Palladium-Catalyzed Synthesis of Ketenimines from Isocyanides and Synthetic Studies Towards the Total Synthesis of Mersilongine

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Abstract

In the first chapter of this thesis, the development of two new reactions for the synthesis of vinyl ketenimines and α-oxo-ketenimines from isocyanides is presented. These palladium-catalyzed transformations both feature an isocyanide insertion / β-hydride elimination sequence. Vinyl ketenimines were generated from allyl carbonates and were then hydrolyzed to β,γ-unsaturated carboxamides or converted to 1,5-disubstituted tetrazoles by treatment with hydrazoic acid. α-Oxo-ketenimines were efficiently prepared from α-halocarbonyl compounds with broad functional group tolerance and their reactivity profile was investigated. This led to the development of a one-pot three-component synthesis of pharmaceutically relevant tetrasubstituted 5-aminopyrazoles and to the synthesis of β-ketoamidines in high yields.

In the second chapter, synthetic studies towards the total synthesis of the alkaloid Mersilongine are presented. An advanced intermediate containing the quinolinic / bridged aminal core of this natural product was synthesized from vanillin in 20 steps. Three key transformations were successfully exploited or developed in this synthetic sequence : 1) A high yielding Tsuji-Trost reaction to create two adjacent tertiary carbon centers with high diastereoselectivity, 2) a substrate-controlled fully diastereoselective α-allylation of a lactone to form a quaternary center, 3) the first application of the iORC sequence for the synthesis of a quinolinic scaffold having three contiguous chiral centers. (iORC = integrated Oxidation / Reduction / Cyclization)

Keywords

Catalysis, palladium, isocyanide, ketenimine, total synthesis, natural product, alkaloid, Mersilongine, iORC

Résumé

Le premier chapitre de cette thèse présente le développement de nouvelles réactions pour la synthèse de céténimines vinyliques et d'α-oxo-céténimines. Ces transformations catalysées par du palladium suivent toutes les deux une séquence composée d'une insertion d'isonitrile suivie par une β-élimination d'hydrure. Les céténimines vinyliques ont été générés à partir de carbonates allyliques et ont ensuite été hydrolysés en amides α,β-insaturés ou convertis en tetrazoles 1,5-disubstitués par traitement avec de l'acide hydrazoïque. Les α-oxo-céténimines ont été préparés efficacement à partir de composés α-halocarbonylés avec une large tolérance de groupes fonctionnels et leur réactivité a été étudiée. Ces investigations ont conduit au développement d'une synthèse monotope tricomposants de 5-aminopyrazoles tetrasubstitués potentiellement intéressants pharmacologiquement. La synthèse de β-cétoamidines a aussi été effectuée avec des rendements élevés.

Le second chapitre présente les avancées en vue de la synthèse totale de l'alcaloïde Mersilongine. Un intermédiaire avancé a été synthétisé en 20 étapes à partir de la vanilline et contient le motif quinoléinique principal constitué également d'un aminal ponté. Trois transformations clés ont été exploitées ou développées avec succès dans cette séquence synthétique : 1) Une réaction de Tsuji-Trost pour créer deux centres tertiaires adjacents avec hauts rendement et diastéréosélectivité, 2) une α-allylation de lactone totalement diastéréosélective controllée par le substrat pour former un centre quaternaire, 3) la première application de la séquence iORC pour la synthèse d'un motif quinoléinique portant trois centres chiraux contigus. (iORC = integrated Oxidation / Reduction / Cyclization)

Mots-clés :

Catalyse, palladium, isonitrile, céténimine, synthèse totale, produit naturel, alcaloïde, Mersilongine, iORC

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List of Abbreviations

AAC	Azide-Alkyne cycloaddition
Ac	Acetyl
AD	Asymmetric dihydroxylation
Aq.	Aqueous
Ar	Aryl
atm	Atmosphere
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
brsm	Based on recovery of starting material
Bu	Butyl
cacld	Calculated
Cat.	Catalytic
Conc.	Concentrated
COSY	Correlation spectroscopy
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DavePhos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
Dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azidocarboxylate
DEPT	Distortionless enhancement by polarization transfer
DFT	Density functional theory
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethylsulfoxide
DPAS	Dihydroprecondylocarpine synthase
DPPA	Diphenyl phosphoryl azide
dppe	1,2-Bis(diphenylphosphino) ethane
dppf	1,1′-Ferrocenediyl-bis(diphenyl phosphine)
dppp	1,3-Bis(diphenylphosphino) propane
dr	Diastereomeric ratio
EDC	*N*-Ethyl-*N*′-(3-dimethyl aminopropyl)carbodiimide hydrochloride
ee	Enantiomeric excess
equiv.	Equivalents
ESI	Electron-spray ionization
Et	Ethyl
FCC	Flash column chromatography
GPP	Geranyl pyrophosphate
HFIP	Hexafluoroisopropanol
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
HWE	Horner-Wadsworth-Emmons
iORC	integrated Oxidation / Reduction / Cyclization
***i*Pr**	Isopropyl
IR	Infrared
LDA	Lithium diisopropylamide
mCPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Mes	Mesityl

m.p.	Melting point
Ms	Mesyl
MS	Molecular sieves
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine oxide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Spectroscopy
Nu	Nucleophile
PAS	Precondylocarpine Ace tate Synthase
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PE	Petroleum ether
PEPPSI-IPr	1,3-Bis(2,6-Diisopropylphenyl) imidazol-2-ylidene
Ph	Phenyl
Phen	Phenantroline
Pin	Pinacol
Rf.	Retention factor
rt	Room temperature
S_N	Nucleophilic substitution
***t*Bu**	*tert*-Butyl
TBA	Tetrabutylammonium
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
Tf	Triflate
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
Tol	Tolyl
Ts	Tosylate
TS	Tabersonine Synthase
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

List of Schemes

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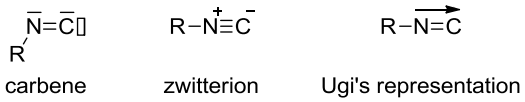
CHAPTER 1 Palladium-Catalyzed Synthesis of Ketenimines from Isocyanides

1.1 Introduction

1.1.1 Structure and Synthesis of Isocyanides

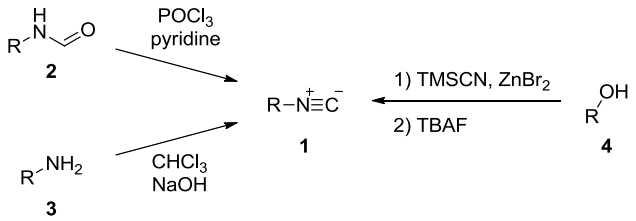
Isocyanides have been known since the 1850s and their electronic structure is usually described in the literature by either a carbenic form or a zwitterionic form (Scheme 1). In 2012, Fleurat-Lessart and coworkers performed high level Valence Bond calculations which supported predominantly the carbenoic structure, with a secondary zwitterionic character, although isocyanides exhibit a linear geometry.[1] π-Back donation of the nitrogen π lone pair to the carbon vacancy would explain this linear geometry. Therefore, the representation of isocyanides proposed by Ugi pointing out this electron donation would be the ideal picture.[2] The carbenoic nature of the terminal carbon atom is highlighted in the famous three-component Passerini[3] and the four-component Ugi[4] reactions. Interestingly, the isocyano group is isoelectronic with carbon monoxide, which has already found a broad scope of applications in organometallic chemistry, paving the way for isocyanides. Furtheremore, compared to carbon monoxide, isocyanides offer the advantage of bearing a tunable substituent for the synthesis of more complex products.



Scheme 1 : *Possible representations of the electronic structure of isocyanides*

[1] Ramozzi, R.; Chéron, N.; Braïda, B.; Hiberty, P. C.; Fleurat-Lessard, P. *New J. Chem.* **2012**, *36* (5), 1137–1140.
[2] Ugi, I. *Isonitrile Chemistry*, Academic Press, New York, 1971, 1–67.
[3] a) Passerini, M.; Simone, L. *Gazz. Chim. Ital.* **1921**, *51*, 126-129. b) For a review, see : Banfi, L.; Riva, R., The Passerini Reaction, *Organic Reactions*, John-Wiley & Sons, Inc., **2004**.
[4] Ugi, I.; Felzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.

