O_2^+$ 419.2442; Found 419.2452.

IR (ν_{max}, cm^{-1}) 2972 (w), 2931 (m), 2877 (w), 2858 (w), 2090 (s), 1747 (s), 1535 (m), 1510 (m), 1468 (m), 1454 (m), 1346 (m), 1288 (m), 1252 (m), 1200 (m), 1184 (s), 1146 (s), 1117 (m), 1093 (m), 1065 (s), 1016 (m), 825 (m), 760 (s), 733 (m).



2.3.24ad, 3-(6-benzamidohexyl)-2-(p-tolyl)-3H-indol-3-yl isobutyrate

This compound was prepared following general procedure **K** using compound **2.3.4ad** (60 mg, 0.11 mmol) as starting material. Yield: 51% (28 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.48 (PE/EtOAc 60:40).

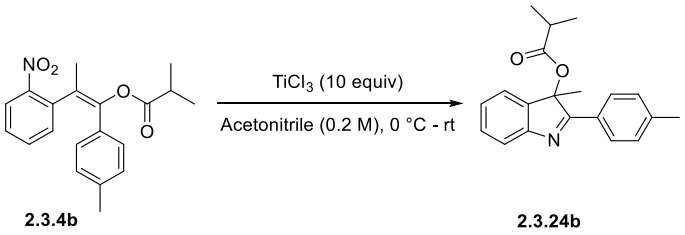
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.38 (td, *J* = 7.5, 1.4 Hz, 1H), 7.27 – 7.24 (m, 3H), 7.20 (t, *J* = 7.4 Hz, 1H), 5.98 (t, *J* = 5.2 Hz, 1H, NH), 3.32 (dt, *J* = 12.7, 6.7 Hz, 2H), 2.56 (hept, *J* = 7.0 Hz, 1H), 2.40 (s, 3H), 2.29 (td, *J* = 12.7, 4.3 Hz, 1H), 2.00 (td, *J* = 12.7, 4.7 Hz, 1H), 1.41 (p, *J* = 7.2 Hz, 2H), 1.21 – 1.11 (m, 4H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.05-0.96 (m, 1H), 0.91 – 0.82 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.6, 174.2, 167.6, 153.7, 141.9, 138.4, 134.9, 131.5, 129.7, 129.6, 129.0, 128.7, 127.9, 126.9, 126.1, 121.2, 120.9, 90.0, 40.0, 37.6, 34.1, 29.5, 29.2, 26.6, 22.0, 21.8, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{37}N_2O_3^+$ 497.2799; Found 497.2815.

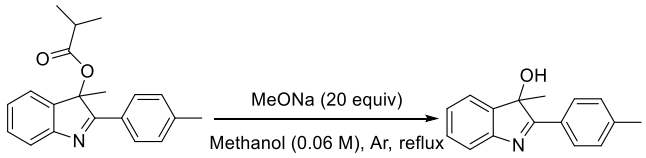
IR (ν_{max}, cm^{-1}) 2933 (w), 2852 (w), 1737 (m), 1645 (s), 1532 (s), 1457 (m), 1309 (m), 1152 (m), 720 (s).

6.2.7. **Gram-scale reaction**



In a 100 mL pressure resistant round bottomed flask was charged the enol ester **2.3.4b** (1.0 g, 2.95 mmol, 1 equiv) in MeCN (14.7 mL, 0.2 M). Then $TiCl_3$ (22.3 mL, 30 mmol, 1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc 95/5) to give the desired 3-acyloxyindolenines **2.3.24b**. Yield: 86% (780 mg), isolated as white solid.

6.2.8. **Post-modification**



2.3.24b **2.3.32b**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask was charged **2.3.24b** (100 mg, 0.325 mmol, 1.0 equiv) in dry methanol (5.3 mL, 0.06 M). Then 1.1 mL of a suspension of MeONa (351 mg, 6.5 mmol, 20 equiv) in MeOH was added and the mixture was stirred under reflux (oil bath) for 1 h. The solution was then cooled to rt and worked up by dropwise addition of a 2M HCl solution, then basified with a $NaHCO_3$ solution. Then the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. Yield: 95% (76 mg), isolated as white solid (mp = 134 – 135 °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.28 (PE/EtOAc 80:20).

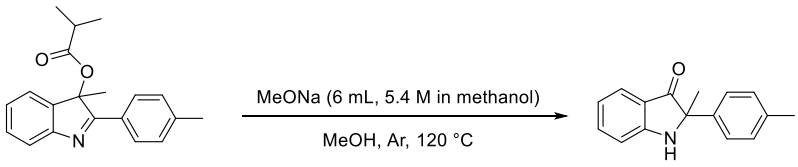
2.3.32b, 3-methyl-2-(p-tolyl)-3H-indol-3-ol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.3 Hz, 2H), 7.47 – 7.39 (m, 2H), 7.31 (td, J = 7.6, 1.4 Hz, 1H), 7.25 – 7.18 (m, 3H), 2.97 (s, 1H), 2.42 (s, 3H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.3, 152.3, 142.7, 141.9, 129.8, 129.4, 129.0, 128.8, 126.4, 121.8, 121.0, 84.2, 25.3, 21.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO^+$ 238.1226; Found 238.1229.

IR (ν_{max}, cm^{-1}) 3313 (w), 3222 (w), 3055 (w), 1608 (m), 1535 (s), 1510 (m), 1458 (m), 1184 (m), 1096 (m), 825 (m).



2.3.24b **2.3.33b**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask were charged **2.3.24b** (100 mg, 0.33 mmol) and a 5.4 M solution of MeONa in MeOH (6 mL). The mixture was stirred at 120 °C (oil bath) overnight, then cooled down to rt, quenched by a dropwise addition of a 6 M HCl solution at 0 °C, and basified with a saturated $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated at reduced pressure obtaining a solid. Yield: 94% (74 mg), isolated as bright yellow solid (mp = 97 – 98 °C). Purification: Flash chromatography (PE/DCM, 1:1), R_f = 0.24 (PE/EtOAc 90:10).

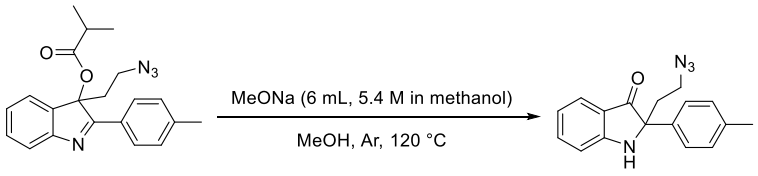
2.3.33b, 2-methyl-2-(p-tolyl)indolin-3-one

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.48 (ddd, *J* = 8.4, 7.1, 1.4 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.2 Hz, 1H), 6.83 (td, *J* = 7.4, 0.8 Hz, 1H), 5.15 (s, 1H), 2.32 (s, 3H), 1.72 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.7, 160.3, 137.5, 137.4, 137.3, 129.4, 125.6, 125.5, 119.1, 119.0, 112.3, 68.4, 24.5, 21.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO^+$ 260.1046; Found 260.1046.

IR (ν_{max}, cm^{-1}) 3346 (m), 3027 (w), 1685 (s), 1611 (s), 1489 (s), 1468 (m), 1324 (s), 969 (m), 752 (m).



2.3.24z **2.3.33z**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask were charged **2.3.24z** (100 mg, 0.27 mmol) and a 2 M solution of MeONa in MeOH (6 mL). The mixture was stirred at 100 °C (oil bath) for 2 h until completion of the reaction monitored by TLC analysis (9:1, DCM:Hex). The reaction mixture was cooled to rt and worked up by addition, in an ice bath, of 30 mL of EtOAc followed by dropwise addition of a 1 M HCl solution, then a saturated Na_2CO_3 solution until basic pH. The mixture was extracted with EtOAc (4 x10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to afford a solid. Yield: 75% (60 mg), isolated as yellow solid (mp = 75 – 76 °C). Purification: Flash chromatography (PE/DCM, 10:10), R_f = 0.21 (PE/EtOAc 90:10).

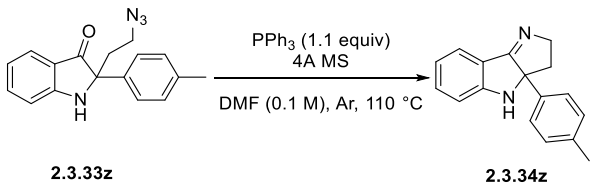
2.3.33z, 2-(2-azidoethyl)-2-(p-tolyl)indolin-3-one

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.7 Hz, 1H), 7.49 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.82 (t, *J* = 7.4 Hz, 1H), 5.54 (s, 1H), 3.46 (ddd, *J* = 12.3, 6.5, 4.4 Hz, 1H), 3.28 (ddd, *J* = 12.3, 9.3, 5.9 Hz, 1H), 2.41 (ddd, *J* = 14.4, 5.9, 4.4 Hz, 1H), 2.32 (s, 3H), 2.23 (ddd, *J* = 14.2, 9.3, 6.5 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.3, 160.4, 137.8, 137.7, 134.9, 129.7, 125.6, 125.5, 119.3, 119.2, 112.4, 70.7, 47.9, 36.9, 21.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}N_4NaO^+$ 315.1216; Found 315.1213.

IR (ν_{max}, cm^{-1}) 2973 (w), 2926 (w), 2362 (m), 2337 (m), 2094 (s), 1747 (s), 1461 (m), 1265 (m), 1187 (m), 1144 (m), 1080 (m), 755 (s).



2.3.33z **2.3.34z**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 10 mL pressure resistant round bottomed flask were charged **2.3.33z** (28.5 mg, 0.097 mmol, 1 equiv), triphenylphosphine (28.2, 0.107 mmol, 1.1 equiv) and activated 4Å molecular sieves in dry DMF (1 mL, 0.1 M). The mixture was stirred at 110 °C (oil bath) for 1 h until the reaction was complete shown by TLC analysis (94:5:1, DCM:MeOH:TEA). The reaction mixture was then cooled to rt and worked up by adding 20 mL of EtOAc. The resulting mixture was washed with brine (2x10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to afford a solid. Yield: 58% (14 mg), isolated as yellow solid (mp = 134 – 135 °C). Purification: Flash chromatography (DCM/MeOH/Et_3N, 98.5:1.25:0.25), R_f = 0.11 (PE/EtOAc 80:20).

2.3.34z, 3a-(p-tolyl)-2,3,3a,4-tetrahydropyrrolo[3,2-b]indole

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.90 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 8.1 Hz, 1H), 4.58 (s, 1H), 4.29 (dd, J = 14.7, 7.2 Hz, 1H), 3.92 (ddd, J = 14.8, 10.6, 4.4 Hz, 1H), 2.54 (dd, J = 11.5, 4.3 Hz, 1H), 2.37 (td, J = 11.1, 7.4 Hz, 1H), 2.30 (s, 3H).

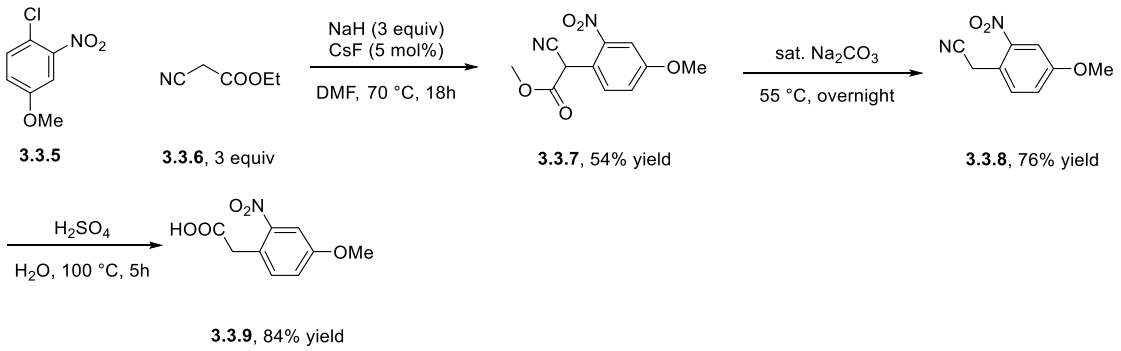
^{13}C NMR (101 MHz, $CDCl_3$): δ 183.4, 159.0, 138.3, 137.8, 133.1, 129.7, 125.2, 123.7, 120.5, 120.0, 113.3, 80.1, 64.5, 43.6, 21.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{17}N_2^+$ 249.1386; Found 249.1394.

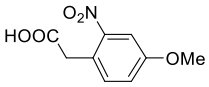
IR (ν_{max}, cm^{-1}) 3226 (w), 3054 (m), 2944 (w), 2859 (w), 1645 (s), 1612 (s), 1510 (m), 1462 (s), 1323 (s), 1285 (m), 818 (m), 752 (s).

6.3. **Studies towards the total synthesis of trigonoliimine C**

6.3.1. **Synthesis of enol ester 3.3.36**



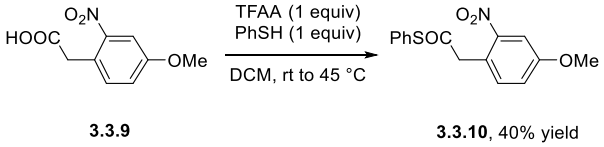
To a solution of NaH (60% suspension in mineral oil, 6.4 g, 160 mmol, 3.0 equiv) in DMF (50 mL, 1.0 M) was added dropwise methyl cyanoacetate **3.3.6** (14 mL, 160 mmol, 3.0 equiv). The mixture was stirred for 1 h at room temperature. Then CsF (400 mg, 2. mmol, 0.05 equiv) and a solution of 4-chloro-3-nitro-anisole **3.3.5** (10 g, 53 mmol, 1.0 equiv) in DMF (50 mL, 1.0 M) were added and the mixture was heated at reflux for 24 hours at 70 ºC. Upon completion of the reaction, the mixture was cooled to room temperature and poured into water (100 mL). It was acidified with 1.0 N sulfuric acid and extracted with EtOAc. The combined organic layers were dried and evaporated. The residual oil **3.3.7** (7.0 g, 28 mmol) was dissolved in 100 mL of a saturated solution of Na_2CO_3 and the mixture was heated overnight at 55 ºC. After cooling to room temperature the mixture was extracted with EtOAc. The combined organic layers were dried and the solvent was removed in vacuo. The solid was recrystallized from diethyl ether. The obtained nitrile **3.3.8** (3.0 g, 15.6 mmol) was heated at reflux in a mixture of water (33 mL, 0.5 M) and concentrated solution of sulfuric acid (22 mL) for 20 minutes. The reaction mixture was then poured onto ice. The solid was collected, washed with water and purified by flash chromatography.



3.3.9, 2-(4-methoxy-2-nitrophenyl)acetic acid, known in the literature.[298]

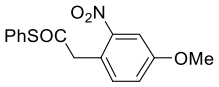
Yield: 35% over 3 steps, isolated as yellow solid (mp = 152 °C).

^{1}H NMR (400 MHz, DMSO) δ 7.59 (d, J = 2.7 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.30 (dd, J = 8.5, 2.8 Hz, 1H), 3.90 (s, 2H), 3.85 (s, 3H).



[298] Lowe, W.; Witzel, S.; Tappmeyer, S.; Albuschat, R. *J. Heterocyclic Chem.* **2004**, *41*, 317 – 326.

To a solution of acid **3.3.9** (4.0 g, 19 mmol, 1.0 equiv) in DCM (60 mL, 0.3 M) was added phenylthiol (1.93 mL, 19 mmol, 1.0 equiv) and TFAA (2.6 mL, 19 mmol, 1.0 equiv). The reaction mixture was stirred overnight at 45 °C. At the end of the reaction, the mixture was quenched with aqueous solution of $NaHCO_3$, followed by extraction with Et_2O. The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to silica gel column chromatography to afford the desired thioester **3.3.10.**



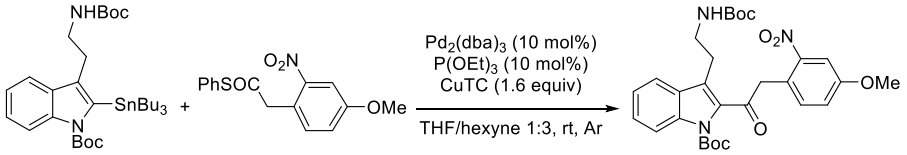
3.3.10, S-phenyl 2-(4-methoxy-2-nitrophenyl)ethanethioate

Yield: 40% (560 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.40 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.7 Hz, 1H), 7.45 – 7.36 (m, 5H), 7.30 (d, J = 8.5 Hz, 1H), 7.15 (dd, J = 8.5, 2.7 Hz, 1H), 4.26 (s, 2H), 3.88 (s, 3H).

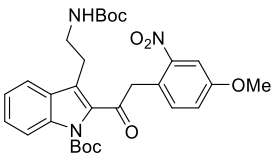
^{13}C NMR (101 MHz, $CDCl_3$): δ 194.4, 159.8, 149.3, 134.8, 134.6, 129.7, 129.3, 127.5, 120.9, 120.3, 110.3, 56.1, 47.4.

IR (ν_{max}, cm^{-1}) 2929 (w), 2856 (w), 1525 (s), 1346 (m), 1248 (s), 1134 (s), 829 (s), 781 (s).



3.3.4, 2.0 equiv **3.3.10**, 1.0 equiv **3.3.18**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump-Thaw technique. To a solution of stannyl **3.3.4** (860 mg, 1.3 mmol, 2.0 equiv) and thioester **3.3.10** (200 mg, 0.66 mmol, 1.0 equiv) in dry THF/hexanes (20 mL, 1:3, 0.067 M), were added Pd_2dba_3 (60 mg, 0.066 mmol, 10 mol%), $P(OEt)_3$ (0.011 mL, 0.066 mmol, 10 mol%) and CuTC (200 mg, 1.1 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature overnight. After completion of the reaction, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2 M HCl, 10% NH_4OH and brine, dried, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography to yield the desired compound **3.3.18**.



3.3.18, tert-butyl 3-(2-((tert-butoxycarbonyl)amino)ethyl)-2-(2-(4-methoxy-2-nitrophenyl)acetyl)-1H-indole-1-carboxylate

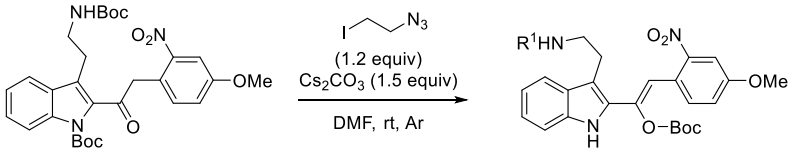
Yield: 58% (200 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.38 (PE/EtOAc 85:15).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 2.7 Hz, 1H), 7.45 – 7.39 (m, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.16 (dd, J = 8.5, 2.8 Hz, 1H), 5.11 (br s, 1H), 4.44 (s, 2H), 3.87 (s, 3H), 3.39 (q, J = 6.4 Hz, 2H), 2.86 (t, J = 6.7 Hz, 2H), 1.72 (s, 9H), 1.39 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1, 159.3, 156.2, 150.5, 149.8, 136.0, 134.5, 129.8, 127.1, 124.4, 123.7, 121.9, 121.1, 120.3, 115.7, 109.9, 85.6, 79.0, 56.0, 46.8, 41.1, 28.6, 28.4, 24.4.

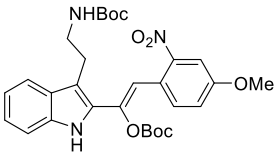
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{35}N_3NaO_8^+$ 576.2316; Found 576.2311.

IR (ν_{max}, cm^{-1}) 2927 (w), 2850 (w), 1677 (m), 1519 (s), 1348 (s), 1226 (m), 987 (m), 808 (s), 730 (s).



3.3.18 **3.3.22**

To a solution of ketone **3.3.18** (20 mg, 0.04 mmol, 1.0 equiv) in DMF (0.1 mL, 0.5 M), Cs_2CO_3 (18 mg, 0.06 mmol, 1.5 equiv) was added, followed by addition of Alk-I (8.5 mg, 0.05 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol **3.3.22**.



3.3.22, tert-butyl (Z)-(2-(2-(1-((tert-butoxycarbonyl)oxy)-2-(4-methoxy-2-nitrophenyl)vinyl)-1H-indol-3-yl)ethyl)carbamate

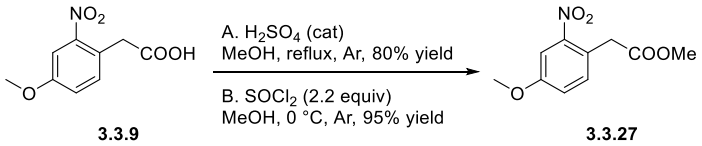
Isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (br s, 1H), 7.78 – 7.73 (m, 1H), 7.54 (d, J = 2.8 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.37 – 7.34 (m, 2H), 7.17 – 7.12 (m, 2H), 6.01 (s, 1H), 4.78 (brs, 1H), 3.86 (s, 3H), 3.49 – 3.17 (m, 4H), 1.45 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 185.8, 167.1, 159.9, 156.1, 149.7, 136.8, 132.9, 130.7, 127.4, 124.3, 123.7, 121.8, 121.1, 120.0, 112.2, 110.4, 83.6, 79.3, 57.4, 56.1 41.5, 28.6, 28.0.

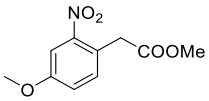
HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{35}N_3NaO_8^+$ 576.2316; Found 576.2311.

IR (ν_{max}, cm^{-1}) 2919 (s), 2859 (m), 1754 (s), 1519 (s), 1344 (s), 1205 (s), 1076 (m), 825 (m).



3.3.9 **3.3.27**

To a solution of acid **3.3.9** (200 mg, 0.95 mmol, 1.0 equiv) in MeOH (1.0 mL, 1.0 M) was added H_2SO_4 (8 µL). The reaction mixture was heated at reflux for 6 h. Upon completion of the reaction, a solution of $NaHCO_3$ was added to the reaction mixture to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **3.3.27**.



3.3.27, methyl 2-(4-methoxy-2-nitrophenyl)acetate

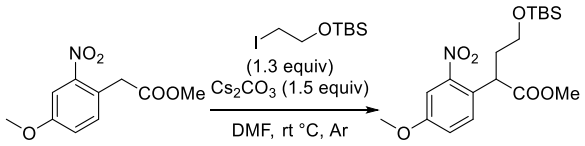
Yield: 80% (300 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.8 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.16 (dd, J = 8.5, 2.7 Hz, 1H), 3.97 (s, 2H), 3.90 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 170.9, 159.5, 149.3, 134.2, 121.8, 120.2, 110.2, 56.0, 52.3, 39.0.

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{12}NO_5^+$ 226.0710; Found 226.1783.

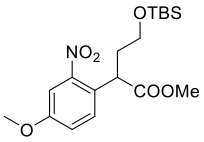
IR (ν_{max}, cm^{-1}) 2972 (w), 1743 (m), 1525 (m), 1346 (m), 1112 (s), 756 (m).



3.3.27 **3.3.32**

To a solution of ester **3.3.27** (2.5 g, 11 mmol, 1.0 equiv) in DMF (100 mL, 0.1 M), Cs_2CO_3 (5.4 g, 16.7 mmol, 1.5 equiv) was added, followed by addition of Alk-I **3.3.31** (4.0 g, 14 mmol, 1.2 equiv). The reaction

mixture was heated at 45 °C for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **3.3.32**.



3.3.32, methyl 4-((tert-butyldimethylsilyl)oxy)-2-(4-methoxy-2-nitrophenyl)butanoate

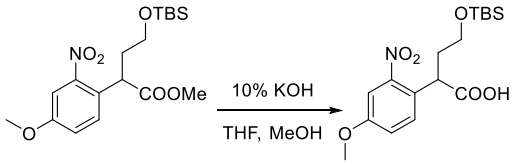
Yield: 78% (3.0 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.22 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.37 (m, 2H), 7.11 (dd, J = 8.7, 2.8 Hz, 1H), 4.32 (t, J = 7.2 Hz, 1H), 3.85 (s, 3H), 3.68 – 3.59 (m, 4H), 3.55 – 3.46 (m, 1H), 2.46 – 2.35 (m, 1H), 2.02 – 1.91 (m, 1H), 0.87 (s, 9H), 0.00 (s, 3H), -0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.6, 158.9, 149.9, 131.7, 125.6, 119.7, 109.6, 60.5, 56.0, 52.3, 42.7, 35.6, 26.0, 18.4, -5.37, -5.38.

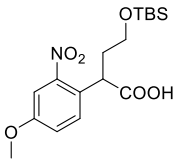
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{29}NNaO_6Si^+$ 406.1656; Found 406.1662.

IR (ν_{max}, cm^{-1}) 2937 (w), 2856 (w), 1736 (m), 1531 (s), 1354 (m), 1252 (s), 1167 (m), 1101 (s), 833 (s).



3.3.32 **3.3.33**

To a solution of ester **3.3.32** (2.9 g, 7.6 mmol, 1.0 equiv) in THF (76 mL, 1.0 M), a 0.1 M solution of KOH (13.5 mL, 24 mmol, 3.0 equiv) was added at 0 °C. The reaction mixture was stirred overnight. After completion of the reaction, the reaction mixture was acidified to pH 3-4 with 1.0 M solution of citric acid. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired acid **3.3.33**.



3.3.33, 4-((tert-butyldimethylsilyl)oxy)-2-(4-methoxy-2-nitrophenyl)butanoic acid

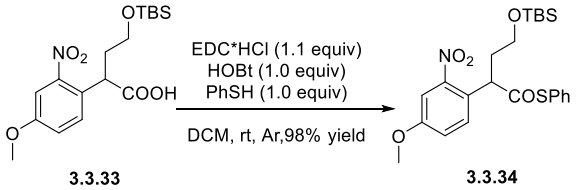
Yield: 97% (2.7 g), isolated as yellow solution, R_f = 0.13 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.8 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.12 (dd, J = 8.7, 2.7 Hz, 1H), 4.35 (t, J = 6.9 Hz, 1H), 3.86 (s, 3H), 3.73 – 3.65 (m, 1H), 3.57 – 3.49 (m, 1H), 2.50 – 2.39 (m, 1H), 2.03 – 1.94 (m, 1H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H).

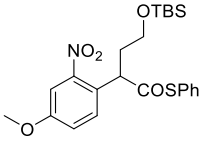
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.2, 159.1, 149.7, 132.1, 125.3, 119.9, 109.8, 60.7, 56.0, 43.3, 35.1, 26.0, 18.4, -5.4.

HRMS (ESI/QTOF) m/z: $[M - COOH]^-$ Calcd for $C_{16}H_{26}NO_4Si^+$ 324.1636; Found 324.1635

IR (ν_{max}, cm^{-1}) 2989 (w), 1685 (s), 1524 (s), 1348 (s), 1211 (m), 966 (m), 702 (m).



To a solution of acid **3.33** (2.7 g, 7.3 mmol, 1.0 equiv) and HOBt (1.1 g, 8.0 mmol, 1.1 equiv) in DCM (28 mL, 0.25 M) EDC (1.6 g, 8.0 mmol, 1.1 equiv) was added portion-wise at 0 °C. After stirring for 30 min at 0 °C, PhSH (0.75 mL, 7.3 mmol, 1.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. After completion of the reaction, the reaction mixture was quenched with saturated solution of $NaHCO_3$. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired thioester **3.3.34**.



3.3.34, S-phenyl 4-((tert-butyldimethylsilyl)oxy)-2-(4-methoxy-2-nitrophenyl)butanethioate

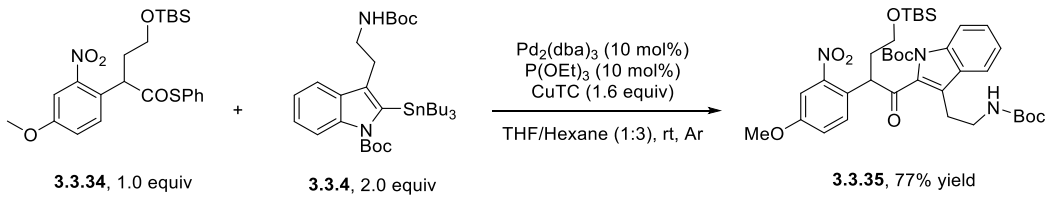
Yield: 95% (3.2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.31 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.43 (m, 2H), 7.41 – 7.29 (m, 5H), 7.14 (dd, J = 8.8, 2.8 Hz, 1H), 4.73 (t, J = 7.1 Hz, 1H), 3.88 (s, 3H), 3.71 – 3.58 (m, 1H), 3.54 – 3.46 (m, 1H), 2.49 – 2.38 (m, 1H), 2.06 – 1.93 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.9, 159.3, 150.3, 134.6, 131.8, 129.5, 129.3, 127.8, 124.5, 119.9, 109.7, 60.2, 56.0, 50.1, 36.2, 26.0, 18.4, -5.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{31}NNaO_5SSi^+$ 484.1594; Found 484.1585.

IR (ν_{max}, cm^{-1}) 2967 (w), 2873 (w), 1681 (s), 1608 (m), 1522 (s), 1349 (s), 1186 (m), 741 (m).

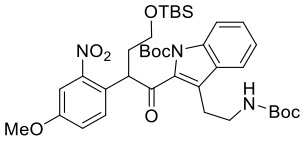


3.3.34, 1.0 equiv

3.3.4, 2.0 equiv

3.3.35, 77% yield

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump-Thaw technique. To a solution of stannyl **3.3.4** (7.6 g, 11.7 mmol, 2.0 equiv) and thioester **3.3.34** (2.7 g, 5.9 mmol, 1.0 equiv) in dry degassed THF/hexanes (87 mL, 1:3, 0.067 M), were added Pd_2dba_3 (540 mg, 0.6 mmol, 10 mol%), $P(OEt)_3$ (0.1 mL, 0.6 mmol, 10 mol%) and CuTC (1.8 g, 9.4 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature overnight. After completion of reaction, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2M HCl, 10% NH_4OH and brine, dried, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography to yield the desired compound **3.3.35**.



3.3.35, tert-butyl 3-(2-((tert-butoxycarbonyl)amino)ethyl)-2-(4-((tert-butyldimethylsilyl)oxy)-2-(4-methoxy-2-nitrophenyl)butanoyl)-1H-indole-1-carboxylate

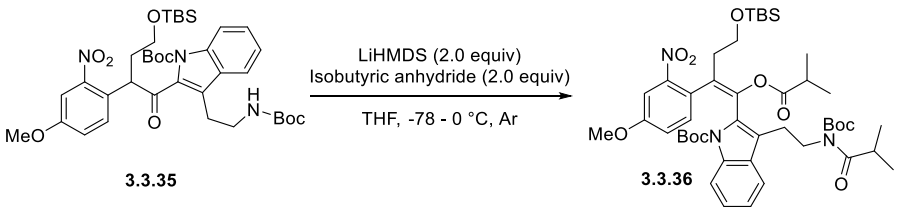
Yield: 87% (3.6 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.29 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.27 – 7.18 (m, 1H), 7.14 (d, J = 2.8 Hz, 1H), 7.08 (dd, J = 8.7, 2.7 Hz, 1H), 5.15 – 5.07 (m, 2H), 3.79 (s, 3H), 3.61 – 3.54 (m, 1H), 3.51 – 3.40 (m, 1H), 3.28 – 3.15 (m, 2H), 2.69 – 2.58 (m, 1H), 2.54 – 2.42 (m, 1H), 2.37 – 2.12 (m, 2H), 1.73 (s, 9H), 1.43 (s, 9H), 0.82 (s, 9H), -0.04 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.6, 158.7, 156.2, 150.9, 150.6, 135.6, 134.8, 130.9, 129.4, 126.8, 124.0, 123.4, 120.6, 119.4, 115.9, 109.4, 85.6, 79.1, 60.9, 55.9, 41.0, 35.3, 28.6, 28.3, 26.1, 18.4, -5.36, -5.41.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{37}H_{53}N_3NaO_9Si^+$ 734.3454; Found 734.3444.

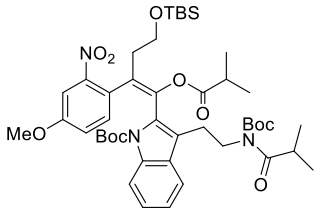
IR (ν_{max}, cm^{-1}) 2926 (w), 2860 (w), 1714 (m), 1531 (m), 1358 (m), 1248 (s), 1145 (s), 1024 (m), 833 (s), 767 (m).



3.3.35

3.3.36

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask was charged a solution of ketone **3.3.35** (800 mg, 1.1 mmol, 1.0 equiv) in THF (11 mL, 0.1 M). Then a solution of LiHMDS (2.5 mL, 2.3 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 1h before warming to -40 °C. Then isobutyric anhydride (0.4 mL, 2.3 mmol, 2.0 equiv) was added to the reaction mixture. The reaction mixture was slowly warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted from the aqueous phase with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **3.3.36**.



3.3.36, tert-butyl (E)-3-(2-(N-(tert-butoxycarbonyl)isobutyramido)ethyl)-2-(4-((tert-butyldimethylsilyl)oxy)-1-(isobutyryloxy)-2-(4-methoxy-2-nitrophenyl)but-1-en-1-yl)-1H-indole-1-carboxylate

Yield: 38% (360 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 97:3).

E-isomer

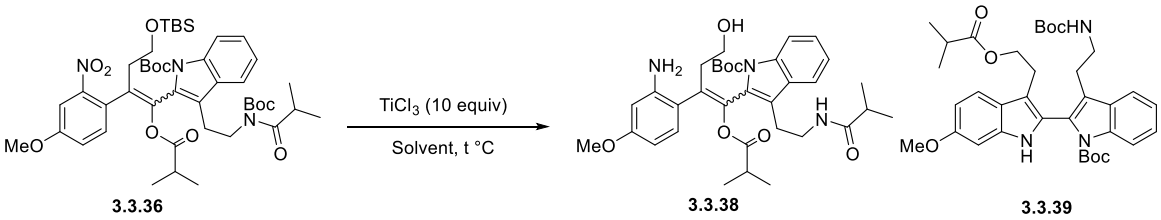
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.86 (m, 2H), 7.60 – 7.51 (m, 1H), 7.32 – 7.05 (m, 3H), 6.83 – 6.72 (m, 1H), 3.89 – 3.47 (m, 7H), 3.02 – 2.86 (m, 2H), 2.63 (p, J = 7.0 Hz, 1H), 2.46 – 2.30 (m, 2H), 1.73 (s, 9H), 1.57 (s, 9H), 1.24 – 1.10 (m, 12H), 0.81 (s, 9H), 0.02 – -0.10 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 181.0, 173.5, 159.0, 153.6, 149.9, 148.3, 137.7, 136.0, 134.0, 129.4, 129.1, 127.1, 125.0, 122.8, 122.3, 121.4, 119.8, 115.0, 110.0, 83.9, 83.3, 60.9, 55.8, 43.5, 34.9, 34.3, 28.4, 28.1, 26.0, 20.0, 19.9, 19.1, 18.8, 18.4, -5.29, -5.31.

HRMS HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{45}H_{66}N_3O_{11}Si^+$ 852.4462; Found 852.4468.

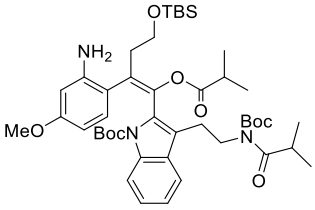
IR (ν_{max}, cm^{-1}) 2933 (w), 1718 (s), 1531 (s), 1358 (s), 1328 (s), 1248 (s), 1149 (s), 1101 (s), 1028 (m), 833 (s), 774 (s).

6.3.2. **Ti-mediated reductive cyclization of enol ester 3.3.36**



3.3.36 **3.3.38** **3.3.39**

In a 10 mL pressure resistant round bottomed flask was charged the enol ester **3.3.36** (1.0 equiv) in MeCN (0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the aniline **3.3.38** and bisindole **3.3.39**.

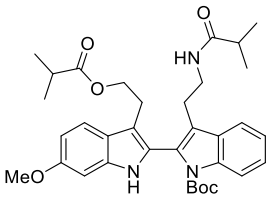


3.3.38, tert-butyl (E)-2-(2-(2-amino-4-methoxyphenyl)-4-((tert-butyldimethylsilyl)oxy)-1-(isobutyryloxy)but-1-en-1-yl)-3-(2-(N-(tert-butoxycarbonyl)isobutyramido)ethyl)-1H-indole-1-carboxylate

Isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.36 (dd, J = 8.5, 2.4 Hz, 1H), 6.04 – 5.94 (m, 2H), 3.83 – 3.73 (m, 1H), 3.71 (s, 3H), 3.65 – 3.58 (m, 1H), 3.06 – 3.00 (m, 1H), 2.95 – 2.89 (m, 2H), 2.85 – 2.77 (m, 1H), 2.69 (p, J = 7.0 Hz, 1H), 2.59 – 2.54 (m, 1H), 2.50 – 2.45 (m, 1H), 2.28 – 2.22 (m, 1H), 1.74 (s, 9H), 1.25 (d, J = 7.0 Hz, 6H), 1.20 (d, J = 7.0 Hz, 6H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{36}N_3O_7^+$ 608.3313; Found 608.3331.