Isocyanides **1** are classically synthesized by dehydration of formamides **2**,[5] reaction of primary amines **3** with dichlorocarbene (called carbylamine reaction or Hofmann isocyanide synthesis),[6] or S_N2 reaction of tertiary alcohols **4** with TMSCN followed by cleavage of the silyl group (Scheme 2).[7,8]

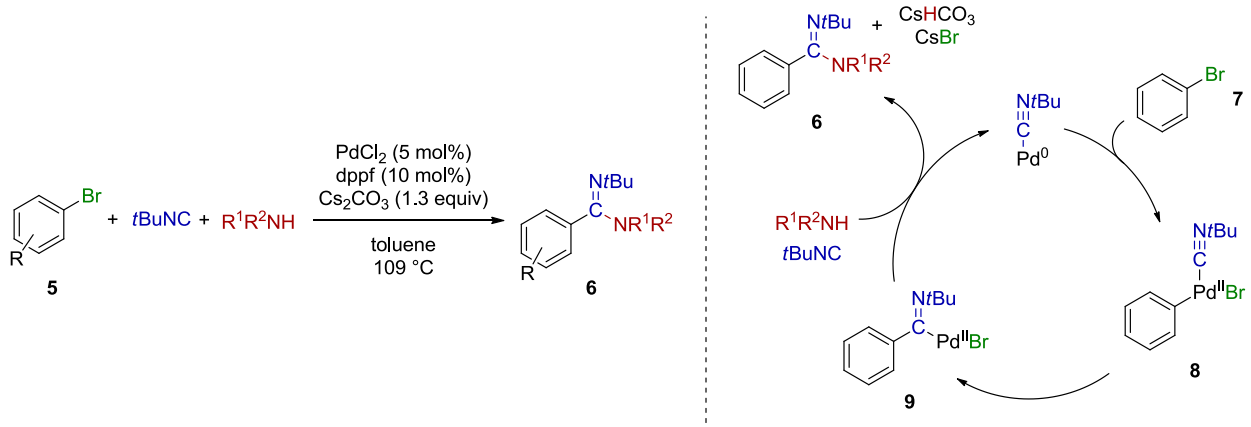


Scheme 2 : *Classical syntheses of isocyanides*

1.1.2 Palladium-Catalyzed Insertions of Isocyanides

Isocyanides have recently been exploited as C1-building blocks in palladium-catalyzed reactions.[9] After the first example of Kosugi and Migita published in 1986,[10] Whitby and coworkers initiated this growing research field in 2000 (Scheme 3).[11] They reported a multicomponent reaction between aryl bromides **5**, *tert*-butyl isocyanide and amines for the synthesis of imidates **6**. The following simplified mechanism was proposed for this transformation : after oxidative addition of a palladium(0)-species into aryl bromide **7**, migratory insertion of the isocyanide from complex **8** would give imidoylpalladium intermediate **9**. This electrophilic complex would finally be trapped by amines to deliver imidates **6** and regenerate the active catalyst. For clarity purposes, only one isocyanide was represented on the scheme, but in reality the palladium may accommodate several isocyanides.

[5] For example, see : Ugi, I.; Meyr, R.; Lipinski, M.; Bodesheim, F.; Rosendahl, F. *Org. Synth.* **1961**, *41*, 13.
[6] For example, see : Gokel, G. W.; Widera, R. P.; Weber, W. P. *Org. Synth.* **1976**, *55*, 96.
[7] For an example with $ZnBr_2$, see : Kitano, Y.; Chiba, K.; Tada, M. *Tetrahedron Lett.* **1998**, *39* (14), 1911–1912.
[8] For examples with other reaction conditions, see : a) Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1981**, *46* (26), 5445–5447. b) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. *Nature* **2013**, *501* (7466), 195–199.
[9] For reviews, see : a) Tobisu, M.; Imoto, S.; Ito, S.; Chatani, N. *J. Org. Chem.* **2010**, *75* (14), 4835–4840. b) Lygin, A. V.; de Meijere, A. *Angew. Chem. Int. Ed.* **2010**, *49* (48), 9094–9124. c) Lang, S. *Chem. Soc. Rev.* **2013**, *42* (12), 4867-4880. d) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2013**, *52* (28), 7084–7097. e) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42* (12), 5257–5269.
[10] Kosugi, M.; Ogata, T.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1986**, *15* (7), 1197–1200.
[11] a) Saluste, C. G.; Whitby, R. J.; Furber, M. A Palladium-Catalyzed Synthesis of Amidines from Aryl Halides. *Angew. Chem. Int. Ed.* **2000**, *39* (22), 4156–4158. b) Saluste, C. G.; Crumpler, S.; Furber, M.; Whitby, R. J. *Tet. Lett.* **2004**, *45* (38), 6995–6996. c) Tetala, K. K. R.; Whitby, R. J.; Light, M. E.; Hurtshouse, M. B. *Tet. Lett.* **2004**, *45* (38), 6991–6994.

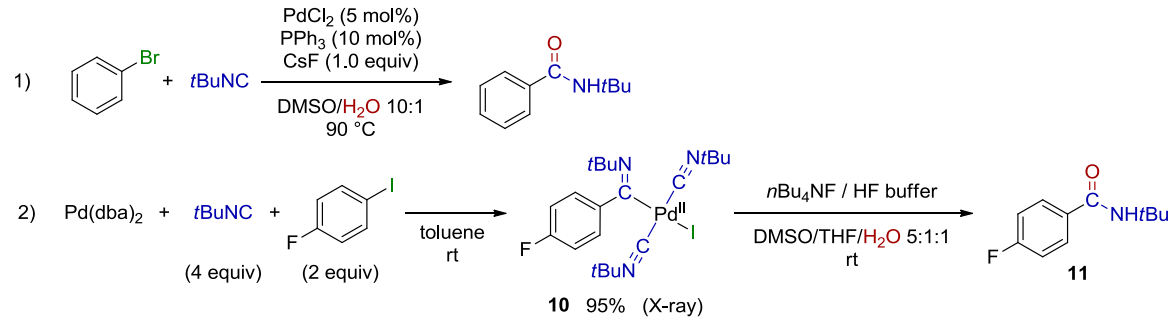


Scheme 3 : *Whitby and coworkers' pionneering work on palladium-catalyzed isocyanide insertions*

This reaction is closely related to palladium-catalyzed carbon monoxide insertions. Although isocyanides exist with hundreds of different substituents, many reactions only tolerate *tert*-butyl isocyanide : isocyanides being excellent σ-donor ligands, less bulky isocyanides tend to irreversibly saturate all coordination sites of the palladium, rendering the catalyst inactive. Contiguous poly-insertions may also occur with less bulky isocyanides and electron-poor isocyanides may not insert.

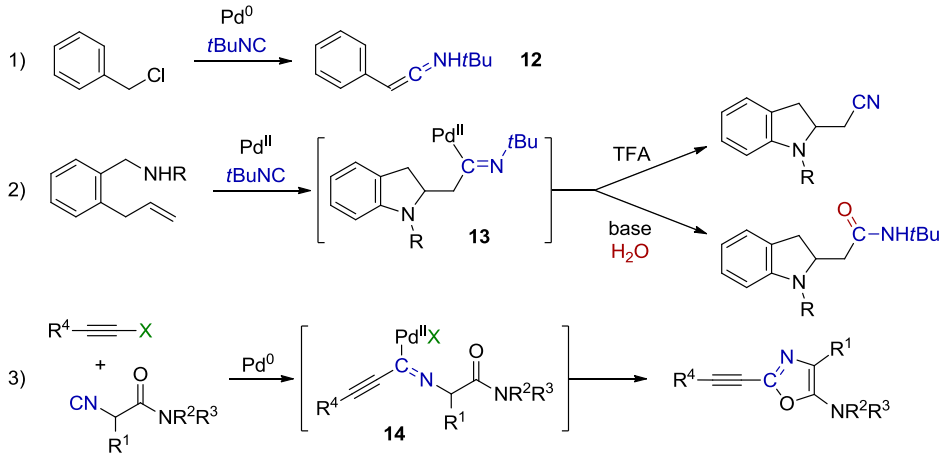
In 2016, Ciofini, El Kaïm, Grimaud and coworkers studied in detail the multiple roles of isocyanides in imidoylative couplings.[12] Their work was based on a reaction depicted in Scheme 4 (equation 1). They first showed that PPh_3 was not necessary because isocyanides are able to reduce Pd(II) to Pd(0)[13] and act as ligands to stabilize the metal center. DFT calculations also revealed that complex [Pd^0(*t*BuNC)$_2$] bearing two isocyanides is the most stable species. This is in accordance with the interpretation of kinetic data showing that dissociation of an isocyanide is not necessary for the oxidative addition step. Then, preparation of complex **10** and analysis of its structure by X-ray diffraction exhibited a *trans* square planar geometry. Isolation of this complex demonstrated that migratory insertion is faster than oxidative addition under these reaction conditions (confirmed by DFT calculations). No reaction was observed when complex **10** was stirred in DMSO with 10 equivalents of *t*BuNC for 72 h, showing its stability towards poly-insertion of *t*BuNC. However, when complex **10** was submitted to an F^-/HF buffer in an aqueous-organic solvent mixture, amide **11** was obtained exclusively, as expected. Similar computational mechanistic studies were carried out by Ren and coworkers.[14]

[12] Perego, L. A.; Fleurat-Lessard, P.; El Kaïm, L.; Ciofini, I.; Grimaud, L. *Chem. Eur. J.* **2016**, *22* (43), 15491–15500.
[13] a) Ito, Y.; Suginome, M.; Matsuura, T.; Murakami, M. *J. Am. Chem. Soc.* **1991**, *113* (23), 8899–8908. b) Liu, Y.-J.; Xu, H.; Kong, W.-J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Nature* **2014**, *515* (7527), 389–393.
[14] Liang, Y.; Ren, Y.; Jia, J.; Wu, H.-S. *J Mol Model* **2016**, *22* (3), 53.



Scheme 4 : *Mechanistic studies for the palladium-catalyzed imidoylative coupling of aryl halides with isocyanides*

Most of the reactions developed in this field involved migratory insertions of isocyanides into C(sp^2)-Pd bonds. Beside the contributions of our research group, insertions into C(sp^3)-Pd or C(sp)-Pd bonds remain scarce (Scheme 5). In 1977, Saegusa and coworkers reported the synthesis of ketenimine **12** from benzyl chloride and proposed an insertion into a benzylic C(sp^3)-Pd bond (equation 1).[15] The reaction depicted in equation 2 featuring a σ-alkylpalladium complex **13** reported by Jiang and coworkers in 2014 is a notable example.[16] In 2014 was also disclosed the first insertion into a C(sp)-Pd bond giving intermediate **14** by Zhu and coworkers (equation 3).[17]

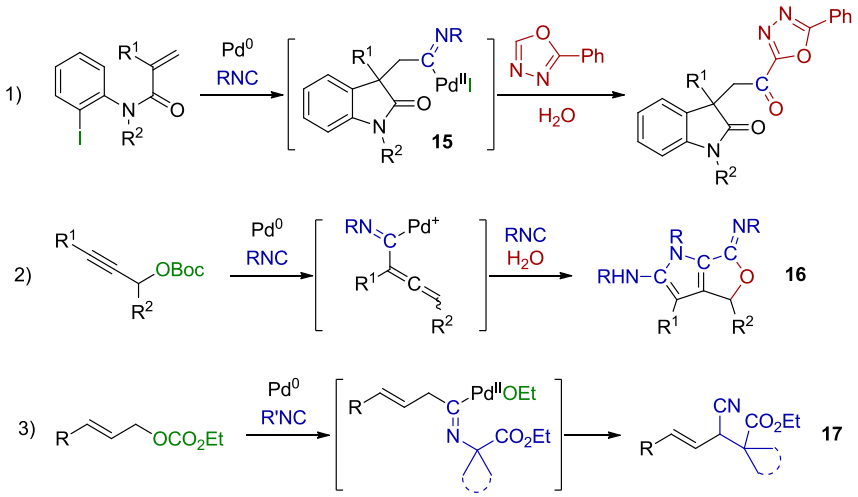


Scheme 5 : *Palladium-catalyzed isocyanide insertions into C(sp^3)-Pd and C(sp) bonds*

Over the last years and in parallel to the work presented in this thesis, our research group reported three novel methodologies involving palladium-catalyzed isocyanide insertions (Scheme 6). 3,3-Disubstituted oxindoles were synthesized, featuring the migratory insertion of an isocyanide into a C(sp^3)-Pd intermediate giving imidoylpalladium complex **15** (equation 1).[18] Reaction of isocyanides with

[15] Ito, Y.; Hirao, T.; Ohta, N.; Saegusa, T. *Tet. Lett.* **1977**, *18* (11), 1009–1012.
[16] Jiang, H.; Gao, H.; Liu, B.; Wu, W. *Chem. Commun.* **2014**, *50* (97), 15348–15351.
[17] Wang, J.; Luo, S.; Huang, J.; Mao, T.; Zhu, Q. *Chem. Eur. J.* **2014**, *20* (35), 11220–11224.
[18] Kong, W.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55* (33), 9714–9718.

propargyl carbonates delivered bicyclic pyrroles **16** after a complex reaction pathway in which three isocyanides were incorporated into the final products (equation 2).[19] Concurrently, an almost identical reaction was published by Jiang and coworkers.[20] An intriguing 1,1-carbocyanation of allyl carbonates was also reported (equation 3).[21] This work was derived from the methodology presented in chapter 1.2. A radical pathway was proposed to account for the formation of the products **17**.

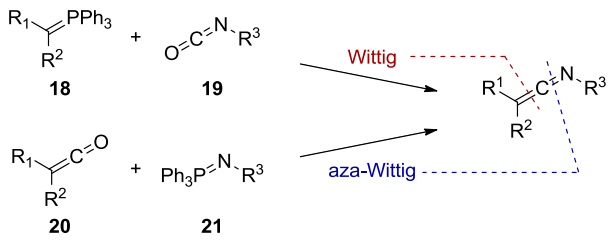


Scheme 6 : *Our research group's contributions to the field of palladium-catalyzed isocyanide insertions*

1.1.3 Synthesis and Reactivity of Ketenimines

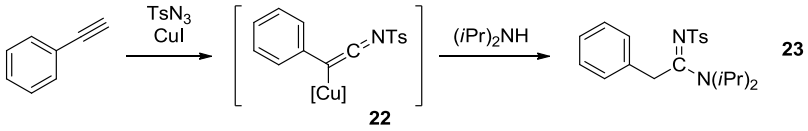
Ketenimines have been known for a long time, mostly as reactive building blocks for the preparation of various products.[22] Several approaches have been developed to access these compounds, the most common being Wittig reactions between phosphonium ylides **18** and isocyanates **19** or aza-Wittig reactions between ketenes **20** and iminophosphoranes **21** (Scheme 7).[23]

[19] Qiu, G.; Wang, Q.; Zhu, J. *Org. Lett.* **2017**, *19* (1), 270–273.
[20] Peng, J.; Gao, Y.; Hu, W.; Gao, Y.; Hu, M.; Wu, W.; Ren, Y.; Jiang, H. *Org. Lett.* **2016**, *18* (22), 5924–5927.
[21] Qiu, G.; Sornay, C.; Savary, D.; Zheng, S.-C.; Wang, Q.; Zhu, J. *Tetrahedron* **2018**, *74* (49), 6966–6971.
[22] For recent reviews, see : a) Lu, P.; Wang, Y. *Chem. Soc. Rev.* **2012**, *41* (17), 5687–5705. b) Alajarin, M.; Marin-Luna, M.; Vidal, A. E*ur. J. Org. Chem.* **2012**, *2012* (29), 5637–5653.
[23] a) Zhou, X.; Fan, Z.; Zhang, Z.; Lu, P.; Wang, Y. *Org. Lett.* **2016**, *18* (18), 4706–4709. b) Capuano, L.; Djokar, K.; Schneider, N.; Wamprecht, C. *Liebigs Ann. Chem.* **1987**, *1987* (3), 183–187.



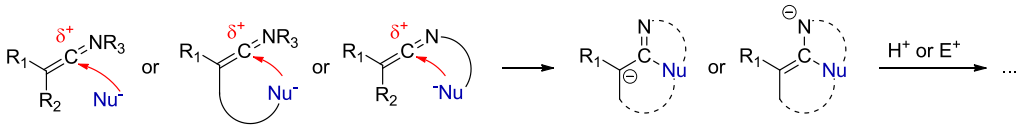
Scheme 7 : *Synthesis of ketenimines via Wittig and aza-Wittig reactions*

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) was then developed by Chang and coworkers to generate ketenimines *in situ* from alkynes (Scheme 8).[24] This strategy allowed the generation under mild conditions of very reactive *N*-sulfonyl ketenimines **22** that could react further, for example with amines to give amidines in high yields **23**.



Scheme 8 : *Generation of ketenimines by copper-catalyzed azide-alkyne cycloaddition (CuAAC)*

Ketenimines were typically engaged as electrophilic partners in inter- or intramolecular reactions with various nucleophiles (Scheme 9). After nucleophilic addition, the resulting intermediates were protonated or trapped by electrophiles. Cycloadditions with ketenimines are also an important class of transformations. In most cases, stepwise mechanisms were proposed for the formation of the products, following the reaction sequence depicted in Scheme 9.

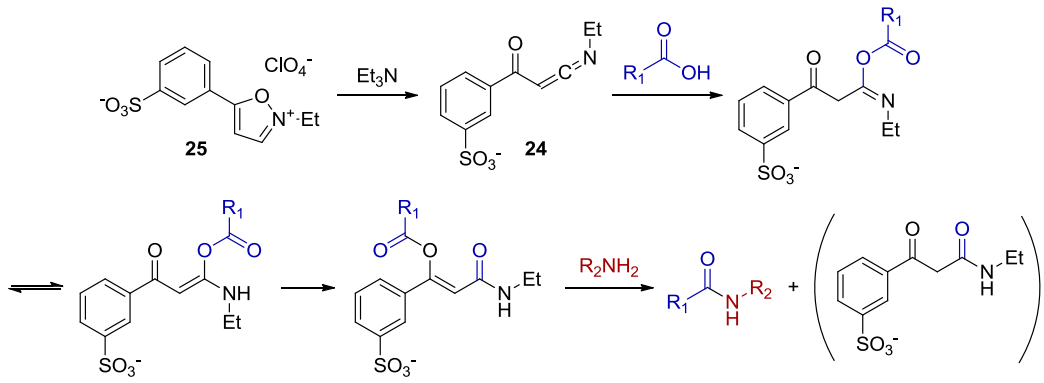


Scheme 9 : *Reactivity profile of ketenimines towards nucleophiles and electrophiles*

Despite extensive studies involving ketenimines with different substitutents at the *C*- and the *N*-terminus of the ketenimine group, to date, the synthesis and reactivity of α-oxo-ketenimines are almost unexplored. As pioneering work, Woodward and coworkers reported in 1961 the generation of α-oxo-