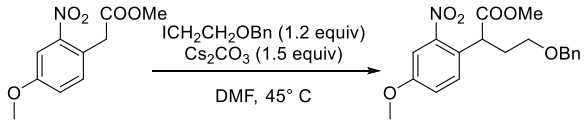
3.3.39, tert-butyl 3-(2-isobutyramidoethyl)-3'-(2-(isobutyryloxy)ethyl)-6'-methoxy-1H,1'H-[2,2'-biindole]-1-carboxylate

Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

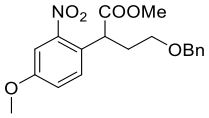
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 8.29 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.71 – 7.61 (m, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.38 (ddd, *J* = 8.5, 7.2, 1.3 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.82 (dd, *J* = 8.6, 2.2 Hz, 1H), 5.54 (t, *J* = 6.4 Hz, 1H), 4.22 – 4.14 (m, 2H), 3.87 (s, 3H), 3.71 – 3.58 (m, 1H), 3.25 – 3.14 (m, 1H), 2.98 – 2.78 (m, 2H), 2.78 – 2.65 (m, 1H), 2.45 (p, *J* = 7.0 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.17 (s, 9H), 1.08 (dd, *J* = 7.0, 1.5 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{43}N_3NaO_6^+$ 612.3045; Found 612.3058.

6.3.3. Synthesis of Bn-protected enol ester 3.3.47



To a solution of ester **3.3.27** (2.3 g, 10 mmol, 1.0 equiv) in DMF (100 mL, 0.1 M), Cs_2CO_3 (4.7 g, 14.4 mmol, 1.5 equiv) was added, followed by addition of Alk-I (2.11 mL, 13.3 mmol, 1.2 equiv). The reaction mixture was heated at 45 °C for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **3.3.43**.



3.3.43, methyl 4-(benzyloxy)-2-(4-methoxy-2-nitrophenyl)butanoate

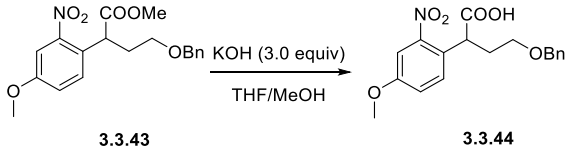
Yield: 74% (2.7 g), isolated as white solid (mp = °C). Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.13 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 7H), 7.09 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.44 (d, *J* =6.7 Hz, 1H), 4.43 (d, *J* =6.7 Hz, 1H), 4.32 (t, *J* = 7.3 Hz, 1H), 3.86 (s, 3H), 3.63 (s, 3H), 3.52 (dt, *J* = 9.6, 5.6 Hz, 1H), 3.40 – 3.31 (m, 1H), 2.60 – 2.48 (m, 1H), 2.13 – 2.02 (m, 1H).

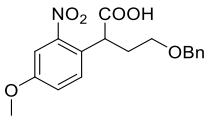
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 159.0, 149.9, 138.3, 131.7, 128.5, 127.8, 127.7, 125.4, 119.8, 109.7, 73.1, 67.6, 56.0, 52.3, 43.2, 32.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{21}NNaO_6^+$ 382.1262; Found 382.1256.

IR (ν_{max}, cm^{-1}) 2926 (w), 2849 (w), 1732 (s), 1531 (s), 1354 (m), 1248 (s), 1098 (m), 1028 (m).



To a solution of ester **3.3.43** (2.7 g, 7.5 mmol, 1.0 equiv) in THF (75 mL, 1.0 M), a 0.1 M solution of KOH (13.0 mL, 25 mmol, 3.0 equiv) was added at 0 °C. The reaction mixture was stirred overnight. After completion of the reaction, the reaction mixture was acidified to pH 3-4 with 1.0 M solution of citric acid. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired acid **3.3.44**.



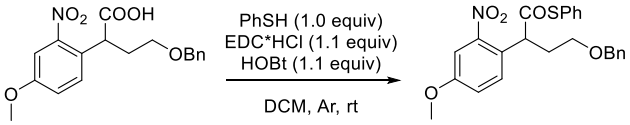
3.3.44, 4-(benzyloxy)-2-(4-methoxy-2-nitrophenyl)butanoic acid

Yield: 92% (2.4 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.22 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.7 Hz, 1H), 7.39 – 7.22 (m, 6H), 7.09 (dd, J = 8.7, 2.8 Hz, 1H), 4.43 (s, 2H), 4.35 (dd, J = 7.7, 6.6 Hz, 1H), 3.86 (s, 3H), 3.53 (dt, J = 9.6, 5.4 Hz, 1H), 3.39 – 3.28 (m, 1H), 2.62 – 2.46 (m, 1H), 2.13 – 2.03 (m, 1H).

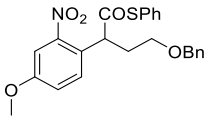
^{13}C NMR (101 MHz, $CDCl_3$): δ 177.3, 159.2, 149.7, 138.1, 132.1, 128.5, 127.9, 127.8, 124.9, 120.0, 109.8, 73.1, 67.4, 56.0, 43.6, 32.3.

IR (ν_{max}, cm^{-1}) 2978 (w), 1718 (s), 1523 (s), 1340 (s), 1278 (s), 1201 (s), 1105 (m), 1014 (m), 752 (m).



3.3.44 **3.3.45**

To a solution of acid **3.3.44** (2.3 g, 6.7 mmol, 1.0 equiv) and HOBt (1.0 g, 7.3 mmol, 1.1 equiv) in DCM (27 mL, 0.25 M) EDC (1.4 g, 7.3 mmol, 1.1 equiv) was added portion-wise at 0 °C. After stirring for 30 min at 0 °C, PhSH (0.68 mL, 6.7 mmol, 1.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. After completion of the reaction, the reaction mixture was quenched with saturated solution of $NaHCO_3$. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired thioester **3.3.45**.



3.3.45, S-phenyl 4-(benzyloxy)-2-(4-methoxy-2-nitrophenyl)butanethioate

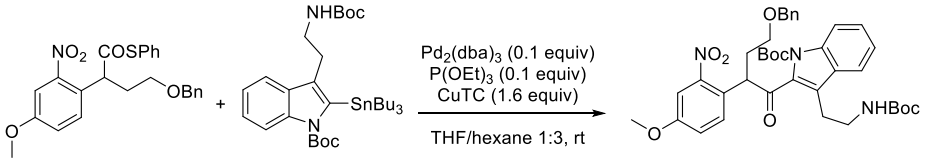
Yield: 80% (2.4 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.63 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.42 (m, 2H), 7.40 – 7.27 (m, 10H), 7.12 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.85 – 4.57 (m, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.41 (d, *J* = 11.9 Hz, 1H), 3.88 (s, 3H), 3.52 (dt, *J* = 9.6, 5.6 Hz, 1H), 3.39 – 3.31 (m, 1H), 2.61 – 2.51 (m, 1H), 2.15 – 2.06 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.7, 159.3, 150.4, 138.2, 134.6, 131.6, 129.6, 129.3, 128.5, 127.9, 127.73, 127.68, 124.2, 119.9, 109.7, 73.2, 67.4, 56.0, 50.5, 33.4.

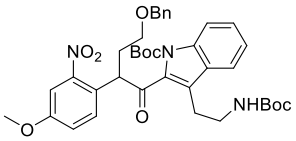
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_5S^+$ 460.1189; Found 460.1198

IR (ν_{max}, cm^{-1}) 2961 (w), 2865 (w), 1702 (m), 1528 (s), 1349 (m), 1252 (m), 1094 (m), 1036 (m), 748 (m).



3.3.45, 1.0 equiv **3.3.4**, 2.0 equiv **3.3.46**, 57% yield

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump-Thaw technique. To a solution of stannyl **3.3.4** (6.6 g, 10 mmol, 2.0 equiv) and thioester **3.3.45** (2.3 g, 5.0 mmol, 1.0 equiv) in dry mixture of solvents THF/hexanes (76 mL, 1:3, 0.067 M), were added Pd_2dba_3 (460 mg, 0.5 mmol, 10 mol%), $P(OEt)_3$ (0.08 mL, 0.5 mmol, 10 mol%) and CuTC (1.55 g, 8.0 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature overnight. After completion of reaction, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2M HCl, 10% NH_4OH and brine, dried, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography to yield the desired compound **3.3.46**.



3.3.46, tert-butyl 2-(4-(benzyloxy)-2-(4-methoxy-2-nitrophenyl)butanoyl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

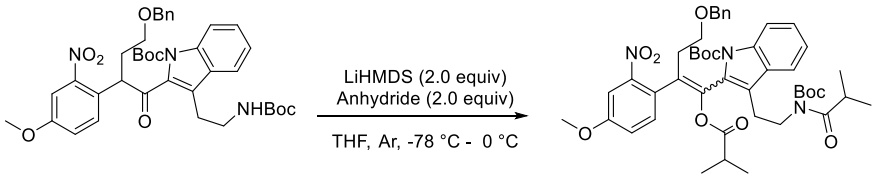
Yield: 57% (2.0 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.14 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.33 – 7.19 (m, 7H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.06 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.18 (dd, *J* = 10.0, 4.6 Hz, 1H), 5.08 (br s, 1H), 4.38 (d, *J* = 11.8 Hz, 1H), 4.33 (d, *J* = 11.8 Hz, 1H), 3.78 (s, 3H), 3.53 – 3.43 (m, 1H), 3.33 – 3.15 (m, 3H), 2.72 – 2.48 (m, 2H), 2.36 – 2.15 (m, 2H), 1.67 (s, 9H), 1.42 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 195.5, 158.8, 155.9, 151.5, 150.5, 138.5, 135.7, 128.3, 127.8, 127.5, 126.9, 123.8, 123.7, 123.4, 120.6, 119.4, 115.9, 109.4, 85.7, 73.0, 67.7, 55.9, 47.8, 41.0, 32.5, 28.6, 28.2.

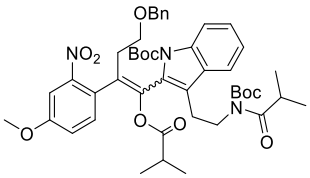
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{38}H_{45}N_3NaO_9^+$ 710.3048; Found 710.3060.

IR (ν_{max}, cm^{-1}) 2979 8w), 1751 (s), 1525 (s), 1346 (s), 1108 (s), 1054 (m), 752 (s), 698 (s).



3.3.46 **3.3.47**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask was charged a solution of ketone **3.3.46** (800 mg, 1.2 mmol, 1.0 equiv) in THF (12 mL, 0.1 M). Then a solution of LiHMDS (2.6 mL, 2.3 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 1h before warming to -40 °C. Then isobutyric anhydride (0.4 mL, 2.3 mmol, 2.0 equiv) was added to the reaction mixture. The reaction mixture was slowly warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted from the aqueous phase with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **3.3.47**.



3.3.47, tert-butyl 2-(4-(benzyloxy)-1-(isobutyryloxy)-2-(4-methoxy-2-nitrophenyl)but-1-en-1-yl)-3-(2-(N-(tert-butoxycarbonyl)isobutyramido)ethyl)-1H-indole-1-carboxylate

Yield: 36% (320 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 92:8), R_f = 0. (PE/EtOAc :).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.5 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.32 – 7.21 (m, 3H), 7.23 – 7.10 (m, 5H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.99 (s, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.6 Hz, 1H), 4.12 (dt, *J* = 9.7, 6.9 Hz, 1H), 3.78 (s, 3H), 3.56 (d, *J* = 8.1 Hz, 1H), 3.49 – 3.38 (m, 3H), 3.00 (q, *J* = 8.9, 8.0 Hz, 3H), 2.80 (dd, *J* = 14.4, 7.9 Hz, 1H), 2.63 (p, *J* = 7.8, 7.2 Hz, 1H), 2.57 (q, *J* = 8.4, 7.4 Hz, 1H), 2.52 – 2.46 (m, 1H), 2.29 – 2.17 (m, 1H), 1.70 (d, *J* = 3.2 Hz, 10H), 1.56 (d, *J* = 3.2 Hz, 13H), 1.25 – 1.19 (m, 4H), 1.16 (dd, *J* = 7.2, 3.1 Hz, 4H), 1.07 (dd, *J* = 7.3, 3.2 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 177.32, 174.85, 159.33, 149.88, 148.05, 138.3, 137.7, 136.2, 134.24, 130.30, 129.04) 128.92, 128.32, 127.82, 127.60, 126.64, 125.40, 122.82, 122.39, 120.82, 120.34, 115.09, 109.54, 84.23, 72.99, 67.73, 55.86, 38.11, 35.39, 34.27, 31.39, 28.37, 23.85, 19.66, 19.56, 18.93, 18.87.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.60 (br s, 1H), 7.63 – 7.47 (m, 4H,), 7.35 (t, J = , 1H), 7.31 – 7.05 (m, 14H), 6.79 (d, *J* = 8.6 Hz, 1H), 5.09 (s, 1H, NH), 4.82 (s, 1H, NH), 4.36 (d, *J* = 11.7 Hz, 1H), 4.37-4.20 (m, 3H) (4.36 (d, *J* = 11.7 Hz, 1H), 4.27 (d, *J* = 11.7 Hz, 1H), 4.25 (d, *J* = 11.7 Hz, 1H), 4.22 (d, *J* = 11.7 Hz, 1H), 3.87 (s, 3H), 3.76 (s, 3H), 3.60-3.43 (m, 4H), 3.39 (t, J

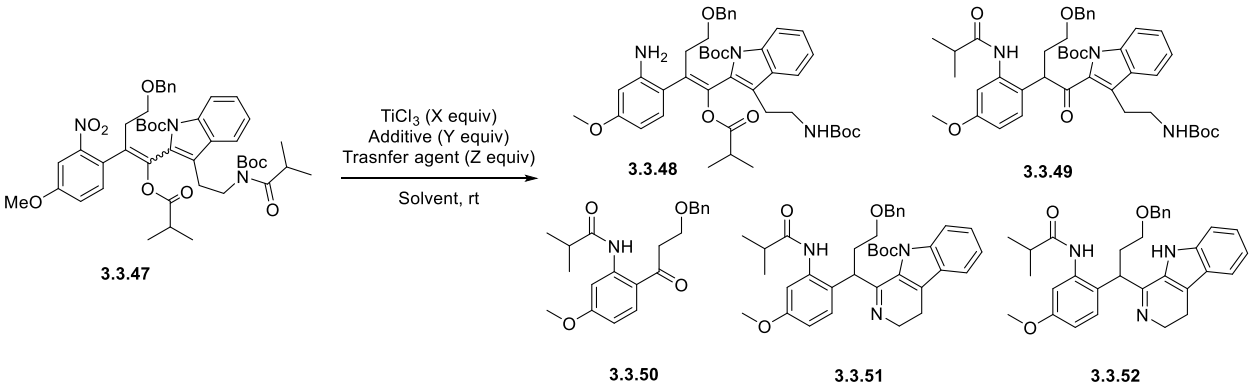
= Hz, 2H), 3.31 – 3.20 (m, 2H), 3.14 (m, 1H), 3.00 (dt, *J* = 14.2, 6.8 Hz, 1H), 2.88-2.78 (m, 2H), 2.72 (t, J = , 1H), 2.69-2.52 (m, 4H), 2.20 (hept, *J* = 8.9, 8.0 Hz, 1H), 1.70 (s, 9H), 1.67 (s, 9H), 1.44 (s, 9H), 1.41 (s, 9H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.26, 159.29, 159.21, 156.27, 156.10, 149.76, 149.36, 148.34, 148.14, 138.22, 138.08, 137.61, 136.56, 136.14, 135.97, 134.08, 133.46, 130.18, 129.34, 129.07, 128.8, 128.40, 128.24, 127.94, 127.74, 127.53, 127.45, 126.48, 125.40, 125.25, 122.80, 122.65, 122.21, 121.85, 120.65, 120.04, 119.70, 115.61, 115.12, 109.47, 109.00, 84.12, 83.65, 78.7, 72.91, 72.66, 68.02, 67.66, 55.92, 55.74, 39.88, 39.37, 34.16, 33.84, 33.26, 31.24, 28.54, 28.48, 28.30, 28.27, 25.17, 24.52, 18.84, 18.81, 18.50, 18.38.

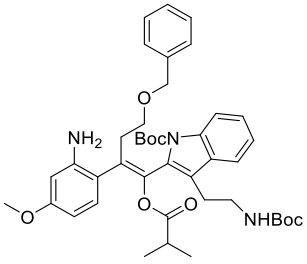
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{46}H_{57}N_3NaO_{11}^+$ 850.3886; Found 850.3891.

IR (ν_{max}, cm^{-1}) 2981 (w), 1726 (s), 1685 (m), 1531 (m), 1454 (m), 1354 (s), 1328 (s), 1145 (s), 760 (m).

6.3.4. **Ti-mediated reductive cyclization of Bn-protected enol ester 3.3.47**



In a 10 mL pressure resistant round bottomed flask was charged the enol ester **7a** (1.0 equiv) in MeCN (0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the aniline **3.3.48**, ketone **3.3.49** and **3.3.50** dihydrocarbazole **3.3.51** and **3.3.52**.



3.3.48, tert-butyl (Z)-2-(2-(2-amino-4-methoxyphenyl)-4-(benzyloxy)-1-(isobutyryloxy)but-1-en-1-yl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

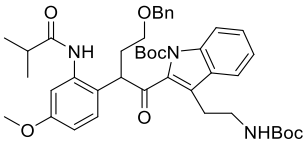
Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.59 – 7.44 (m, 2H), 7.40 – 7.27 (m, 6H), 7.25 – 7.20 (m, 1H), 7.12 – 7.03 (m, 1H), 6.60 (d, J = 8.7 Hz, 1H), 5.05 (br s, 1H), 4.50 – 4.41 (m, 2H), 4.35 (d, J = 11.7 Hz, 1H), 3.75 (s, 3H), 3.59 – 3.51 (m, 1H), 3.17 (td, J = 10.4, 3.6 Hz, 1H), 2.99 – 2.89 (m, 2H), 2.67 – 2.49 (m, 2H), 2.46 – 2.22 (m, 2H), 1.68 (s, 9H), 1.42 (s, 9H), 1.03 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 156.2, 150.8, 138.1, 135.4, 134.9, 134.7, 129.8, 128.5, 127.93, 127.88, 126.8, 123.7, 123.6, 121.2, 115.4, 112.1, 109.2, 85.6, 73.0, 67.6, 55.5, 40.7, 36.4, 29.9, 28.6, 28.3, 24.2, 19.9, 19.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{42}H_{53}N_3NaO_8^+$ 750.3725; Found 750.3737.

IR (ν_{max}, cm^{-1}) 3216 (w), 2933 (w), 1747 (m), 1523 (m), 1351 (m), 1105 (s), 719 (s).



3.3.49, tert-butyl 2-(4-(benzyloxy)-2-(2-isobutyramido-4-methoxyphenyl)butanoyl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

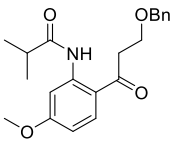
Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.36 – 7.25 (m, 7H), 7.17 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.34 – 6.24 (m, 1H), 5.91 (d, J = 2.5 Hz, 1H), 4.79 (d, J = 6.4 Hz, 1H), 4.51 – 4.36 (m, 2H), 3.67 (s, 3H), 3.57 – 3.49 (m, 1H), 3.41 – 3.29 (m, 1H), 3.05 – 2.95 (m, 1H), 2.88 – 2.75 (m, 2H), 2.71 – 2.58 (m, 2H), 2.56 – 2.46 (m, 1H), 2.39 – 2.25 (m, 1H), 1.68 (s, 9H), 1.41 (s, 9H), 1.19 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.2, 160.1, 156.2, 150.3, 146.2, 138.7, 137.5, 136.2, 130.6, 129.5, 128.8, 128.4, 127.8, 127.6, 125.2, 122.8, 121.6, 121.0, 115.2, 103.6, 100.4, 85.5, 78.9, 72.9, 67.8, 60.6, 55.2, 39.2, 34.2, 33.7, 28.6, 28.3, 26.2, 19.0, 18.8, 14.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{42}H_{54}N_3O_8^+$ 728.3905; Found 728.3918.

IR (ν_{max}, cm^{-1}) 2973 (w), 1754 (s), 1526 (s), 1348 (s), 1108 (s), 1054 (m), 852 (m), 748 (s).



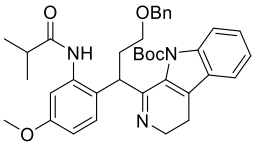
3.3.50, N-(2-(3-(benzyloxy)propanoyl)-5-methoxyphenyl)isobutyramide

Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.15 (s, 1H), 8.50 (d, J = 2.6 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.39 – 7.27 (m, 5H), 6.60 (dd, J = 9.0, 2.7 Hz, 1H), 4.56 (s, 2H), 3.94 – 3.85 (m, 5H), 3.28 (t, J = 6.5 Hz, 2H), 2.63 (hept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H), 1.26 (d, J = 2.6 Hz, 8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 201.1, 177.3, 165.0, 144.4, 138.2, 133.1, 128.6, 127.9, 115.2, 110.1, 103.8, 73.5, 65.9, 55.8, 40.0, 37.8, 19.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{25}NNaO_4^+$ 378.1676; Found 378.1674.



3.3.51, tert-butyl 1-(3-(benzyloxy)-1-(2-isobutyramido-4-methoxyphenyl)propyl)-3,4-dihydro-9H-pyrido[3,4-b]indole-9-carboxylate

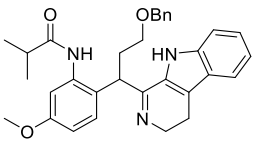
Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.85 (m, 2H), 7.51 (dt, J = 7.9, 1.2 Hz, 1H), 7.39 (ddd, J = 8.5, 7.2, 1.3 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.24 – 7.21 (m, 3H), 6.94 (d, J = 8.5 Hz, 1H), 6.45 (dd, J = 8.5, 2.8 Hz, 1H), 4.60 (t, J = 7.8 Hz, 1H), 4.33 (d, J = 11.7 Hz, 1H), 4.25 (d, J = 11.7 Hz, 1H), 3.98 – 3.86 (m, 1H), 3.75 (s, 3H), 3.68 (td, J = 13.3, 6.1 Hz, 1H), 3.37 (dt, J = 10.1, 5.2 Hz, 1H), 3.25 – 3.17 (m, 1H), 2.73 (dt, J = 17.4, 6.4 Hz, 1H), 2.65 – 2.53 (m, 2H), 2.42 – 2.33 (m, 2H), 1.65 (s, 9H), 1.31 – 1.26 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.8, 159.0, 150.7, 139.3, 138.7, 138.2, 131.4, 129.9, 128.3, 128.0, 127.5, 127.4, 127.2, 123.5, 120.6, 120.3, 116.1, 110.3, 107.2, 85.2, 73.1, 68.2, 55.4, 46.5, 37.1, 28.3, 20.2, 20.0, 19.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{37}H_{44}N_3O_5^+$ 610.3276; Found 610.3286.

IR (ν_{max}, cm^{-1}) 2956 (m), 1751 (m), 1527 (s), 1348 (m), 1097 (s), 820 (m), 742 (m).



3.3.52, N-(2-(3-(benzyloxy)-1-(4,9-dihydro-3H-pyrido[3,4-b]indol-1-yl)propyl)-5-methoxyphenyl)isobutyramide

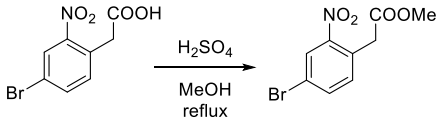
Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (800 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.19 – 7.00 (m, 3H), 6.74 – 6.52 (m, 1H), 5.24 (br s, 1H), 4.54 (d, J = 11.1 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 4.37 – 4.30 (m, 1H), 4.04 (br s, 1H), 3.88 – 3.81 (m, 1H), 3.78 (s, 3H), 1.16 – 1.00 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.6, 159.3, 137.7, 137.2, 128.8, 128.4, 128.36, 125.0, 124.4, 120.0, 119.6, 117.3, 112.8, 73.4, 68.4, 55.6, 51.3, 28.9, 24.7, 19.8, 19.7, 19.5.

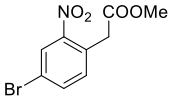
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{32}H_{36}N_3O_3^+$ 510.2752; Found 510.2760.

6.3.5. **Synthesis of enol ester 3.3.60**



3.3.54 **3.3.55**

To a solution of acid **3.3.54** (15 g, 39 mmol, 1.0 equiv) in MeOH (39 mL, 1.0 M) was added H_2SO_4 (500 mg). The reaction mixture was heated at reflux for 6 h. Upon completion of the reaction, a solution of $NaHCO_3$ was added to the reaction mixture to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **3.3.55**.



3.3.55, methyl 2-(4-bromo-2-nitrophenyl)acetate

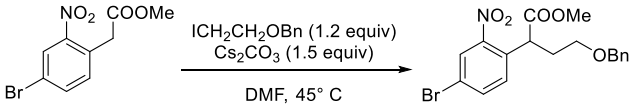
Yield: 87% (13.6 g), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.50 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 2.2 Hz, 1H), 7.68 (dd, J = 8.2, 2.1 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 3.95 (s, 2H), 3.67 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 169.9, 149.1, 136.5, 134.7, 128.7, 128.2, 121.7, 52.4, 39.0.

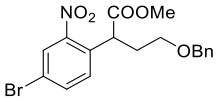
HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_9BrNO_4^+$ 273.9709; Found 273.9714.

IR (ν_{max}, cm^{-1}) 3092 (w), 1732 (s), 1528 (s), 1346 (s), 1214 (s), 1167 (s), 880 (m), 810 (m).



3.3.55 **3.3.56**

To a solution of ester **3.3.55** (10 g, 37 mmol, 1.0 equiv) in DMF (100 mL, 0.1 M), was added Cs_2CO_3 (16.8 g, 67 mmol, 1.5 equiv), followed by addition of Alk-I (7.6 mL, 48 mmol, 1.2 equiv). The reaction mixture was heated at 45 °C for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **3.3.56**.



3.3.56, methyl 4-(benzyloxy)-2-(4-bromo-2-nitrophenyl)butanoate

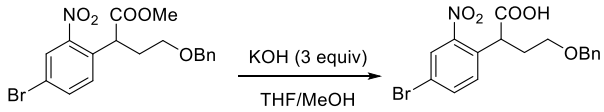
Yield: 60% (8.3 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 93:7), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.4, 2.1 Hz, 1H), 7.40 – 7.12 (m, 7H), 4.41 (m, 2H), 4.34 (t, J = 7.2 Hz, 1H), 3.62 (s, 3H), 3.56 – 3.46 (m, 1H), 3.38 – 3.29 (m, 1H), 2.59 – 2.47 (m, 1H), 2.15 – 1.97 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 149.9, 138.2, 136.2, 132.6, 132.4, 128.5, 127.9, 127.84, 127.79, 121.4, 73.1, 67.3, 52.5, 43.7, 32.8.

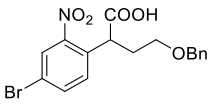
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{18}BrNNaO_5^+$ 430.0261; Found 430.0259.

IR (ν_{max}, cm^{-1}) 2858 (w), 1736 (s), 1530 (s), 1350 (s), 1204 (m), 1098 (s), 1003 (m), 738 (s).



3.3.56 **3.3.57**

To a solution of ester **3.3.56** (8.3 g, 20 mmol, 1.0 equiv) in THF (20 mL, 1.0 M), was added a 0.1 M solution of KOH (36 mL, 70 mmol, 3.0 equiv) at 0 °C. The reaction mixture was stirred overnight. After completion of the reaction, the reaction mixture was acidified to pH 3-4 with 1.0 M of citric acid. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired acid **3.3.57**.



3.3.57, 4-(benzyloxy)-2-(4-bromo-2-nitrophenyl)butanoic acid

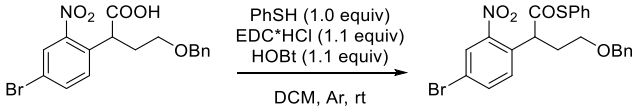
Yield: quant. (8.0 g), isolated as white solid. Purification: used without purification, R_f = 0.08 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.1 Hz, 1H), 7.66 (dd, J = 8.3, 2.1 Hz, 1H), 7.40 – 7.28 (m, 6H), 4.43 (s, 2H), 4.37 (t, J = 7.0 Hz, 1H), 3.58 – 3.50 (m, 1H), 3.38 – 3.31 (m, 1H), 2.61 – 2.50 (m, 1H), 2.14 – 2.00 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 149.6, 137.9, 136.3, 132.7, 132.3, 128.6, 128.1, 127.92, 127.90, 121.7, 73.2, 67.3, 44.0, 32.3.

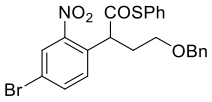
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{16}BrNNaO_5^+$ 416.0104; Found 416.0105.

IR (ν_{max}, cm^{-1}) 2888 (w), 1706 (s), 1528 (s), 1350 (s), 1098 (s), 740 (s), 698 (s).



3.3.57 **3.3.58**

To a solution of acid **3.3.57** (4.0 g, 10.2 mmol, 1.0 equiv) and HOBt (1.5 g, 11.2 mmol, 1.1 equiv) in DCM (30 mL, 0.25 M) was added EDC (2.2 g, 11.2 mmol, 1.1 equiv) portion-wise at 0 °C. After stirring for 30 min at 0 °C, PhSH (1.04 mL, 10.2 mmol, 1.0 equiv) was added to the reaction mixture. The reaction mixture was warmed to room temperature and stirred overnight. After completion of the reaction, the reaction mixture was quenched with saturated solution of $NaHCO_3$. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired thioester **3.3.58**.



3.3.58, S-phenyl 4-(benzyloxy)-2-(4-bromo-2-nitrophenyl)butanethioate

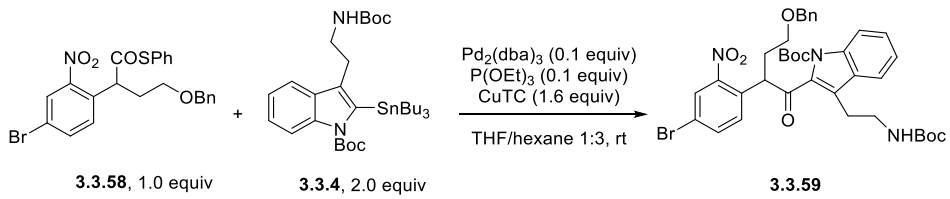
Yield: 74% (3.6 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.73 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 2.1 Hz, 1H), 7.69 (dd, J = 8.4, 2.1 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.41 – 7.27 (m, 10H), 4.76 (t, J = 7.2 Hz, 1H), 4.45 (d, J = 11.8 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 3.57 – 3.48 (m, 1H), 3.38 – 3.30 (m, 1H), 2.61 – 2.49 (m, 1H), 2.15 – 2.05 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 197.1, 150.2, 138.0, 136.2, 134.6, 132.0, 131.5, 129.8, 129.4, 128.5, 127.9, 127.8, 127.3, 121.9, 73.2, 67.2, 50.6, 33.6.

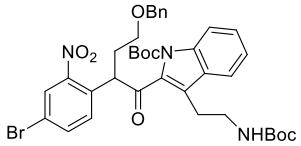
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{20}BrNNaO_4S^+$ 508.0189; Found 508.0196.

IR (ν_{max}, cm^{-1}) 3060 8w), 1670 (m), 1612 (m), 1526 (s), 1346 (s), 1083 (m), 744 (m).



3.3.58, 1.0 equiv **3.3.4**, 2.0 equiv **3.3.59**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump technique. To a solution of stannyl **3.3.4** (8.6 g, 13 mmol, 2.0 equiv) and thioester **3.3.58** (3.2 g, 6.6 mmol, 1.0 equiv) in dry THF/hexanes (69 mL, 1:3, 0.067 M), were added Pd_2dba_3 (600 mg, 0.66 mmol, 10 mol%), $P(OEt)_3$ (0.11 mL, 0.66 mmol, 10 mol%) and CuTC (2.0 g, 10.6 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature overnight. After completion of reaction, the reaction mixture was filtered through a pad of Celite (rinsed with EtOAc). The filtrate was washed with 2M HCl, 10% NH_4OH and brine, dried, filtered and evaporated *in vacuo*. The crude product was purified by flash column chromatography to yield the desired compound **3.3.59**.



3.3.59, tert-butyl 2-(4-(benzyloxy)-2-(4-bromo-2-nitrophenyl)butanoyl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

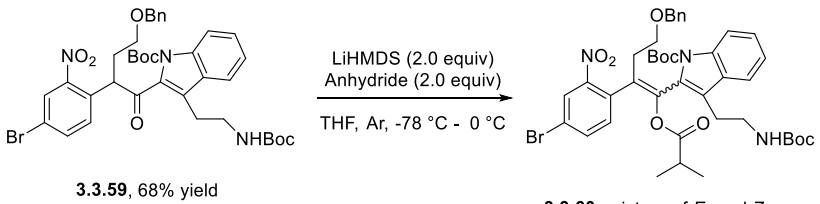
Yield: 68% (3.45 g), isolated as colorless oil Purification: Flash chromatography (PE/EtOAc, 93:7), R_f = 0.13 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.78 (d, *J* = 2.1 Hz, 1H), 7.65 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 7.33 – 7.21 (m, 4H), 7.22 – 7.13 (m, 2H), 5.23 (dd, *J* = 10.0, 4.5 Hz, 1H), 5.08 (br s, 1H), 4.36 (d, *J* = 11.8 Hz, 1H), 4.30 (d, *J* = 11.8 Hz, 1H), 3.46 (dt, *J* = 10.5, 5.6 Hz, 1H), 3.35 – 3.18 (m, 3H), 2.73 – 2.64 (m, 1H), 2.62 – 2.50 (m, 1H), 2.41 – 2.31 (m, 1H), 2.27 – 2.19 (m, 1H), 1.66 (s, 9H), 1.43 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.7, 156.2, 150.9, 150.6, 138.2, 135.7, 135.6, 134.6, 131.4, 129.4, 128.4, 127.8, 127.66, 127.6, 127.2, 124.1, 123.6, 121.2, 120.8, 116.0, 85.9, 79.2, 73.1, 67.5, 48.2, 41.1, 32.9, 28.6, 28.2, 24.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{37}H_{42}BrN_3NaO_8^+$ 758.2047; Found 758.2054.

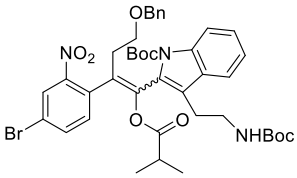
IR (ν_{max}, cm^{-1}) 3048 (w), 1524 (s), 1348 (s), 1048 (m), 885 (m), 823 (m).



3.3.59, 68% yield

3.3.60, mixture of *E*- and *Z*-isomers, 76% yield

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 25 mL pressure resistant round bottomed flask was charged a solution of ketone **3.3.59** (1.0 g, 1.4 mmol, 1.0 equiv) in THF (14 mL, 0.1 M). Then a solution of LiHMDS (2.7 mL, 2.7 mmol, 1.0 M in THF, 2.0 equiv) was added dropwise at -78 °C. The reaction mixture was stirred at this temperature for 1h before warming to -40 °C. Then isobutyric anhydride (0.45 mL, 2.7 mmol, 2.0 equiv) was added to the reaction mixture. The reaction mixture was slowly warmed to rt and stirred for 2 h. After completion of the reaction, $NaHCO_3$ was added slowly to quench the reaction. The mixture was extracted from the aqueous phase with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the enol ester **3.3.60**.



3.3.60, tert-butyl 2-(4-(benzyloxy)-2-(4-bromo-2-nitrophenyl)-1-(isobutyryloxy)but-1-en-1-yl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

Yield: 51% (580 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

Z-isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.12 – 7.06 (m, 2H), 5.08 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 11.7 Hz, 1H), 4.24 (d, J = 11.8 Hz, 1H), 3.60 – 3.52 (m, 1H), 3.52 – 3.44 (m, 1H), 3.41 (t, J = 6.7 Hz, 2H), 3.26 – 3.19 (m, 1H), 3.19 – 3.12 (m, 1H), 2.91 – 2.81 (m, 1H), 2.78 – 2.71 (m, 1H), 2.29 – 2.19 (m, 1H), 1.70 (s, 9H), 1.47 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.2, 156.3, 149.4, 148.2, 137.9, 136.8, 135.9, 134.2, 132.6, 129.3, 128.3, 127.84, 127.79 127.63, 127.58, 125.4, 123.0, 122.0, 121.5, 120.8, 115.7, 83.8, 78.9, 72.8, 68.0, 39.9, 33.9, 33.1, 28.6, 28.3, 25.2, 18.5, 18.4.

E-isomer

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.10 (m, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 – 7.20 (m, 6H), 7.16 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 7.3 Hz, 2H), 4.86 (t, J = 5.6 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 4.23 (d, J = 11.8 Hz, 1H), 3.58 – 3.47 (m, 2H), 3.30 – 3.23 (m, 1H), 3.06 – 2.96 (m, 1H), 2.91 –

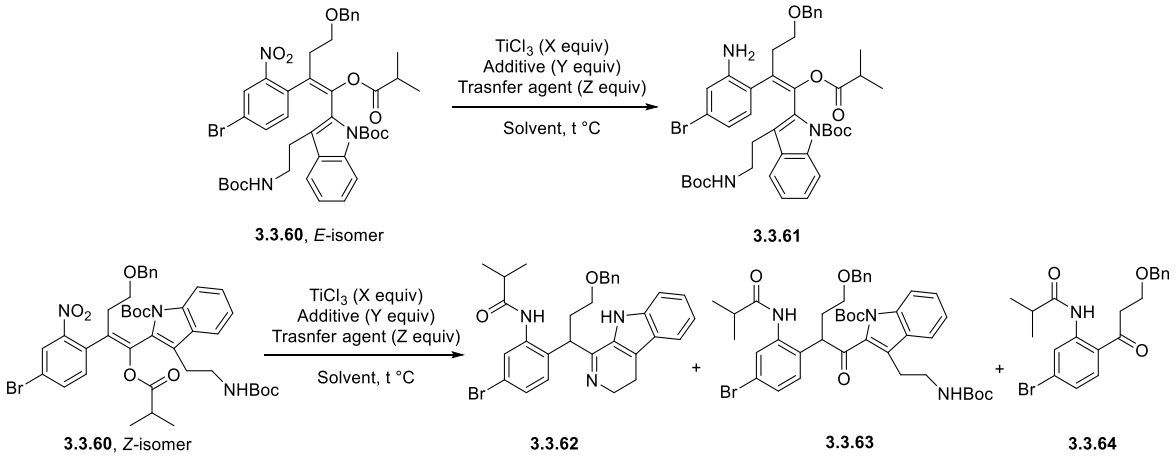
2.76 (m, 2H), 2.63 (p, *J* = 7.0 Hz, 1H), 2.60 – 2.51 (m, 2H), 1.71 (s, 9H), 1.40 (s, 9H), 1.22 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 156.1, 149.8, 147.8, 138.2, 138.0, 136.5, 136.1, 134.6, 133.6, 129.8, 128.9, 128.4, 128.3, 127.9, 127.8, 127.6, 125.5, 122.8, 122.6, 121.7, 120.8, 115.2, 84.3, 78.8, 73.0, 67.5, 39.3, 34.2, 31.1, 28.5, 28.3, 24.5, 18.83, 18.79.

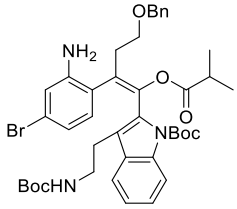
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{41}H_{48}BrN_3NaO_9^+$ 828.2466; Found 828.2475.

IR (ν_{max}, cm^{-1}) 2919 (w), 1754 (m), 1579 (m), 1523 (s), 1189 (m), 1116 (s), 1048 (m), 820 (s).

6.3.6. TiCl$_3$-mediated reductive cyclization of enol ester 3.3.60



In a 10 mL pressure resistant round bottomed flask was charged the enol ester **3.3.60** (1.0 equiv) in MeCN (0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 10 equiv) was added dropwise at 0 °C upon 10 min. The reaction mixture was warmed to rt and stirred overnight. After completion of the reaction, $NaHCO_3$ was added slowly at 0 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give to give the aniline **3.3.61**, ketone **3.3.63** and **3.3.64**, dihydrocarbazole **3.3.62**.



3.3.61, tert-butyl (E)-2-(2-(2-amino-4-bromophenyl)-4-(benzyloxy)-1-(isobutyryloxy)but-1-en-1-yl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

Isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

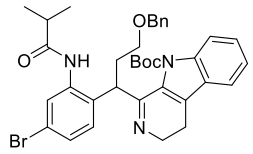
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.26 (m, 7H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.83 – 6.65 (m, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.83 (t, *J* = 5.8

Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.7 Hz, 1H), 4.27 (m, 2H), 3.69 – 3.47 (m, 2H), 3.41 – 3.33 (m, 1H), 3.02 – 2.93 (m, 1H), 2.86 – 2.73 (m, 1H), 2.68 – 2.52 (m, 2H), 2.55 – 2.43 (m, 1H), 1.68 (s, 9H), 1.41 (s, 9H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 175.2, 156.2, 150.3, 146.3, 138.5, 138.0, 136.1, 131.0, 129.3, 128.5, 128.4, 128.4, 127.8, 127.6, 125.4, 122.9, 122.1, 121.8, 121.1, 121.08, 119.8, 118.0, 115.3, 84.6, 78.9, 73.0, 67.6, 39.2, 24.2, 33.3, 28.6, 28.3, 26.1, 19.0, 18.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{41}H_{51}BrN_3O_7^+$ 776.2905; Found 776.2921.

IR (ν_{max}, cm^{-1}) 2967 (w), 1722 (m), 1529 (m), 1353 (m), 1211 (m), 1105 (s), 760 (m).



3.3.62, tert-butyl 1-(3-(benzyloxy)-1-(4-bromo-2-isobutyramidophenyl)propyl)-3,4-dihydro-9H-pyrido[3,4-b]indole-9-carboxylate

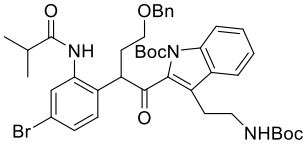
Isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.44 (d, *J* = 2.1 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.41 (ddd, *J* = 8.5, 7.1, 1.3 Hz, 1H), 7.33 – 7.18 (m, 6zH), 7.00 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 4.69 – 4.59 (m, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.79 – 3.64 (m, 1H), 3.39 – 3.31 (m, 1H), 3.24 – 3.14 (m, 1H), 2.78 – 2.67 (m, 1H), 2.67 – 2.55 (m, 2H), 2.42 – 2.25 (m, 2H), 1.65 (s, 9H), 1.32 – 1.21 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 175.7, 150.7, 139.5, 138.5, 138.1, 131.3, 130.1, 128.6, 128.4, 128.0, 127.9, 127.87, 127.63, 127.61, 127.2, 126.4, 125.8, 123.7, 121.4, 120.4, 116.2, 85.3, 73.1, 67.9, 60.5, 46.5, 37.0, 31.8, 28.3, 28.26, 20.1, 19.9, 19.6.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{36}H_{41}BrN_3O_4^+$ 658.2275; Found 658.2291.

IR (ν_{max}, cm^{-1}) 2952 (w), 2859 (w), 1714 (s), 1523 (s), 1417 (s), 1348 (s), 1230 (s), 1154 (s), 1092 (s), 760 (s).



3.3.63, tert-butyl 2-(4-(benzyloxy)-2-(4-bromo-2-isobutyramidophenyl)butanoyl)-3-(2-((tert-butoxycarbonyl)amino)ethyl)-1H-indole-1-carboxylate

Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

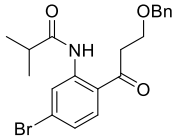
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.24 (s, 1H), 8.03 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.04 (m, 8H), 5.05 (br s, 1H), 4.60 – 4.50 (m, 1H), 4.49 – 4.28 (m, 2H), 3.64 – 3.45 (m, 1H), 3.22 –

2.92 (m, 3H), 2.70 – 2.53 (m, 2H), 2.48 – 2.36 (m, 1H), 2.33 – 2.20 (m, 1H), 1.69 (s, 9H), 1.42 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 175.1, 156.1, 150.7, 138.3, 137.8, 135.5, 128.6, 128.1, 127.9, 127.1, 123.8, 121.8, 121.4, 115.5, 85.7, 79.2, 73.1, 67.4, 40.6, 36.2, 28.6, 28.3, 19.8, 19.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{41}H_{50}BrN_3NaO_7^+$ 798.2724; Found 798.2733.

IR (ν_{max}, cm^{-1}) 2919 (w), 1641 (s), 1531 (s), 1450 (s), 1300 (s), 711 (s).



3.3.64, N-(2-(3-(benzyloxy)propanoyl)-5-bromophenyl)isobutyramide

Isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5).

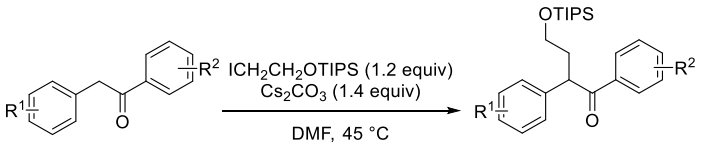
^{1}H NMR (400 MHz, $CDCl_3$) *δ* 11.75 (s, 1H), 9.08 (d, *J* = 2.0 Hz, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.39 – 7.27 (m, 4H), 7.23 (dd, *J* = 8.6, 2.0 Hz, 1H), 4.55 (s, 2H), 3.89 (t, *J* = 6.3 Hz, 2H), 3.28 (t, *J* = 6.3 Hz, 2H), 2.61 (p, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 6H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{22}BrNNaO_3^+$ 426.0675; Found 426.0662.

IR (ν_{max}, cm^{-1}) 2967 (w), 1674 (m), 1587 (m), 1514 (s), 1342 (m), 1263 (s), 1154 (s), 1018 (m), 746 (m).

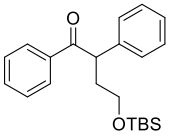
6.4. $TiCl_3$-Mediated Reductive Cyclization of tetrasubstituted *ortho*-nitrostyrene derivatives

6.4.1. General procedure L for the alkylation of ketone 4.5.5



4.5.5 **4.5.6**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **4.5.5** (4.0 g, 20.0 mmol, 1.0 equiv) in DMF (40 mL, 0.5 M), Cs_2CO_3 (9.3 g, 28.6 mmol, 1.4 equiv) was added to the reaction mixture, followed by addition of ((2-iodoethoxy)triisopropylsilane, 8.0 g, 24.5 mmol, 1.2 equiv). The reaction mixture was heated at 45 °C in the oil bath for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.5.6**.



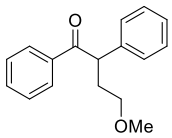
4.3.22, 4-((tert-butyldimethylsilyl)oxy)-1,2-diphenylbutan-1-one

This compound was prepared following the general procedure **L** using substrate 1,2-diphenylethan-1-one (4.0 g, 20.0 mmol) as starting material and tert-butyl(2-iodoethoxy)dimethylsilane as Alk-I. Yield: 60% (4.3 g), isolated as white solid. Purification: Flash chromatography (PE/DCM, 9:1 -> 7:3), R_f = 0.22 (PE/EtOAc 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.53 – 7.45 (m, 1H), 7.43 – 7.35 (m, 2H), 7.34 – 7.27 (m, 4H), 7.22 – 7.16 (m, 1H), 4.89 (t, J = 7.2 Hz, 1H), 3.65 – 3.56 (m, 1H), 3.56 – 3.49 (m, 1H), 2.47 – 2.33 (m, 1H), 2.06 – 1.92 (m, 1H), 0.88 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{30}NaO_2Si^+$ 377.1907; Found 377.1910.

IR (ν_{max}, cm^{-1}) 2958 (w), 2893 (w), 1719 (m), 1679 (m), 1449 (m), 1273 (m), 1119 (m), 1026 (m), 764 (m).



4.3.32, 4-methoxy-1,2-diphenylbutan-1-one

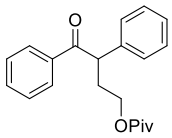
This compound was prepared following the general procedure **L** using substrate 1,2-diphenylethan-1-one (5.2 g, 26.6 mmol) as starting material and 1-iodo-2-methoxyethane as Alk-I. Yield: 71% (4.8 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98.5:1.5), R_f = 0.41 (PE/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.93 (m, 2H), 7.50 – 7.43 (m, 1H), 7.42 – 7.35 (m, 2H), 7.34 – 7.24 (m, 4H), 7.23 – 7.14 (m, 1H), 4.84 (t, *J* = 7.3 Hz, 1H), 3.41 – 3.31 (m, 1H), 3.31 – 3.22 (m, 4H), 2.53 – 2.36 (m, 1H), 2.11 – 2.00 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 139.3, 137.0, 132.9, 129.1, 128.9, 128.6, 128.5, 127.2, 70.1, 58.7, 49.8, 33.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{18}NaO_2^+$ 277.1199; Found 277.1209.

IR (ν_{max}, cm^{-1}) 2968 (m), 2889 (m), 2365 (w), 2340 (w), 1679 (m), 1449 (m), 1270 (m), 1119 (s), 1069 (s).



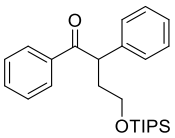
4.3.36, 4-oxo-3,4-diphenylbutyl pivalate

This compound was prepared following the general procedure **L** using substrate 1,2-diphenylethan-1-one (4.0 g, 20.0 mmol) as starting material and 2-iodoethyl pivalate as Alk-I. Yield: 58% (3.8 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.65 (PE/EtOAc 8:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90 (m, 2H), 7.49 – 7.41 (m, 1H), 7.36 (dd, *J* = 8.4, 7.0 Hz, 2H), 7.27 (d, *J* = 4.4 Hz, 5H), 4.69 (t, *J* = 7.3 Hz, 1H), 4.05 (dt, *J* = 11.8, 6.0 Hz, 1H), 3.97 (ddd, *J* = 11.0, 7.5, 5.6 Hz, 1H), 2.51 (dtd, *J* = 14.3, 7.3, 5.9 Hz, 1H), 2.14 (ddt, *J* = 13.7, 7.4, 5.9 Hz, 1H), 1.16 (s, 9H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{24}NaO_3^+$ 347.1618; Found 347.1619.

IR (ν_{max}, cm^{-1}) 2972 (s), 2889 (m), 2365 (w), 1729 (s), 1679 (s), 1449 (m), 1392 (m), 1280 (m), 1155 (s), 1044 (s), 756 (m).



4.5.6a, 1,2-diphenyl-4-((triisopropylsilyl)oxy)butan-1-one

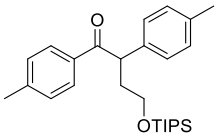
This compound was prepared following the general procedure **L** using substrate 1,2-diphenylethan-1-one (4.0 g, 20.0 mmol) as starting material. Yield: 58% (3.5 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.57 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.97 (m, 2H), 7.53 – 7.47 (m, 1H), 7.44 – 7.35 (m, 2H), 7.38 – 7.27 (m, 4H), 7.22 – 7.16 (m, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 3.73 – 3.66 (m, 1H), 3.65 – 3.57 (m, 1H), 2.50 – 2.38 (m, 1H), 2.07 – 1.95 (m, 1H), 1.06 – 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3, 139.6, 137.1, 132.9, 129.0, 128.9, 128.7, 128.6, 127.1, 60.7, 49.4, 37.1, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{36}NaO_2Si^+$ 419.2377; Found 419.2379.

IR (ν_{max}, cm^{-1}) 2946 (m), 2866 (m), 1720 (m), 1684 (m), 1460 (m), 1272 (m), 1103 (m), 883 (m), 754 (m).



4.5.6b, 1,2-di-p-tolyl-4-((triisopropylsilyl)oxy)butan-1-one

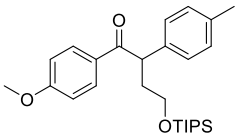
This compound was prepared following the general procedure **L** using substrate 1,2-di-p-tolylethan-1-one (3.0 g, 13.4 mmol) as starting material. Yield: 61% (3.5 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.58 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.83 (m, 2H), 7.24 – 7.13 (m, 4H), 7.08 (d, *J* = 7.8 Hz, 2H), 4.90 (t, *J* = 6.9 Hz, 1H), 3.74 – 3.56 (m, 2H), 2.49 – 2.38 (m, 1H), 2.35 (d, *J* = 3.2 Hz, 3H), 2.27 (s, 2H), 2.04 – 1.88 (m, 1H), 1.12 – 0.98 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 143.6, 136.8, 136.6, 134.6, 129.6, 129.2, 129.0, 128.5, 60.8, 48.8, 37.1, 21.7, 21.2, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{40}NaO_2Si^+$ 447.2690; Found 447.2695.

IR (ν_{max}, cm^{-1}) 2946 (s), 2863 (s), 1676 (s), 1608 (m), 1460 (m), 1266 (m), 1100 (s), 904 (m), 883 (m), 736 (s).



4.5.6c, 1-(4-methoxyphenyl)-2-(p-tolyl)-4-((triisopropylsilyl)oxy)butan-1-one

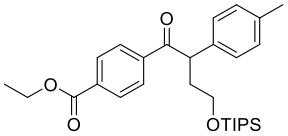
This compound was prepared following the general procedure **L** using substrate 1-(4-methoxyphenyl)-2-(p-tolyl)ethan-1-one (3.0 g, 12.5 mmol) as starting material. Yield: 69% (3.8 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.43 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.92 (m, 2H), 7.24 – 7.16 (m, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 6.91 – 6.82 (m, 2H), 4.88 (t, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 3.71 – 3.57 (m, 2H), 2.45 – 2.33 (m, 1H), 2.28 (s, 3H), 2.03 – 1.91 (m, 1H), 1.11 – 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.9, 163.3, 137.0, 136.6, 131.2, 130.1, 129.6, 128.4, 113.7, 60.8, 55.5, 48.6, 37.2, 21.2, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{40}NaO_3Si^+$ 463.2639; Found 463.2656.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 1672 (s), 1600 (s), 1511 (s), 1258 (s), 1168 (s), 1106 (s), 883 (s), 808 (s).



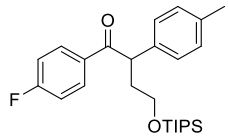
4.5.6d, ethyl 4-(2-(p-tolyl)-4-((triisopropylsilyl)oxy)butanoyl)benzoate

This compound was prepared following the general procedure **L** using substrate ethyl 4-(2-(p-tolyl)acetyl)benzoate (3.2 g, 11.3 mmol) as starting material. Yield: 42% (2.3 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.5:0.5), R_f = 0.53 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 7.96 (m, 4H), 7.21 – 7.13 (m, 2H), 7.11 – 7.05 (m, 2H), 4.92 (t, *J* = 7.1 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.74 – 3.58 (m, 2H), 2.47 – 2.37 (m, 1H), 2.27 (s, 3H), 2.02 – 1.91 (m, 1H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.11 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.0, 166.0, 140.4, 137.0, 136.0, 133.9, 129.8, 129.7, 128.7, 128.5, 61.5, 60.6, 49.5, 36.9, 21.2, 18.2, 14.4, 12.1.

IR (ν_{max}, cm^{-1}) 2918 (s), 2864 (s), 1724 (s), 1273 (s), 1106 (s), 914 (m), 732 (s).



4.5.6e, 1-(4-fluorophenyl)-2-(p-tolyl)-4-((triisopropylsilyl)oxy)butan-1-one

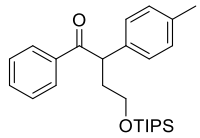
This compound was prepared following the general procedure **L** using substrate 1-(4-fluorophenyl)-2-(p-tolyl)ethan-1-one (2.2 g, 10.3 mmol) as starting material. Yield: 77% (3.4 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.41 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.20 – 7.15 (m, 2H), 7.11 – 7.00 (m, 4H), 4.88 (t, *J* = 7.1 Hz, 1H), 3.74 – 3.58 (m, 2H), 2.46 – 2.33 (m, 1H), 2.28 (s, 3H), 2.02 – 1.91 (m, 1H), 1.06 – 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 196.8, 166.0 (d, *J* = 250.0 Hz), 165.7, 144.5, 134.3, 132.33 (d, *J* = 9.3 Hz), 130.0, 128.4, 126.47 (d, *J* = 3.2 Hz), 115.63 (d, *J* = 22.0 Hz), 60.7, 37.5, 29.9, 21.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{37}FNaO_2Si^+$ 451.2439; Found 451.2447.

IR (ν_{max}, cm^{-1}) 2943 (w), 2866 (w), 1685 (m), 1438 (m), 1277 (m), 1130 (m), 1021 (m), 770 (m).



4.5.6f, 1-phenyl-2-(p-tolyl)-4-((triisopropylsilyl)oxy)butan-1-one

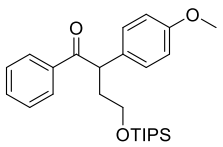
This compound was prepared following the general procedure **L** using substrate 1-phenyl-2-(p-tolyl)ethan-1-one (1.35 g, 6.4 mmol) as starting material. Yield: 76% (2.0 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.91 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.93 (m, 2H), 7.50 – 7.42 (m, 1H), 7.41 – 7.33 (m, 2H), 7.23 – 7.16 (m, 2H), 7.09 (d, *J* = 7.9 Hz, 2H), 4.93 (t, *J* = 7.1 Hz, 1H), 3.74 – 3.51 (m, 2H), 2.48 – 2.36 (m, 1H), 2.28 (s, 3H), 2.02 – 1.90 (m, 1H), 1.11 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.4, 137.1, 136.7, 136.5, 132.8, 129.7, 128.9, 128.6, 128.5, 60.8, 49.0, 37.1, 21.2, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{38}NaO_2Si^+$ 433.2533; Found 433.2527.

IR (ν_{max}, cm^{-1}) 2932 (m), 2863 (m), 1676 (m), 1460 (w), 1266 (w), 1100 (m), 1064 (m), 992 (m), 800 (m).



4.5.6g, 2-(4-methoxyphenyl)-1-phenyl-4-((triisopropylsilyl)oxy)butan-1-one

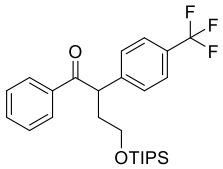
This compound was prepared following the general procedure **L** using substrate 2-(4-methoxyphenyl)-1-phenylethan-1-one (1.4 g, 6.1 mmol) as starting material. Yield: 76% (2.0 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.68 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.95 (m, 2H), 7.50 – 7.43 (m, 1H), 7.42 – 7.34 (m, 2H), 7.25 – 7.19 (m, 2H), 6.82 (d, *J* = 8.7 Hz, 1H), 4.92 (t, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.73 – 3.55 (m, 2H), 2.45 – 2.34 (m, 1H), 2.03 – 1.91 (m, 1H), 1.10 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.5, 158.7, 137.1, 132.8, 131.5, 129.7, 128.9, 128.6, 114.4, 60.7, 55.4, 48.5, 37.1, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{38}NaO_3Si^+$ 449.2482; Found 449.2486.

IR (ν_{max}, cm^{-1}) 2963 (m), 2850 (m), 1677 (m), 1491 (m), 1236 (m), 1108 (m), 865 (m), 760 (s).



4.5.6h, 1-phenyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)butan-1-one

This compound was prepared following the general procedure **L** using substrate 1-phenyl-2-(4-(trifluoromethyl)phenyl)ethan-1-one (1.6 g, 6.0 mmol) as starting material. Yield: 79% (2.2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.88 (PE/EtOAc 90:10).

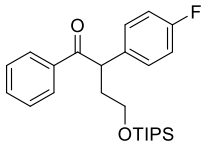
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.63 – 7.36 (m, 7H), 5.08 (t, *J* = 7.2 Hz, 1H), 3.77 – 3.65 (m, 1H), 3.63 – 3.55 (m, 1H), 2.54 – 2.39 (m, 1H), 2.09 – 1.94 (m, 1H), 1.12 – 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.7, 143.6, 136.7, 133.3, 129.1, 129.0, 128.9, 128.8, 125.88 (q, *J* = 3.7 Hz), 60.5, 49.0, 37.2, 18.1, 12.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ 62.5.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{35}F_3NaO_2Si^+$ 487.2251; Found 487.2253.

IR (ν_{max}, cm^{-1}) 2943 (m), 2864 (m), 2344 (w), 1683 (m), 1464 (m), 1324 (s), 1166 (s), 1126 (s), 1069 (s).



4.5.6i, 2-(4-fluorophenyl)-1-phenyl-4-((triisopropylsilyl)oxy)butan-1-one

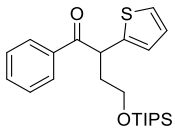
This compound was prepared following the general procedure **L** using substrate 2-(4-fluorophenyl)-1-phenylethan-1-one (2.2 g, 10.3 mmol) as starting material. Yield: 70% (3.0 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.88 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.55 – 7.45 (m, 1H), 7.44 – 7.36 (m, 2H), 7.33 – 7.26 (m, 2H), 7.02 – 6.93 (m, 2H), 4.98 (t, *J* = 7.2 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.62 – 3.54 (m, 1H), 2.46 – 2.36 (m, 1H), 2.02 – 1.92 (m, 1H), 1.15 – 0.87 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3, 162.01 (d, *J* = 245.5 Hz), 136.9, 135.16 (d, *J* = 3.3 Hz), 133.1, 130.20 (d, *J* = 8.0 Hz), 128.9, 128.7, 115.81 (d, *J* = 21.3 Hz), 60.6, 48.4, 37.2, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{35}FNaO_2Si^+$ 437.2283; Found 437.2283.

IR (ν_{max}, cm^{-1}) 2943 (m), 2864 (m), 1683 (s), 1507 (s), 1227 (m), 1105 (s), 998 (m), 882 (s), 814 (m), 728 (s).



4.5.6j, 1-phenyl-2-(thiophen-2-yl)-4-((triisopropylsilyl)oxy)butan-1-one

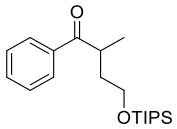
This compound was prepared following the general procedure **L** using substrate 1-phenyl-2-(thiophen-2-yl)ethan-1-one (2.3 g, 11.3 mmol) as starting material. Yield: 55% (2.5 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.69 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.03 (m, 2H), 7.55 – 7.51 (m, 1H), 7.47 – 7.40 (m, 2H), 7.19 – 7.18 (m, 1H), 6.94 – 6.90 (m, 2H), 5.32 (t, *J* = 7.1 Hz, 1H), 3.76 – 3.66 (m, 2H), 2.43 (dddd, *J* = 14.0, 7.6, 6.6, 4.9 Hz, 1H), 2.07 (dddd, *J* = 13.6, 7.6, 5.9, 4.4 Hz, 1H), 1.09 – 1.00 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.2, 141.8, 136.5, 133.2, 129.0, 128.7, 126.9, 126.0, 125.0, 60.5, 43.9, 38.1, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculated for $C_{23}H_{34}NaO_2SSi^+$ 425.1941; Found 425.1951.

IR (ν_{max}, cm^{-1}) 2962 (w), 2941 (w), 2922 (w), 2893 (w), 2864 (m), 2841 (w), 1684 (m), 1597 (w), 1464 (w), 1446 (w), 1427 (w), 1385 (w), 1346 (w), 1327 (w), 1288 (w), 1255 (w), 1236 (m), 1205 (w), 1178 (w), 1157 (w), 1101 (m), 1065 (m), 1032 (w), 1012 (w), 982 (w), 943 (w), 920 (w), 881 (m), 852 (w), 812 (w).



4.5.6k, 2-methyl-1-phenyl-4-((triisopropylsilyl)oxy)butan-1-one

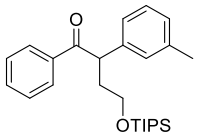
This compound was prepared following the general procedure **L** using substrate propiophenone (1.5 g, 11.0 mmol) as starting material. Yield: 52% (3.6 g), isolated as colorless oil. Purification: Flash chromatography (PE), R_f = 0.73 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.99 (m, 2H), 7.58 – 7.51 (m, 1H), 7.49 – 7.42 (m, 2H), 3.89 – 3.68 (m, 3H), 2.18 – 2.05 (m, 1H), 1.63 – 1.53 (m, 1H), 1.21 (d, *J* = 6.7 Hz, 3H), 1.14 – 1.00 (p, *J* = 5.4, 4.6 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.6, 136.7, 132.9, 128.64, 128.62, 61.0, 37.0, 36.9, 18.1, 16.9, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{34}NaO_2Si^+$ 357.2220; Found 357.2223.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 1684 (s), 1456 (m), 1236 (m), 1104 (s), 980 (m), 883 (s), 754 (s).



4.5.6l, 1-phenyl-2-(m-tolyl)-4-((triisopropylsilyl)oxy)butan-1-one

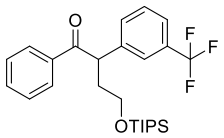
This compound was prepared following the general procedure **L** using substrate 1-phenyl-2-(m-tolyl)ethan-1-one (2.6 g, 12.3 mmol) as starting material. Yield: 79% (4.0 g), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.4 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 2H), 7.51 – 7.43 (m, 1H), 7.42 – 7.34 (m, 2H), 7.20 – 7.08 (m, 3H), 7.05 – 6.96 (m, 1H), 4.93 (t, *J* = 7.2 Hz, 1H), 3.73 – 3.65 (m, 1H), 3.64 – 3.57 (m, 1H), 2.47 – 2.36 (m, 1H), 2.30 (s, 3H), 2.06 - 1.93 (m, 1H), 1.07 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.3, 139.5, 138.6, 137.1, 132.9, 129.3, 128.9, 128.8, 128.6, 127.9, 125.8, 60.7, 49.3, 37.1, 21.6, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{38}NaO_2Si^+$ 433.2533; Found 433.2526.

IR (ν_{max}, cm^{-1}) 2947 (m), 2868 (m), 1679 (m), 1460 (m), 1273 (m), 1101 (s), 1065 (s), 882 (s), 778 (s).



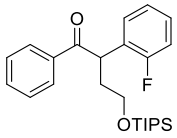
4.5.6m, 1-phenyl-2-(3-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)butan-1-one

This compound was prepared following the general procedure **L** using substrate 1-phenyl-2-(3-(trifluoromethyl)phenyl)ethan-1-one (2.4 g, 9.1 mmol) as starting material. Yield: 61% (2.6 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.4:0.6), R_f = 0.84 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 7.94 (m, 2H), 7.64 – 7.60 (m, 1H), 7.58 – 7.36 (m, 6H), 5.09 (t, J = 7.2 Hz, 1H), 3.76 – 3.66 (m, 1H), 3.60 – 3.52 (m, 1H), 2.50 – 2.40 (m, 1H), 2.07 – 1.97 (m, 1H), 1.13 – 0.93 (m, 21H).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{36}F_3O_2Si^+$ 465.2431; Found 465.2425.

IR (ν_{max}, cm^{-1}) 2943 (m), 2864 (m), 1686 (m), 1449 (m), 1327 (s), 1166 (s), 1126 (s), 1076 (s), 882 (m).



4.5.6n, 2-(2-fluorophenyl)-1-phenyl-4-((triisopropylsilyl)oxy)butan-1-one

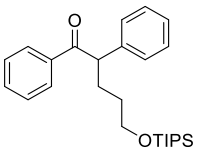
This compound was prepared following the general procedure **L** using substrate 2-(2-fluorophenyl)-1-phenylethan-1-one (2.0 g, 9.3 mmol) as starting material. Yield: 65% (2.5 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.4:0.6), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 7.97 (m, 2H), 7.53 – 7.46 (m, 1H), 7.44 – 7.36 (m, 2H), 7.32 – 7.25 (m, 1H), 7.23 – 7.14 (m, 1H), 7.09 – 6.98 (m, 2H), 5.34 (t, J = 7.0 Hz, 1H), 3.77 – 3.59 (m, 2H), 2.55 – 2.38 (m, 1H), 2.09 – 1.94 (m, 1H), 1.12 – 0.96 (m, 21H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 199.7, 160.32 (d, J = 245.6 Hz), 136.6, 133.1, 129.54 (d, J = 3.7 Hz), 128.8, 128.7, 128.66, 126.69 (d, J = 15.2 Hz), 124.65 (d, J = 3.5 Hz), 115.76 (d, J = 22.9 Hz), 60.9, 41.0, 36.2, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{35}FNaO_2Si^+$ 437.2283; Found 437.2283.

IR (ν_{max}, cm^{-1}) 2947 (m), 2864 (m), 1686 (m), 1489 (m), 1449 (m), 1230 (m), 1108 (m), 882 (m), 756 (s).



4.5.6ai, 1,2-diphenyl-5-((triisopropylsilyl)oxy)pentan-1-one

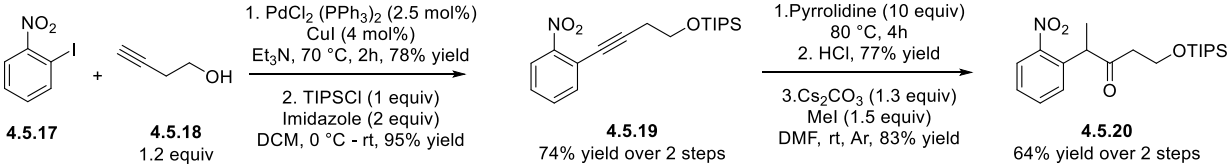
This compound was prepared following the general procedure **L** using substrate propiophenone (3.0 g, 15.3 mmol) as starting material and (3-iodopropoxy)triisopropylsilane as Alk-I. Yield: 76% (4.8 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.5:0.5), R_f = 0.68 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 2H), 7.52 – 7.44 (m, 1H), 7.42 – 7.35 (m, 2H), 7.34 – 7.23 (m, 4H), 7.22 – 7.16 (m, 1H), 4.60 (t, *J* = 7.3 Hz, 1H), 3.68 (td, *J* = 6.4, 1.0 Hz, 2H), 2.30 – 2.18 (m, 1H), 1.98 – 1.87 (m, 1H), 1.62 – 1.40 (m, 2H), 1.10 – 0.98 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 139.8, 137.1, 132.9, 129.0, 128.8, 128.6, 128.5, 127.1, 63.4, 53.5, 31.0, 30.5, 18.2, 12.1.

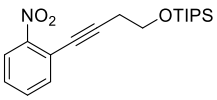
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{38}NaO_2Si^+$ 433.2533; Found 433.2533.

IR (ν_{max}, cm^{-1}) 2942 (m), 2863 (m), 1684 (m), 1456 (m), 1106 (s), 1067 (m), 883 (m), 753 (m).



To a solution of 1-iodo-2-nitrobenzene **4.5.17** (5.0 g, 20.0 mmol, 1.0 equiv) in Et_3N (40 mL, 0.5 M) was added but-3-yn-1-ol **4.5.18** (1.83 mL, 24 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (350 mg, 0.5 mmol, 2.5 mol%) and CuI (150 mg, 0.8 mmol, 4 mol%). The reaction mixture was heated at 70 °C for 3 h, then water was added, the reaction crude was filtered through celite followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step without purification.

To a solution of 4-(2-nitrophenyl)but-3-yn-1-ol (3.0 g, 15.7 mmol, 1.0 equiv) in DCM (35 mL, 0.5 M) was added TIPSCl (3.26 mL, 15.7 mmol, 1.0 equiv), followed by addition of imidazole (2.14 g, 31.4 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at rt for 3 h, then the reaction was quenched with $NaHCO_3$, followed by extraction with DCM (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to silica gel column chromatography to afford the desired protected alcohol **4.5.19.**



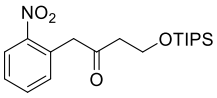
4.5.19, triisopropyl((4-(2-nitrophenyl)but-3-yn-1-yl)oxy)silane

This compound was prepared using substrate 4-(2-nitrophenyl)but-3-yn-1-ol (3.0 g, 15.7 mmol) as starting material. Yield: 95% (5.2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.3, 1.3 Hz, 1H), 7.58 (dd, J = 7.8, 1.6 Hz, 1H), 7.52 (td, J = 7.5, 1.3 Hz, 1H), 7.40 (dd, J = 8.8, 7.3 Hz, 1H), 3.93 (t, J = 7.2 Hz, 2H), 2.73 (t, J = 7.1 Hz, 2H), 1.11 – 0.94 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 135.0, 132.7, 128.2, 124.6, 119.2, 96.3, 61.9, 24.5, 18.1, 12.1.

A solution of triisopropyl((4-(2-nitrophenyl)but-3-yn-1-yl)oxy)silane **4.5.19** (5.2 g, 15 mmol, 1.0 equiv) in pyrrolidine (25 mL, 0.6 M) was heated at 80 °C for 3 h. Upon completion of the reaction, the excess of pyrrolidine was evaporated. The reaction mixture was then acidified with HCl (1.0 N) and stirred for 30 min. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.5.19a**.



4.5.19a, 1-(2-nitrophenyl)-4-((triisopropylsilyl)oxy)butan-2-one

This compound was prepared using substrate triisopropyl((4-(2-nitrophenyl)but-3-yn-1-yl)oxy)silane (5.2 g, 15 mmol) as starting material. Yield: 75% (4.2 g), isolated as colorless crystalls. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.32 (PE/EtOAc 90:10).

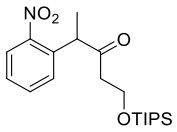
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.2, 1.4 Hz, 1H), 7.58 (td, J = 7.5, 1.4 Hz, 1H), 7.45 (ddd, J = 8.8, 7.5, 1.5 Hz, 1H), 7.29 – 7.22 (m, 1H), 4.19 (s, 2H), 4.04 (t, J = 6.3 Hz, 2H), 2.82 (t, J = 6.3 Hz, 2H), 1.16 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 205.1, 148.9, 133.7, 133.67, 130.5, 128.5, 125.4, 59.3, 49.0, 46.2, 18.1, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{31}NNaO_4Si^+$ 388.1915; Found 388.1919.

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **4.5.19a** (0.75 g, 2.0 mmol, 1.0 equiv) in DMF (4.0 mL, 0.5 M), Cs_2CO_3 (1.0 g, 3.0 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of MeI (8.0 g, 24.5 mmol, 1.2 equiv). The reaction mixture was heated at 45 °C in the oil bath for 1 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined

organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.5.20**.



4.5.20, 4-(2-nitrophenyl)-1-((triisopropylsilyl)oxy)pentan-3-one

This compound was prepared using substrate 1-(2-nitrophenyl)-4-((triisopropylsilyl)oxy)butan-2-one (2.2 g, 10.3 mmol) as starting material. Yield: 83% (650 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.47 (PE/EtOAc 90:10).