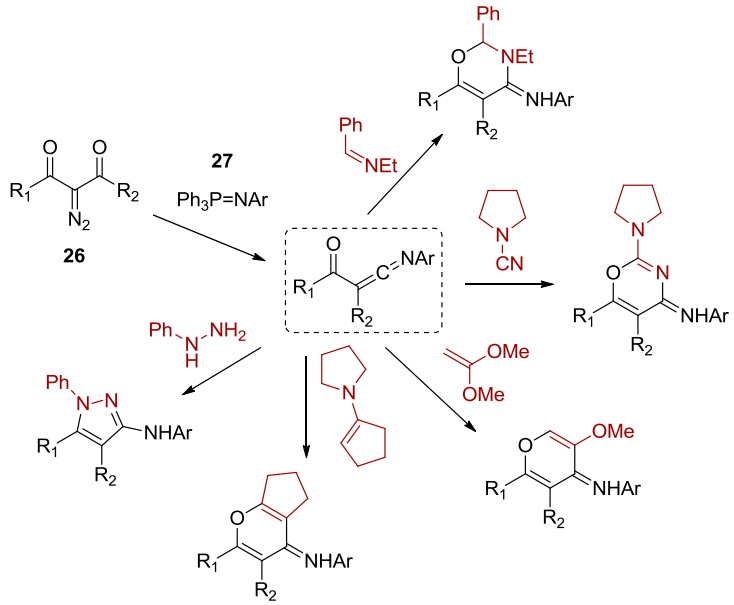
[24] Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127* (7), 2038–2039.

ketenimines **24** from isoxazolium salts **25** (Woodward's reagents K) and their use as activating agents for carboxylic acids in peptide couplings (Scheme 10).[25]



Scheme 10 : *α-Oxo-ketenimines as activating agents in peptide couplings*

Another method for the preparation of α-oxo-ketenimines combined diazomalonates **26** and iminophosphoranes **27** (Scheme 11). Capuano and coworkers then submitted the α-oxo-ketenimines to various reagents to deliver cycloaddition products. Interestingly, the carbonyl group participated in all these reactions.[26]

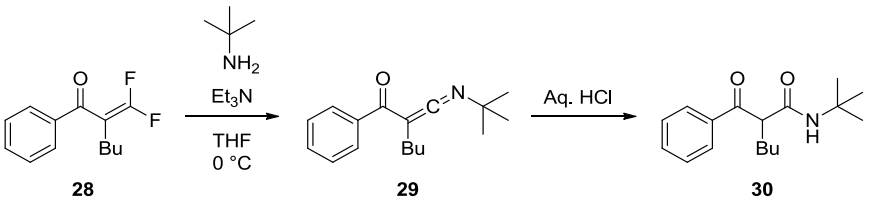


Scheme 11 : *Reactions of α-oxo-ketenimines with various partners*

[25] a) Woodward, R. B.; Olofson, R. A. *J. Am. Chem. Soc.* **1961**, *83* (4), 1007–1009. b) Woodward, R. B.; Olofson, R. A.; Mayer, H. *J. Am. Chem. Soc.* **1961**, *83* (4), 1010–1012. c) Woodman, D. J.; Davidson, A. I. *J. Org. Chem.* **1973**, *38* (25), 4288–4295.

[26] See reference 23b.

To the best of our knowledge, the last appearance of α-oxo-ketenimines in the literature was in 1996. It consisted in the reaction between 2,2-difluorovinyl ketones **28** and amines (Scheme 12).[27] The α-oxo-ketenimines **29** were then simply hydrolyzed to β–ketoamides **30** under aqueous acidic conditions.



28 **29** **30**

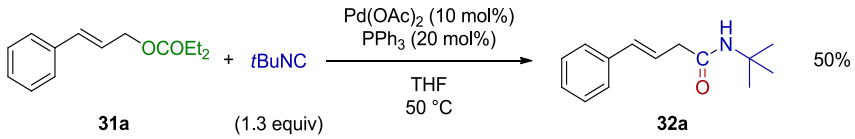
Scheme 12 : *Synthesis of α-oxo-ketenimines from 2,2-difluorovinyl ketones and amines*

[27] Ichikawa, J.; Yokota, N.; Kobayashi, M.; Amano, K.; Minami, T. *Synlett* **1996**, *1996* (03), 243–245.

1.2 Vinyl Ketenimines

1.2.1 Previous Work by Dr. Guanyinsheng Qiu

Aiming at developing new palladium-catalyzed isocyanide insertions with electrophilic partners other than vinyl or aryl halides, our former group member Qiu proposed a reaction between allyl carbonate **31a** an *tert*-butyl isocyanide in the presence of 10 mol% $Pd(OAc)_2$ and 20 mol% of PPh_3 in THF at 50 °C (Scheme 13). After purification of the crude product by column chromatography on silica gel, β,γ-unsaturated carboxamide **32a** was isolated in a promising 50% yield.

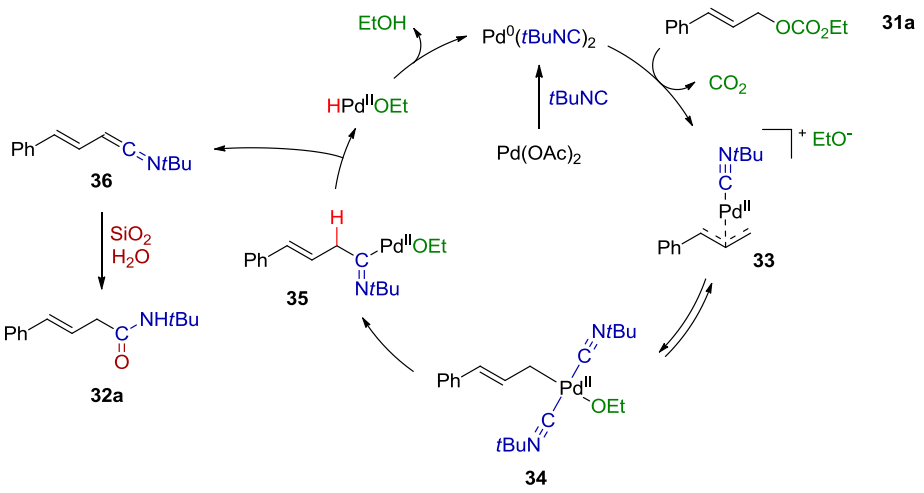


31a **32a**

Scheme 13 : *Discovery of a novel palladium-catalyzed insertion of isocyanide with an allyl carbonate*

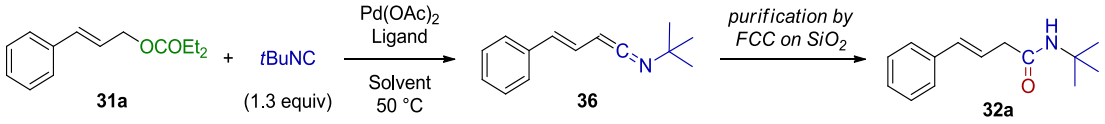
The proposed mechanism for this new transformation is the following (Scheme 14) : as seen in chapter 1.2.1, Pd(II) would be reduced by *t*BuNC to form an active Pd(0)-complex bearing two isocyanides (for clarity purposes, isocyanide ligands may be omitted in the rest of the catalytic cycle). Oxidative addition of palladium to allyl carbonate **31a** would then afford π-allyl Pd complex **33**, which would be in equilibrium with η^1-allyl Pd complex **34**. Detailed kinetic studies by Canovese and coworkers have confirmed that there is an equilibrium between complexes **33** and **34** with isocyanide-ligated Pd(II)-complexes.[28] Migratory insertion from **34** would furnish imidoylpalladium intermediate **35**, which, upon β–hydride elimination would deliver vinyl ketenimine **36** with concurrent regeneration of the active catalyst. To note, no reductive elimination was observed from complex **35**. Hydrolysis of the ketenimine on silica gel upon purification by flash column chromatography finally gave β,γ-unsaturated carboxamide **32a**. Alternative syntheses of vinyl ketenimines by deprotonation of allyl cyanides and *N*-trapping were reported,[29] or by dehydration of α-vinylamides.[30]

[28] Canovese, L.; Visentin, F.; Santo, C.; Bertolasi, V. *Organometallics* **2014**, *33* (7), 1700–1709.
[29] a) Fuks, R.; Baudoux, D.; Piccinni-Leopardi, C.; Declercq, J. P.; Van Meerssche, M. *J. Org. Chem.* **1988**, *53* (1), 18–22. b) Differding, E.; Vandevelde, O.; Roekens, B.; Van, T. T.; Ghosez, L. *Tet. Lett.* **1987**, *28* (4), 397–400.
[30] Sonveaux, E.; Ghosez, L. *J. Am. Chem. Soc.* **1973**, *95* (16), 5417–5419.



Scheme 14 : *Proposed mechanism for the synthesis of β,γ-unsaturated carboxamides from allyl carbonates*

Optimization of the reaction conditions lead to an NMR yield of 87% for β,γ-unsaturated carboxamide **32a** (Table 1, entry 6). The reaction worked better without ligand (entries 1-3) and THF was the best solvent (entries 8-10). The reaction also proceeded at room temperature but with a slightly lower yield and longer reaction time (entry 7). Interestingly, it was observed that reducing the catalyst loading improved the yield (entries 4-6).