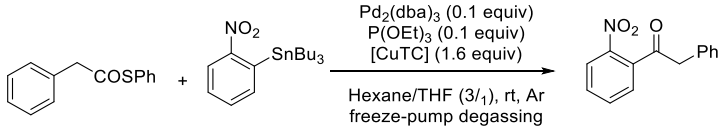
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.58 (td, *J* = 7.6, 1.4 Hz, 1H), 7.42 (ddd, *J* = 8.6, 7.4, 1.4 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.4 Hz, 1H), 4.38 (q, *J* = 7.0 Hz, 1H), 4.05 – 3.86 (m, 2H), 2.80 – 2.69 (m, 1H), 2.69 – 2.56 (m, 1H), 1.48 (d, *J* = 7.0 Hz, 3H), 1.09 – 0.98 (m, 21H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.1, 149.5, 135.1, 133.4, 130.0, 128.1, 124.9, 59.1, 48.3, 44.7, 18.1, 17.1, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{33}NNaO_4Si^+$ 402.2071; Found 402.2076.

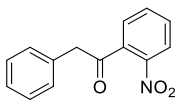
IR (ν_{max}, cm^{-1}) 2946 (m), 2866 (m), 1720 (m), 1525 (s), 1460 (m), 1352 (m), 1099 (s), 883 (s), 746 (s).

6.4.2. Synthesis of the precursor 4.5.9a *via* 2nd synthetic pathway



4.3.20 **4.3.21** 1.6 equiv **4.3.19**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump-Thaw technique. To a mixture of organostannane **4.3.21** (2.5 g, 6.0 mmol, 1.6 equiv), thioester **4.3.20** (0.85 g, 3.7 mmol, 1.0 equiv), $P(OEt)_3$ (0.06 mL, 0.37 mmol, 0.1 equiv), Pd_2dba_3 (340 mg, 0.37 mmol, 0.1 equiv) and CuTC (1.14 g, 6.0 mmol, 1.6 equiv) was added dry and degassed THF (13.5 mL) and hexane (40.4 mL). After being stirred at rt overnight, the reaction mixture was quenched by the addition of water and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.3.19**.



4.3.19, 1-(2-nitrophenyl)-2-phenylethan-1-one

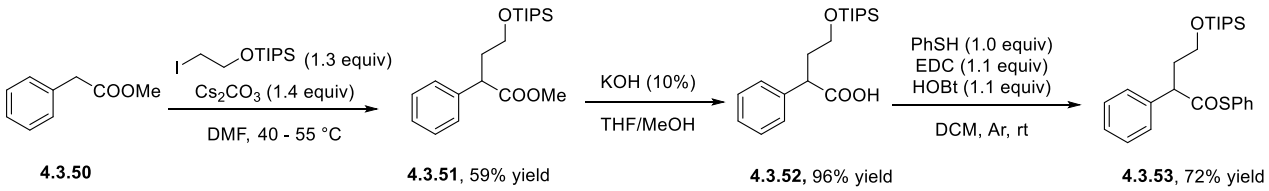
Yield: 68% (550 mg), isolated as white solid. Purification: Flash chromatography (PE), R_f = 0.84 (PE/EtOAc 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J = 8.2, 1.2 Hz, 1H) 7.66 (td, J = 7.5, 1.3 Hz, 1H), 7.58 (ddd, J = 8.2, 7.5, 1.5 Hz, 1H), 7.34 – 7.20 (m, 6H), 4.10 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.4, 145.5, 137.9, 134.4, 133.0, 130.6, 130.0, 128.9, 128.0, 127.5, 124.5, 50.1.

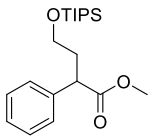
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{11}NNaO_3^+$ 264.0631; Found 264.0638.

IR (ν_{max}, cm^{-1}) 3350 (w), 2964 (m), 1607 (s), 1519 (s), 1460 (s), 1223 (m), 1057 (m), 815 (m), 746 (s).



4.3.50 **4.3.51**, 59% yield **4.3.52,** 96% yield **4.3.53**, 72% yield

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was charged a solution of methyl 2-phenylacetate **4.3.50** (3.0 g, 20.0 mmol, 1.0 equiv) in DMF (40 mL, 0.5 M), Cs_2CO_3 (9.2 g, 28.0 mmol, 1.4 equiv) was added to the reaction mixture, followed by addition of (2-iodoethoxy)triisopropylsilane (8.5 g, 26.0 mmol, 1.3 equiv). The reaction mixture was heated at 45 °C in the oil bath for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ester **4.3.51**.



4.3.51, methyl 2-phenyl-4-((triisopropylsilyl)oxy)butanoate

Yield: 59% (4.1 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.4:0.6), R_f = 0.69 (PE/EtOAc 90:10).

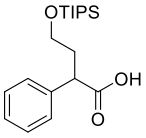
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.21 (m, 5H), 3.89 (t, J = 7.5 Hz, 1H), 3.70 – 3.63 (m, 1H), 3.65 (s, 3H), 3.58 (ddd, J = 10.1, 7.2, 5.1 Hz, 1H), 2.37 – 2.29 (m, 1H), 1.99 – 1.91 (m, 1H), 1.12 - 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 139.2, 128.8, 128.2, 127.3, 60.7, 52.1, 47.6, 36.6, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{34}NaO_3Si^+$ 373.2169; Found 373.2172.

IR (ν_{max}, cm^{-1}) 2946 (m), 2866 (m), 1734 (s), 1456 (m), 1262 (m), 1164 (s), 1103 (s), 1067 (s), 883 (s), 746 (m).

To a solution of ester **4.3.51** (3.2 g, 9.0 mmol, 1.0 equiv) in THF/MeOH (10:1, 90 mL, 0.1 M) was added KOH (16 mL, 10 % solution). After being stirred overnight, the reaction was acidified to pH = 3 by the addition of 1M HCl and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude product **4.3.52** was used without purification.



4.3.52, 2-phenyl-4-((triisopropylsilyl)oxy)butanoic acid

Yield: 97% (2.9 g), isolated as colorless oil.

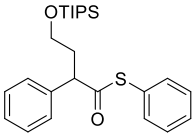
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.26 – 7.09 (m, 5H), 3.73 (t, *J* = 7.4 Hz, 1H), 3.64 – 3.54 (m 1H), 3.52 – 3.41 (m, 1H), 2.26 – 2.18 (m, 1H), 1.91 – 1.79 (m, 1H), 1.10 – 0.73 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 180.0, 139.1, 128.7, 128.4, 127.3, 60.8, 48.3, 36.2, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{32}NaO_3Si^+$ 359.2013; Found 359.2012.

IR (ν_{max}, cm^{-1}) 2946 (m), 2870 (m), 1730 (s), 1528 (s), 1464 (m), 1352 (m), 1272 (m), 1154 (s), 1013 (m), 883 (m), 808 (m).

To a solution of acid **4.3.52** (2.9 g, 8.6 mmol, 1.0 equiv), HOBt (1.3 g, 9.5 mmol, 1.1 equiv) and PhSH (0.88 mL, 8.6 mmol, 1.0 equiv) in dry DCM (25 mL, 0.3 M) was added EDC·HCl (1.8 g, 9.5 mmol, 1.1 equiv) at 0 °C. After being stirred at room temperature for 3h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired thioester **4.3.53**.



4.3.53, *S*-phenyl 2-phenyl-4-((triisopropylsilyl)oxy)butanethioate

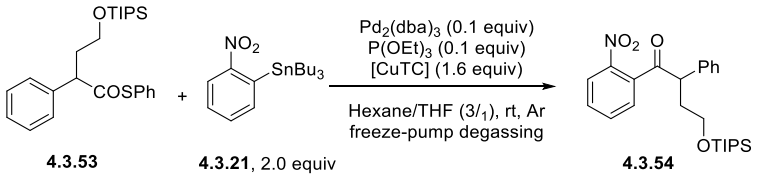
Yield: 72% (2.7 g), isolated as colorless oil. Purification: Flash chromatography (PE), R_f = 0.31 (PE/EtOAc 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 10H), 4.23 (t, *J* = 7.4 Hz, 1H), 3.72 (ddd, *J* = 10.1, 6.2, 5.2 Hz, 1H), 3.57 (ddd, *J* = 10.1, 7.3, 5.0 Hz, 1H), 2.40 (dtd, *J* = 14.2, 7.2, 5.2 Hz, 1H), 2.01 (dddd, *J* = 13.8, 7.8, 6.2, 4.9 Hz, 1H), 1.14 – 0.99 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 198.7, 138.2, 134.6, 129.4, 129.2, 128.9, 128.7, 128.2, 127.7, 60.4, 56.1, 36.7, 18.2, 12.1.

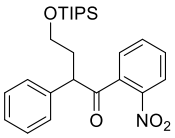
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{36}NaO_2SSi^+$ 451.2097; Found 451.2099.

IR (ν_{max}, cm^{-1}) 2954 (m), 2868 (m), 1704 (m), 1464 (m), 1252 (m), 1101 (s), 1066 (s), 882 (s), 742 (s).



4.3.53 **4.3.21**, 2.0 equiv **4.3.54**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. THF and hexane were degassed with Freeze-pump technique. To a mixture of organostannane **4.3.21** (5.2 g, 12.6 mmol, 2.0 equiv), thioester **4.3.53** (2.7 g, 6.3 mmol, 1.0 equiv), $P(OEt)_3$ (0.1 mL, 0.63 mmol, 0.1 equiv), Pd_2dba_3 (600 mg, 0.63 mmol, 0.1 equiv) and CuTC (1.92 g, 10 mmol, 1.6 equiv) was added dry and degassed THF (20 mL) and hexane (60 mL). After being stirred at rt overnight, the reaction mixture was quenched by the addition of water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.3.54**.



4.3.54, 1-(2-nitrophenyl)-2-phenyl-4-((triisopropylsilyl)oxy)butan-1-one

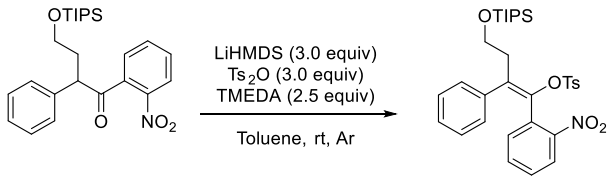
Yield: 73% (190 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.41 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 – 8.05 (m, 1H), 7.50 – 7.42 (m, 2H), 7.28 – 7.20 (m, 3H), 7.19 – 7.15 (m, 2H), 6.84 – 6.82 (m, 1H), 4.31 (dd, J = 9.5, 5.1 Hz, 1H), 3.71 (ddd, J = 10.4, 6.1, 4.5 Hz, 1H), 3.50 (ddd, J = 10.1, 8.8, 5.1 Hz, 1H), 2.54 (dddd, J = 13.9, 8.8, 6.1, 5.0 Hz, 1H), 2.18 (ddt, J = 14.1, 9.6, 4.8 Hz, 1H), 1.08 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5, 145.8, 137.7, 137.1, 133.8, 130.3, 129.4, 128.94, 128.89, 127.7, 124.3, 60.3, 55.3, 35.4, 18.1, 12.1.

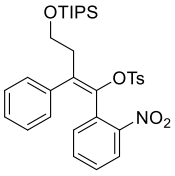
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{35}NNaO_4Si^+$ 464.2228; Found 464.2229.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 1705 (m), 1528 (s), 1345 (s), 1106 (s), 1067 (s), 883 (m), 760 (m).



4.3.54 **4.3.55**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. To a solution of LiHMDS (1.0 M in toluene, 0.23 mL, 0.23 mmol, 2.0 equiv) was added TMEDA (0.06 mL, 0.56 mmol, 5.0 equiv). After stirring for 15 min, a solution of ketone **4.3.54** (50 mg, 0.11 mmol, 1.0 equiv) in toluene (0.5 mL, 1.0 M) was added dropwise at 0 °C. After stirring for 1 h, recrystallized Ts_2O (110 mg, 0.34 mmol, 3.0 equiv) was added portion-wise. The reaction was stirred vigorously for 3 h. After completion of the reaction, water was added slowly. The reaction mixture was extracted with DCM. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol tosylate **4.3.55**.



4.3.55, (*E*)-1-(2-nitrophenyl)-2-phenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

Yield: 40% (27 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.41 (PE/EtOAc 85:15).

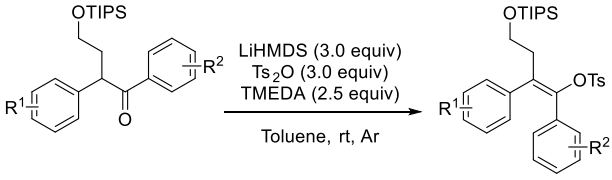
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.60 (m, 1H), 7.47 – 7.45 (m, 2H), 7.25 – 7.21 (m, 2H), 7.15 – 7.06 (m, 8H), 3.78 (td, *J* = 9.1, 6.3 Hz, 1H), 3.63 (td, *J* = 9.2, 5.8 Hz, 1H), 3.15 (ddd, *J* = 13.1, 8.7, 6.2 Hz, 1H), 2.76 – 2.70 (m, 1H), 2.38 (s, 3H), 1.07 – 0.93 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.3, 144.9, 139.9, 137.7, 134.7, 133.9, 132.4, 129.64, 129.62, 129.3, 129.1, 128.3, 127.9, 127.8, 60.9, 36.4, 21.8, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{41}NNaO_6SSi^+$ 618.2316; Found 618.2348.

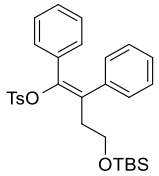
IR (ν_{max}, cm^{-1}) 3399 (w), 2936 (w), 2868 (w), 1694 (w), 1528 (m), 1374 (m), 1349 (m), 1176 (m), 1034 (m), 750 (s).

6.4.3. **General procedure M for the synthesis of enol tosylate 4.5.7**



4.5.6 **4.5.7**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. To a solution of LiHMDS (1.0 M in toluene, 7.6 mL, 7.6 mmol, 3.0 equiv) was added TMEDA (0.8 mL, 7.6 mmol, 3.0 equiv). After stirring for 15 min., a solution of ketone **4.5.6a** (1.0 g, 2.5 mmol, 1.0 equiv) in toluene (2.5 mL, 1.0 M) was added dropwise. After stirring for 1 h, the reaction mixture was placed in a 23 °C water bath and recrystallized Ts_2O (2.06 g, 6.0 mmol, 2.5 equiv) was added portion-wise. The reaction was stirred vigorously for 3 h. After completion of the reaction, water was added slowly. The reaction mixture was extracted with DCM. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol tosylate **4.5.7a**.



4.3.25, (*E*)-4-((*tert*-butyldimethylsilyl)oxy)-1,2-diphenylbut-1-en-1-yl 4-methylbenzenesulfonate

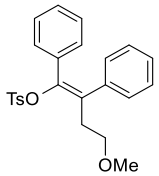
This compound was prepared following the general procedure **M** using substrate **4.3.22** (1.0 g, 2.8 mmol) as starting material. Yield: 53% (750 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.35 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.17 – 7.12 (m, 3H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.05 – 6.97 (m, 3H), 6.93 – 6.86 (m, 4H), 3.55 (t, *J* = 7.0 Hz, 2H), 2.87 (t, *J* = 7.0 Hz, 2H), 2.36 (s, 3H), 0.85 (s, 9H), -0.03 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.54, 144.46, 138.4, 134.5, 134.0, 132.4, 130.0, 129.6, 129.4, 128.2, 128.1, 127.8, 127.5, 127.2, 60.5, 36.5, 26.0, 21.7, 18.3, -5.3.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{36}NaO_4SSi^+$ 531.1996; Found 531.1998.

IR (ν_{max}, cm^{-1}) 2962 (m), 2889 (m), 2356 (m), 1372 (s), 1252 (m), 1189 (s), 1179 (s), 1099 (s), 834 (s), 780 (s).



4.3.33, (*E*)-4-methoxy-1,2-diphenylbut-1-en-1-yl 4-methylbenzenesulfonate

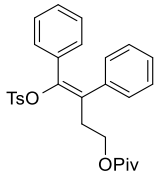
This compound was prepared following the general procedure **M** using substrate **4.3.32** (0.5 g, 2.0 mmol) as starting material. Yield: 69% (550 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.28 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.13 (m, 3H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.06 – 6.96 (m, 3H), 6.91 – 6.86 (m, 4H), 3.32 (t, *J* = 7.0 Hz, 2H), 3.24 (s, 3H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.6, 138.2, 134.3, 133.8, 132.2, 130.0, 129.5, 129.4, 128.3, 128.2, 127.9, 127.5, 127.3, 69.7, 58.5, 33.0, 21.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{24}NaO_4S^+$ 431.1288; Found 431.1290.

IR (ν_{max}, cm^{-1}) 2982 (m), 2896 (m), 1371 (s), 1188 (s), 1176 (s), 1080 (s), 1048 (s), 782 (s).



4.3.38, (*E*)-3,4-diphenyl-4-(tosyloxy)but-3-en-1-yl pivalate

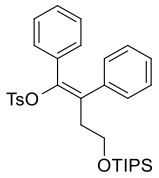
This compound was prepared following the general procedure **M** using substrate **4.3.36** (1.0 g, 3.1 mmol) as starting material. Yield: 37% (550 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.47 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.17 – 7.13 (m, 3H), 7.11 – 7.07 (m, 2H), 7.04 – 6.98 (m, 3H), 6.94 – 6.86 (m, 4H), 3.98 (t, *J* = 6.5 Hz,2), 3.00 (t, *J* = 6.5 Hz, 2H), 2.36 (s, 3H), 1.14 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.4, 144.9, 144.7, 137.7, 134.3, 133.8, 131.5, 129.9, 129.5, 129.4, 128.5, 128.1, 128.0, 127.59, 127.55, 61.7, 38.8, 32.3, 27.3, 21.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{30}NaO_5S^+$ 501.1706; Found 501.1709.

IR (ν_{max}, cm^{-1}) 2972 (s), 2896 (s), 1722 (s), 1367 (s), 1156 (s), 1054 (s), 814 (m), 778 (s).



4.5.7a, (*E*)-1,2-diphenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

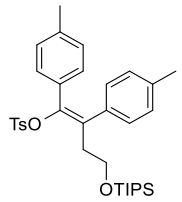
This compound was prepared following the general procedure **M** using substrate **4.5.6a** (1.0 g, 2.5 mmol) as starting material. Yield: 64% (800 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.48 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.09 (m, 5H), 7.04 – 6.98 (m, 3H), 6.93 – 6.88 (m, 4H), 3.61 (t, *J* = 6.9 Hz, 2H), 2.88 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 1.01 – 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.48, 144.45, 138.4, 134.5, 134.2, 132.5, 130.0, 129.6, 129.4, 128.20, 128.15, 127.8, 127.5, 127.2, 60.8, 36.6, 21.7, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{42}NaO_4SSi^+$ 573.2465; Found 573.2477.

IR (ν_{max}, cm^{-1}) 3356 (w), 2954 (m), 2868 (m), 1367 (m), 1187 (m), 1176 (s), 1044 (s), 878 (m), 782 (s).



4.5.7b, (*E*)-1,2-di-p-tolyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

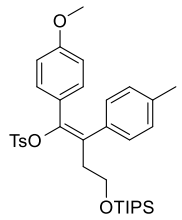
This compound was prepared following the general procedure **M** using substrate **4.5.6b** (2.5 g, 5.9 mmol) as starting material. Yield: 37% (1.3 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.32 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 2H), 7.12 – 7.10 (m, 2H), 6.97 – 6.90 (m, 4H), 6.80 (d, J = 8.2 Hz, 2H), 6.73 (d, J = 7.9 Hz, 2H), 3.57 (t, J = 7.0 Hz, 2H), 2.81 (t, J = 7.0 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H), 1.00 – 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4, 144.3, 137.6, 136.7, 135.5, 134.7, 131.4, 129.9, 129.4, 129.3, 128.9, 128.22, 128.17, 60.9, 36.7, 21.7, 21.4, 21.3, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}NaO_4SSi^+$ 601.2778; Found 601.2783.

IR (ν_{max}, cm^{-1}) 3381 (w), 2936 (w), 2864 (m), 1507 (m), 1367 (m), 1176 (s), 1044 (m), 969 (m), 825 (s).



4.5.7c, (*E*)-1-(4-methoxyphenyl)-2-(p-tolyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

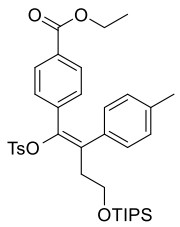
This compound was prepared following the general procedure **M** using substrate **4.5.6c** (2.5 g, 5.7 mmol) as starting material. Yield: 47% (1.6 g), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.3 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.3 Hz, 2H), 7.13 – 7.11 (m, 2H), 6.96 – 6.89 (m, 4H), 6.83 (d, J = 8.8 Hz, 2H), 6.45 (d, J = 8.9 Hz, 2H), 3.68 (s, 3H), 3.58 (t, J = 7.0 Hz, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 3H), 1.00 – 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 159.0, 144.3, 144.2, 136.7, 135.6, 134.8, 131.3, 130.9, 129.4, 129.3, 128.9, 128.2, 126.8, 113.0, 60.9, 55.2, 36.6, 21.7, 21.3, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{34}H_{46}NaO_5SSi^+$ 617.2727; Found 617.2726.

IR (ν_{max}, cm^{-1}) 3385 (w), 2938 (w), 2863 (w), 1669 (w), 1601 (m), 1510 (w), 1258 (s), 1172 (s), 1125 (s), 1035 (s), 1009 (s), 814 (s).



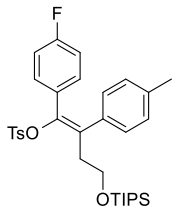
4.5.7d, ethyl (*E*)-4-(2-(p-tolyl)-1-(tosyloxy)-4-((triisopropylsilyl)oxy)but-1-en-1-yl)benzoate

This compound was prepared following the general procedure **M** using substrate **4.5.6d** (2.0 g, 4.1 mmol) as starting material. Yield: 43% (1.1 g), isolated as orange solid. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.24 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.97 – 6.88 (m, 6H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.58 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.36 (s, 3H), 2.26 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.01 – 0.97 (m, 21H).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{48}NaO_6SSi^+$ 659.2833; Found 659.2847.

IR (ν_{max}, cm^{-1}) 2968 (m), 2868 (m), 1722 (m), 1683 (m), 1468 (m), 1406 (m), 1273 (s), 1101 (s), 1019 (s), 878 (m), 731 (s).



4.5.7e, (*E*)-1-(4-fluorophenyl)-2-(p-tolyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

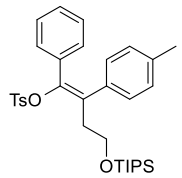
This compound was prepared following the general procedure **M** using substrate **4.5.6e** (3.0 g, 7.0 mmol) as starting material. Yield: 49% (2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.4 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.15 – 7.13 (m, 2H), 6.97 – 6.87 (m, 6H), 6.61 (t, *J* = 8.8 Hz, 2H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.38 (s, 3H), 2.26 (s, 3H), 1.05 – 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.0 (d, *J* = 248.3 Hz), 144.7, 143.2, 137.0, 135.1, 134.6, 132.6, 131.8 (d, *J* = 8.2 Hz), 130.5 (d, *J* = 3.4 Hz), 129.4, 129.3, 129.0, 128.1, 114.6 (d, *J* = 21.7 Hz), 60.7, 36.6, 21.7, 21.3, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{43}FNaO_4SSi^+$ 605.2528; Found 605.2537.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 2358 (m), 1507 (m), 1370 (m), 1229 (m), 1189 (s), 1179 (s), 1106 (s), 840 (s), 814 (s), 757 (s).



4.5.7f, (*E*)-1-phenyl-2-(p-tolyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

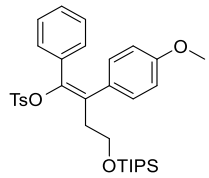
This compound was prepared following the general procedure **M** using substrate **4.5.6f** (2.0 g, 4.9 mmol) as starting material. Yield: 22% (600 mg), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.55 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.03 – 6.97 (m, 1H), 6.97 – 6.88 (m, 8H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 2.25 (s, 3H), 1.02 – 0.95 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4, 144.2, 136.8, 135.3, 134.6, 134.4, 132.3, 130.0, 129.4, 129.36, 128.9, 128.1, 127.7, 127.5, 60.8, 36.7, 21.7, 21.3, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{44}NaO_4SSi^+$ 587.2622; Found 587.2631.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 1464 (m), 1374 (m), 1189 (s), 1179 (s), 1106 (s), 1049 (m), 883 (s), 818 (s), 760 (s).



4.5.7g, (*E*)-2-(4-methoxyphenyl)-1-phenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

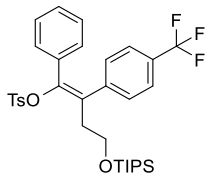
This compound was prepared following the general procedure **M** using substrate **4.5.6g** (1.9 g, 4.5 mmol) as starting material. Yield: 48% (1.25 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.39 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.03 – 6.97 (m, 1H), 6.96 – 6.88 (m, 6H), 6.68 (d, *J* = 8.7 Hz, 2H), 3.73 (s, 3H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 1.01 – 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.7, 144.4, 144.1, 134.6, 134.4, 131.9, 130.7, 130.5, 130.0, 129.4, 128.1, 127.6, 127.5, 113.7, 60.9, 55.3, 36.6, 21.7, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{44}NaO_5SSi^+$ 603.2571; Found 603.2580.

IR (ν_{max}, cm^{-1}) 2954 (m), 2864 (m), 1510 (m), 1374 (m), 1248 (m), 1176 (s), 1094 (m), 1044 (s), 753 (m).



4.5.7h, (*E*)-1-phenyl-2-(4-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

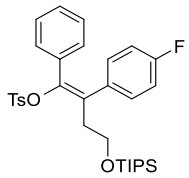
This compound was prepared following the general procedure **M** using substrate **4.5.6h** (2.0 g, 4.3 mmol) as starting material. Yield: 31% (830 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.07 – 7.00 (m, 1H), 6.93 (t, J = 7.6 Hz, 2H), 6.88 (d, J = 7.3 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 2.36 (s, 3H), 1.03 – 0.89 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.4, 144.6, 142.6, 134.4, 133.5, 131.6, 130.0, 129.2 (q, J = 32.4 Hz), 128.2, 128.1, 127.7, 125.1 (q, J = 3.7 Hz), 124.1 (q, J = 272.0 Hz), 60.8, 36.4, 21.7, 18.1, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{41}F_3NNaO_4Si^+$ 641.2340; Found 641.2357.

IR (ν_{max}, cm^{-1}) 2945 (m), 2830 (m), 1383 (m), 1167 (s), 1103 (m), 883 (m), 754 (s).



4.5.7i, (*E*)-2-(4-fluorophenyl)-1-phenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

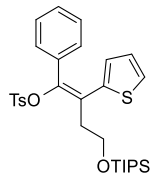
This compound was prepared following the general procedure **M** using substrate **4.5.6i** (2.8 g, 6.8 mmol) as starting material. Yield: 55% (2.1 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.29 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 7.05 – 6.97 (m, 3H), 6.96 – 6.80 (m, 6H), 3.62 (t, J = 6.7 Hz, 2H), 2.88 (t, J = 6.7 Hz, 2H), 2.36 (s, 3H), 1.04 – 0.94 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.1 (d, J = 247.1 Hz), 145.4, 144.8, 134.1 133.8 (d, J = 3.6 Hz), 133.4, 131.4, 131.2 (d, J = 8.1 Hz), 130.0, 129.4, 128.1, 128.07, 127.6, 115.5 (d, J = 21.4 Hz), 60.1, 36.3, 21.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{41}FNaO_4SSi^+$ 591.2371; Found 591.2387.

IR (ν_{max}, cm^{-1}) 3553 (w), 3374 (w), 2950 (m), 2864 (m), 1507 (m), 1367 (m), 1227 (m), 1191 (s), 1176 (s), 1051 (m), 836 (m), 754 (s).



4.5.7j, (*E*)-1-phenyl-2-(thiophen-2-yl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

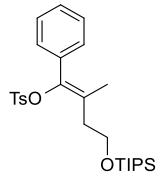
This compound was prepared following the general procedure **M** using substrate **4.5.6j** (2.3 g, 5.8 mmol) as starting material. Yield: 65% (2.1 g), isolated as green oil, mixture of *E*- and *Z*-isomers (7 to 1 ratio). Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.57 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.45 (m, 2/7H), 7.35-6.99 (m, 12H + 8/7H), 6.79 (dd, *J* = 5.1, 3.6 Hz, 1/7H), 6.71 (dd, *J* = 3.6, 1.2 Hz, 1/7H), 3.77 (t, *J* = 7.2 Hz, 2/7H), 3.66 (t, *J* = 7.2 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2/7H), 2.70 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3/7H), 2.33 (s, 3H), 1.06-0.93 (m, 21H + 21/7H).

^{13}C NMR (101 MHz, $CDCl_3$) (for only major isomer): δ 144.2, 143.4, 138.3, 134.4, 133.3, 130.4, 129.1, 128.8, 128.0, 128.0, 126.7, 126.4, 122.8, 62.1, 36.4, 21.7, 18.0, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculated for $C_{30}H_{40}NaO_4S_2Si^+$ 579.2029; Found 579.2037.

IR (ν_{max}, cm^{-1}) 2962 (w), 2925 (w), 2891 (w), 2864 (w), 1464 (w), 1444 (w), 1373 (m), 1257 (w), 1190 (m), 1174 (s), 1097 (m), 1065 (m), 1036 (m), 1018 (m), 989 (m), 943 (w), 918 (w), 881 (m), 856 (w), 839 (m), 808 (s).



4.5.7k, (*Z*)-2-methyl-1-phenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

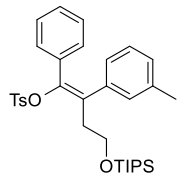
This compound was prepared following the general procedure **M** using substrate **4.5.6k** (2.0 g, 6.0 mmol) as starting material. Yield: 30% (850 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99.5:0.5), R_f = 0.55 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.09 (m, 5H), 7.04 (d, *J* = 8.3 Hz, 2H), 3.88 (t, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 6.7 Hz, 2H), 2.33 (s, 3H), 1.80 (s, 3H), 1.10 – 0.94 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.2, 142.2, 134.7, 133.9, 129.8, 129.3, 128.1, 128.04, 127.97, 127.8, 62.0, 36.0, 21.7, 18.9, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{40}NaO_4SSi^+$ 511.2309; Found 511.2310.

IR (ν_{max}, cm^{-1}) 2942 (m), 2866 (m), 1464 (w), 1374 (m), 1176 (s), 1089 (s), 984 (m), 811 (m).



4.5.7l, (*E*)-1-phenyl-2-(m-tolyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

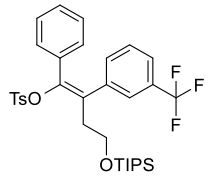
This compound was prepared following the general procedure **M** using substrate **4.5.6l** (3.5 g, 8.5 mmol) as starting material. Yield: 35% (1.7 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.25 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.12 – 7.07 (m, 2H), 7.03 – 6.96 (m, 2H), 6.96 – 6.86 (m, 6H), 6.77 (dt, *J* = 7.7, 1.8 Hz, 1H), 3.60 (t, *J* = 6.9 Hz, 2H), 2.87 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H), 2.19 (s, 3H), 1.01 – 0.97 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4, 144.3, 138.3, 137.7, 134.6, 134.2, 132.5, 130.1, 129.9, 129.4, 128.1, 128.0, 127.9, 127.7, 127.4, 126.7, 60.8, 36.6, 21.7, 21.4, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{44}NaO_4SSi^+$ 587.2622; Found 587.2640.

IR (ν_{max}, cm^{-1}) 2961 (m), 2864 (m), 1468 (m), 1367 (m), 1176 (s), 1047 (s), 828 (s), 753 (s).



4.5.7m, (*E*)-1-phenyl-2-(3-(trifluoromethyl)phenyl)-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

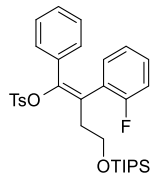
This compound was prepared following the general procedure **M** using substrate **4.5.6m** (2.6 g, 5.6 mmol) as starting material. Yield: 46% (1.6 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.45 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.34 (m, 1H), 7.32 – 7.19 (m, 3H), 7.12 – 7.07 (m, 2H), 7.06 – 7.00 (m, 1H), 6.95 – 6.88 (m, 2H), 6.88 – 6.84 (m, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 6.5 Hz, 2H), 2.36 (s, 3H), 1.01 – 0.92 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 145.6, 144.6, 139.5, 134.4, 133.5, 133.1, 131.5, 130.6 (q, *J* = 32.3 Hz), 130.0, 129.4, 128.6, 128.2, 128.1, 127.7, 126.5 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.1 Hz), 123.9 (q, *J* = 3.8 Hz),60.8, 36.2, 21.7, 18.0, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{41}F_3NaO_4SSi^+$ 641.2339; Found 641.2351.

IR (ν_{max}, cm^{-1}) 2939 (w), 2864 (w), 1460 (m), 1374 (m), 1338 (s), 1176 (s), 1126 (s), 997 (m), 807 (s), 756 (m).



4.5.7n, (*E*)-2-(2-fluorophenyl)-1-phenyl-4-((triisopropylsilyl)oxy)but-1-en-1-yl 4-methylbenzenesulfonate

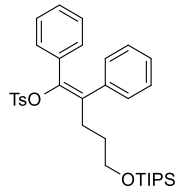
This compound was prepared following the general procedure **M** using substrate **4.5.6n** (1.8 g, 4.4 mmol) as starting material. Yield: 48% (1.2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.25 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.14 – 7.12 (m, 3H), 7.06 – 7.01 (m, 1H), 7.00 – 6.86 (m, 7H), 3.63 (t, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 6.9 Hz, 2H), 2.37 (s, 3H), 1.04 – 0.98 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1 (d, *J* = 246.7 Hz), 145.8, 144.6, 134.0 (d, *J* = 2.5 Hz), 131.7 (d, *J* = 3.6 Hz), 129.4, 129.3, 129.28, 129.26, 128.2, 128.1, 127.5, 127.0, 126.0 (d, *J* = 15.7 Hz), 123.9 (d, *J* = 3.5 Hz), 115.5 (d, *J* = 21.7 Hz), 60.7, 35.6, 21.7, 18.0, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{41}FNaO_4SSi^+$ 591.2371; Found 591.2390.

IR (ν_{max}, cm^{-1}) 3384 (w), 2939 (m), 2864 (m), 1446 (m), 1371 (m), 1176 (s), 1054 (s), 818 (s), 757 (s).



4.5.7ai, (*E*)-1,2-diphenyl-5-((triisopropylsilyl)oxy)pent-1-en-1-yl 4-methylbenzenesulfonate

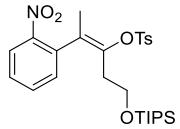
This compound was prepared following the general procedure **M** using substrate **4.5.6ai** (3.0 g, 7.3 mmol) as starting material. Yield: 40% (1.57 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.49 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.17 – 7.11 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.04 – 6.96 (m, 3H), 6.93 – 6.86 (m, 4H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.73 – 2.69 (m, 2H), 2.35 (s, 3H), 1.59 – 1.49 (m, 2H), 1.04 – 0.99 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.4, 143.3, 138.5, 135.4, 134.5, 134.2, 130.0, 129.5, 129.4, 128.3, 128.2, 127.7, 127.5, 127.2, 63.1, 30.7, 29.4, 21.7, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{33}H_{44}NaO_4SSi^+$ 587.2622; Found 587.2628.

IR (ν_{max}, cm^{-1}) 2938 (m), 2866 (m), 1377 (m), 1176 (s), 1103 (m), 974 (m), 779 (s), 757 (s).



4.5.22, (*E*)-2-(2-nitrophenyl)-5-((triisopropylsilyl)oxy)pent-2-en-3-yl 4-methylbenzenesulfonate

This compound was prepared following the general procedure **M** using substrate **4.5.20** (0.67 g, 1.8 mmol) as starting material. Yield: 43% (440 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.34 (PE/EtOAc 90:10).

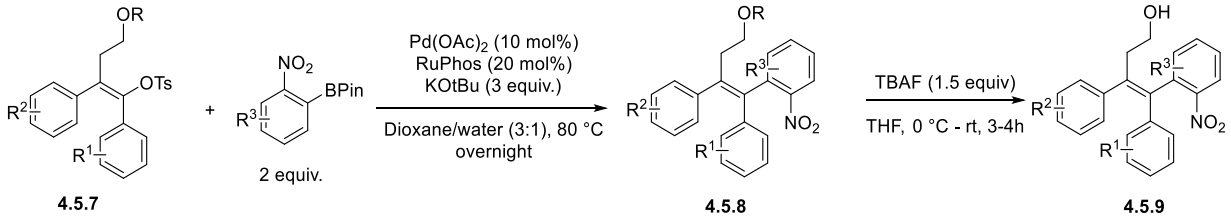
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.57 (td, *J* = 7.5, 1.3 Hz, 1H), 7.45 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.33 (dd, *J* = 7.7, 1.5 Hz, 1H), 3.75 (dt, *J* = 9.7, 7.5 Hz, 1H), 3.57 (ddd, *J* = 9.7, 7.3, 5.3 Hz, 1H), 2.46 (s, 3H), 2.32 – 2.26 (m, 2H), 1.73 (s, 3H), 1.00 – 0.93 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 145.6, 142.7, 135.3, 134.0, 133.9, 131.7, 130.1, 129.5, 129.0, 128.2, 125.1, 59.0, 35.2, 21.9, 18.9, 18.0, 17.8, 12.4.

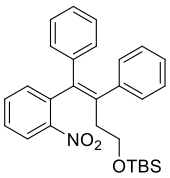
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{39}NNaO_6SSi^+$ 556.2160; Found 556.2155.

IR (ν_{max}, cm^{-1}) 2965 (s), 2889 (s), 1528 (s), 1367 (s), 1176 (s), 1058 (s), 878 (s), 754 (s).

6.4.4. **General procedure N for the synthesis of alcohol 4.5.9**



Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Dioxane and water were degassed with Freeze-pump technique. To a solution of enol tosylate **4.5.7a** (1.6 g, 3.0 mmol, 1.0 equiv) in dioxane/water (3:1, 0.06 M) were added 2-nitrophenyl boronic acid pinacol ester (1.5 g, 6.0 mmol, 2.0 equiv), $Pd(OAc)_2$ (67 mg, 0.3 mmol, 10 mol%), RuPhos (280 mg, 0.6 mmol, 20 mol%), KOH (510 mg, 9.0 mmol, 3.0 equiv) and *t*-BuOH (0.86 mL, 9.0 mmol, 3.0 equiv). The reaction mixture was heated at 80 °C overnight, then water was added, followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step after separation from Pd-nanoparticles by silica gel column chromatography. To a solution of alkene **4.5.8a** (270 mg, 0.5 mmol, 1.0 equiv) in THF (5 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.8 mL, 0.8 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 hours at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9a**.



4.3.29, (*E*)-*tert*-butyldimethyl((4-(2-nitrophenyl)-3,4-diphenylbut-3-en-1-yl)oxy)silane

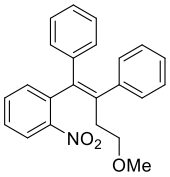
This compound was prepared following the general procedure **N** using substrate **4.3.25** (51 mg, 0.1 mmol) as starting material. Yield: 18% (NMR yield), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0. (PE/EtOAc :).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.50 – 7.44 (m, 1H), 7.20 – 7.08 (m, 5H), 7.00 – 6.96 (m, 3H), 6.92 – 6.85 (m, 2H), 3.51 – 3.38 (m, 2H), 2.68 – 2.51 (m, 2H), 0.82 (s, 9H), -0.11 (s, 3H), -0.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 140.8, 140.0, 138.4, 138.0, 136.3, 133.4, 133.0, 130.8, 129.7, 128.2, 128.06, 127.5, 126.9, 126.5, 124.9, 61.0, 40.0, 26.0, 18.4, -5.3, -5.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{33}NNaO_3Si^+$ 482.2122; Found 482.2141.

IR (ν_{max}, cm^{-1}) 3380 (w), 3064 (w), 2930 (w), 2855 (w), 1546 (s), 1329 (m), 1045 (m), 764 (m), 702 (s).



4.3.34, (*E*)-(4-methoxy-1-(2-nitrophenyl)but-1-ene-1,2-diyl)dibenzene

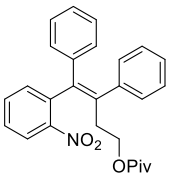
This compound was prepared following the general procedure **N** using substrate **4.3.33** (41 mg, 0.1 mmol) as starting material. Yield: 58% (NMR yield), isolated as white solid (mp = °C). Purification: Flash chromatography (PE/EtOAc, :), R_f = 0. (PE/EtOAc :).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.23 – 7.12 (m, 5H), 7.03 – 6.97 (m, 3H), 6.95 – 6.90 (m, 2H), 3.24 – 3.12 (m, 5H), 2.71 – 2.49 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 140.9, 140.1, 138.0, 137.9, 136.3, 133.2, 132.9, 130.8, 129.6, 128.3, 128.2, 127.6, 126.9, 126.6, 124.9, 70.4, 58.7, 36.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1419.

IR (ν_{max}, cm^{-1}) 3398 (w), 2955 (w), 2889 (w), 1728 (s), 1540 (s), 1363 (s), 1053 (m), 746 (s).



4.3.40, (*E*)-4-(2-nitrophenyl)-3,4-diphenylbut-3-en-1-yl pivalate

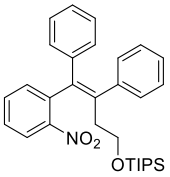
This compound was prepared following the general procedure **N** using substrate **4.3.38** (48 mg, 0.1 mmol) as starting material. Yield: 61% (NMR yield), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.44 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.69 (td, *J* = 7.5, 1.3 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.22 – 7.10 (m, 5H), 7.04 – 6.96 (m, 3H), 6.94 – 6.83 (m, 2H), 3.91 (dd, *J* = 7.4, 6.7 Hz, 2H), 2.71 (td, *J* = 7.5, 7.0, 1.4 Hz, 2H), 1.13 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 178.5, 148.7, 140.2, 139.7, 137.62, 137.57, 137.0, 133.2, 132.6, 130.6, 129.5, 128.5, 128.3, 127.6, 127.2, 126.8, 125.1, 62.6, 38.8, 35.2, 27.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{30}NaO_5S^+$ 501.1706; Found 501.1709.

IR (ν_{max}, cm^{-1}) 3438 (w), 2973 (w), 2889 (w), 1745 (s), 1530 (s), 1356 (s), 1230 (m), 910 (m), 752 (s).



4.5.8a, (*E*)-triisopropyl((4-(2-nitrophenyl)-3,4-diphenylbut-3-en-1-yl)oxy)silane

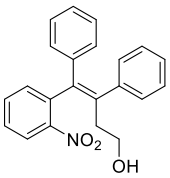
This compound was prepared following the general procedure **N** using substrate XX (1.7 g, 3.0 mmol) as starting material. Yield: 60% (910 mg), isolated as orange solid. Purification: Flash chromatography (PE/EtOAc, 98:2), Rf = 0.69 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.70 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.20 – 7.10 (m, 5H), 7.03 – 6.95 (m, 3H), 6.94 – 6.85 (m, 2H), 3.62 – 3.48 (m, 2H), 2.76 – 2.53 (m, 2H), 0.99 – 0.91 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 140.9, 140.1, 138.6, 138.0, 136.3, 133.3, 132.9, 130.7, 129.7, 128.2, 128.0, 127.5, 126.8, 126.5, 124.9, 61.2, 40.0, 18.12, 18.10, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{39}NNaO_3Si^+$ 524.2591; Found 524.2598.

IR (ν_{max}, cm^{-1}) 3415 (w), 2900 (m), 1625 (m), 1530 (s), 1506 (s), 1250 (m), 1180 (m), 1037 (s), 835 (m), 754 (s).



4.5.9a, (*E*)-4-(2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

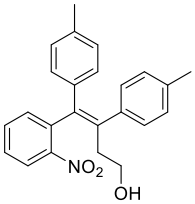
This compound was prepared following the general procedure **N** using substrate **4.5.8** (270 mg, 0.5 mmol) as starting material. Yield: 93% (174 mg), isolated as yellow crystals. Purification: Flash chromatography (PE/EtOAc, 82:18), R_f = 0.13 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.56 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.48 (td, *J* = 7.8, 1.4 Hz, 1H), 7.23 – 7.14 (m, 5H), 7.04 – 6.99 (m, 3H), 6.96 – 6.92 (m, 2H), 3.56 – 3.44 (m, 2H), 2.70 – 2.56 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 140.7, 139.9, 138.0, 137.8, 137.0, 133.3, 132.8, 130.7, 129.5, 128.4, 128.3, 127.6, 127.1, 126.7, 125.0, 60.6, 39.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{19}NNaO_3^+$ 368.1257; Found 368.1258.

IR (ν_{max}, cm^{-1}) 3360 (w), 3015 (w), 2955 (w), 2334 (w), 1615 (w), 1540 (s), 1348 (s), 1027 (m), 756 (s).



4.5.9b, (*E*)-4-(2-nitrophenyl)-3,4-di-p-tolylbut-3-en-1-ol

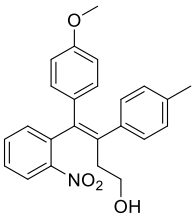
This compound was prepared following the general procedure **N** using substrate **4.5.7b** (1.1 g, 1.9 mmol) as starting material. Yield: 48% over 2 steps (340 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.26 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 2H), 6.84 – 6.78 (m, 4H), 3.55 – 3.41 (m, 2H), 2.64 – 2.55 (m, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 1.26 (t, *J* = 7.2 Hz, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 138.3, 137.9, 137.24, 137.17, 136.6, 136.5, 136.3, 133.2, 132.8, 130.5, 129.3, 129.1, 128.4, 128.2, 124.9, 60.8, 39.4, 21.3, 21.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_3^+$ 396.1570; Found 396.1578.

IR (ν_{max}, cm^{-1}) 3381 (w), 2947 (m), 2365 (w), 1525 (s), 1345 (m), 1047 (m), 814 (m), 757 (s).



4.5.9c, (*E*)-4-(4-methoxyphenyl)-4-(2-nitrophenyl)-3-(p-tolyl)but-3-en-1-ol

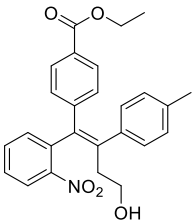
This compound was prepared following the general procedure **N** using substrate **4.5.7c** (1.4 g, 2.4 mmol) as starting material. Yield: 34% over 2 steps (312 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 78:22), R_f = 0.27 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.49 – 7.44 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 2H), 3.67 (s, 3H), 3.48 (sext, *J* = 6.5 Hz, 2H), 2.59 (t, *J* = 6.7 Hz, 2H), 2.29 (s, 3H), 1.25 (br s, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.1, 148.8, 138.3, 137.9, 136.8, 136.6, 136.2, 133.2, 132.8, 132.6, 131.9, 129.4, 129.1, 128.2, 125.0, 113.0, 60.8, 55.2, 39.4, 21.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{24}H_{23}NNaO_4^+$ 412.1519; Found 412.1518.

IR (ν_{max}, cm^{-1}) 3402 (w), 2922 (m), 1604 (m), 1525 (s), 1507 (s), 1349 (m), 1288 (m), 1245 (s), 1173 (m), 1037 (s), 828 (m), 754 (s).



4.5.9d, ethyl (*E*)-4-(4-hydroxy-1-(2-nitrophenyl)-2-(p-tolyl)but-1-en-1-yl)benzoate

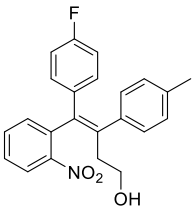
This compound was prepared following the general procedure **N** using substrate **4.5.7d** (1.0 g, 1.6 mmol) as starting material. Yield: 22% over 2 steps (145 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 78:22), R_f = 0.20 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.73 – 7.64 (m, 3H), 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 7.03 – 6.96 (m, 4H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.57 – 3.43 (m, 2H), 2.68 – 2.55 (m, 2H), 2.29 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.28 – 1.21 (m, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.5, 148.8, 144.9, 139.6, 137.3, 137.23, 137.16, 135.8, 133.4, 133.0, 130.7, 129.3, 128.9, 128.6, 128.4, 125.1, 61.0, 60.6, 39.4, 21.3, 14.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{26}H_{25}NNaO_5^+$ 454.1625; Found 454.1625.

IR (ν_{max}, cm^{-1}) 3454 (w), 2964 (m), 2870 (m), 2365 (w), 1716 (s), 1604 (m), 1528 (s), 1348 (m), 1276 (s), 1107 (m), 1020 (m), 854 (m), 743 (m).



4.5.9e, (*E*)-4-(4-fluorophenyl)-4-(2-nitrophenyl)-3-(p-tolyl)but-3-en-1-ol

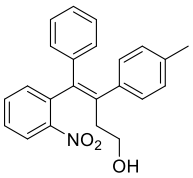
This compound was prepared following the general procedure **N** using substrate **4.5.7e** (1.4 g, 2.4 mmol) as starting material. Yield: 45% 2 steps (400 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.25 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 2H), 6.93 – 6.85 (m, 2H), 6.76 – 6.65 (m, 2H), 3.56 – 3.40 (m, 2H), 2.67 – 2.53 (m, 2H), 2.29 (s, 3H), 1.26 (t, *J* = 7.1 Hz, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.36 (d, *J* = 246.7 Hz), 148.8, 138.2, 137.7, 137.4, 136.9, 136.11 (d, *J* = 3.6 Hz), 135.5, 133.4, 132.8, 132.31 (d, *J* = 8.0 Hz), 129.3, 129.2, 128.4, 125.1, 114.62 (d, *J* = 21.3 Hz), 60.7, 39.3, 21.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}NFO_3^+$ 378.1500; Found 378.14995.

IR (ν_{max}, cm^{-1}) 3404 8w), 2928 (m), 2354 (w), 2257 (w), 1604 (m), 1525 (m), 1507 (m), 1352 (m), 1233 (m), 1160 (m), 1046 (m), 904 (s), 732 (s).



4.5.9f, (*E*)-4-(2-nitrophenyl)-4-phenyl-3-(p-tolyl)but-3-en-1-ol

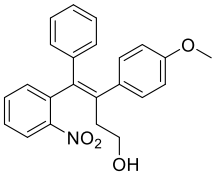
This compound was prepared following the general procedure **N** using substrate **4.5.7f** (570 mg, 1.0 mmol) as starting material. Yield: 33% over 2 steps (120 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 75:25), R_f = 0.25 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 7.04 – 6.97 (m, 5H), 6.97 – 6.89 (m, 2H), 3.57 – 3.40 (m, 2H), 2.68 – 2.55 (m, 2H), 2.28 (s, 3H), 1.26 (br s, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 140.1, 138.0, 137.9, 137.6, 136.7, 136.6, 133.3, 132.9, 130.7, 129.3, 129.1, 128.3, 127.6, 126.6, 125.0, 60.8, 39.3, 21.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1414.

IR (ν_{max}, cm^{-1}) 3393 (w), 3061 (w), 2920 (w), 2866 (w), 2358 (w), 2332 (w), 1608 (w), 1521 (s), 1442 (m), 1352 (s), 1031 (m), 757 (s).



4.5.9g, (*E*)-3-(4-methoxyphenyl)-4-(2-nitrophenyl)-4-phenylbut-3-en-1-ol

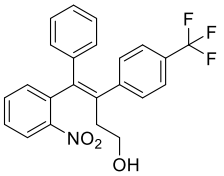
This compound was prepared following the general procedure **N** using substrate **4.5.7g** (1.2 g, 2.1 mmol) as starting material. Yield: 24% over 2 steps (150 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.18 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.04 – 6.98 (m, 3H), 6.98 – 6.89 (m, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H), 3.56 – 3.40 (m, 2H), 2.67 – 2.56 (m, 2H), 1.26 (br s, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.6, 148.8, 140.2, 138.1, 137.5, 136.4, 133.3, 132.9, 130.74, 130.66, 128.3, 127.7, 126.6, 125.0, 113.8, 60.8, 55.3, 39.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_4^+$ 398.1363; Found 398.1377.

IR (ν_{max}, cm^{-1}) 3402 (w), 3030 (w), 2934 (w), 2846 (w), 2358 (w), 2322 (w), 1604 (m), 1525 (s), 1507 (s), 1349 (m), 1284 (m), 1248 (s), 1176 (m), 1033 (m), 832 (m), 756 (s).



4.5.9h, (*E*)-4-(2-nitrophenyl)-4-phenyl-3-(4-(trifluoromethyl)phenyl)but-3-en-1-ol

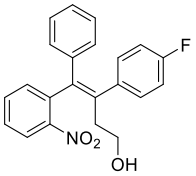
This compound was prepared following the general procedure **N** using substrate **4.5.7h** (830 g, 1.3 mmol) as starting material. Yield: 63% (200 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.25 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.68 (td, *J* = 7.5, 1.3 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.06 – 6.98 (m, 3H), 6.95 – 6.88 (m, 2H), 3.57 – 3.40 (m, 2H), 2.72 – 2.57 (m, 2H), 1.28 – 1.23 (m, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 144.8, 139.3, 138.5, 137.3, 136.7, 133.4, 132.6, 130.6, 129.9, 128.7, 127.9, 127.2, 125.27 (q, *J* = 4.0 Hz), 125.1, 60.3, 39.1, 22.63 (d, *J* = 28.2 Hz).

HRMS $[M + Na]^+$ Calcd for $C_{23}H_{18}NF_3NaO_3^+$ 436.1131; Found 436.1139.

IR (ν_{max}, cm^{-1}) 3428 (w), 3058 (w), 2929 (w), 2358 (w), 1611 (w), 1521 (s), 1352 (m), 1324 (s), 1166 (m), 1123 (s), 1062 (m), 1019 (m), 846 (m), 753 (m), 706 (m).



4.5.9i, (*E*)-3-(4-fluorophenyl)-4-(2-nitrophenyl)-4-phenylbut-3-en-1-ol

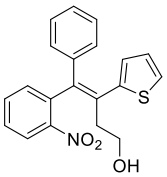
This compound was prepared following the general procedure **N** using substrate **4.5.7i** (1.4 g, 2.4 mmol) as starting material. Yield: 44% over 2 steps (380 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.10 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.20 – 7.10 (m, 2H), 7.05 – 6.98 (m, 3H), 6.96 – 6.81 (m, 4H), 3.56 – 3.39 (m, 2H), 2.69 – 2.52 (m, 2H), 0.91 (td, *J* = 7.4, 1.2 Hz, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.77 (d, *J* = 246.3 Hz), 148.6, 139.8, 137.6, 137.3, 136.9, 136.59 (d, *J* = 3.4 Hz), 133.3, 132.7, 131.10 (d, *J* = 7.9 Hz), 130.6, 128.4, 127.7, 126.8, 125.0, 115.26 (d, *J* = 21.3 Hz), 60.4, 39.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}FNNaO_3^+$ 386.1163; Found 386.1165.

IR (ν_{max}, cm^{-1}) 3407 (w), 2927 (w), 2848 (w), 2351 (w), 2250 (w), 1604 (w), 1525 (s), 1507 (s), 1352 (m), 1222 (m), 1160 (m), 1045 (m), 908 (s), 843 (m), 735 (s).



4.5.9j, (*E*)-4-(2-nitrophenyl)-4-phenyl-3-(thiophen-2-yl)but-3-en-1-ol

This compound was prepared following the general procedure **N** using substrate **4.5.7j** (1.0 g, 1.8 mmol) as starting material. Yield: 82% (514 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.1 and 0.16 (PE/EtOAc 80:20).

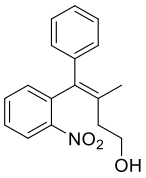
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.6, 7.4, 1.5 Hz, 1H), 7.17 – 7.07 (m, 6H), 6.88 – 6.80 (m, 2H), 3.72 – 3.61 (m, 2H), 2.74-2.61 (m, 2H).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.45 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 – 7.28 (m, 7H), 7.14 (dd, *J* = 5.0, 1.2 Hz, 1H), 6.83 – 6.74 (m, 2H), 3.75 – 3.57 (q, *J* = 7.1 Hz, 2H), 3.65 (br s, OH), 3.00 – 2.86 (m, 1H), 2.83 – 2.72 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5, 142.71, 140.1, 138.4, 137.6, 133.4, 132.6, 130.7, 130.4, 128.5, 128.1, 127.9, 127.4, 126.8, 125.9, 125.1, 61.1, 40.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{17}NNaO_3S^+$ 374.0821; Found 374.0814.

IR (ν_{max}, cm^{-1}) 1604 (w), 1523 (s), 1491 (w), 1442 (w), 1346 (m), 1311 (w), 1294 (w), 1275 (w), 1240 (w), 1080 (w), 1032 (m), 1012 (w), 1001 (w), 908 (w), 852 (m), 833 (w).



4.5.9k, (*Z*)-3-methyl-4-(2-nitrophenyl)-4-phenylbut-3-en-1-ol

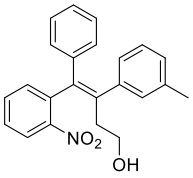
This compound was prepared following the general procedure **N** using substrate **4.5.7k** (850 mg, 1.7 mmol) as starting material. Yield: 31% over 2 steps (150 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.2 (PE/EtOAc 75:25).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.60 (td, *J* = 7.5, 1.3 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.30 – 7.22 (m, 2H), 7.22 – 7.11 (m, 3H), 3.84 – 3.74 (m, 1H), 3.74 – 3.64 (m, 1H), 2.55 – 2.44 (m, 1H), 2.31 – 2.21 (m, 1H), 1.90 (s, 3H), 1.78 – 1.66 (m, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.0, 139.9, 137.6, 135.5, 133.3, 133.0, 132.8, 129.9, 128.1, 128.0, 127.1, 124.8, 60.6, 39.3, 19.4.

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_3^+$ 306.1101; Found 306.1105.

IR (ν_{max}, cm^{-1}) 3374 (w), 2914 (w), 1521 (s), 1345 (m), 1047 (m), 850 (m), 764 (m), 749 (m).



4.5.9l, (*E*)-4-(2-nitrophenyl)-4-phenyl-3-(m-tolyl)but-3-en-1-ol

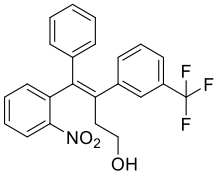
This compound was prepared following the general procedure **N** using substrate **4.5.7l** (1.4 g, 2.5 mmol) as starting material. Yield: 35% (310 mg), isolated as orange solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.27 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.66 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 7.04 – 6.81 (m, 8H), 3.55 – 3.42 (m, 2H), 2.68 – 2.57 (m, 2H), 2.24 (s, 3H), 1.28 – 1.23 (t, *J* = 7.1 Hz, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.8, 140.6, 140.0, 138.1, 137.90, 137.87, 136.8, 133.3, 132.8, 130.6, 130.0, 128.3, 128.2, 127.9, 127.6, 126.7, 125.0, 60.8, 39.4, 21.5.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1413.

IR (ν_{max}, cm^{-1}) 3382 (w), 3021 (w), 2920 (w), 2344 (w), 1604 (w), 1525 (s), 1442 (w), 1348 (s), 1031 (m), 793 (m), 753 (s).



4.5.9m, (*E*)-4-(2-nitrophenyl)-4-phenyl-3-(3-(trifluoromethyl)phenyl)but-3-en-1-ol

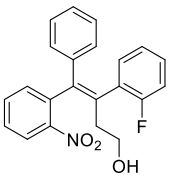
This compound was prepared following the general procedure **N** using substrate **4.5.7m** (1.4 g, 2.3 mmol) as starting material. Yield: 55% (500 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.13 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.45 – 7.27 (m, 4H), 7.06 – 6.98 (m, 3H), 6.96 – 6.86 (m, 2H), 3.61 – 3.49 (m, 2H), 2.72 – 2.61 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 141.7, 139.3, 138.6, 137.3, 136.5, 133.5, 133.1, 132.6, 130.6, 128.69 (d, *J* = 11.2 Hz), 127.9, 127.1, 126.30 (d, *J* = 4.1 Hz), 125.1, 123.81 (d, *J* = 4.0 Hz), 60.4, 38.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}NF_3O_3^+$ 414.1312; Found 414.1316.

IR (ν_{max}, cm^{-1}) 3394 (w), 3038 (w), 2955 (w), 2886 (w), 2359 (m), 1605 (w), 1524 (s), 1338 (s), 1168 (s), 1124 (s), 1073 (m), 1030 (m), 765 (m).



4.5.9n, (*E*)-3-(2-fluorophenyl)-4-(2-nitrophenyl)-4-phenylbut-3-en-1-ol

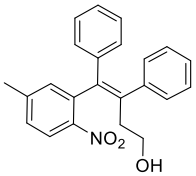
This compound was prepared following the general procedure **N** using substrate **4.5.7n** (1.2 g, 2.1 mmol) as starting material. Yield: 21% over 2 steps (150 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.33 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.67 (td, *J* = 7.4, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.21 – 7.13 (m, 2H), 7.05 – 6.89 (m, 7H), 3.61 – 3.40 (m, 2H), 2.74 – 2.51 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.14 (d, *J* = 244.5 Hz), 148.5, 139.8, 139.6, 137.0, 133.4, 132.8, 131.65 (d, *J* = 4.0 Hz), 129.7, 129.12 (d, *J* = 8.1 Hz), 128.5, 128.14 (d, *J* = 16.3 Hz), 127.7, 127.0, 125.0, 124.14 (d, *J* = 3.4 Hz), 115.51 (d, *J* = 22.3 Hz), 60.3, 38.69 (d, *J* = 1.6 Hz).

HRMS HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}FNNaO_3^+$ 386.1163; Found 386.1172.

IR (ν_{max}, cm^{-1}) 3362 (w), 2958 (w), 2893 (w), 2363 (m), 1527 (s), 1487 (m), 1444 (m), 1349 (m), 1215 (m), 1048 (m), 758 (s).



4.5.9o, (*E*)-4-(5-methyl-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

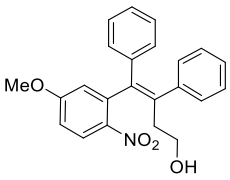
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 4,4,5,5-tetramethyl-2-(5-methyl-2-nitrophenyl)-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 50% over 2 steps (260 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1->90:10), R_f = 0.12 (PE/EtOAc 85:15).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.30 (brs, 1H), 7.27 – 7.12 (m, 6H), 7.03 – 6.92 (m, 5H), 3.53 – 3.43 (m, 2H), 2.67-2.56 (m, 2H), 2.47 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 146.4, 144.6, 140.9, 140.0, 137.9, 137.4, 137.3, 133.1, 130.6, 129.5, 129.0, 128.3, 127.6, 127.0, 126.6, 125.2, 60.7, 39.4, 21.7.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculated for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1417.

IR (ν_{max}, cm^{-1}) 3235 (w), 2959 (w), 2922 (w), 2156 (w), 1599 (w), 1582 (m), 1518 (s), 1510 (s), 1491 (m), 1442 (m), 1340 (s), 1055 (m), 1043 (m), 1029 (m), 1017 (m), 827 (m).



4.5.9p, (*E*)-4-(5-methoxy-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

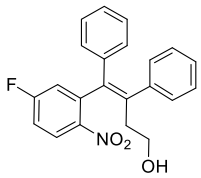
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 2-(5-methoxy-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 50% over 2 steps (274 mg), isolated as grey solid. Purification: Flash chromatography (PE/EtOAc, 99:1->85:15), R_f = 0.21 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 9.1 Hz, 1H), 7.23 – 7.14 (m, 5H), 7.05 – 6.89 (m, 7H), 3.93 (s, 3H), 3.55 – 3.45 (m, 2H), 2.70-2.59 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 141.6, 140.7, 140.6, 139.65, 137.6, 137.1, 130.6, 129.5, 128.3, 127.8, 127.6, 127.0, 126.7, 117.7, 113.17, 60.6, 56.1, 39.4.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculate d for $C_{23}H_{21}NNaO_4^+$ 398.1363; Found 398.1355.

IR (ν_{max}, cm^{-1}) 2154 (w), 1512 (s), 1334 (s), 1228 (s), 1028 (s).



4.5.9q, (*E*)-4-(5-fluoro-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

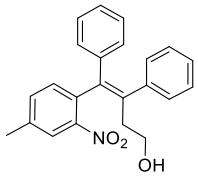
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 2-(5-fluoro-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 52% over 2 steps (280 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1->85:15), R_f = 0.27 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* = 9.0, 5.1 Hz, 1H), 7.29 (dd, *J* = 8.6, 2.8 Hz, 1H), 7.24 – 7.12 (m, 6H), 7.04 – 7.00 (m, 3H), 6.96 – 6.91 (m, 2H), 3.56 – 3.44 (m, 2H), 2.70 – 2.57 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.7 (d, *J* = 257.9 Hz), 144.9 (d, *J* = 3.0 Hz), 141.1 (d, *J* = 9.1 Hz), 140.3, 139.4, 138.4, 136.2, 130.6, 129.4, 128.4, 127.8 (d, *J* = 10.0 Hz), 127.8, 127.2, 127.0, 119.8 (d, *J* = 23.0 Hz), 115.4 d, *J* = 23.2 Hz), 60.4, 39.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}FNNaO_3^+$ 386.1163; Found 386.1168**.**

IR (ν_{max}, cm^{-1}) 1616 (w), 1579 (m), 1523 (s), 1493 (w), 1473 (w), 1442 (w), 1344 (m), 1304 (w), 1271 (m), 1209 (w), 1072 (w), 1045 (m), 1030 (m), 1014 (w), 908 (m), 868 (w), 835 (w).



4.5.9r, (*E*)-4-(4-methyl-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

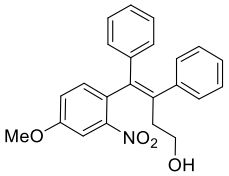
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 24,4,5,5-tetramethyl-2-(4-methyl-2-nitrophenyl)-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 68% over 2 steps (360 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.19 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (brs, 1H), 7.48 – 7.41 (m, 2H), 7.22 – 7.13 (m, 5H), 7.02 – 6.91 (m, 5H), 3.55 – 3.44 (m, 2H), 2.69 – 2.58 (m, 2H), 2.46 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.6, 140.9, 140.1, 138.9, 137.1, 137.0, 134.9, 134.1, 132.5, 130.6, 129.5, 128.3, 127.6, 127.0, 126.6, 125.3, 60.7, 39.4, 21.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculated for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1410.

IR (ν_{max}, cm^{-1}) 2958 (w), 2925 (w), 2360 (s), 2337 (m), 2312 (w), 1525 (s), 1491 (m), 1350 (m), 1047 (m), 1030 (m).



4.5.9s, (*E*)-4-(4-methoxy-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

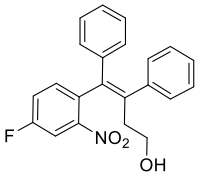
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 2-(4-methoxy-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 48% over 2 steps (260 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 98:2->80:20), R_f = 0.06 (PE/EtOAc 85:15).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 9.1 Hz, 1H), 7.23 – 7.12 (m, 5H), 7.05 – 6.89 (m, 7H), 3.93 (s, 3H), 3.55– 3.44 (m, 2H), 2.70-2.59 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 163.3, 141.6, 140.8, 140.6, 139.6, 137.6, 137.1, 130.6, 129.54, 128.31, 127.82, 127.56, 127.03, 126.7, 117.70, 113.2, 60.6, 56.1, 39.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calculated for $C_{23}H_{21}NNaO_4^+$ 398.1363; Found 398.1349.

IR (ν_{max}, cm^{-1}) 2960 (w), 2362 (m), 2339 (w), 1603 (m), 1442 (m), 1334 (s), 1288 (m), 1275 (m), 1248 (m), 1225 (m), 1097 (m), 1070 (m), 1047 (m), 1028 (s), 833 (m).



4.5.9t, (*E*)-4-(4-fluoro-2-nitrophenyl)-3,4-diphenylbut-3-en-1-ol

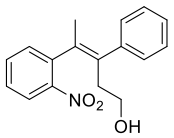
This compound was prepared following the general procedure **N** using substrate **4.5.7a** (0.6 g, 1.1 mmol) as starting material and 2-(4-fluoro-2-nitrophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as the nitrophenyl boronic ester. Yield: 36% over 2 steps (190 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1->85:15), R_f = 0.27 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.59 (dd, *J* = 8.5, 5.6 Hz, 1H), 7.40 (td, J = 8.1, 2.7 Hz, 1H), 7.23-7.13 (m, 5H), 7.03-6.97 (m, 3H), 6.93-6.88 (m, 2H), 3.55 – 3.44 (m, 2H), 2.68-2.56 (m, 2H), 2.68-2.56 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.0 (d, *J* = 251.7 Hz), 149.0 (d, *J* = 9.0 Hz), 140.4, 139.6, 138.5, 135.9, 134.4 (d, *J* = 7.5 Hz), 133.8 (d, *J* = 4.0 Hz) 130.5, 129.3, 128.2, 127.6, 127.1, 126.7, 120.5 (d, *J* = 20.8 Hz), 112.4 (d, *J* = 26.4 Hz), 60.3, 39.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{22}H_{18}FNNaO_3^+$ 386.1163; Found 386.1161.

IR (ν_{max}, cm^{-1}) 2962 (w), 1533 (s), 1493 (m), 1442 (w), 1348 (m), 1263 (m), 1211 (m), 1045 (m), 1030 (m), 1012 (w), 908 (m), 876 (w), 841 (w), 806 (m).



4.5.9z, (*E*)-4-(2-nitrophenyl)-3-phenylpent-3-en-1-ol.

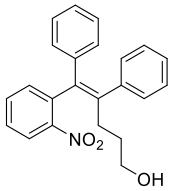
This compound was prepared following the general procedure **N** using substrate **4.5.22** (400 mg, 0.75 mmol) as starting material. Yield: 49% over 2 steps (100 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.4 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.65 (td, *J* = 7.5, 1.3 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.44 – 7.35 (m, 3H), 7.34 – 7.20 (m, 3H), 3.34 (t, *J* = 6.5 Hz, 2H), 2.44 – 2.27 (m, 2H), 1.86 (s, 3H), 1.26 (t, *J* = 7.1 Hz, OH).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.3, 140.8, 139.2, 135.0, 133.6, 133.0, 131.4, 128.7, 128.6, 128.0, 127.1, 124.9, 60.4, 38.7, 22.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{17}NNaO_3^+$ 306.1101; Found 306.1108.

IR (ν_{max}, cm^{-1}) 3374 (w), 2954 (w), 2857 (w), 1521 (s), 1439 (m), 1349 (s), 1037 (s), 858 (m), 754 (s), 703 (s).



4.5.9ai, (*E*)-5-(2-nitrophenyl)-4,5-diphenylpent-4-en-1-ol

This compound was prepared following the general procedure **N** using substrate **4.5.7ai** (1.2 g, 2.1 mmol) as starting material. Yield: 26% over 2 steps (200 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.32 (DCM).

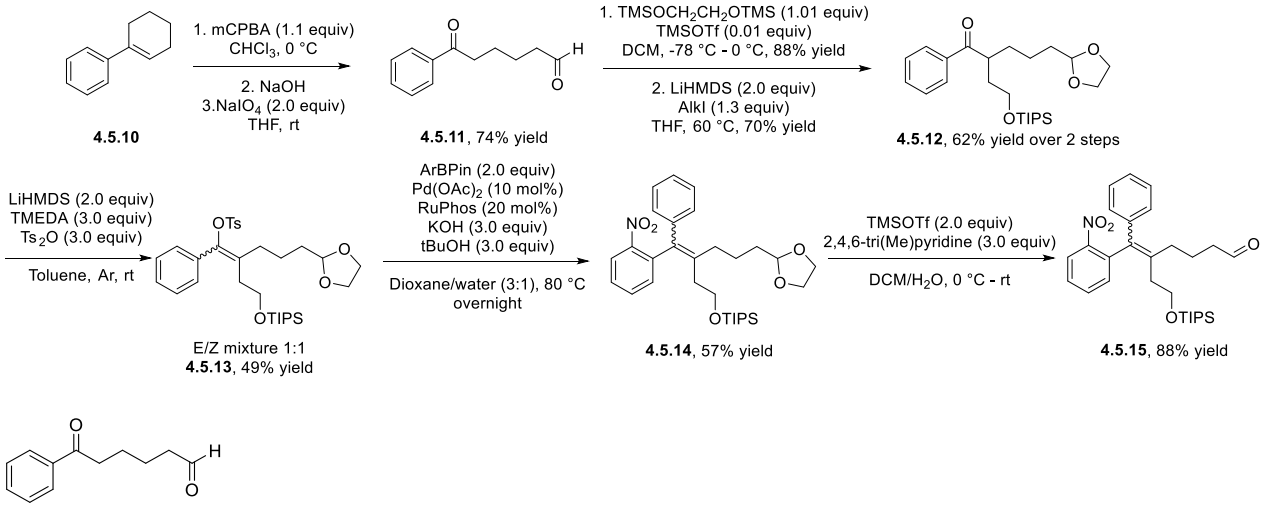
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.63 (td, *J* = 7.5, 1.3 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.23 – 7.09 (m, 5H), 7.05 – 6.92 (m, 5H), 3.54 – 3.39 (m, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.52 – 1.35 (m, 2H), 1.26 (br s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 141.1, 141.0, 140.3, 138.0, 134.7, 133.2, 132.5, 130.8, 129.5, 128.3, 128.2, 127.6, 126.9, 126.6, 124.8, 62.8, 32.6, 31.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{23}H_{21}NNaO_3^+$ 382.1414; Found 382.1414.

IR (ν_{max}, cm^{-1}) 3367 (w), 2954 (w), 2882 (w), 1525 (s), 1442 (m), 1345 (m), 1072 (m), 764 (m), 699 (s).

6.4.5. **Synthesis of alcohols 4.5.9u-y**

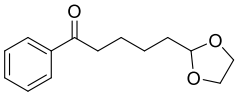


4.5.11, 6-oxo-6-phenylhexanal

6-Oxo-6-phenylhexanal **4.5.11** was prepared according to literature method:[299] To a stirred solution of m-CPBA (8.5 g, 34.8 mmol, 1.1 equiv) in $CHCl_3$ (150 mL) was added dropwise 1-phenyl-cyclohexene **4.5.10** (5.0 g, 31.6 mmol, 1.0 equiv) at 0 ºC. The mixture was stirred at room temperature for 4 h before 10 % NaOH aq. (85 mL) was added at 0 ºC. The organic layer was separated and washed sequentially with saturated $NaHSO_3$ and brine. Then the solvent was removed, and the residue was dissolved in THF (5.6 mL). The resulting mixture was added dropwise to a solution of sodium periodate (13.5 g, 63 mmol, 2.0 equiv) in THF/H_2O (v/v 2:1, 84 mL). Upon reaction completion after 3 h, the white precipitate was filtered away. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by flash chromatography (PE/EtOAc, 9:1), R_f = 0.32, to yield 6-oxo-6-phenylhexanal **4.5.11** as a white solid (4.4 g, 74 %).