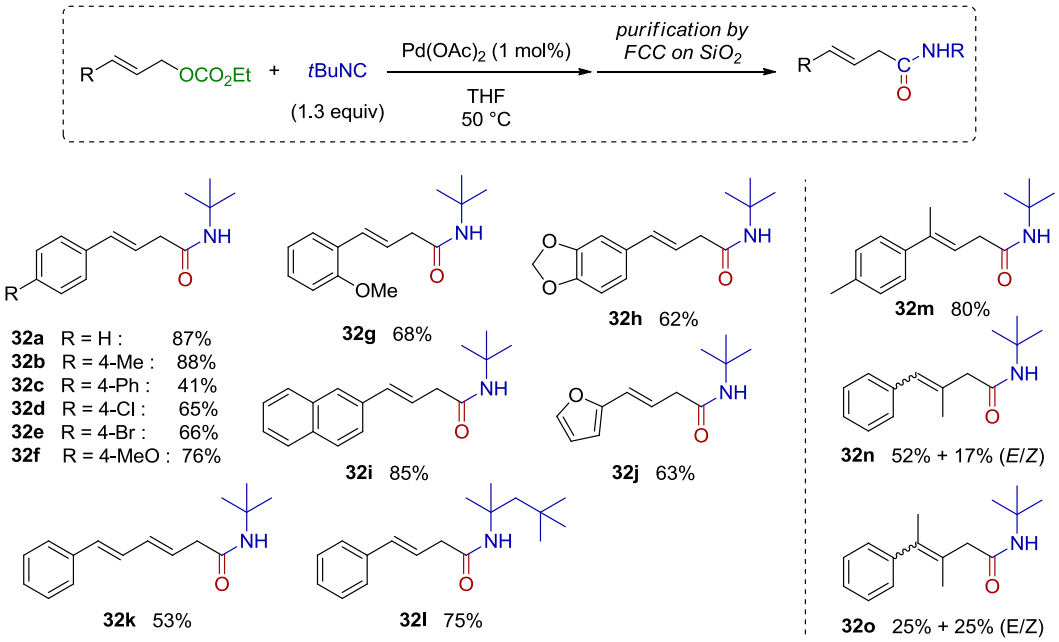


	Solvent	$Pd(OAc)_2$ (equiv)	Ligand (20 mol%)	Yield[a]
1	THF	10 mol%	PPh_3	50%
2	THF	10 mol%	PCy_3, dppf, dppp, Phen	< 60%
3	THF	10 mol%	---	66%
4	THF	5 mol%	---	69%
5	THF	2 mol%	---	71%
6	THF	1 mol%	---	87%
7	THF	1 mol%	---	83%[b]
8	Toluene	1 mol%	---	76%
9	DCE	1 mol%	---	32%
10	MeCN	1 mol%	---	trace

Reaction conditions : Allyl carbonate **31a** (0.2 mmol), *t*BuNC (0.26 mmol), $Pd(OAc)_2$, ligand (20 mol%), solvent (1 mL), 50 °C, filtration through SiO_2 (typical reaction time : 6 h) / [a] NMR yield of **32a** / [b] 25 °C

Table 1 : *Optimization of the conditions for the synthesis of β,γ-unsaturated carboxamides from allyl carbonates*

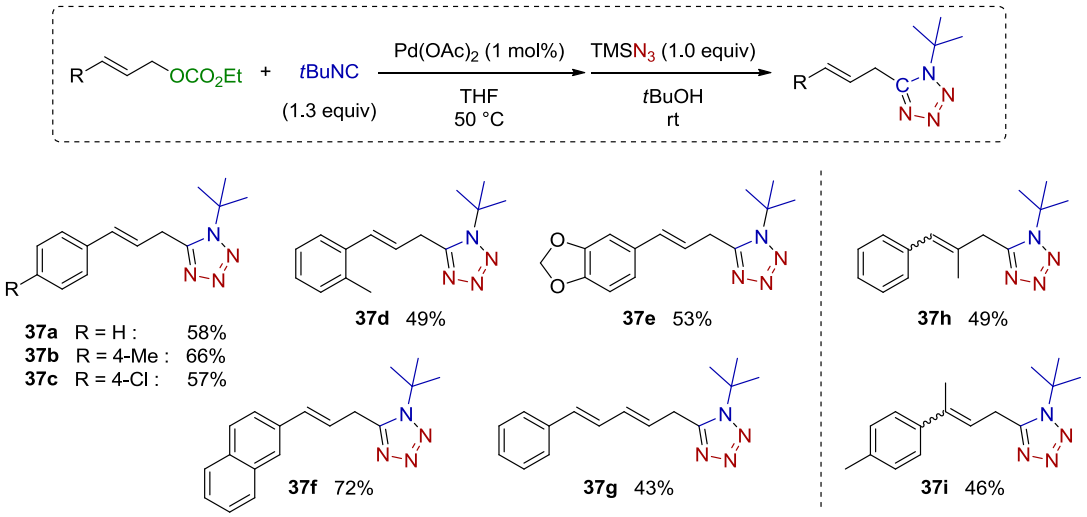
With the optimized reaction conditions in hand, the scope of the reaction was investigated and allowed the synthesis of β,γ-unsaturated carboxamides in good to excellent yields (Scheme 15).



Scheme 15 : *Scope of the synthesis of β,γ-unsaturated carboxamides from allyl carbonates*

The conversion of ketenimines into tetrazoles was then envisaged. It was found that 1,5-disubstituted tetrazole **37a** could be synthesized in 58% yield by treatment of ketenimine **36** with $TMSN_3$ at room temperature for 24 h in *t*BuOH (after the generation of the vinyl ketenimine, THF was evaporated and replaced by *t*BuOH). The use of protic solvents was found necessary for the reaction to proceed. A few 1,5-disubstituted tetrazoles were synthesized and revealed lower yields than the corresponding β,γ-unsaturated carboxamides (Scheme 16). The geometries of the trisubstituted double bonds of products **37h** and **37i** were not determined. A very recent review of multicomponent reactions for the synthesis of tetrazoles was published by Dömling and coworkers.[31]

[31] Neochoritis, C. G.; Zhao, T.; Dömling, A. *Chem. Rev.* **2019**. (10.1021/acs.chemrev.8b00564)



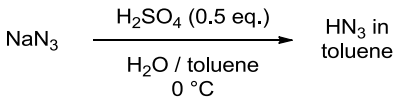
Scheme 16 : *Scope of the synthesis of 1,5-disubstituted tetrazoles from allyl carbonates*

1.2.2 Synthesis of 1,5-Disubstituted Tetrazoles with Hydrazoic Acid

Disappointed by the modest yields for the synthesis of tetrazoles, it was decided to re-investigate the reaction conditions. Two factors were proposed to explain the difference in yields between the β,γ-unsaturated carboxamides and the 1,5-disubstituted tetrazoles. On one hand, the solvent switch from THF to *t*BuOH could partially decompose the vinyl ketenimines. On the other hand, the [3+2]-cycloaddition with $TMSN_3$ could be inefficient. Presuming that *t*BuOH played the role of proton donor, the use of hydrazoic acid HN_3 in THF was envisaged as HN_3 is both an azide source and a proton donor. Furthermore, by avoiding the solvent switch, this reaction could be made in one-pot.

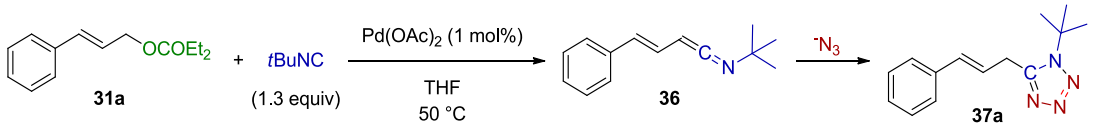
The preparation and the use of HN_3 required extreme care, as this low boiling point and volatile liquid is both explosive and highly toxic. In fact, only a few procedures have been published to date for its preparation,[32] which consists in adding H_2SO_4 to a solution of NaN_3 (Scheme 17). A solution of HN_3 in toluene was obtained and its concentration was determined by acid-base titration. In the best case, a concentration of 1.7 M was obtained.

[32] a) Breton, G. W.; Kropp, P. J.; Banert, K. *Hydrazoic Acid, Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2013. b) Alonso-Gómez, J. L.; Pazos, Y.; Navarro-Vázquez, A.; Lugtenburg, J.; Cid, M. M. *Org. Lett.* **2005**, *7* (17), 3773–3776.



Scheme 17 : *Preparation of a stock solution of HN_3 in toluene*

In order to compare the reactivities of $TMSN_3$ and HN_3 for the synthesis of tetrazoles, three reactions were run (Table 2). When solvent switches were made, almost identical yields were obtained with both $TMSN_3$ and HN_3 (entries 1 and 2). However, when the solution of HN_3 in toluene was added in one-pot to the cooled reaction mixture of vinyl ketenimine **36**, an improved yield of 69% was obtained for 1,5-disubstituted tetrazole **37a**. These three experiments confirmed our initial hypothesis that partial degradation of vinyl ketenimine **36** occurs during solvent switches.