Known compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (t, J = 1.6 Hz, 1H), 7.99 – 7.90 (m, 2H), 7.59 – 7.52 (m, 1H), 7.46 (dd, J = 8.2, 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 2.50 (td, J = 7.1, 1.6 Hz, 2H), 1.87 – 1.64 (m, 4H).



4.5.11a, 5-(1,3-dioxolan-2-yl)-1-phenylpentan-1-one

To a stirred solution of **4.5.11** (10 g, 53 mmol, 1.0 equiv) was added 1,2-bis(trimethylsiloxy)ethane (13 mL, 53 mmol, 1.01 equiv) in dry DCM (250 mL) at room temperature. The solution was cooled to -78℃ and TMSOTf (0.14 mL, 5 mmol, 0.01 equiv) was added. The resulting mixture was stirred for 15 minutes at -78℃ and then slowly warmed to 0℃. The reaction was quenched with pyridine (50 mL) and diluted with

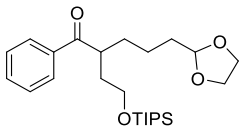
[299] Wang, Y.; Du, H. *J. Org. Chem.* **2010**, *75*, 3503-3506

DCM. The mixture was washed with water and brine and the organic layer dried and concentrated under reduced pressure. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.25 (PE/EtOAc 80:20). Yield: 88% (13 g), isolated as white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.91 (m, 2H), 7.60 – 7.50 (m, 1H), 7.50 – 7.40 (m, 2H), 4.87 (t, *J* = 4.7 Hz, 1H), 4.00 – 3.91 (m, 2H), 3.91 – 3.81 (m, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 1.85 – 1.68 (m, 4H), 1.56 – 1.46 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.4, 137.2, 133.1, 128.7, 128.2, 104.5, 65.0, 38.6, 33.8, 24.3, 23.9.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{18}NaO_3^+$ 257.1148; Found 257.1141.



4.5.12, 5-(1,3-dioxolan-2-yl)-1-phenyl-2-(2-((triisopropylsilyl)oxy)ethyl)pentan-1-one

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 500 mL pressure resistant round bottomed flask under argon was charged ketone **4.5.11a** (13 g, 68 mmol, 1.0 equiv) in THF (360 mL, 0.2 M), LiHMDS (1.0 M in THF, 111 mL, 136 mmol, 2.0 equiv) was added to the reaction mixture, followed by addition of alkyl iodide (31 g, 96 mmol, 1.4 equiv). The reaction mixture was heated at 65 °C in the oil bath for 2-3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the desired ketone **4.5.12**.

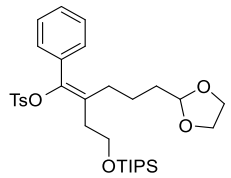
Yield: 41% (12 g), isolated as white solid (mp = °C). Purification: Flash chromatography (PE/EtOAc, 92:8), R_f = 0.37 (PE/EtOAc 85:15).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 7.97 (m, 2H), 7.57 – 7.50 (m, 1H), 7.47 – 7.40 (m, 2H), 4.79 (t, *J* = 4.8 Hz, 1H), 3.97 – 3.56 (m, 5H), 2.09 – 1.98 (m, 1H), 1.90 – 1.75 (m, 1H), 1.75 – 1.47 (m, 6H), 1.47 – 1.34 (m, 2H), 1.08 – 0.94 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 204.5, 137.6, 133.0, 128.7, 128.6, 104.5, 65.0, 61.1, 42.4, 35.7, 34.1, 32.2, 22.3, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{48}NaO_6SSi^+$ 611.2833; Found 611.2851.

IR (ν_{max}, cm^{-1}) 2944 (m), 2868 (m), 1676 (m), 1466 (m), 1364 (m), 1240 (m), 1102 (s), 1000 (s), 884 (s).



4.5.13, (*Z*)-5-(1,3-dioxolan-2-yl)-1-phenyl-2-(2-((triisopropylsilyl)oxy)ethyl)pent-1-en-1-yl 4-methylbenzenesulfonate

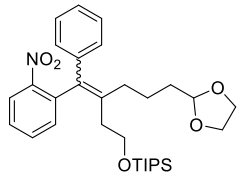
Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 500 mL pressure resistant round bottomed flask under argon was charged LiHMDS (1.0 M in toluene, 12.6 mL, 12.6 mmol, 2.0 equiv), TMEDA (2.0 mL, 18.9 mmol, 3.0 equiv) was added dropwise to the reaction mixture. The reaction mixture was placed in a water bath and a solution of ketone **4.5.12** (2.7 g, 6.3 mmol, 1.0 equiv) was added via syringe. After stirring for 20 min, Ts_2O (6.2 g, 19 mmol, 3.0 equiv) was added over 5 min. The reaction mixture was stirred for 2-3 h. After completion of the reaction, water was added to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the desired enol tosylate **4.5.13**.

Yield: 59% (2.2 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.39 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.37 (m, 2 + 1.6H), 7.22 – 7.09 (m, 5 + 4H), 7.07 – 7.02 (m, 2 + 1.6H), 4.88 (t, *J* = 4.6 Hz, 1H), 4.75 (t, *J* = 4.3 Hz, 0.8H), 4.04 – 3.73 (m, 9.2H), 3.70 (t, *J* = 7.0 Hz, 2H), 2.55 (t, *J* = 6.7 Hz, 1.6H), 2.40 – 2.28 (m, 10.2H), 2.17 – 2.10 (m, 1.6H), 1.74 – 1.57 (m, 6.0H), 1.10 – 1.05 (m, 16.8H), 1.02 - 0.96 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 144.2, 143.7, 143.2, 134.7, 134.66, 133.9, 133.8, 131.6, 130.7, 130.0, 129.8, 129.3, 128.3, 128.2, 127.94, 127.89, 127.87, 127.6, 104.6, 104.3, 64.99, 64.96, 62.2, 61.9, 33.8, 33.7, 33.5, 32.6., 31.2, 29.8, 29.5, 22.8, 22.2, 21.7, 18.2, 18.1, 12.1, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{32}H_{48}NaO_6SSi^+$ 611.2833; Found 611.2851.

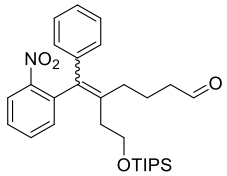


4.5.14, ((6-(1,3-dioxolan-2-yl)-3-((2-nitrophenyl)(phenyl)methylene)hexyl)oxy)triisopropylsilane
Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Dioxane and water were degassed with Freeze-pump technique. To a solution of enol tosylate **4.5.13** (790 mg, 1.3 mmol, 1.0 equiv) in dioxane/water (22 mL, 3:1, 0.06 M) were added 2-nitrophenyl boronic acid pinacol ester (670 mg, 2.6 mmol, 2.0 equiv), $Pd(OAc)_2$ (30 mg, 0.13 mmol, 10 mol%), RuPhos (125 mg, 0.27 mmol, 20 mol%), KOH (230 mg, 4.0 mmol, 3.0 equiv) and *t*-BuOH (0.38 mL, 4.0 mmol, 3.0 equiv). The reaction mixture was heated at 80 °C overnight, then water was added, followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and

dried over sodium sulfate. The residue was subjected to silica gel column chromatography to afford the desired alkene **4.5.14**.
Yield: 59% (430 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.19 (PE/EtOAc 90:10).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.84 (m, 1 + 0.8H), 7.59 – 7.49 (m, 1 + 0.8H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.39 – 7.31 (m, 1 + 1.6H), 7.29 – 7.13 (m, 4 + 4H), 4.7 – 4.70 (m, 1 + 0.8H), 4.03 – 3.60 (m, 10.8H), 2.54 – 2.43 (m, 2 + 0.8H), 2.38 – 2.21 (m, 1 + 1.6H), 2.14 – 1.95 (m, 2 + 0.8H), 1.64 – 1.43 (m, 4.4H), 1.02 – 0.95 (m, 21 + 16.8H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 140.6, 140.5, 137.9, 135.1, 135.0, 132.9, 132.8, 132.5, 130.0, 129.8, 129.7, 128.3, 128.2, 127.8, 127.7, 127.01, 126.97, 124.6, 124.5, 104.5, 104.4, 65.0, 64.9, 61.9, 61.7, 35.9, 34.8, 33.7, 33.5, 33.2, 31.7, 29.9, 22.7, 22.5, 18.14, 18.12, 17.9, 12.1, 11.8.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{45}NNaO_5Si^+$ 562.2959; Found 562.2965.



4.5.15, 5-((2-nitrophenyl)(phenyl)methylene)-7-((triisopropylsilyl)oxy)heptanal

To a solution of dioxolane **4.5.14** (2.21 g, 2.77 mmol) in CH_2Cl_2 (50 mL) were added 2,4,6-trimethylpyridine (1.10 mL, 8.31 mmol) and TMSOTf (1.00 mL, 5.54 mmol) at 0 °C. After stirring for 1 h at this temperature, water (50 mL) was added and stirring continued for 2 h at ambient temperature. The layers were separated and the aqueous phase was extracted with EtOAc. The combined extracts were dried over Na_2SO_4, filtered and concentrated. The residue was subjected to silica gel column chromatography to afford the desired aldehyde **4.5.15**.

Yield: 88% (1.5 g), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.19 (PE/EtOAc 90:10).

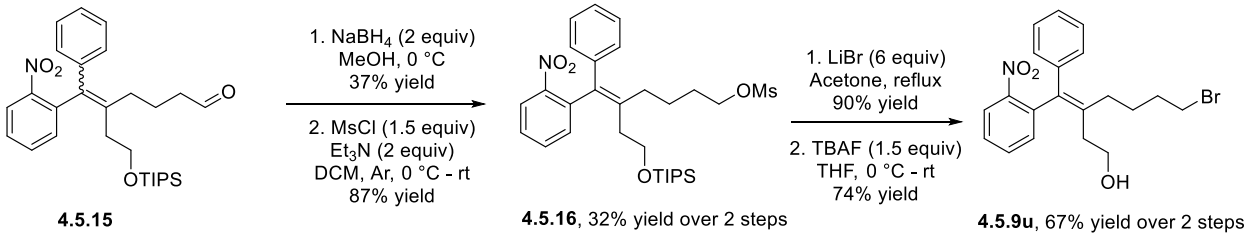
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (t, *J* = 1.6 Hz, 1H), 7.87 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.54 (td, *J* = 7.5, 1.3 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.30 – 7.26 (m, 2H), 7.23 – 7.18 (m, 3H), 3.75 – 3.59 (m, 2H), 2.42 – 2.14 (m, 6H), 1.87 – 1.69 (m, 2H), 1.03 – 0.93 (m, 21H).

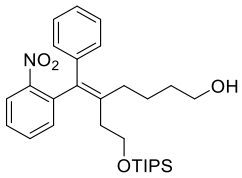
^{13}C NMR (101 MHz, $CDCl_3$): δ 202.5, 148.8, 140.5, 137.6, 137.3, 135.7, 132.9, 132.7, 129.6, 128.4, 127.9, 127.2, 124.6, 93.0, 61.7, 43.3, 35.8, 31.0, 20.6, 18.1, 12.0.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.65 (d, *J* = 1.7 Hz, 1H), 7.88 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.56 (td, *J* = 7.6, 1.3 Hz, 1H), 7.39 (td, *J* = 7.8, 1.4 Hz, 1H), 7.34 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.29 – 7.22 (m, 4H), 7.19 (tt, *J* = 5.6, 2.5 Hz, 1H), 3.76 – 3.63 (m, 2H), 2.59 – 2.25 (m, 4H), 2.16 – 2.00 (m, 2H), 1.76 (p, *J* = 7.5 Hz, 2H), 0.99 (d, *J* = 2.3 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 202.3, 148.8, 140.3, 137.6, 137.2, 135.7, 132.9, 132.4, 129.8, 128.3, 128.0, 127.1, 124.7, 61.9, 43.5, 34.7, 32.7, 20.5, 18.1, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{41}NNaO_4Si^+$ 518.2698; Found 518.2693.





4.5.15a, 5-((2-nitrophenyl)(phenyl)methylene)-7-((triisopropylsilyl)oxy)heptan-1-ol

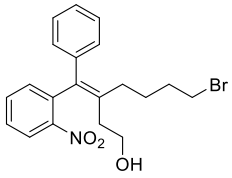
To a solution of aldehyde **4.5.15** (1.2 g, 2.4 mmol, 1.0 equiv) in MeOH (24 mL, 0.1 M) was added sodium borohydride (180 mg, 4.8 mmol, 2 equiv) at 0 °C, and the resulting mixture was stirred for 2 hours. The solvent was removed under reduced pressure, and the resulting residue was transferred to a separatory funnel containing ethyl acetate and water. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with water, and brine. The organic layer was then dried over sodium sulfate, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the desired alcohol **4.5.15a**.

Yield: 37% (450 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.32 (DCM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 1H), 7.57 – 7.50 (m, 1H), 7.42 – 7.31 (m, 2H), 7.30 – 7.10 (m, 5H), 3.79 – 3.61 (m, 2H), 3.52 (t, J = 6.1 Hz, 2H), 2.59 – 2.41 (m, 2H), 2.38 – 2.20 (m, 1H), 2.12 – 1.93 (m, 2H), 1.50 – 1.38 (m, 4H), 0.99 (d, J = 3.7 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 140.6, 138.0, 137.9, 134.9, 132.8, 132.5, 129.8, 128.3, 127.8, 127.0, 124.6, 62.8, 62.0, 34.9, 33.1, 32.7, 24.3, 18.2, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{43}NNaO_4Si^+$ 520.2854; Found 520.2856.



4.5.9u, 7-bromo-3-((2-nitrophenyl)(phenyl)methylene)heptan-1-ol

To a solution of alcohol **4.5.15a** (400 mg, 0.8 mmol, 1.0 equiv) in DCM (8 mL, 0.1 M) were added MsCl (0.1 mL, 1.2 mmol, 1.5 equiv) and triethylamine (0.22 mL, 1.6 mmol, 2.0 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl

acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to a next step without purification.

To a solution of alkene **4.5.16** (200 mg, 0.35 mmol, 1.0 equiv) in acetone (1.1 mL, 0.3 M) was added LiBr (180 mg, 2.1 mmol, 6.0 equiv) at room temperature. The reaction mixture was heated 3 h at 50 °C, then water was added, followed by extraction with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to a next step without purification.

To a solution of alkene **4.5.16a** (270 mg, 0.5 mmol, 1.0 equiv) in THF (5 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.8 mL, 0.8 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9u**.

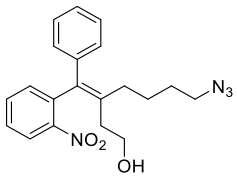
Yield: 74% (93 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.36 and 0.24 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.79 (m, 1 + 0.7H), 7.62 – 7.52 (m, 1 + 0.7H), 7.44 – 7.35 (m, 2 + 0.7H), 7.35 – 7.30 (m, 1.0H), 7.29 – 7.09 (m, 4 + 4.2H), 3.76 – 3.58 (m, 3.5H), 3.31 – 3.21 (m, 3H), 2.65 – 2.55 (m, 1H), 2.52 – 2.14 (m, 4.3H), 2.12 – 1.93 (m, 2H), 1.82– 1.46 (m, 6.6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.7, 140.4, 140.0, 137.6, 137.5, 136.9, 136.83, 136.80, 136.2, 133.2, 133.1, 132.6, 132.3, 129.74, 129.69, 128.5, 128.3, 128.2, 128.1, 127.34, 127.33, 124.9, 124.6, 61.2, 60.8, 35.7, 34.5, 33.6, 33.5, 32.4, 32.2, 31.8, 30.3, 26.6, 26.4.

HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}BrNO_3^+$ 404.0856; Found 404.0858.

IR (ν_{max}, cm^{-1}) 2922 (w), 2849 (w), 2363 (w), 1716 (w), 1357 (w), 1062 (w), 910 (s), 728 (s).



4.5.9v, 7-azido-3-((2-nitrophenyl)(phenyl)methylene)heptan-1-ol

To a solution of alkene **4.5.16** (200 mg, 0.35 mmol, 1.0 equiv) in a mixture DMF/H_2O (8:1, 1.1 mL, 0.3 M) was added NaN_3 (45 mg, 0.7 mmol, 2.0 equiv) at room temperature. The reaction mixture was heated 3 h at 50 °C, then water was added, followed by extraction with EtOAc (3 times). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to a next step without purification.

To a solution of alkene **4.5.16b** (160 mg, 0.3 mmol, 1.0 equiv) in THF (3 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.46 mL, 0.46 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic

layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9v**.

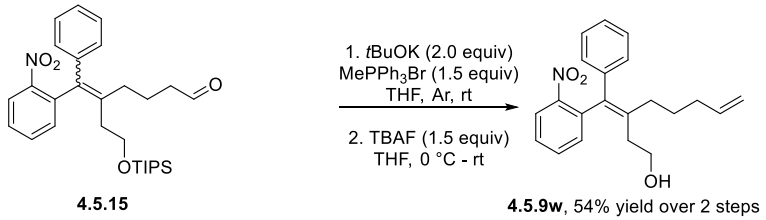
Yield: 89% (100 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.31 and 0.21 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 1 + 0.6H), 7.62 – 7.52 (m, 1 + 0.6H), 7.43 – 7.35 (m, 1 + 1.2H), 7.32 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.29 – 7.13 (m, 9H), 3.77 – 3.46 (m, 2 + 1.2H), 3.19 – 3.08 (m, 2 + 1.2H), 2.59 (dt, *J* = 13.9, 7.0 Hz, 1H), 2.50 - 2.37 (ddt, *J* = 16.1, 13.3, 6.6 Hz, 1.6H), 2.36 – 2.18 (m, 2H), 2.15 – 1.94 (m, 2H), 1.48 (tdd, *J* = 9.3, 5.6, 2.2 Hz, 6.2H).

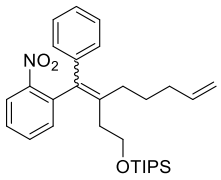
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.8, 140.4, 140.0, 137.6, 137.5, 137.0, 136.83, 136.81, 136.2, 133.14, 133.06, 132.6, 132.3, 129.74, 129.68, 128.5, 128.3, 128.2, 128.1, 127.3, 124.9, 124.6, 61.2, 60.8, 51.2, 51.1, 35.7, 34.5, 32.2, 30.7, 28.7, 28.4, 25.2, 25.1.

HRMS (Sicrit plasma/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_4O_3^+$ 367.1765; Found 367.1764.

IR (ν_{max}, cm^{-1}) 2922 (m), 2849 (w), 2101 (m), 1734 (w), 1523 (w), 1353 (w), 914 (s), 739 (s).



4.5.15 **4.5.9w**, 54% yield over 2 steps



4.5.15b, triisopropyl((3-((2-nitrophenyl)(phenyl)methylene)oct-7-en-1-yl)oxy)silane

To a solution of *t*-BuOK (86 mg, 0.8 mmol, 2.0 equiv) in THF (4 mL, 0.1 M) was added methyltriphenylphosphonium bromide (210 mg, 0.6 mmol, 1.5 equiv) at 0 °C. After 20 min, aldehyde (190 mg, 0.4 mmol, 1.0 equiv) was added and the mixture was stirred at room temperature for 2 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford the desired alkene **4.5.15b**.

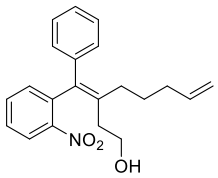
Yield: 57% (110 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.67 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 1 + 0.3H), 7.57 – 7.50 (m, 1 + 0.3H), 7.45 – 7.31 (m, 2 + 0.9H), 7.29 – 7.14 (m, 6.2H), 5.76 – 5.60 (m, 1 + 0.3H), 4.96 – 4.82 (m, 2 + 0.6H), 3.76 – 3.61 (m, 2 +

0.6H), 2.59 – 2.15 (m, 2 + 1.2H), 2.08 – 1.85 (m, 4 + 0.6H), 1.62 – 1.38 (m, 2.6H), 0.99 (d, J = 4.3 Hz, 27.3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.8, 140.65, 14.64, 138.7, 138.5, 138.1, 138.06, 137.9, 137.88, 134.9, 134.8, 132.8, 132.78, 132.5, 132.4, 129.8, 129.7, 128.3, 128.2, 127.8, 127.7, 127.0, 126.9, 124.6, 124.5, 114.8, 114.7, 62.0, 61.8, 36.2, 35.1, 33.8, 33.7, 33.0, 31.6, 27.7, 27.5, 18.2, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{30}H_{43}NNaO_3Si^+$ 516.2904; Found 516.2910.



4.5.9w, 3-((2-nitrophenyl)(phenyl)methylene)oct-7-en-1-ol

To a solution of alkene **4.5.15b** (110 mg, 0.22 mmol, 1.0 equiv) in THF (2.2 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.33 mL, 0.33 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9w**.

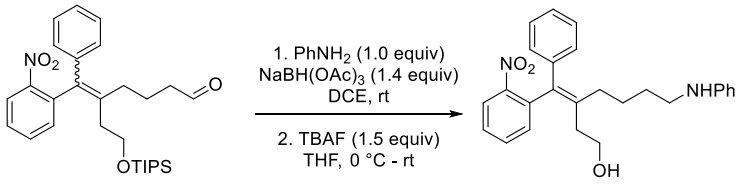
Yield: 94% (73 mg), isolated as orange oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.44 and 0.62 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.84 (m, 1 + 0.4H), 7.64 – 7.50 (m, 1 + 0.4H), 7.44 – 7.36 (m, 2.0H), 7.35 – 7.11 (m, 7.8H), 5.74 – 5.58 (m, 1 + 0.4H), 4.98 – 4.80 (m, 2.8H), 3.85 – 3.55 (m, 2 + 1.2H), 2.68 – 2.56 (m, 1H), 2.55 – 1.82 (m, 8.4H), 1.57 – 1.39 (m, 1 + 0.4H), 1.26 (br s, 1 + 0.4H).

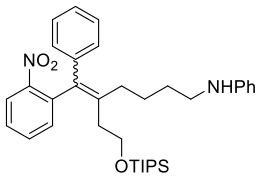
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.8, 140.6, 140.0, 138.4, 138.3, 137.8, 137.7, 137.4, 136.4, 135.9, 133.1, 133.0, 132.7, 132.4, 129.8, 129.7, 128.5, 128.2, 128.1, 127.9, 127.3, 127.2, 124.9, 124.6, 115.0, 114.9, 61.2, 60.8, 35.9, 34.6, 33.6, 33.56, 32.2, 31.0, 27.6, 27.3.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_3^+$ 360.1571; Found 360.1584.

IR (ν_{max}, cm^{-1}) 3396 (w), 3076 (w), 2924 (w), 2866 (w), 2361 (w), 1524 (s), 1348 (m), 1038 (m), 916 (m), 750 (m), 702 (s).



4.5.15 **4.5.9x**, 78% yield over 2 steps



4.5.15c, *N*-(5-((2-nitrophenyl)(phenyl)methylene)-7-((triisopropylsilyl)oxy)heptyl)aniline

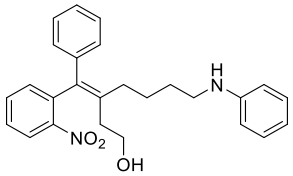
To a solution of aldehyde **4.5.15** (200 mg, 0.4 mmol, 1.0 equiv) and amine (0.04 mL, 0.4 mmol, 1.0 equiv) in DCE (2.0 mL, 0.2 M) was added dropwise $NaBH(OAc)_3$ (120 mg, 0.56 mmol, 1.4 equiv) at 0 °C under inert atmosphere of Ar. After being stirred for 2 h at room temperature, the reaction mixture was quenched with 1.0 M solution NaOH and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography to give the amine **4.5.15c**.

Yield: 87% (200 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.33 and 0.47 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 1 + 0.2H), 7.56 – 7.47 (m, 1 + 0.2H), 7.43 – 7.08 (m, 14.4H), 6.71 – 6.65 (m, 1 + 0.2H), 6.57 – 6.51 (m, 2 + 0.4H), 3.75 – 3.63 (m, 2 + 0.4H), 3.02 – 2.90 (m, 2 + 0.4H), 2.59 – 1.97 (m, 4 + 0.8H), 1.66 – 1.42 (m, 4 + 0.8H), 0.99 (d, *J* = 4.5 Hz, 21 + 4.2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.87, 148.6, 148.5, 140.7, 140.6, 138.0, 137.9, 137.8, 137.76, 135.0, 134.9, 132.8, 132.78, 132.4, 129.8, 129.7, 129.3, 128.3, 127.8, 127.1, 124.6, 124.5, 117.3, 117.2, 112.9, 112.8, 62.0, 61.8, 43.7, 36.1, 35.0, 33.1, 31.5, 29.4, 29.1, 25.8, 25.7, 18.2, 18.1, 12.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{35}H_{49}N_2O_3Si^+$ 573.3507; Found 573.3503.



4.5.9x, 3-((2-nitrophenyl)(phenyl)methylene)-7-(phenylamino)heptan-1-ol

To a solution of amine **4.5.15c** (200 mg, 0.35 mmol, 1.0 equiv) in THF (3.5 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.52 mL, 0.52 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9x**.

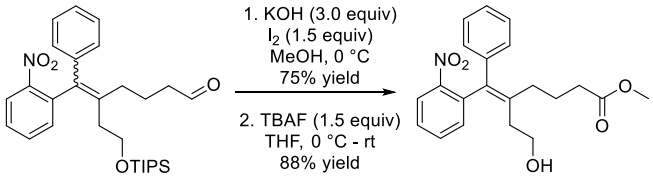
Yield: 90% (131 mg), isolated as orange oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 70:30), R_f = 0.21 and 0.32 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 1 + 0.2H), 7.58 (td, *J* = 7.5, 1.4 Hz, 0.4H), 7.50 (td, *J* = 7.6, 1.3 Hz, 1H), 7.44 – 7.11 (m, 14.2H), 6.73 – 6.64 (m, 1 + 0.2H), 6.56 – 6.51 (m, 2 + 0.4H), 3.78 – 3.59 (m, 2 + 0.4H), 3.02 – 2.89 (m, 2 + 0.4H), 2.68 – 2.21 (m, 3 + 0.4H), 2.15 – 1.93 (m, 2H), 1.6 – 1.4 (m, 4.2H).

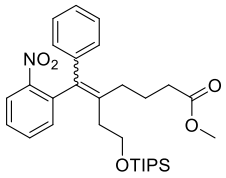
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.9, 148.8, 148.44, 148.4, 140.5, 140.1, 137.6, 137.2, 137.19, 136.0, 133.1, 133.0, 132.7, 132.3, 129.8, 129.7, 129.4, 128.5, 128.3, 128.1, 128.0, 127.3, 124.9, 124.6, 117.4, 117.3, 112.92, 112.89, 61.2, 60.9, 43.62, 43.60, 35.8, 34.6, 32.4, 30.9, 29.3, 29.0, 25.6, 25.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{29}N_2O_3^+$ 417.2173; Found 417.2176.

IR (ν_{max}, cm^{-1}) 3417 (w), 2943 (w), 2853 (w), 2347 (w), 2258 (w), 1600 (m), 1521 (m), 1352 (m), 1033 (m), 907 (s), 739 (s).



4.5.15 **4.5.9y**, 67% yield over 2 steps



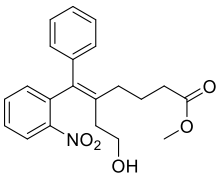
4.5.15d, methyl 5-((2-nitrophenyl)(phenyl)methylene)-7-((triisopropylsilyl)oxy)heptanoate

To a solution of aldehyde **4.5.15** (180 mg, 0.36 mmol, 1.0 equiv) in MeOH (5.4 mL, 0.07 M) was added dropwise a solution of KOH in MeOH (0.2 M, 61 mg, 0.9 mmol, 2.6 equiv) followed by addition of a solution of I_2 in MeOH (0.2 M, 69 mg, 1.3 equiv) at 0 °C. After being stirred for 2 hat room temperature, the reaction mixture was quenched with saturated solution of NH_4Cl and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography to give the ester **4.5.15d**.

Yield: 75% (150 mg), isolated as yellow oil, mixture of *E* and *Z* isomers. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.27 and 0.4 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 – 7.83 (m, 1 + 0.2H), 7.58 – 7.50 (m, 1 + 0.4H), 7.42 – 7.33 (m, 2 + 0.4H), 7.25 – 7.16 (m, 5.8H), 3.77 – 3.61 (m, 4H), 3.58 (s, 3 + 0.6H), 2.56 – 2.19 (m, 2H), 2.12 – 1.97 (m, 2 + 0.4H), 0.99 (s, 21 + 4.2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.8, 148.8, 140.4, 137.7, 137.3, 135.5, 132.9, 132.5, 129.8, 128.3, 127.9, 127.1, 124.6, 61.9, 51.6, 34.8, 33.9, 32.8, 23.4, 18.1, 12.0.



4.5.9y, methyl 7-hydroxy-5-((2-nitrophenyl)(phenyl)methylene)heptanoate

To a solution of ester **4.5.15d** (145 mg, 0.27 mmol, 1.0 equiv) in THF (2.7 mL, 0.1 M) was added dropwise TBAF (1 M in THF, 0.4 mL, 0.4 mmol, 1.5 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9y**.

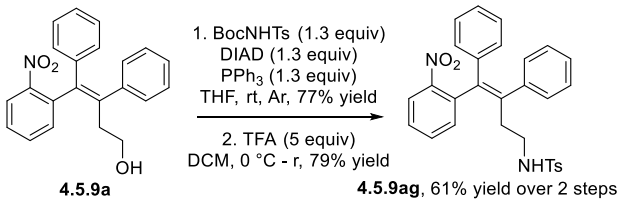
Yield: 88% (110 mg), isolated as brown oil, mixture of E and Z isomers. Purification: Flash chromatography (PE/EtOAc, 65:35), R_f = 0.15 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.85 (m, 1.6H), 7.63 – 7.52 (m, 1.6H), 7.44 – 7.37 (m, 2.2H), 7.35 – 7.13 (m, 9H), 3.78 – 3.64 (m, 3.2H), 3.63 – 3.57 (br s, 4.8H), 2.6 8 – 2.58 (m, 1H), 2.52 – 1.95 (m, 3.8H), 1.84 – 1.66 (m, 4.2H), 1.32 – 1.23 (br t, 1.6OH).

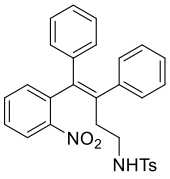
^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 173.8, 148.8, 148.7, 140.4, 139.9, 137.6, 137.5, 137.1, 136.7, 136.6, 136.5, 133.2, 133.1, 132.6, 132.3, 129.8, 129.7, 128.5, 128.3, 128.2, 128.0, 127.4, 127.3, 124.9, 124.6, 61.1, 60.8, 51.7, 51.6, 35.6, 34.4, 33.7, 33.6, 32.1, 30.7, 23.4, 23.2.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{21}H_{23}NNaO_5^+$ 392.1468; Found 392.1477.

IR (ν_{max}, cm^{-1}) 3458 (w), 2960 (w), 2870 (w), 1738 (s), 1525 (s), 1352 (s), 1200 (m), 1045 (m), 908 (m), 743 (s).



4.5.9a **4.5.9ag**, 61% yield over 2 steps



4.5.9ag, 4-methyl-N-(4-(2-nitrophenyl)-3,4-diphenylbut-3-en-1-yl)benzenesulfonamide

To a solution of alcohol **4.5.9a** (200 mg, 0.58 mmol, 1.0 equiv), PPh_3 (200 mg, 0.75 mmol, 1.3 equiv) and BocNHTs (200 mg, 0.75 mmol, 1.3 equiv) in THF (6.0 mL, 0.07 M) was added dropwise DIAD (0.15 mL, 0.75 mmol, 1.3 equiv) at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was quenched with saturated solution of H_2O and extracted with EtOAc. The organic layers were combined,

washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography to give the carbamate. Yield: 77% (270 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.17 (PE/EtOAc 90:10).

To a solution of carbamate (260 mg, 0.44 mmol, 1.0 equiv) in DCM (4.4 mL, 0.1 M) was added dropwise TFA (0.17 mL, 2.2 mmol, 5.0 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alcohol **4.5.9ag**.

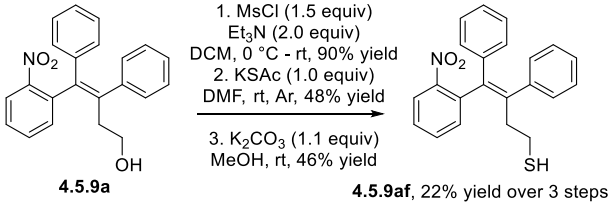
Yield: 79% (170 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.47 (PE/EtOAc 70:30).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.95 (m, 1H), 7.71 – 7.66 (m, 1H), 7.58 – 7.47 (m, 4H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.17 – 7.12 (m, 3H), 7.06 – 7.02 (m, 2H), 7.01 – 6.96 (m, 3H), 6.90 – 6.86 (m, 2H), 4.35 (t, *J* = 6.3 Hz, 1H), 2.82 (q, *J* = 6.9 Hz, 2H), 2.64 – 2.50 (m, 2H), 2.41 (s, 3H).

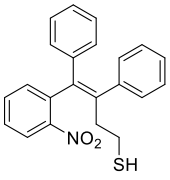
^{13}C NMR (101 MHz, $CDCl_3$): δ 148.5, 143.4, 139.9, 139.5, 137.5, 137.4, 137.2, 136.8, 133.5, 132.5, 130.5, 129.7, 129.3, 128.6, 128.4, 127.7, 127.2, 127.1, 126.9, 125.0, 41.3, 36.4, 21.6.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{26}N_2NaSO_4^+$ 521.1506; Found 521.1522.

IR (ν_{max}, cm^{-1}) 3295 (w), 3064 (w), 2927 (w), 2354 (w), 2253 (w), 1525 (s), 1326 (s), 1160 (s), 1092 (s), 912 (s), 732 (s).



4.5.9a **4.5.9af**, 22% yield over 3 steps



4.5.9af, 4-(2-nitrophenyl)-3,4-diphenylbut-3-ene-1-thiol

To a solution of alcohol **4.5.9a** (200 mg, 0.58 mmol, 1.0 equiv) in DCM (6.0 mL, 0.1 M) was added MsCl (0.07 mL, 0.87 mmol, 1.5 equiv) and triethylamine (0.09 mL, 1.2 mmol, 2.0 equiv) at 0 °C. After being stirred 3 h at room temperature, the reaction mixture was quenched with 2 M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was subjected to a next step without purification.

The crude sulfonate (220 mg, 0.52 mmol, 1.0 equiv) was added to cesium thioacetate (62 mg, 0.55 mmol, 1.05 equiv) in DMF (3.5 mL, 0.15 M). The reaction mixture was heated at 50 °C overnight, then diluted

with DCM and washed with water. The combined organics were concentrated in vacuo. The crude product was filtered through a short plug of silicagel, delivering the title compound as an oil.

To a suspension of K_2CO_3 (38 mg, 0.27 mmol, 1.1 equiv) in MeOH (1.2 mL, 0.2 M) stirred 20 min at rt, was added the crude thioacetate (100 mg, 0.25 mmol, 1.0 equiv). After 20 min of stirring, the reaction mixture was quenched with 0.1 M HCl and extracted with DCM. The organic layer was washed with aq NaCl, dried over $MgSO_4$, filtered, and concentrated in vacuo.

Yield: 46% (82 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 85:15), R_f = 0.42 (PE/EtOAc 80:20).

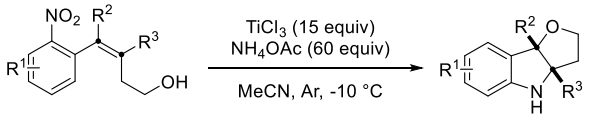
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.2 Hz, 1H), 7.6 5 – 7.56 (m, 1H), 7.50 – 7.35 (m, 2H), 7.23 – 7.07 (m, 5H), 7.05 – 6.86 (m, 5H), 2.63 – 2.52 (m, 2H), 2.32 – 2.21 (m, 2H), 1.26 (br s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.52 (d, J = 5.3 Hz), 140.34 (d, J = 8.6 Hz), 139.82 (d, J = 4.6 Hz), 139.03 (d, J = 3.8 Hz), 137.57, 136.09 (d, J = 4.1 Hz), 133.34 (d, J = 6.2 Hz), 132.52 (d, J = 3.5 Hz), 130.64, 129.53 (d, J = 2.9 Hz), 128.4, 128.3, 127.6, 127.11 (d, J = 2.0 Hz), 126.8, 124.9, 36.3, 36.0, 35.7, 35.5.

HRMS (Nanochip-based ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}NO_2S^+$ 362.1209; Found 362.1205.

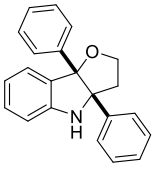
IR (ν_{max}, cm^{-1}) 3015 (w), 2918 (w), 1686 (w), 1525 (m), 1345 (m), 1213 (m), 749 (s).