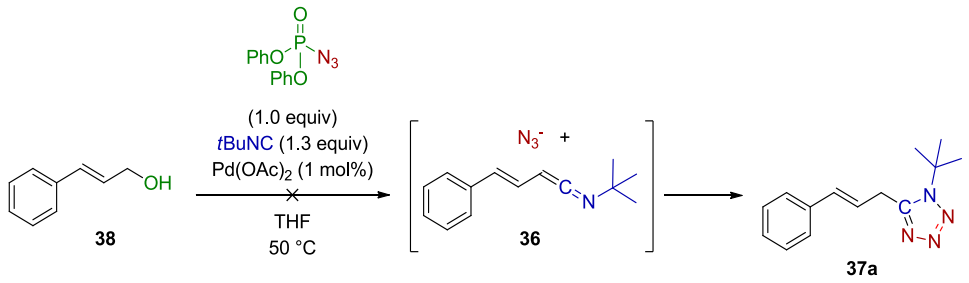
	Conditions after full consumption of 31a	Yield[a]
1	Evaporation of THF, addition of *t*BuOH and $TMSN_3$ (1.3 equiv)	57%
2	Evaporation of THF, addition of toluene and HN_3 in toluene (1.5 equiv)	61%
3	One-pot addition of HN_3 in toluene at room temperature (1.5 equiv)	69%

Reaction conditions to generate **36** : Allyl carbonate **31a** (0.2 mmol), *t*BuNC (0.26 mmol), $Pd(OAc)_2$ (1 mol%), THF (1 mL), 50 °C / [a] NMR yield of **37a**

Table 2 : *Comparison of $TMSN_3$ and HN_3 for the synthesis of 1,5-disubstituted tetrazoles from ketenimines*

It was later hypothesized that 1,5-disubstituted tetrazole **37a** could be obtained from allyl alcohol **38** in one-pot with the use of diphenylphosphoryl azide (Scheme 18).[33] First, allyl alcohol **38** would be converted to a phosphoryl alcohol, rendering it a suitable electrophilic partner for Pd(0). Secondly, the azide that would have been released in the phosphorylation process would react with vinyl ketenimine **36**. Unfortunately, no consumption of allyl alcohol **38** was observed, probably because the phosphorylation of alcohols usually requires special reaction conditions.[34]

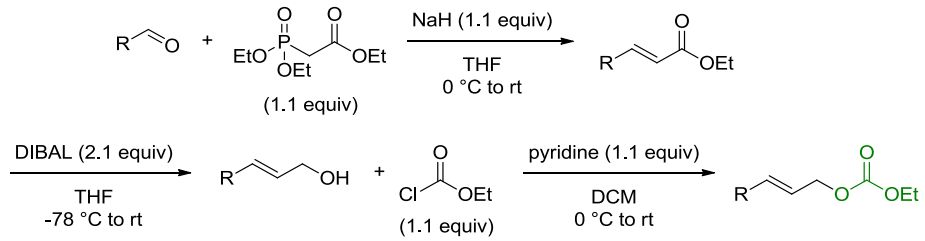
[33] This was kindly proposed by Prof. Alex Szpilman.
[34] Murray, J. I.; Woscholski, R.; Spivey, A. C. *Chem. Commun.* **2014**, *50* (88), 13608–13611.



Scheme 18 : *Attempted synthesis of 1,5-disubstituted tetrazole from an unactivated allyl alcohol*

1.2.3 Synthesis of Allyl Carbonates as Starting Materials

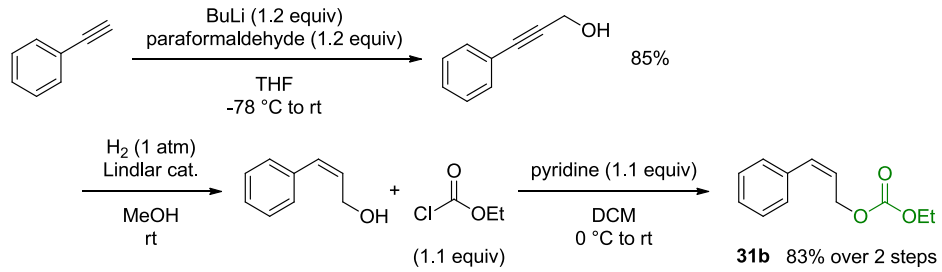
Most of the allyl carbonates for the investigation of the scope were prepared in three steps from the corresponding aldehydes (Scheme 19). First, Horner-Wadsworth-Emmons reaction afforded α,β-unsaturated esters,[35] which were reduced to allyl alcohols before final treatment with ethyl chloroformate to give allyl carbonates in high yields. In most cases, no purification was necessary after the first two steps. Some α,β-unsaturated esters and allyl alcohols were obtained by other methods and their preparation is reported hereafter.



Scheme 19 : *Three-step synthesis of allyl carbonates from aldehydes*

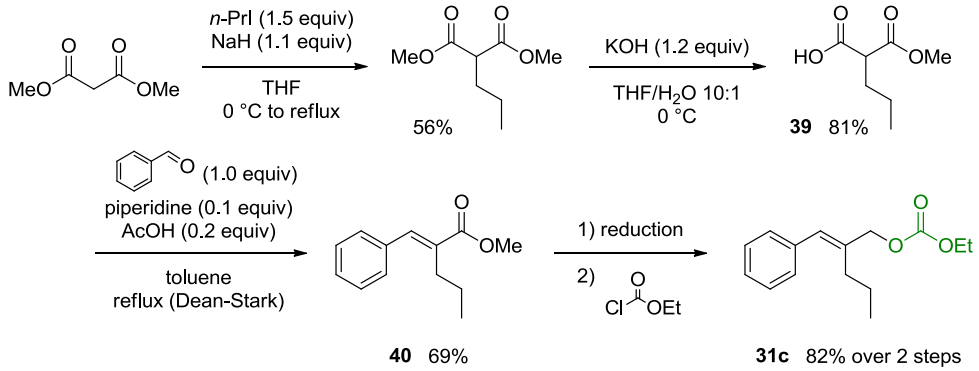
(*Z*)-allyl carbonate **31b** was made in three steps : reaction of phenylacetylene with formaldehyde in 85% yield, (*Z*)-selective reduction and formation of the carbonate in 83% yield over two steps (Scheme 20).

[35] Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125* (37), 11176–11177.



Scheme 20 : *Synthesis of a (Z)-allyl carbonate*

Allyl carbonate **31c** was prepared by Knoevenagel condensation as key step (Scheme 21). Mono-acid **39** and benzaldehyde were refluxed in toluene with catalytic amount of piperidine and AcOH to afford α,β-unsaturated ester **40** in 69% yield.[36] Reduction of the ester and formation of the carbonate then afforded the desired product.

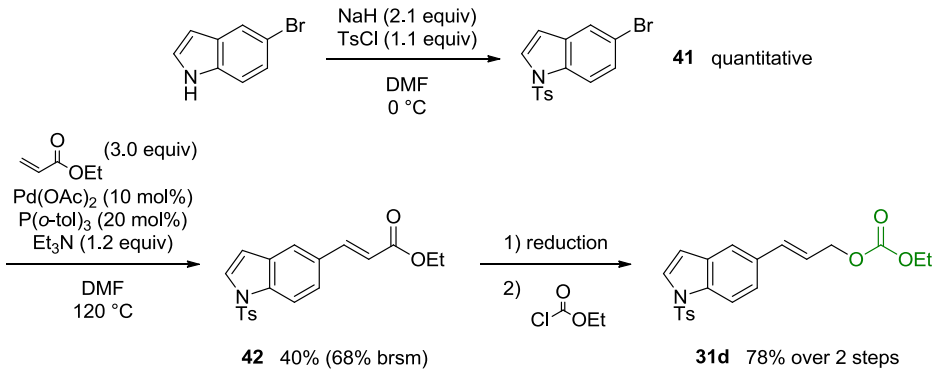


Scheme 21 : *Synthesis of a trisubstituted allyl carbonate*

The synthesis of indolenic allyl carbonate **31d** was achieved in four steps (Scheme 22). After quantitative protection of 5-bromoindole, *N*-tosyl-5-bromoindole **41** was engaged in a Heck reaction with ethyl acrylate that gave α,β-unsaturated ester **42** in a modest 40% yield (68% brsm).[37] Reduction and formation of the carbonate delivered the product **31d** in 78% over 2 steps.

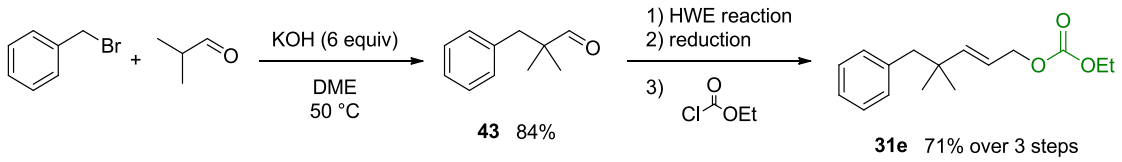
[36] For reaction conditions with a similar substrate, see : Leber, J.; Christensen, S.; Daines, R.; Li, M.; Weinstock, J.; Head, M. WO/2001/090099, November 30, 2001.

[37] For reaction conditions with a similar substrate, see : Tomoo, T.; Nakatsuka, T.; Katayama, T.; Hayashi, Y.; Fujieda, Y.; Terakawa, M.; Nagahira, K. *J. Med. Chem.* **2014**, *57* (17), 7244–7262.