6.4.6. General procedure O for the reductive cyclization of *ortho*-nitrostyrenes 4.5.9



4.5.9 **4.5.23**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. MeCN and the solution of $TiCl_3$ were degassed with Freeze-pump technique. In a 10 mL pressure resistant round bottomed flask was charged the *o*-nitrostyrene **4.5.9** (1.0 equiv) in MeCN (0.2 M). Then $TiCl_3$ (1.3 M solution in HCl, 10 equiv) was added dropwise at -10 °C upon 10 min. The reaction mixture was stirred at -10 °C for 3 h. After completion of the reaction, $NaHCO_3$ was added slowly at -10 °C to quench the reaction. The mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the desired furo[3,2-*b*]indolenine **4.5.23**.



4.5.23a, 3a,8b-diphenyl-3,3a,4,8b-tetrahydro-*2H*-furo[3,2-*b*]indole

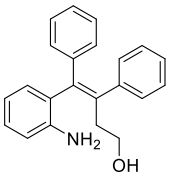
This compound was prepared following the general procedure **O** using substrate **4.5.9a** (34.5 mg, 0.1 mmol) as starting material. Yield: 59% (18.5 mg), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.38 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 7.3 Hz, 2H), 7.05 – 6.97 (m, 8H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.77 (t, *J* = 7.4 Hz, 1H), 4.45 (t, *J* = 8.1 Hz, 1H), 4.28 (br, 1H), 4.07 (ddd, *J* = 11.1, 8.5, 5.2 Hz, 1H), 2.92 (td, *J* = 11.9, 7.6 Hz, 1H), 2.28 (dd, *J* = 12.8, 5.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 142.1, 140.9, 130.5, 130.0, 127.8, 127.6, 127.1, 126.83, 126.80, 126.76, 126.5, 119.4, 108.6, 98.5, 80.4, 67.3, 41.5.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + H]^+$ Calcd for $C_{22}H_{20}NO^+$ 314.1539; Found 314.1530.

IR (ν_{max}, cm^{-1}) 3352 (w), 3016 (w), 2830 (w), 1614 (m), 1507 (m), 1382 (m), 1259 (m), 1031 (m), 753 (s).



4.5.24, (*E*)-4-(2-aminophenyl)-3,4-diphenylbut-3-en-1-ol

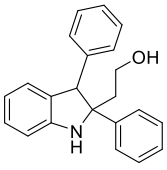
This compound was prepared following the general procedure **O** using substrate **4.5.9a** (34.5 mg, 0.1 mmol) as starting material. Yield: 98% (NMR yield), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.22 (PE/EtOAc 80:20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.09 (m, 7H), 7.05 – 6.94 (m, 5H), 6.84 (t, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 3.61 – 3.46 (m, 2H), 3.45 – 3.28 (br s, 2H), 2.82 – 2.55 (m, 2H), 1.31 – 1.21 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 143.2, 141.2, 141.1, 140.1, 137.6, 130.7, 130.1, 129.7, 129.5, 128.4, 128.3, 127.8, 126.9, 126.4, 119.5, 116.5, 60.4, 39.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}NO^+$ 316.1696; Found 316.1691.

IR (ν_{max}, cm^{-1}) 3345 (w), 2959 (m), 2832 (m), 1604 (s), 1512 (s), 1475 (s), 1216 (m), 1054 (m), 810 (m), 746 (s).



4.6.9, 2-(2,3-diphenylindolin-2-yl)ethan-1-ol

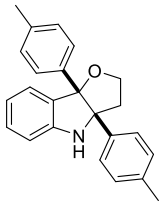
This compound was prepared following the general procedure **O** using substrate **4.5.9a** (34.5 mg, 0.1 mmol) as starting material. Yield: 30% (NMR yield), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, :), R_f = 0. (PE/EtOAc :).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.12 (m, 1H), 7.06 – 6.93 (m, 8H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.76 – 6.66 (m, 3H), 4.57 (s, 1H), 3.95 – 3.88 (m, 1H), 3.71 – 3.62 (m, 1H), 2.58 – 2.49 (m, 1H), 2.41 – 2.32 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.4, 142.2, 139.8, 131.6, 129.7, 128.3, 127.73, 127.70, 127.1, 126.6, 126.4, 125.9, 119.4, 109.5, 74.7, 60.8, 60.4, 42.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{22}NO^+$ 316.1696; Found 316.1699.

IR (ν_{max}, cm^{-1}) 3354 (w), 2999 (m), 2916 (m), 1617 (m), 1460 (m), 1410 (m), 1278 (s), 1057 (s), 754 (s).



4.5.23b, 3a,8b-di-p-tolyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

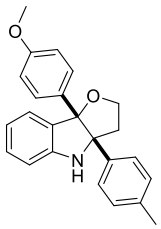
This compound was prepared following the general procedure **O** using substrate **4.5.9b** (43.8 mg, 0.1 mmol) as starting material. Yield: 54% (18.4 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, *J* = 7.6, 1.3 Hz, 1H), 6.97 (d, *J* = 8.3 Hz, 2H), 6.96 – 6.93 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 6.85 – 6.78 (m, 5H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 4.41 (ddd, *J* = 8.6, 7.7, 1.2 Hz, 1H), 4.26 (br, 1H), 4.05 (ddd, *J* = 11.2, 8.3, 5.1 Hz, 1H), 2.87 (ddd, *J* = 12.5, 11.2, 7.6 Hz, 1H), 2.24 (ddd, *J* = 12.6, 5.1, 1.2 Hz, 1H), 2.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 139.1, 137.9, 136.4, 136.2, 130.9, 129.9, 128.5, 127.8, 127.5, 126.8, 126.4, 119.2, 108.5, 98.1, 80.3, 67.2, 41.3, 21.1, 21.0.

HRMS HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO^+$ 342.1852; Found 342.1856.

IR (ν_{max}, cm^{-1}) 3368 (w), 3032 (w), 2863 (w), 1604 (m), 1511 (m), 1482 (m), 1467 (m), 1323 (w), 1215 (w), 1046 (m), 804 (m), 746 (s).



4.5.23c, 8b-(4-methoxyphenyl)-3a-(p-tolyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

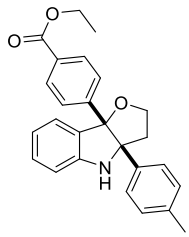
This compound was prepared following the general procedure **O** using substrate **4.5.9c** (46.4 mg, 0.1 mmol) as starting material. Yield: 52% (18.6 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.23 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (td, *J* = 7.7, 1.3 Hz, 1H), 6.99 – 6.93 (m, 3H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.1 Hz, 2H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 6.54 (d, *J* = 9.0 Hz, 2H), 4.43 – 4.37 (m, 1H), 4.25 (brs, 1H), 4.04 (ddd, *J* = 11.2, 8.3, 5.1 Hz, 1H), 3.69 (s, 3H), 2.87 (ddd, *J* = 12.5, 11.2, 7.6 Hz, 1H), 2.24 (ddd, *J* = 12.6, 5.1, 1.2 Hz, 1H), 2.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 151.7, 139.0, 136.4, 133.2, 130.8, 130.0, 128.8, 128.6, 126.8, 126.4, 119.2, 112.5, 108.5, 98.0, 80.2, 67.2, 55.3, 41.1, 21.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO_2^+$ 358.1802; Found 358.1803.

IR (ν_{max}, cm^{-1}) 3411 (w), 3025 (w), 2841 (w), 1604 (m), 1521 (m), 1507 (m), 1352 (m), 1251 (m), 1179 (m), 1031 (m), 829 (m), 753 (s).



4.5.23d, ethyl 4-(3a-(p-tolyl)-2,3,3a,4-tetrahydro-8b*H*-furo[3,2-*b*]indol-8b-yl)benzoate

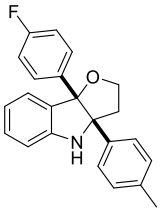
This compound was prepared following the general procedure **O** using substrate **4.5.9d** (43.2 mg, 0.1 mmol) as starting material. Yield: 56% (22.3 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.25 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.88 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.84 – 6.81 (m, 3H), 6.75 (td, *J* = 7.4, 1.0 Hz, 1H), 4.44 (td, *J* = 8.1, 1.3 Hz, 1H), 4.35 – 4.22 (m, 3H), 4.04 (ddd, *J* = 11.1, 8.4, 5.2 Hz, 1H), 2.88 (ddd, *J* = 12.7, 11.1, 7.7 Hz, 1H), 2.28 (ddd, *J* = 12.7, 5.3, 1.3 Hz, 1H), 2.16 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 151.5, 146.3, 138.6, 136.7, 130.2, 130.20, 128.8, 128.7, 128.4, 127.6, 126.6, 126.3, 119.4, 108.8, 98.0, 80.5, 67.3, 60.9, 42.0, 21.0, 14.4.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{26}NO_3^+$ 400.1907; Found 400.1908.

IR (ν_{max}, cm^{-1}) 3370 (w), 2990 (m), 2904 (m), 1712 (m), 1607 (m), 1485 (m), 1468 (m), 1407 (m), 1278 (s), 1105 (s), 1047 (s), 1022 (s), 754 (s).



4.5.23e, 8b-(4-fluorophenyl)-3a-(p-tolyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

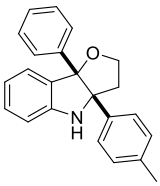
This compound was prepared following the general procedure **O** using substrate **4.5.9e** (40 mg, 0.106 mmol) as starting material. Yield: 66% (24.3 mg), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.4 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, *J* = 7.7, 1.4 Hz, 1H), 6.99 – 6.94 (m, 4H), 6.93 (dd, *J* = 7.8, 1.2 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.79 – 6.74 (m, 1H), 6.68 (t, *J* = 8.9 Hz, 2H), 4.41 (ddd, *J* = 8.7, 7.6, 1.3 Hz, 1H), 4.26 (br, 1H), 4.03 (ddd, *J* = 11.2, 8.4, 5.1 Hz, 1H), 2.87 (ddd, *J* = 12.7, 11.2, 7.7 Hz, 1H), 2.25 (ddd, *J* = 12.6, 5.1, 1.3 Hz, 1H), 2.18 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.8 (d, *J* = 244.9 Hz), 151.6, 138.8, 136.9 (d, *J* = 3.0 Hz), 136.6, 130.3, 130.2, 129.3 (d, *J* = 8.1 Hz), 128.7, 126.7, 126.3, 119.3, 113.9 (d, *J* = 21.3 Hz), 108.7, 97.9, 80.2, 67.3, 41.3, 21.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}FNO^+$ 346.1602; Found 346.1604.

IR (ν_{max}, cm^{-1}) 3370 (w), 2975 (m), 2882 (m), 1604 (s), 1507 (s), 1482 (s), 1468 (s), 1220 (m), 1044 (m), 807 (m), 746 (s).



4.5.23f, 8b-phenyl-3a-(p-tolyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

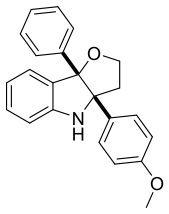
This compound was prepared following the general procedure **O** using substrate **4.5.9f** (36.0 mg, 0.1 mmol) as starting material. Yield: 42% (14 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.41 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.00 – 6.94 (m, 8H), 6.83 – 6.79 (m, 3H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 4.43 (ddd, *J* = 8.7, 7.7, 1.2 Hz, 1H), 4.27 (br, 1H), 4.06 (ddd, *J* = 11.1, 8.3, 5.1 Hz, 1H), 2.89 (ddd, *J* = 12.5, 11.1, 7.6 Hz, 1H), 2.25 (ddd, *J* = 12.6, 5.1, 1.3 Hz, 1H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 140.9, 138.9, 136.4, 130.6, 130.0, 128.5, 127.6, 127.0, 126.8, 126.7, 126.4, 119.2, 108.6, 98.2, 80.4, 67.3, 41.3, 20.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO^+$ 328.1696; Found 328.1696.

IR (ν_{max}, cm^{-1}) 3377 (w), 3033 (w), 2922 (w), 2864 (w), 1607 (m), 1482 (m), 1468 (m), 1152 (m), 1047 (m), 742 (s).



4.5.23g, 3a-(4-methoxyphenyl)-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

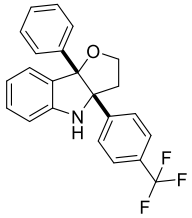
This compound was prepared following the general procedure **O** using substrate **4.5.9g** (37.5 mg, 0.1 mmol) as starting material. Yield: 27% (9.2 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.31 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, *J* = 7.6, 1.4 Hz, 1H), 7.03 – 6.97 (m, 7H), 6.96 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 6.55 (d, *J* = 8.9 Hz, 2H), 4.42 (ddd, *J* = 8.6, 7.7, 1.2 Hz, 1H), 4.28 (s, 1H), 4.06 (ddd, *J* = 11.2, 8.4, 5.1 Hz, 1H), 3.67 (s, 3H), 2.86 (ddd, *J* = 12.6, 11.2, 7.6 Hz, 1H), 2.25 (ddd, *J* = 12.6, 5.1, 1.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 158.4, 151.7, 140.9, 134.0, 130.6, 130.0, 127.64, 127.60, 127.1, 126.84, 126.80, 119.3, 113.1, 108.6, 98.2, 80.2, 67.3, 55.3, 41.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO_2^+$ 344.1645; Found 344.1646.

IR (ν_{max}, cm^{-1}) 3374 (w), 3044 (w), 2932 (w), 2868 (w), 2831 (w), 2358 (w), 1607 (s), 1511 (s), 1482 (m), 1468 (m), 1320 (m), 1299 (m), 1252 (s), 1180 (s), 1033 (s), 746 (s).



4.5.23h, 8b-phenyl-3a-(4-(trifluoromethyl)phenyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

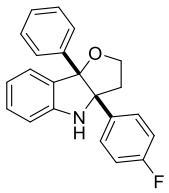
This compound was prepared following the general procedure **O** using substrate **4.5.9h** (41 mg, 0.1 mmol) as starting material. Yield: 58% (22 mg), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.38 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 5H), 7.01 – 6.95 (m, 6H), 6.84 (dt, *J* = 7.9, 0.8 Hz, 1H), 6.80 (td, *J* = 7.4, 0.9 Hz, 1H), 4.46 (ddd, *J* = 9.1, 7.8, 1.4 Hz, 1H), 4.46 (ddd, *J* = 9.1, 7.8, 1.4 Hz, 1H), 4.03 (ddd, *J* = 11.0, 8.6, 5.4 Hz, 1H), 2.89 (ddd, *J* = 12.7, 11.0, 7.7 Hz, 1H), 2.32 (ddd, *J* = 12.8, 5.4, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.0, 146.7, 140.5, 130.2, 130.1, 128.9 (q, *J* = 32.4 Hz), 127.3, 127.1, 127.0, 126.7, 124.5 (q, *J* = 3.9 Hz), 124.2 (q, *J* = 271.9 Hz), 119.8, 108.9, 98.9, 79.9, 67.1, 43.0.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}F_3NO^+$ 382.1413; Found 382.1415.

IR (ν_{max}, cm^{-1}) 3359 (w), 3054 (w), 2954 (w), 2875 (w), 2358 (w), 1607 (m), 1485 (m), 1471 (m), 1327 (s), 1162 (s), 1116 (s), 1069 (s), 1015 (s), 746 (s).



4.5.23i, 3a-(4-fluorophenyl)-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

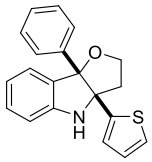
This compound was prepared following the general procedure **O** using substrate **4.5.9i** (40 mg, 0.11 mmol) as starting material. Yield: 64% (23.3 mg), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.38 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (td, *J* = 7.4, 1.3 Hz, 1H), 7.10 – 7.05 (m, 2H), 7.02 – 6.96 (m, 6H), 6.82 – 6.76 (m, 2H), 6.70 (t, *J* = 8.7 Hz, 2H), 4.43 (td, *J* = 8.1, 1.3 Hz, 1H), 4.23 (br, 1H), 4.03 (ddd, *J* = 11.1, 8.5, 5.2 Hz, 1H), 2.86 (ddd, *J* = 12.7, 11.1, 7.7 Hz, 1H), 2.28 (ddd, *J* = 12.7, 5.2, 1.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 161.64 (d, *J* = 245.8 Hz), 151.3, 140.8, 137.98 (d, *J* = 3.3 Hz), 130.2, 130.1, 128.16 (d, *J* = 8.0 Hz), 127.5, 127.2, 126.9, 126.8, 119.5, 114.44 (d, *J* = 21.3 Hz), 108.7, 98.4, 79.8, 67.1, 42.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}FNO^+$ 332.1445; Found 332.1453

IR (ν_{max}, cm^{-1}) 3359 (w), 3061 (w), 2943 (w), 2864 (w), 1607 (m), 1507 (s), 1482 (m), 1468 (m), 1227 (m), 1044 (m), 746 (s).



4.5.23j, 8b-phenyl-3a-(thiophen-2-yl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

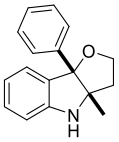
This compound was prepared following the general procedure **O** using substrate **4.5.9j** (840 mg, 2.4 mmol) as starting material. Yield: 70% (531 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (brs 1H), 7.42 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.18-7.15 (m, 1H), 7.12 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.00-6.96 (m, 2H), 6.87 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.76 (dd, *J* = 3.6, 1.2 Hz, 1H), 4.59 (ddd, *J* = 8.7, 7.5, 1.2 Hz, 1H), 4.19 (ddd, *J* = 11.4, 8.5, 4.9 Hz, 1H), 2.96 (ddd, *J* = 12.9, 11.3, 7.6 Hz, 1H), 2.61 (ddd, *J* = 12.7, 4.9, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.0, 148.1, 140.8, 130.1, 129.9, 127.5, 127.2, 127.1, 127.0, 126.9, 124.7, 124.3, 119.7, 108.8, 98.5, 79.0, 67.0, 42.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{18}NOS^+$ 320.1104; Found 320.1112.

IR (ν_{max}, cm^{-1}) 3363 (w), 3053 (w), 2972 (w), 2877 (w), 1608 (m), 1483 (m), 1468 (m), 1446 (w), 1390 (w), 1313 (w), 1265 (w), 1236 (m), 1207 (w), 1174 (w), 1082 (w), 1047 (m), 1020 (w), 978 (w), 947 (w), 908 (m), 885 (w), 849 (w), 831 (w).



4.5.23k, 3a-methyl-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

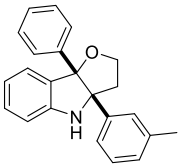
This compound was prepared following the general procedure **O** using substrate **4.5.9k** (28 mg, 0.1 mmol) as starting material. Yield: 72% (18 mg), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.24 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 7.19 (td, *J* = 7.6, 1.4 Hz, 1H), 7.03 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.78 (td, *J* = 7.4, 1.0 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 4.21 (ddd, *J* = 8.8, 5.8, 3.2 Hz, 1H), 3.87 – 3.71 (m, 2H), 2.15 – 2.05 (m, 2H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 141.7, 130.9, 129.9, 127.8, 127.6, 127.3, 126.7, 119.3, 109.6, 96.4, 74.1, 66.6, 42.1, 25.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO^+$ 252.1383; Found 252.1380.

IR (ν_{max}, cm^{-1}) 3352 (w), 3058 (w), 2975 (w), 2925 (w), 2871 (w), 2358 (w), 1609 (m), 1482 (m), 1468 (m), 1446 (m), 1309 (s), 1270 (m), 1213 (w), 1151 (w), 1044 (m), 986 (m), 943 (m), 746 (s).



4.5.23l, 8b-phenyl-3a-(m-tolyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

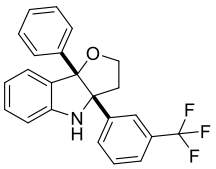
This compound was prepared following the general procedure **O** using substrate **4.5.9l** (40 mg, 0.11 mmol) as starting material. Yield: 61% (22.0 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.5 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ δ 7.24 (td, *J* = 7.7, 1.3 Hz, 1H), 7.00 (apparent s, 5H), 6.97 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.94 – 6.90 (m, 2H), 6.86 (brs, 1H), 6.83 – 6.79 (m, 2H), 6.77 (td, *J* = 7.4, 1.0 Hz, 1H), 4.44 (ddd, *J* = 8.6, 7.6, 1.2 Hz, 1H), 4.27 (br, 1H), 4.05 (ddd, *J* = 11.1, 8.4, 5.1 Hz, 1H), 2.90 (ddd, *J* = 12.6, 11.2, 7.6 Hz, 1H), 2.27 (ddd, *J* = 12.6, 5.1, 1.3 Hz, 1H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.6, 142.0, 140.9, 137.2, 130.4, 130.0, 127.62, 127.57, 127.42, 127.37, 126.9, 126.8, 126.7, 123.5, 119.2, 108.5, 98.5, 80.3, 67.2, 41.7, 21.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{22}NO^+$ 328.1696; Found 328.1699.

IR (ν_{max}, cm^{-1}) 3367 (w), 3029 (w), 2950 (w), 2878 (w), 1607 (m), 1482 (m), 1468 (m), 1317 (w), 1267 (w), 1217 (w), 1044 (m), 742 (s).



4.5.23m, 8b-phenyl-3a-(3-(trifluoromethyl)phenyl)-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

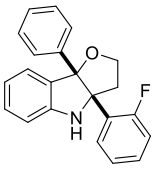
This compound was prepared following the general procedure **O** using substrate **4.5.9m** (42 mg, 0.1 mmol) as starting material. Yield: 53% (20.6 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.37 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.00 – 6.89 (m, 6H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.80 (td, *J* = 7.4, 0.9 Hz, 1H), 4.46 (ddd, *J* = 8.8, 7.7, 1.3 Hz, 1H), 4.22 (br, 1H), 4.00 (ddd, *J* = 11.0, 8.7, 5.4 Hz, 1H), 2.88 (ddd, *J* = 12.9, 11.0, 7.7 Hz, 1H), 2.34 (ddd, *J* = 12.9, 5.4, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.9, 143.8, 140.6, 130.2, 129.9 (q, *J* = 32.0 Hz), 129.9, 129.88 (br), 128.0, 127.3, 127.2, 127.0, 126.7, 124.1 (q, *J* = 270.7 Hz), 123.6 (q, *J* = 3.9 Hz), 123.4 (q, *J* = 3.8 Hz), 119.8, 108.9, 99.0, 79.6, 66.8, 43.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{19}F_3NO^+$ 382.1413; Found 382.1413.

IR (ν_{max}, cm^{-1}) 3375 (w), 3039 (w), 2960 (w), 2874 (w), 1720 (w), 1604 (m), 1482 (m), 1334 (m), 1164 (m), 1121 (m), 1078 (m), 746 (s).



4.5.23n, 3a-(2-fluorophenyl)-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

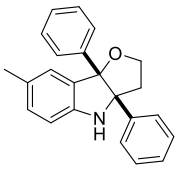
This compound was prepared following the general procedure **O** using substrate **4.5.9n** (36 mg, 0.1 mmol) as starting material. Yield: 24% (8.0 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.33 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (td, *J* = 8.0, 1.9 Hz, 1H), 7.21 (td, *J* = 7.6, 1.3 Hz, 1H), 7.13-7.06 (m, 2H), 7.06-6.9 (m, 4H), 6.96-6.90 (m, 2H), 6.79 – 6.74 (m, 2H), 6.61 (dd, *J* = 12.3, 8.0 Hz, 1H), 4.43 (t, *J* = 8.2 Hz, 1H), 4.12 (br, 1H), 3.94 – 3.86 (m, 1H), 3.17 (ddd, *J* = 12.6, 10.9, 7.9 Hz, 1H), 2.26 – 2.18 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 160.1 (d, *J* = 248.3 Hz), 150.7, 140.8, 130.9, 130.0 (d, *J* = 11.0 Hz), 129.9, 129.1 (d, *J* = 8.8 Hz), 128.8 (d, *J* = 4.3 Hz), 127.3, 126.9, 126.8, 126.5, 123.4 (d, *J* = 3.4 Hz), 119.6, 116.1 (d, *J* = 23.8 Hz), 108.7, 98.6, 78.7 (d, *J* = 4.3 Hz), 66.5, 42.8 (d, *J* = 5.8 Hz).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{22}H_{19}FNO^+$ 332.1445; Found 332.1444.

IR (ν_{max}, cm^{-1}) 3364 (w), 3051 (w), 2922 (w), 2864 (w), 1609 (m), 1486 (m), 1446 (m), 1320 (m), 1270 (w), 1216 (m), 1044 (m), 749 (s).



4.5.23o, 7-methyl-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

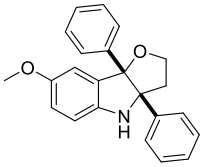
This compound was prepared following the general procedure **O** using substrate **4.5.9o** (35 mg, 0.1 mmol) as starting material. Yield: 53% (17 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.51 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13-7.11 (m, 2H), 7.08-6.99 (m, 9H), 6.80 (brs, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.46 (t, *J* = 8.0 Hz, 1H), 4.19 (brs, 1H), 4.09 (ddd, *J* = 11.0, 8.3, 5.1 Hz, 1H), 2.92 (ddd, *J* = 12.5, 11.1, 7.6 Hz, 1H), 2.28 (ddd, *J* = 12.6, 5.3, 1.3 Hz, 1H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.3, 142.2, 140.8, 130.6, 130.5, 128.7, 127.7, 127.5, 127.0, 126.7, 126.6, 126.4, 108.6, 98.4, 80.5, 67.2, 41.4, 20.8.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{23}H_{22}NO^+$ 328.1696; Found 328.1694.

IR (ν_{max}, cm^{-1}) 3367 (w), 3032 (w), 2927 (w), 2862 (w), 2158 (w), 1711 (w), 1614 (m), 1495 (s), 1446 (m), 1045 (m), 1034 (m).



4.5.23p, 7-methoxy-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

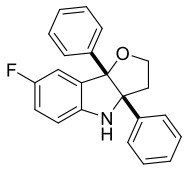
This compound was prepared following the general procedure **O** using substrate **4.5.9p** (36.5 mg, 0.1 mmol) as starting material. Yield: 41% (14 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.31 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 7.06 – 6.96 (m, 8H), 6.85 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.77 (m, 1H), 6.57 (brs, 1H), 4.45 (td, *J* = 8.0, 1.4 Hz, 1H), 4.15 (brs, 1H), 4.09 (ddd, *J* = 11.0, 8.4, 5.4 Hz, 1H), 3.67 (s, 3H), 2.91 (m, 1H), 2.28 (dd, *J* = 12.7, 5.1 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 153.9, 145.4, 142.2, 140.6, 131.5, 127.7, 127.4, 127.0, 126.7, 126.4, 116.8, 111.3, 109.8, 98.6, 80.9, 70.6, 55.9, 41.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{23}H_{22}NO_2^+$ 344.1645; Found 344.1637.

IR (ν_{max}, cm^{-1}) 3348 (w), 2927 (w), 2868 (w), 1493 (s), 1466 (m), 1448 (m), 1433 (m), 1263 (m), 1234 (m), 1213 (m), 1147 (m), 1047 (m), 1032 (m).



4.5.23q, 7-fluoro-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

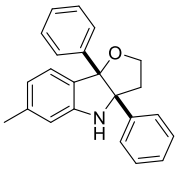
This compound was prepared following the general procedure **O** using substrate **4.5.9q** (36 mg, 0.1 mmol) as starting material. Yield: 65% (21.5 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.43 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.08 (m, 2H), 7.05-6.92 (m, 9H), 6.74 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.7 Hz, 1H), 4.46 (ddd, *J* = 8.7, 7.7, 1.4 Hz, 1H), 4.21 (br s, 1H), 4.07 (ddd, *J* = 11.1, 8.4, 5.3 Hz, 1H), 2.91 (ddd, *J* = 12.7, 11.0, 7.7 Hz, 1H), 2.29 (ddd, *J* = 12.7, 5.3, 1.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 157.4 (d, *J* = 235.9 Hz), 147.6, 142.0, 140.4, 132.1 (d, *J* = 7.0 Hz), 127.9, 127.5, 127.3, 127.1, 127.0, 126.5, 116.7 (d, *J* = 23.8 Hz), 113.6 (d, *J* = 23.8 Hz), 109.3 (d, *J* = 7.8 Hz), 98.3, 81.2, 67.5, 41.8.

HRMS HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{22}H_{19}FNO^+$ 332.1445; Found 332.1441.

IR (ν_{max}, cm^{-1}) 127.8, 127.4, 127.2, 127.0, 126.9, 126.4, 116.7, 116.5, 113.6, 113.4, 109.2, 109.1, 98.3, 81.2, 67.5, 41.8. IR: ᵛ (cm-1) 2920 (w), 1489 (s), 1446 (m), 1254 (m), 1203 (m), 1186 (m), 1138 (m), 1078 (m), 1045 (m), 1030 (m), 933 (m), 868 (m).



4.5.23r, 6-methyl-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

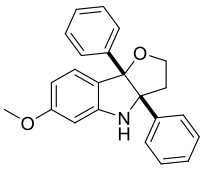
This compound was prepared following the general procedure **O** using substrate **4.5.9r** (36 mg, 0.1 mmol) as starting material. Yield: 53% (17.3 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.48 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.08 (m, 2H), 7.05 – 6.95 (m, 8H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.65 (s, 1H), 6.61 (dt, *J* = 7.6, 1.1 Hz, 1H), 4.44 (ddd, *J* = 8.7, 7.6, 1.2 Hz, 1H), 4.26 (br s, 1H), 4.07 (ddd, *J* = 11.2, 8.4, 5.1 Hz, 1H), 2.91 (ddd, *J* = 12.7, 11.2, 7.6 Hz, 1H), 2.37 (s, 3H), 2.26 (ddd, *J* = 12.6, 5.1, 1.2 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.9, 142.2, 141.0, 140.2, 127.7, 127.7, 127.6, 127.0, 126.8, 126.7, 126.5, 120.3, 109.3, 98.3, 80.6, 67.2, 41.4, 21.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{23}H_{22}NO^+$ 328.1696; Found 328.1706.

IR (ν_{max}, cm^{-1}) 2920 (w), 1616 (w), 1593 (w), 1496 (w), 1466 (w), 1444 (w), 1317 (w), 1304 (w), 1281 (w), 1259 (w), 1228 (w), 1182 (w), 1153 (w), 1117 (w), 1080 (w), 1030 (w), 997 (w), 976 (w), 957 (w), 935 (w), 906 (s), 881 (w), 849 (w), 802 (w).



4.5.23s, 6-methoxy-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

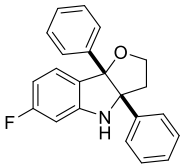
This compound was prepared following the general procedure **O** using substrate **4.5.9s** (37 mg, 0.1 mmol) as starting material. Yield: 40% (13.7 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.34 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 2H), 7.06 – 6.95 (m, 8H), 6.85 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.81-6.73 (m, 1H), 6.57 (d, *J* = 2.6 Hz, 1H), 4.45 (t, *J* = 8.0 Hz, 1H), 4.16 (brs, 1H), 4.09 (ddd, *J* = 11.0, 8.4, 5.4 Hz, 1H), 3.68 (s, 3H), 2.96-2.85 (m, 1H), 2.28 (dd, *J* = 12.6, 5.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 154.0, 145.6, 142.3, 140.7, 131.6, 127.8, 127.5, 127.1, 126.8, 126.5, 116.9, 111.4, 109.9, 98.8, 81.0, 67.4, 56.1, 41.7.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{23}H_{22}NO_2^+$ 344.1645; Found 344.1653.

IR (ν_{max}, cm^{-1}) 2922 (s), 2852 (m), 2158 (m), 2048 (m), 1493 (s), 1444 (m), 1263 (m), 1215 (m), 1034 (m).



4.5.23t, 6-fluoro-3a,8b-diphenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

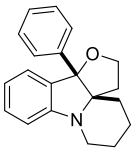
This compound was prepared following the general procedure **O** using substrate **4.5.9t** (36 mg, 0.1 mmol) as starting material. Yield: 85% (28.2 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.46 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 6.96 (m, 10H), 6.87 (dd, *J* = 8.2, 5.7 Hz, 1H), 6.49 (dd, *J* = 9.8, 2.3 Hz, 1H), 6.44 (td, *J* = 8.8, 2.3 Hz, 1H), 4.45 (t, *J* = 8.0 Hz, 1H), 4.37 (brs, 1H), 4.06 (ddd, *J* = 11.2, 8.4, 5.0 Hz, 1H), 2.91 (td, *J* = 12.0, 7.6 Hz, 1H), 2.27 (dd, *J* = 12.7, 5.0 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.9 (d, *J* = 243.9 Hz), 152.9 (d, *J* = 2.2 Hz), 141.6, 140.6, 127.9, 127.8, 127.8 (d, *J* = 11.0 Hz), 127.6, 127.1, 127.0, 126.9, 126.0 (d, *J* = 2.2 Hz), 105.8 (d, *J* = 23.1 Hz), 97.8, 95.9 (d, *J* = 26.3 Hz), 81.3, 67.2, 41.3.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calculated for $C_{22}H_{19}FNO^+$ 332.1445; Found 332.1443.

IR (ν_{max}, cm^{-1})) 1618 (m), 1601 (m), 1495 (m), 1464 (w), 1444 (m), 1325 (w), 1288 (w), 1248 (w), 1227 (w), 1215 (w), 1173 (w), 1144 (m), 1099 (w), 1084 (w), 1043 (m), 999 (w), 980 (w), 962 (m), 941 (w), 906 (s), 881 (w), 829 (m).



4.5.23u, 12b-phenyl-2,3,4,5,6,7-hexahydro-12b*H*-furo[3,2-*b*]pyrido[1,2-*a*]indole

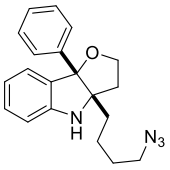
This compound was prepared following the general procedure **O** using substrate **4.5.9u** (31.5 mg, 0.08 mmol) as starting material. Yield: 51% (14.8 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 93:7), R_f = 0.57 (PE/EtOAc 80:20).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 5H), 7.19 (td, *J* = 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.62 (td, *J* = 7.3, 1.0 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 4.26 (td, *J* = 8.2, 2.0 Hz, 1H), 3.76 (ddd, *J* = 10.7, 8.5, 5.9 Hz, 1H), 3.70 – 3.64 (m, 2H), 3.00 (td, *J* = 13.0, 3.2 Hz, 1H), 2.39 (ddd, *J* = 12.6, 5.9, 2.0 Hz, 1H), 1.91 (ddd, *J* = 12.6, 10.7, 7.9 Hz, 1H), 1.72-1.67 (m, 1H), 1.52 – 1.35 (m, 3H), 1.03 (td, *J* = 13.1, 3.8 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.8, 141.0, 130.3, 129.9, 127.9, 127.7, 127.3, 126.4, 116.6, 105.0, 95.6, 67.5, 40.7, 34.3, 32.7, 29.9, 24.8, 22.5.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{22}NO^+$ 292.1696; Found 292.1719.

IR (ν_{max}, cm^{-1}) 3378 (w), 2964 (m), 2881 (m), 2336 (w), 1524 (s), 1356 (m), 1262 (m), 1179 (m), 1042 (m), 739 (s), 706 (s).



4.5.23v, 3a-(4-azidobutyl)-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

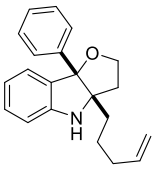
This compound was prepared following the general procedure **O** using substrate **4.5.9v** (30 mg, 0.08 mmol) as starting material. Yield: 66% (18 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 96:4), R_f = 0.2 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 5H), 7.18 (td, *J* = 7.7, 1.3 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.77 (td, *J* = 7.4, 1.0 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.25 – 4.20 (m, 1H), 4.00 (brs, 1H), 3.79 – 3.73 (m, 1H), 3.14 (t, *J* = 6.3 Hz, 2H), 2.08 – 2.05 (m, 2H), 1.45 – 1.23 (m, 4H), 1.19 – 1.10 (m, 1H), 0.90 – 0.79 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 141.2, 130.7, 130.0, 127.8, 127.5, 126.6, 119.3, 109.4, 96.9, 76.3, 66.5, 51.3, 40.2, 38.3, 29.4, 22.9.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{20}H_{23}N_4O^+$ 335.1866; Found 335.1871.

IR (ν_{max}, cm^{-1}) 3365 (w), 2922 (m), 2843 (m), 2363 (w), 2094 (s), 1611 (s), 1483 (s), 1466 (s), 1269 (m), 1052 (m), 906 (m), 750 (s).



4.5.23w, 3a-(pent-4-en-1-yl)-8b-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

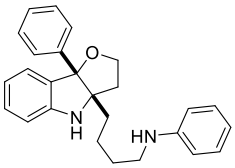
This compound was prepared following the general procedure **O** using substrate **4.5.9w** (25 mg, 0.08 mmol) as starting material. Yield: 88% (20 mg), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 95:5), R_f = 0.77 (PE/EtOAc 65:35).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 7.18 (td, *J* = 7.6, 1.3 Hz, 1H), 7.02 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 6.67 (dt, *J* = 8.0, 0.8 Hz, 1H), 5.66 (ddt, *J* = 16.0, 10.8, 6.7 Hz, 1H), 4.91-4.85 (m, 2H), 4.23 (ddd, *J* = 8.7, 6.3, 2.4 Hz, 1H), 3.98 (br s, 1H), 3.78 (ddd, *J* = 9.9, 8.5, 6.1 Hz, 1H), 2.11 – 2.00 (m, 2H), 1.89 – 1.83 (m, 2H), 1.48 – 1.28 (m, 2H), 1.15 (ddd, *J* = 13.5, 11.8, 4.6 Hz, 1H), 0.81 (ddd, *J* = 13.5, 12.2, 4.6 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.2, 141.3, 138.3, 130.8, 129.9, 127.8, 127.7, 127.4, 126.6, 119.2, 114.8, 109.3, 96.9, 76.6, 66.7, 40.1, 38.2, 34.2, 25.1.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO^+$ 306.1852; Found 306.1852.