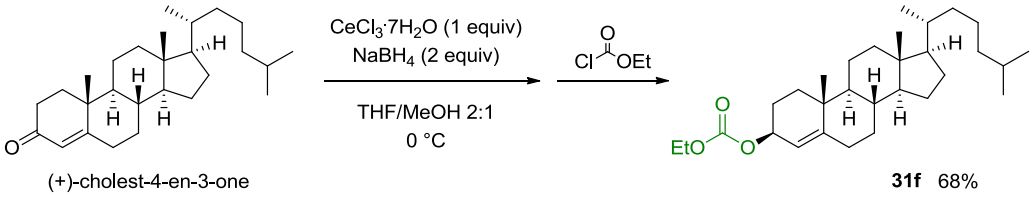
Scheme 22 : *Synthesis of an indolenic allyl carbonate*

The preparation of non-conjugated allyl carbonates was then undertaken. Aldehyde **43** was synthesized[38] and converted in three steps to allyl carbonate **31e** in a high overall yield (Scheme 23). A similar substrate was prepared starting from cyclohexane carboxaldehyde instead of isobutyraldehyde.



Scheme 23 : *Synthesis of a non-conjugated allyl carbonate*

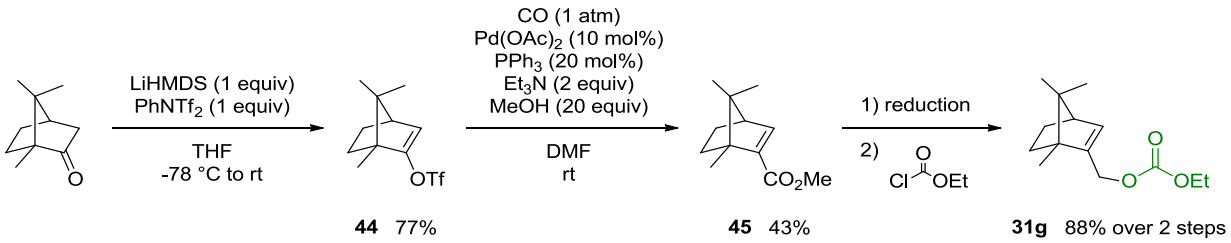
Transformation of (+)-cholest-4-en-3-one into allyl carbonate **31f** was completed in two steps, the first being a diastereoselective reduction under Luche conditions to give cholest-4-en-3β-ol in 86% yield (Scheme 24).[39] The second step afforded the desired carbonate **31f** in 68% yield.



Scheme 24 : *Synthesis of a steroidic allyl carbonate*

The preparation of camphoric allyl carbonate **31g** was the most challenging as it involved a novel carbonylation of camphor triflate **44** (Scheme 25).[40] This carbonylation gave only 43% yield of α,β–unsaturated ester **45**, but the last two steps afforded the desired product in overall decent yield.

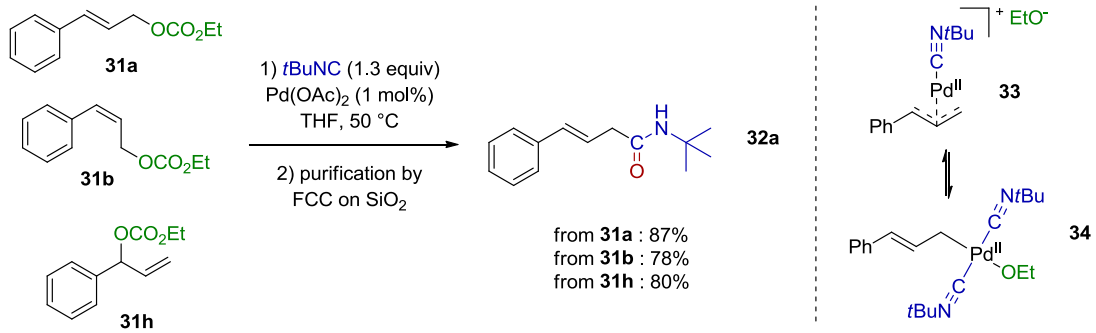
[38] Artaud, I.; Torossian, G.; Viout, P. *Tetrahedron* **1985**, *41* (21), 5031–5037.
[39] For reaction conditions with a similar substrate, see : Carvalho, J. F. S.; Cruz Silva, M. M.; Moreira, J. N.; Simões, S.; Sá e Melo, M. L. *J. Med. Chem.* **2009**, *52* (13), 4007–4019.
[40] For the synthesis of camphor triflate : Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52* (11), 3272–3276.



Scheme 25 : *Synthesis of a camphoric allyl carbonate*

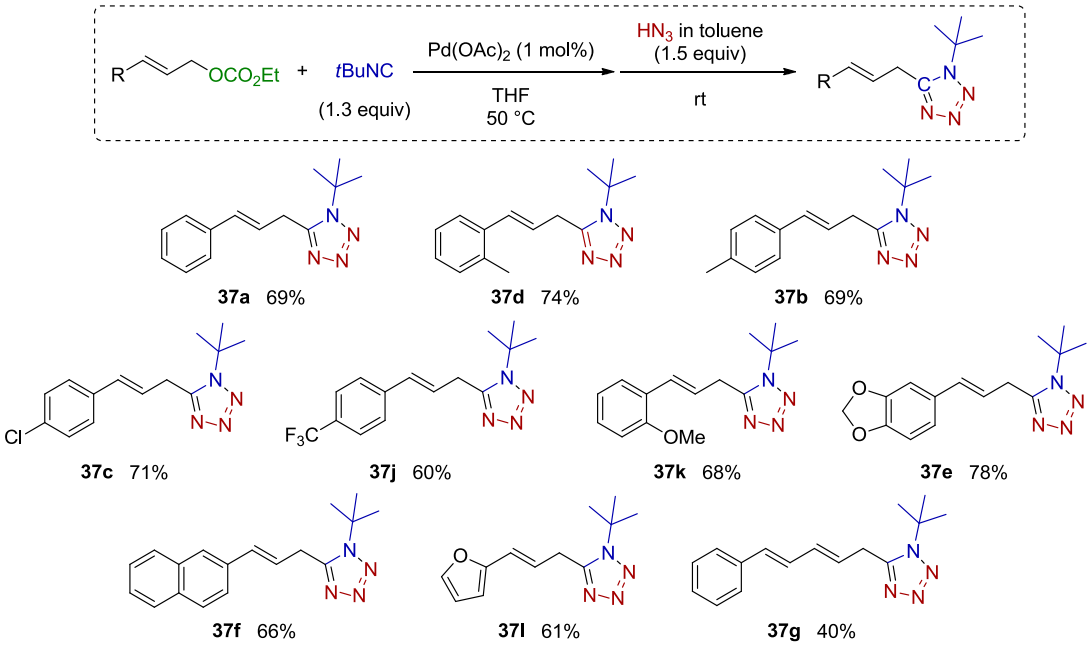
1.2.4 Scope of the Synthesis of 1,5-Disubstituted Tetrazoles

As seen previously, (*E*)-allyl carbonate **31a** was converted to β,γ-unsaturated carboxamide **32a** in 87% yield under the optimized reaction conditions (Scheme 26). The same product could be formed from (*Z*)-allyl carbonate **31b** or from branched allyl carbonate **31h** in similar yields. Isomerization of the double bond most probably occured in the equilibrium between π-allyl Pd complex **33** and η^1-allyl Pd complex **34**.



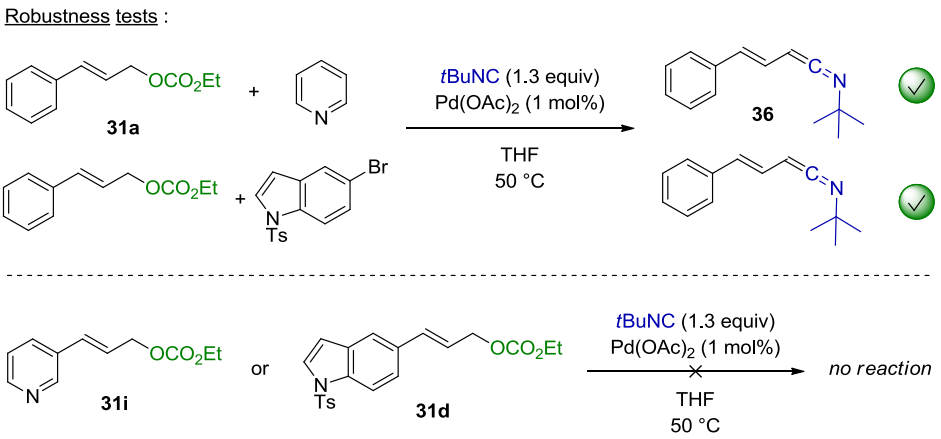
Scheme 26 : *Reactivity of different types of allyl carbonates for the synthesis of β,γ-unsaturated carboxamides*

The generality of the three-component synthesis of 1,5-disubstituted tetrazoles from allyl carbonates, isocyanides and HN_3 was then investigated. Gratifyingly, in all cases, the method using HN_3 was superior to that using $TMSN_3$, allowing the synthesis of 1,5-disubstituted tetrazoles in good 60% to 68% yields for aryl-substituted allyl carbonates (Scheme 27). Electron-withdrawing and donating groups at various positions were well tolerated. Even furan derivative **37l** and diene **37g** could be synthesized, although a lower yield of 40% was obtained for compound **37g**. It is noteworthy that 1,5-disubstituted tetrazole **37a** was prepared in 80% yield at gram-scale (1.03 g of starting material).