IR (ν_{max}, cm^{-1}) 3374 (w), 3051 (w), 2939 (m), 2871 (m), 1607 (m), 1485 (m), 1468 (m), 1317 (w), 1270 (w), 1223 (w), 1048 (m), 907 (m), 746 (s), 702 (s).



4.5.23x, N-(4-(8b-phenyl-2,3,4,8b-tetrahydro-3a*H*-furo[3,2-*b*]indol-3a-yl)butyl)aniline

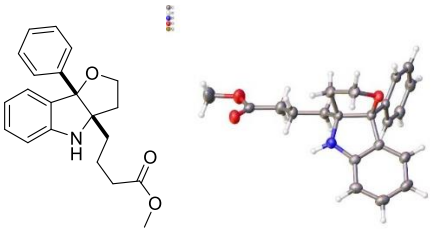
This compound was prepared following the general procedure **O** using substrate **4.5.9x** (35 mg, 0.09 mmol) as starting material. Yield: 66% (21.3 mg), isolated as brown oil. Purification: Flash chromatography (PE/EtOAc, 90:10), R_f = 0.58 (PE/EtOAc 65:35).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 7.22 – 7.12 (m, 3H), 7.03 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.77 (td, *J* = 7.4, 1.0 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.67 (d, *J* =7.9 Hz, 1H), 6.53 (d, *J* =8.6 Hz, 2H), 4.23 (ddd, *J* = 8.7, 5.2, 3.6 Hz, 1H), 3.77 (td, *J* = 8.8, 7.4 Hz, 1H), 3.71 (brs, 1H), 2.98 (t, *J* = 6.5 Hz, 2H), 2.14 – 1.99 (m, 2H), 1.50 – 1.28 (m, 4H), 1.23 – 1.14 (m, 1H), 0.90 – 0.83 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 151.1, 148.4, 141.3, 130.7, 129.9, 129.4, 127.84, 127.77, 127.5, 126.6, 119.2, 117.4, 112.8, 109.4, 96.9, 76.4, 66.6, 43.8, 40.2, 38.6, 30.1, 23.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{29}N_2O^+$ 385.2274; Found 385.2271.

IR (ν_{max}, cm^{-1}) 3392 (w), 3029 (w), 2936 (m), 2864 (m), 1600 (m), 1508 (m), 1478 (m), 1468 (m), 1317 (m), 1255 (m), 1173 (m), 1054 (m), 746 (s).



4.5.23y, methyl 4-(8b-phenyl-2,3,4,8b-tetrahydro-3a*H*-furo[3,2-*b*]indol-3a-yl)butanoate

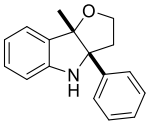
This compound was prepared following the general procedure **O** using substrate **4.5.9y** (30 mg, 0.08 mmol) as starting material. Yield: 58% (15.7 mg), isolated as purple crystals. Purification: Flash chromatography (PE/EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 7.18 (ddd, *J* = 8.0, 7.4, 1.3 Hz, 1H), 7.01 (ddd, *J* = 7.5, 1.4, 0.6 Hz, 1H), 6.76 (td, *J* = 7.4, 1.0 Hz, 1H), 6.68 (dt, *J* = 7.9, 0.8 Hz, 1H), 4.23 (ddd, *J* = 8.7, 6.3, 2.4 Hz, 1H), 4.13 (brs, 1H), 3.77 (ddd, *J* = 9.9, 8.6, 6.2 Hz, 1H), 3.60 (s, 3H), 2.15 – 2.05 (m, 4H), 1.73 – 1.53 (m, 2H), 1.12 (ddd, *J* = 13.5, 11.8, 4.6 Hz, 1H), 0.82 (ddd, *J* = 13.5, 12.2, 4.9 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 151.2, 141.2, 130.6, 129.9, 127.79, 127.76, 127.4, 126.6, 119.2, 109.4, 96.9, 76.3, 66.6, 51.6, 40.1, 38.1, 34.1, 21.0.

HRMS HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{21}H_{24}NO_3^+$ 338.1751; Found 338.1756.

IR (ν_{max}, cm^{-1}) 3381 (w), 3033 (w), 2943 (m), 2853 (w), 1737 (m), 1607 (m), 1482 (m), 1263 (m), 1170 (m), 1054 (m), 746 (s).



4.5.23z, 8b-methyl-3a-phenyl-3,3a,4,8b-tetrahydro-2*H*-furo[3,2-*b*]indole

This compound was prepared following the general procedure **O** using substrate **4.5.9z** (30 mg, 0.11 mmol) as starting material. Yield: 45% (12 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 96.4:3.6), R_f = 0.39 (PE/EtOAc 90:10).

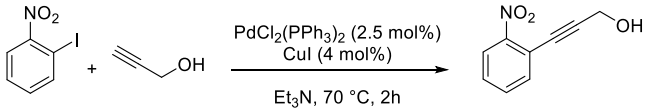
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.25 (m, 1H), 7.24 – 7.15 (m, 2H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 4.25 – 4.11 (m, 2H), 3.81 – 3.73 (m, 1H), 2.93 – 2.81 (m, 1H), 2.26 – 2.16 (m, 1H), 1.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.6, 142.8, 130.5, 129.9, 128.5, 127.5, 126.4, 124.6, 119.1, 108.6, 93.1, 77.6, 66.1, 41.1, 23.2.

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{18}NO^+$ 252.1383; Found 252.1380.

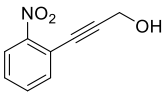
IR (ν_{max}, cm^{-1}) 3345 (w), 2968 (m), 2925 (m), 2878 (m), 1607 (m), 1484 (m), 1468 (m), 1446 (m), 1267 (m), 1105 (m), 1040 (m), 746 (s).

6.4.7. **Studies towards the total synthesis of phalarine**



4.7.9 **4.7.10** **4.7.11**

To a solution of 1-iodo-2-nitrobenzene **4.7.9** (20.0 g, 80.0 mmol, 1.0 equiv) in Et_3N (160 mL, 0.5 M) was added prop-2-yn-1-ol **4.7.10** (5.55 mL, 96 mmol, 1.2 equiv), $PdCl_2(PPh_3)_2$ (1.4 g, 2.0 mmol, 2.5 mol%) and CuI (610 mg, 3.2 mmol, 4 mol%). The reaction mixture was heated at 70 °C for 3 h, then water was added, the reaction crude was filtered through celite followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a next step without purification.

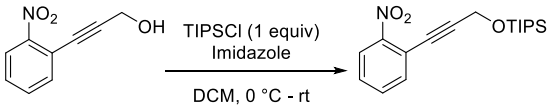


4.7.11, 3-(2-nitrophenyl)prop-2-yn-1-ol, known compound in the literature.

Yield: 67% (9.5 g), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 80:20), R_f = 0.31 (PE/EtOAc 70:30).

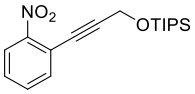
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, J = 8.3, 1.3 Hz, 1H), 7.62 (dd, J = 7.7, 1.6 Hz, 1H), 7.56 (td, J = 7.5, 1.3 Hz, 1H), 7.45 (ddd, J = 8.3, 7.3, 1.6 Hz, 1H), 4.55 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.8, 134.9, 133.0, 129.0, 124.7, 118.1, 95.4, 80.9, 51.8.



4.7.11 **4.7.12**

To a solution of 4-(2-nitrophenyl)but-3-yn-1-ol **4.7.11** (9.5 g, 54 mmol, 1.0 equiv) in DCM (120 mL, 0.5 M) was added TIPSCl (11.1 mL, 54 mmol, 1.0 equiv), followed by addition of imidazole (7.3 g, 107 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at rt for 3 h, then the reaction was quenched with $NaHCO_3$, followed by extraction with DCM (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to silica gel column chromatography to afford the desired protected alcohol **4.7.12.**



4.7.12, triisopropyl((3-(2-nitrophenyl)prop-2-yn-1-yl)oxy)silane

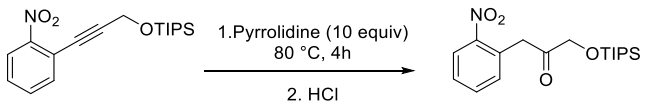
Yield: 90% (16.0 g), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.42 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.56 (td, *J* = 7.5, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.8, 7.3, 1.6 Hz, 1H), 4.67 (s, 2H), 1.14 – 1.05 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.9, 135.0, 132.8, 128.7, 124.7, 118.5, 96.3, 79.7, 52.7, 18.1, 12.2.

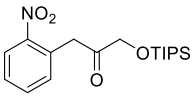
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{27}NNaO_3Si^+$ 356.1652; Found 356.1651.

IR (ν_{max}, cm^{-1}) 2947 (m), 2868 (m), 1608 (m), 1528 (s), 1460 (m), 1342 (s), 1263 (m), 1098 (s), 882 (s), 782 (m), 746 (s).



4.7.12 **4.7.13**

A solution of triisopropyl((3-(2-nitrophenyl)prop-2-yn-1-yl)oxy)silane **4.7.12** (8.0 g, 24 mmol, 1.0 equiv) in pyrrolidine (20 mL, 0.4 M) was heated at 80 °C for 3 h. Upon completion of the reaction, the excess of pyrrolidine was evaporated. The reaction mixture was then acidified with 1N HCl and stirred for 30 min. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.7.13**.



4.7.13, 1-(2-nitrophenyl)-3-((triisopropylsilyl)oxy)propan-2-one

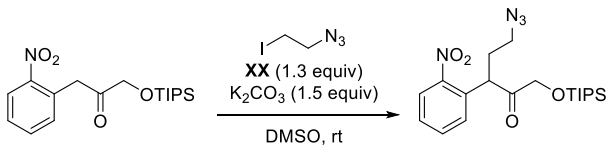
Yield: 88% (7.4 g), isolated as brown solid. Purification: Flash chromatography (PE/EtOAc, 97:2), R_f = 0.18 (PE/EtOAc 95:5).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46 (ddd, *J* = 8.9, 7.5, 1.5 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.5 Hz, 1H), 4.42 (s, 2H), 4.34 (s, 2H), 1.12 – 1.05 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 207.2, 148.8, 133.9, 133.7, 130.7, 128.5, 125.5, 70.1, 44.6, 18.1, 12.0.

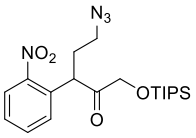
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{30}NO_4Si^+$ 352.1939; Found 352.1942.

IR (ν_{max}, cm^{-1}) 2954 (w), 2868 (w), 1726 (m), 1525 (m), 1464 (w), 1346 (m), 1162 (w), 1105 (m), 1058(w), 754 (s).



4.7.13 **4.7.14**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **4.7.13** (3.0 g, 8.7 mmol, 1.0 equiv) in DMSO (30 mL, 0.3 M), K_2CO_3 (1.8 g, 13 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of Alk-I (1-azido-2-iodoethane, 2.4 g, 12.2 mmol, 1.4 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.7.14**.



4.7.14, 5-azido-3-(2-nitrophenyl)-1-((triisopropylsilyl)oxy)pentan-2-one

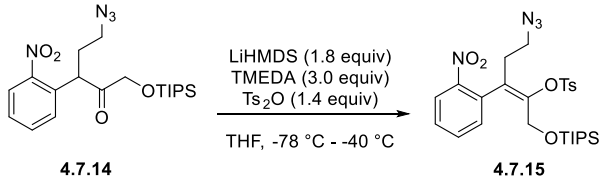
Yield: 75% (2.7 g), isolated as yellow solid. Purification: Flash chromatography (PE/EtOAc, 99.5:0.5), R_f = 0.9 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, J = 8.1, 1.4 Hz, 1H), 7.58 (td, J = 7.6, 1.4 Hz, 1H), 7.43 (ddd, J = 8.6, 7.5, 1.4 Hz, 1H), 7.38 (dd, J = 7.8, 1.4 Hz, 1H), 4.77 (t, J = 7.1 Hz, 1H), 4.32 (d, J = 0.8 Hz, 2H), 3.29 (t, J = 6.9 Hz, 2H), 2.48 – 2.36 (m, 1H), 2.09 – 1.93 (m, 1H), 0.98 (t, J = 7.1 Hz, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.0, 149.7, 133.4, 132.2, 129.8, 128.5, 125.3, 69.2, 49.5, 45.1, 31.4, 17.9, 12.0.

HRMS (nanochip-ESI/LTQ-Orbitrap) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{32}N_4NaO_4Si^+$ 443.2085; Found 443.2082.

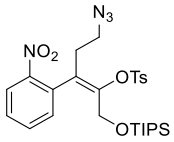
IR (ν_{max}, cm^{-1}) 3349 (w), 3051 (w), 2968 (m), 2871 (m), 1607 (m), 1482 (m), 1263 (w), 1102 (w), 1044 (w), 846 (w), 742 (s).



4.7.14 **4.7.15**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. To a solution of LiHMDS (1.0 M in toluene, 0.22 mL, 0.22 mmol, 1.8 equiv) was added TMEDA (0.04 mL, 0.36 mmol, 3.0 equiv). After stirring for 15 min., a solution of ketone **4.7.14** (50 mg, 0.12 mmol, 1.0 equiv) in toluene (0.5 mL, 0.25 M) was added dropwise. After stirring for 1 h, the reaction

mixture was placed in a 23 °C water and recrystallized Ts_2O (54 mg, 0.17 mmol, 1.4 equiv) was added portion-wise. The reaction was stirred vigorously for 3 h. After completion of the reaction, water was added slowly. The reaction mixture was extracted with DCM. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol tosylate **4.7.15**.



4.7.15, (E)-5-azido-3-(2-nitrophenyl)-1-((triisopropylsilyl)oxy)pent-2-en-2-yl 4-methylbenzenesulfonate

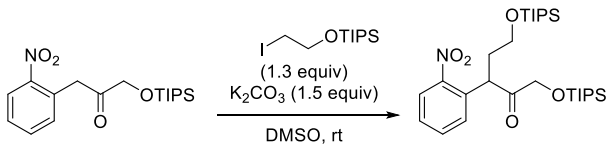
Yield: 55% (38 mg), isolated as yellow oil. Purification: Flash chromatography (PE/DCM, 65:35), R_f = 0.36 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.62 (td, *J* = 7.5, 1.4 Hz, 1H), 7.52 (td, *J* = 7.8, 1.5 Hz, 1H), 7.44 – 7.32 (m, 3H), 4.12 (d, *J* = 12.7 Hz, 1H), 3.94 (d, *J* = 12.7 Hz, 1H), 3.18 – 3.07 (m, 2H), 2.78 – 2.67 (m, 1H), 2.47 (s, 3H), 2.45 – 2.31 (m, 1H), 0.94 – 0.81 (m, 21H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.0, 146.2, 145.6, 134.0, 133.4, 132.27, 132.25, 130.2, 129.9, 129.6, 128.3, 125.1, 61.3, 48.7, 31.3, 21.9, 17.9, 12.0.

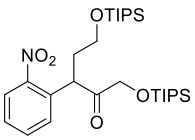
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{38}N_4NaO_6SSi^+$ 597.2174; Found 597.2179.

IR (ν_{max}, cm^{-1}) 2964 (m), 2906 (m), 2098 (m), 1727 (w), 1525 (s), 1348 (s), 1180 (s), 1064 (s), 912 (s), 758 (s).



4.7.13 **4.7.27**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **4.7.13** (2.0 g, 5.7 mmol, 1.0 equiv) in DMSO (20 mL, 0.3 M), K_2CO_3 (1.2 g, 8.5 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of Alk-I ((2-iodoethoxy)triisopropylsilane, 2.6 g, 7.9 mmol, 1.4 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.7.27**.



4.7.27, 3,3,11,11-tetraisopropyl-2,12-dimethyl-7-(2-nitrophenyl)-4,10-dioxa-3,11-disilatridecan-6-one

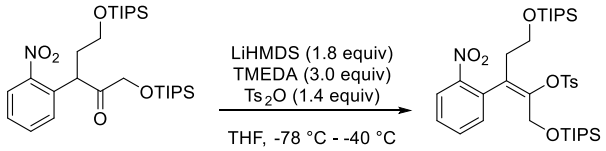
Yield: 46% (1.25 g), isolated as orange solid. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.53 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.1, 1.4 Hz, 1H), 7.55 (td, J = 7.6, 1.4 Hz, 1H), 7.48 (dd, J = 7.9, 1.5 Hz, 1H), 7.38 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 4.79 (t, J = 7.1 Hz, 1H), 4.44 (d, J = 1.1 Hz, 2H), 3.73 – 3.47 (m, 2H), 2.43 – 2.32 (m, 1H), 2.02 – 1.90 (m, 1H), 1.11 – 0.92 (m, 42H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 208.1, 149.9, 133.1, 133.0, 130.5, 128.0, 124.9, 69.3, 60.9, 44.3, 35.4, 18.1, 17.94, 17.91, 12.0.

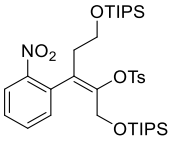
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{29}H_{53}NNaO_5Si_2^+$ 574.3354; Found 574.3358.

IR (ν_{max}, cm^{-1}) 2965 (m), 2864 (m), 1726 (w), 1528 (m), 1464 (m), 1349 (m), 1245 (m), 1101 (s), 1066 (s), 882 (s).



4.7.27 **4.7.28**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. To a solution of LiHMDS (1.0 M in toluene, 2.2 mL, 2.2 mmol, 1.8 equiv) was added TMEDA (0.38 mL, 3.6 mmol, 3.0 equiv). After stirring for 15 min., a solution of ketone **4.7.27** (670 mg, 1.2 mmol, 1.0 equiv) in toluene (5.0 mL, 0.25 M) was added dropwise. After stirring for 1 h, the reaction mixture was placed in a 23 °C water and recrystallized Ts_2O (550 mg, 1.7 mmol, 1.4 equiv) was added portion-wise. The reaction was stirred vigorously for 3 h. After completion of the reaction, water was added slowly. The reaction mixture was extracted with DCM. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol tosylate **4.7.28**.



4.7.28, (*E*)-3,3,11,11-tetraisopropyl-2,12-dimethyl-7-(2-nitrophenyl)-4,10-dioxa-3,11-disilatridec-6-en-6-yl 4-methylbenzenesulfonate

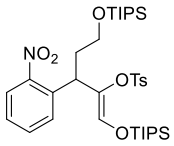
Yield: 15% (130 mg), isolated as yellow oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.73 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.00 (m, 1H), 7.94 (d, *J* = 8.7 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 4.19 (d, *J* = 12.4 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.58 – 3.48 (m, 1H), 3.48 – 3.39 (m, 1H), 2.73 – 2.63 (m, 1H), 2.45 (s, 3H), 2.23 – 2.09 (m, 1H), 1.00 – 0.80 (m, 42H)

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.9, 145.7, 145.2, 134.4, 133.1, 132.9, 132.88, 131.4, 130.0, 129.0, 128.4 124.7, 61.5, 60.8, 35.0, 21.8, 18.0, 17.9, 12.0.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{59}NNaO_7SSi_2^+$ 728.3443; Found 728.3464.

IR (ν_{max}, cm^{-1}) 2944 (s), 2868 (s), 1531 (s), 1462 (s), 1375 (s), 1350 (s), 1194 (s), 1106 (s), 1066 (s), 914 (s), 881 (s), 815 (s), 746 (s).



4.7.29, (*Z*)-3,3,11,11-tetraisopropyl-2,12-dimethyl-7-(2-nitrophenyl)-4,10-dioxa-3,11-disilatridec-5-en-6-yl 4-methylbenzenesulfonate

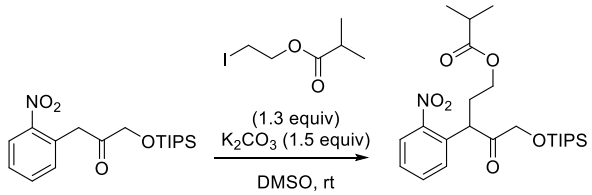
Yield: 21% (180 mg), isolated as orange oil. Purification: Flash chromatography (PE/EtOAc, 99:1), R_f = 0.69 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.35 (s, 1H), 4.39 (dd, *J* = 8.5, 6.2 Hz, 1H), 3.78 – 3.63 (m, 2H), 2.41 (s, 3H), 2.21 – 2.13 (m, 1H), 1.95 – 1.88 (m, 1H), 1.08 – 0.97 (m, 42H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 150.0, 144.4, 135.6, 135.2, 134.1, 132.5, 132.3, 130.2, 129.5, 127.7, 127.5, 124.6, 60.6, 36.8, 35.6, 21.7, 18.1, 17.8, 17.7, 17.6, 12.4, 12.03, 11.99.

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{36}H_{59}NNaO_7SSi_2^+$ 728.3443; Found 728.3459.

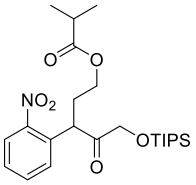
IR (ν_{max}, cm^{-1}) 2941 (m), 2865 (m), 1528 (s), 1462 (m), 1354 (s), 1191 (s), 1094 (s), 920 (s), 880 (s), 815 (s), 742 (s).



4.7.13 **4.7.31**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Into a 50 mL pressure resistant round bottomed flask was prepared a solution of ketone **4.7.13** (2.0 g, 5.6 mmol, 1.0 equiv) in DMSO (20 mL, 0.3 M), K_2CO_3 (1.2 g, 8.5 mmol, 1.5 equiv) was added to the reaction mixture, followed by addition of Alk-I (2-iodoethyl isobutyrate, 1.9 g, 7.9 mmol, 1.4 equiv). The reaction mixture was stirred for 3 h. After completion of the reaction, NH_4Cl was added slowly

at 0 °C to quench the reaction. The reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired ketone **4.7.31**.



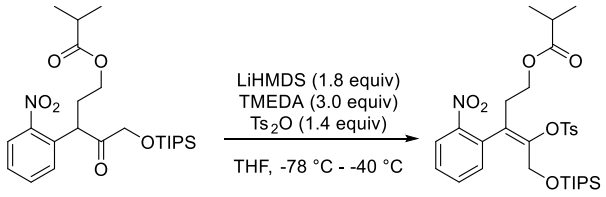
4.7.31, 3-(2-nitrophenyl)-4-oxo-5-((triisopropylsilyl)oxy)pentyl isobutyrate

Yield: 49% (1.3 g), isolated as white solid. Purification: Flash chromatography (PE/EtOAc, 97:3), R_f = 0.46 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.55 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 – 7.34 (m, 2H), 4.80 (t, *J* = 7.2 Hz, 1H), 4.32 (s, 2H), 4.10 – 3.90 (m, 2H), 2.55 – 2.34 (m, 2H), 2.15 – 2.03 (m, 1H), 1.12 (dd, *J* = 7.0, 1.4 Hz, 6H), 0.98 – 0.91 (m, 21H).

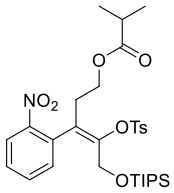
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{45}NNaO_8SSi^+$ 642.2527; Found 642.2536.

IR (ν_{max}, cm^{-1}) 2938 (m), 2870 (m), 1730 (s), 1528 (s), 1471 (s), 1348 (s), 1153 (s), 1110 (s), 1071 (s), 883 (s), 790 (s), 746 (s).



4.7.31 **4.7.32**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. To a solution of LiHMDS (1.0 M in toluene, 1.0 mL, 1.0 mmol, 1.8 equiv) was added TMEDA (0.3 mL, 1.6 mmol, 3.0 equiv). After stirring for 15 min., a solution of ketone **4.7.31** (250 mg, 0.54 mmol, 1.0 equiv) in toluene (2.0 mL, 0.25 M) was added dropwise. After stirring for 1 h, the reaction mixture was placed in a 23 °C water and recrystallized Ts_2O (250 mg, 0.8 mmol, 1.4 equiv) was added portion-wise. The reaction was stirred vigorously for 3 h. After completion of the reaction, water was added slowly. The reaction mixture was extracted with DCM. The combined organic layers were dried, filtered and concentrated under reduced pressure. The residue was directly subjected to silica gel column chromatography to afford the desired enol tosylate **4.7.32**.



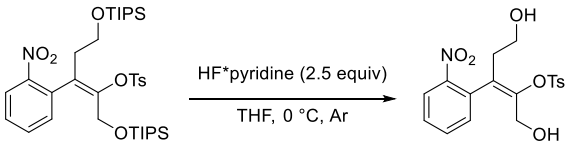
4.7.32, (*E*)-3-(2-nitrophenyl)-4-(tosyloxy)-5-((triisopropylsilyl)oxy)pent-3-en-1-yl isobutyrate

Yield: 25% (80 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2), R_f = 0.19 (PE/EtOAc 90:10).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.59 (td, *J* = 7.5, 1.4 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.42 – 7.35 (m, 2H), 4.17 (d, *J* = 12.5 Hz, 1H), 4.00 – 3.87 (m, 2H), 3.81 – 3.71 (m, 1H), 2.88 – 2.76 (m, 1H), 2.46 (s, 3H), 2.37 (p, *J* = 7.0 Hz, 1H), 2.11 – 2.01 (m, 1H), 1.07 – 1.04 (m, 6H), 0.96 – 0.79 (m, 21H).

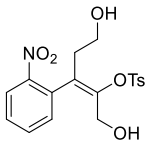
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{31}H_{45}NNaO_8SSi^+$ 642.2527; Found 642.2536.

IR (ν_{max}, cm^{-1}) 2942 (w), 2866 (w), 1723 (m), 1528 (m), 1467 (m), 1360 (m), 1269 (m), 1186 (m), 1070 (m), 916 (m), 754 (s).



4.7.28 **4.7.36**

To a solution of alkene **4.7.28** (210 mg, 0.3 mmol, 1.0 equiv) in THF (3 mL, 0.1 M) at 0 °C was added dropwise HF·pyridine (0.72 mL). After being stirred overnight at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layers were combined, washed with brine and dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the diol **4.7.36**.



4.7.36, (*E*)-1,5-dihydroxy-3-(2-nitrophenyl)pent-2-en-2-yl 4-methylbenzenesulfonate

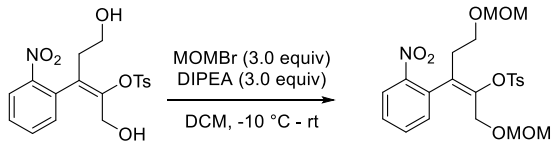
Yield: 33% (40 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 10:10.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.66 (td, *J* = 7.5, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.49 – 7.39 (m, 3H), 3.99 (d, *J* = 14.0 Hz, 1H), 3.96 (d, *J* = 14.0 Hz, 1H), 3.63 – 3.53 (m, 1H), 3.44 – 3.36 (m, 1H), 2.90 – 2.80 (m, 1H), 2.49 (s, 3H), 2.44 – 2.36 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.1, 146.1, 145.8, 133.6, 133.1, 132.4, 131.9, 131.5, 130.3, 129.6, 128.4, 125.1, 60.9, 59.7, 34.8, 22.0.

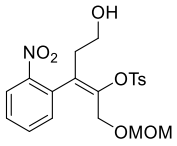
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{19}NNaO_7S^+$ 416.0774; Found 416.0780.

IR (ν_{max}, cm^{-1}) 2934 (m), 2360 (m), 1528 (s), 1353 (s), 1179 (s), 1040 (s), 906 (s), 765 (s).



4.7.36 **4.7.37**

To a solution of the diol **4.7.36** (40 mg, 0.1 mmol, 1.0 equiv) in dry DCM (0.4 mL, 1.0 M) was added dropwise DIPEA (0.02 mL, 0.3 mmol, 3.0 equiv) at 0 °C under Ar. The solution was stirred for 15 min at room temperature, cooled back to 0 °C then MOMBr (0.05 mL, 0.3 mmol, 3.0 equiv) was added dropwise. The reaction mixture was warmed to room temperature and stirred until full conversion (3 h). The reaction was quenched with a satd. aq. NH_4Cl solution and extracted with DCM. The combined organic layers were washed with cold water, dried and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography (PE:EtOAc) to give the alkene **4.7.37**.



4.7.37, (*E*)-7-(2-nitrophenyl)-2,4,10,12-tetraoxatridec-6-en-6-yl 4-methylbenzenesulfonate

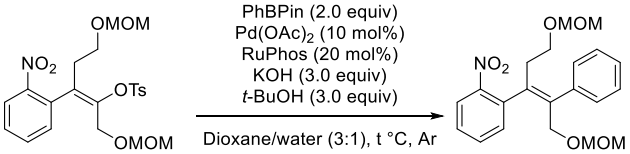
Yield: 39% (20 mg), isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 99:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.01 (m, 1H), 7.96 (d, *J* = 8.1 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 7.6, 1.4 Hz, 1H), 4.40 (d, *J* = 6.6 Hz, 1H), 4.38 (d, *J* = 6.6 Hz, 1H), 4.02 (dd, *J* = 14.0, 6.1 Hz, 1H), 3.94 (dd, *J* = 14.0, 6.7 Hz, 1H), 3.35 – 3.27 (m, 2H), 3.22 (s, 3H), 2.72 (dt, *J* = 14.6, 7.3 Hz, 1H), 2.56 (t, *J* = 7.0 Hz, 1H), 2.49 (s, 3H), 2.35 (dt, *J* = 15.2, 6.4 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 148.2, 145.9, 145.7, 133.5, 133.3, 132.4, 132.0, 131.2, 130.3, 129.5, 128.4, 125.1, 96.4, 64.9, 60.9, 55.4, 53.6, 31.8, 22.8, 21.9, 14.3.

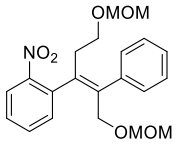
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{23}NNaO_8S^+$ 460.1037; Found 460.1044.

IR (ν_{max}, cm^{-1}) 2929 (m), 2858 (m), 2363 (m), 1528 (m), 1354 (m), 1080 (m), 910 (m).



4.7.37 **4.7.38**

Glassware and stirring bar were stored in the oven and the reaction was carried out under inert atmosphere and dry conditions. Dioxane and water were degassed with Freeze-pump technique. To a solution of enol tosylate **4.7.37** (6.0 mg, 0.013 mmol, 1.0 equiv) in dioxane/water (3:1, 0.02 M) were added phenyl boronic acid (5.0 mg, 0.026 mmol, 2.0 equiv), $Pd(OAc)_2$ (0.4 mg, 0.001 mmol, 10 mol%), RuPhos (1.2 mg, 0.03 mmol, 20 mol%), KOH (2.1 mg, 0.04 mmol, 3.0 equiv) and *t*-BuOH (0.004 mL, 0.04 mmol, 3.0 equiv). The reaction mixture was heated at 80 °C overnight, then water was added, followed by extraction with EtOAc (3 times). The organic layers were combined, washed with brine and dried over sodium sulfate. The residue was subjected to a silica gel column chromatography (PE:EtOAc) to give the alkene **4.7.38**.



4.7.38, (*Z*)-7-(2-nitrophenyl)-6-phenyl-2,4,10,12-tetraoxatridec-6-ene

Yield: 34%, isolated as colorless oil. Purification: Flash chromatography (PE/EtOAc, 98:2).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.56 – 7.47 (m, 1H), 7.47 – 7.34 (m, 5H), 7.30 (t, *J* = 6.1 Hz, 1H), 4.41 (d, *J* = 6.6 Hz, 1H), 4.40 (d, *J* = 6.6 Hz, 1H), 4.35 (d, *J* = 6.6 Hz, 1H), 4.32 (d, *J* = 6.6 Hz, 1H), 3.92 (d, *J* = 11.1 Hz, 1H), 3.88 (d, *J* = 11.2 Hz, 1H), 3.47 – 3.40 (m, 1H), 3.37 – 3.28 (m, 1H), 3.21 (s, 3H), 3.00 (s, 3H), 2.82 – 2.72 (m, 1H), 2.51 – 2.41 (m, 1H).

IR (ν_{max}, cm^{-1}) 2947 (m), 2868 (m), 1607 (m), 1510 (m), 1374 (m), 1245 (m), 1176 (s), 1048 (s), 756 (s).

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Curriculum Vitae

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EDUCATION

October 2018 – October 2022 **PhD** in Organic Chemistry – **École Polytechnique Fédérale de Lausanne**, Switzerland

September 2016 – May 2018 **Master** in Organic chemistry – **École Polytechnique**, Paris, France.

September 2012 – May 2016 **Bachelor** in Organic chemistry – **Saint-Petersburg State University**, Saint-Petersburg, Russia.

RESEARCH EXPERIENCE

October 2018 – October 2022 **PhD** (4 years, EPFL, Lausanne, Switzerland)
Professor Jieping Zhu

- Synthesis of indolenines and furo[3,2-*b*]indoles by $TiCl_3$-mediated reductive cyclization of tetrasubstituted alkenes and enol ester bearing a 2-nitrophenyl substitutent
- Synthetic studies towards the total synthesis of Trigonoliimine C

February 2018 – August 2018 **Master Thesis** (7 months, Institut de Chimie des Substances Naturelles CNRS, Paris, France)
Professor Géraldine Masson

- Tritylium assisted iodine catalysis for the synthesis of unsymmetrical triarylmethanes
- Visible light-triggered C–C and C–N bonds formation by C–S bonds cleavage of benzylic thioethers

April 2017 – July 2017 **Internship Master 1** (4 months, Institut de Chimie des Substances Naturelles CNRS, Paris, France)
Professor Ali Al-Mourabit

- Synthesis of new inhibitors of Aurora kinase B

June 2015 – September 2015 **Internship** (4 months, Bowling Green State University, Bowling Green, Ohio, US)
Professor Jeremy K. Klosterman

- Synthesis of new mixed Metal-Organic Materials of Zn and Cu

March 2011 – August 2016 **Bachelor thesis** (4 years, Saint-Petersburg State University, Saint-Petersburg, Russia)
Professor Vadim Yu. Kukushkin

- New acyclic diaminocarbene complexes of Pd(II): synthesis, photophysical properties and catalytic activity in Sonogashira reaction

PUBLICATIONS:

1. **Boyarskaya, D.V.;** Ongaro, A.; Piemontesi, C.; Wang, Q.; Zhu, J. *Org. Lett.* **2022**, *24*, 7004–7008.
2. Juillet C.; Ermolenko, L.; **Boyarskaya, D.V.**; Baratte, B.; Josselin, B.; Nedev, H.; Bach, S.; Iorga, B.I.; Bignon, J.; Ruchaud, S.; Al-Mourabit, A. *J.Med.Chem.* **2021**, *64*, 1197-1219.
3. **Boyarskaya, D.V.**; Chulkova, T.G. *Rus. J .Org. Chem.* **2020**, *56*, 1937-1941.
4. Courant T.; Lombard, M.; **Boyarskaya, D.V.**; Neuville, L.; Masson, G. *Org.Biomol.Chem.* **2020**, *18*, 6502-6508.
5. **Boyarskaya, D.V.**; Bulatov, E.; Boiarskaia, I.A.; Chulkova, T.G.; Rassadin, V.A.; Tolstopjatova, E.G.; Kolesnikov, I.E.; Avdovtceva, M.S.; Panikorovskii, T.L.; Suslonov, V.V.; Haukka, M. *Organometallics* **2019**, *38*, 300-309.
6. Lanzi, M.; Merad, J.; **Boyarskaya, D.V.**; Maestri, G.; Allain, C.; Masson, G. *Org. Lett.* **2018**, *20*, 5247–5250.
7. **Boyarskaya, D.V.**; Kinzhalov, M.; Suslonov, V.; Boyarskiy, V.P. *Inorg. Chim. Acta* **2017**, *458*, 190-198.
8. Afanasenko, A.M.; **Boyarskaya, D.V.**; Boiarskaia, I.A.; Chulkova, T.G.; Grigoriev, Y.; Kolesnilov, I.E.; Avdovtceva, M.S.; Panikorovskii, T.L.; Panin, A.; Vereshchagin, A.; Elinson, M. *J.Mol.Struc.* **2017**, *1146*, 554-561.
9. **Boyarskaya D.V.**, Boyarskii V.P. *Rus. J. Gen. Chem.* **2016**, *86*, 2033–2036.

POSTER PRESENTATIONS:

1. Boyarskaya D.V., Piemontesi C.; Wang, Q.; Zhu, J. *17th Belgian Organic Synthesis Symposium*. **3.07-8.07.2022**, Namur, Belgium. Book of abstracts.
2. Boyarskaya D.V., Boyarskaya I. A., Chulkova T.G. *Cluster of Conferences of Organic Chemistry* "OrgChem-2016". **27.06-01.07.16**, Saint-Petersburg, Russia. Book of abstracts.
3. Boyarskaya D.V., Chulkova T.G. *IV Russian conference of organic chemistry* – **22.11–27.11.15**, Moscow, Russia. Book of abstracts.

AWARDS

September 2017	Grand prize for research internship of Ecole Polytechnique
September 2016 – August 2018	Scholarship from Ecole Polytechnique Foundation
September 2014 – August 2016	Advanced academic scholarship of SPbSU

MANAGEMENT AND TEACHING EXPERIENCE

- Mentorship of a Master student in the laboratory during his thesis work (6 months)
- Teaching assistant for undergraduate practical and theoretical organic chemistry courses and M.Sc. seminars on total synthesis