Scheme 27 : *Scope of the synthesis of 1,5-disubstituted tetrazoles from conjugated allyl carbonates*

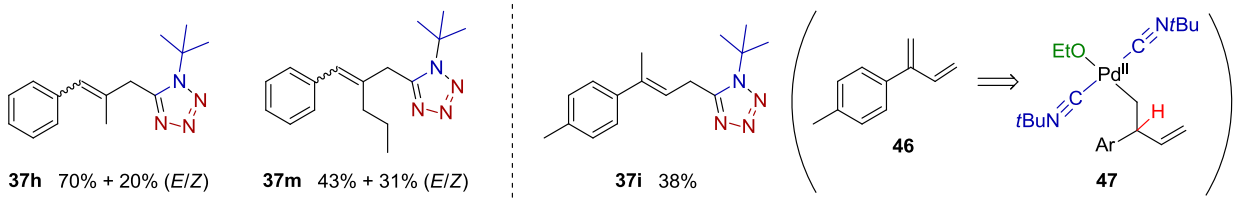
Glorius' robustness tests[41] were carried out by adding pyridine and *N*-tosyl 5-bromoindole to our model reaction (Scheme 28). In both cases, the desired vinyl ketenimine **36** was formed exclusively from allyl carbonate **31a**. According to the principles of this robustness test, allyl carbonates bearing pyridyl and *N*-tosyl indole moietes should be suitable starting materials for the generation of vinyl ketenimines. Pyridine derivative **31i** and indolenic allyl carbonate **31d** were therefore prepared and submitted to the optimized reaction conditions. Unfortunately, they both proved unsuitable for this transformation despite the positive results of the tests.



Scheme 28 : *Positive Glorius' robustness tests but unsuitable allyl carbonates for the generation of vinyl ketenimines*

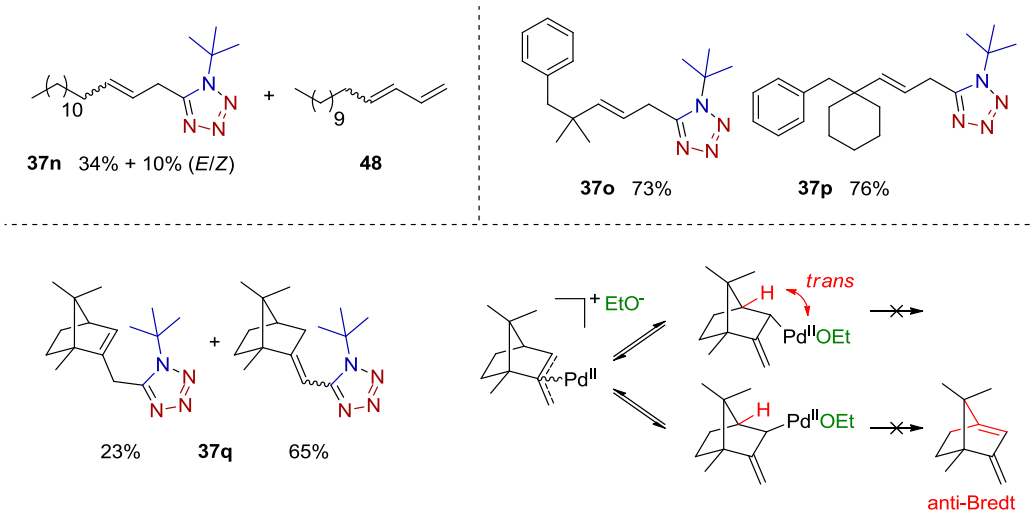
[41] Collins, K. D.; Glorius, F. *Nat Chem* **2013**, *5* (7), 597–601.

The reactivity of substrates having trisubstituted double bonds was then probed. 1,5-Disubstituted tetrazoles **37h** were isolated separately in 70% and 20% yields from a pure (*E*)-allyl carbonate precursor (Scheme 29). Monitoring of the reaction by TLC and ^{1}H NMR showed that isomerization of the double bond occurred during the palladium-catalyzed step, before treatment with HN_3. The corresponding β,γ-unsaturated carboxamides were also synthesized in 68% and 22% yields, showing a reproducible *E*/*Z* ratio. Similar yields and ratios for products **37m** were observed. 1,5-Disubstituted tetrazole **37i** was only obtained in 38% yield, with diene **46** identified as side-product probably arising from β–hydride elimination of η^{1}-allyl Pd complex **47** before isocyanide insertion.



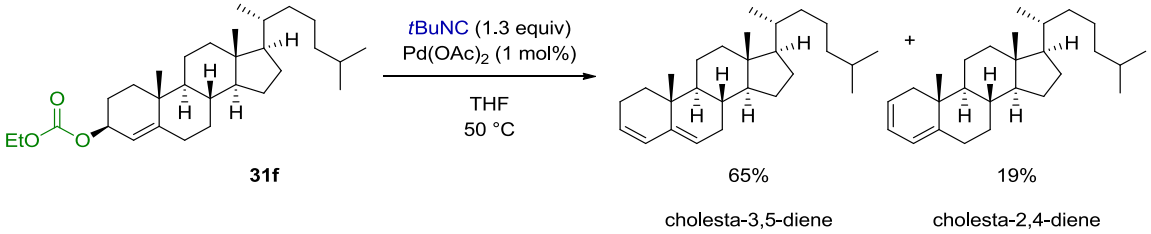
Scheme 29 : *Reactivity of trisubstituted allyl carbonates for the synthesis of 1,5-disubstituted tetrazoles*

Our attention next focused on non-conjugated allyl carbonates (Scheme 30). An overall yield of 44% was obtained for products **37n** along with high amounts of terminal dienes **48**, resulting from β–hydride elimination before isocyanide insertion. To avoid this undesired side-reaction, non-conjugated allyl carbonates from which no β-hydride elimination would be possible were prepared. Gratifyingly, 1,5-disubstituted tetrazoles **37o** and **37p** were obtained in good 73% and 76% yields. The synthesis of the corresponding β,γ-unsaturated amides was achieved in 70% and 83% yields. Finally, camphoric tetrazole and its isomerized form **37q** were isolated separately in 23% and 65% yields. As expected, the β–H was not eliminated for geometrical reasons.



Scheme 30 : *Reactivity of non-conjugated allyl carbonates for the synthesis of 1,5-disubstituted tetrazoles*

Although steroidic allyl carbonate **31f** was a challenging substrate because of possible β-hydride elimination before isocyanide insertion, the pharmaceutically relevant tetrazole that could be formed prompted us to prepare it (Scheme 31). Unfortunately, cholesta-3,5-diene and cholesta-2,4-diene were isolated in overall 84% yield as an inseparable mixture from compounds.

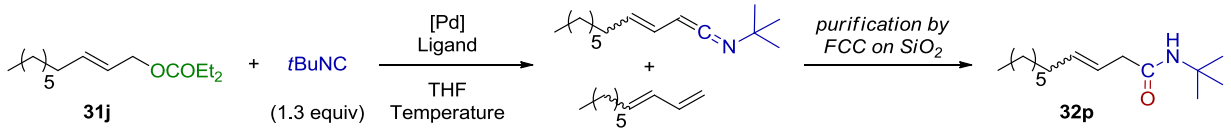


Scheme 31 : *Reactivity of a steroidic allyl carbonate for the synthesis of 1,5-disubstituted tetrazole*

Disappointed by the limitation of our methodology for non-conjugated allyl carbonates, we decided to re-investigate the reaction conditions for this type of starting material.

1.2.5 Reactivity of Non-Conjugated Allyl Carbonates

Using non-conjugated allyl carbonate **31j** as model substrate, re-investigation of the reaction conditions was undertaken (Table 3). The previously optimized reaction conditions gave only 30% NMR yield of β,γ-unsaturated carboxamides **32p** along with 1,3-decadiene (entry 1). Carrying out the reaction at room temperature did not improve the result (entry 2). No conversion was observed using PEPSSI-IPr as catalyst, even at 75 °C (entry 3). Monophosphine ligands gave similar yields (entry 4). The same outcome was observed for the dppe, dppp and dppf diphosphine ligands (entry 5). The ligands with large bite angles (±)-BINAP and XantPhos showed lower performances (entry 6). Finally, slow addition of *t*BuNC over 4 hours was also failure (entry 7).



	Conditions	Yield[a]
1	Standard	30%
2	Room temperature	25%
3	PEPPSI-IPr instead of $Pd(OAc)_2$	---
4	[*t*-$Bu_3PH]BF_4$, Xphos, DavePhos (2 mol%)	30-34%
5	dppe, dppp, dppf (2 mol%)	33-36%
6	(±)-BINAP, XantPhos (2 mol%)	21-28%
7	5 mol% $Pd(OAc)_2$, 10 mol% dppe, *t*BuNC over 4 hours	7%

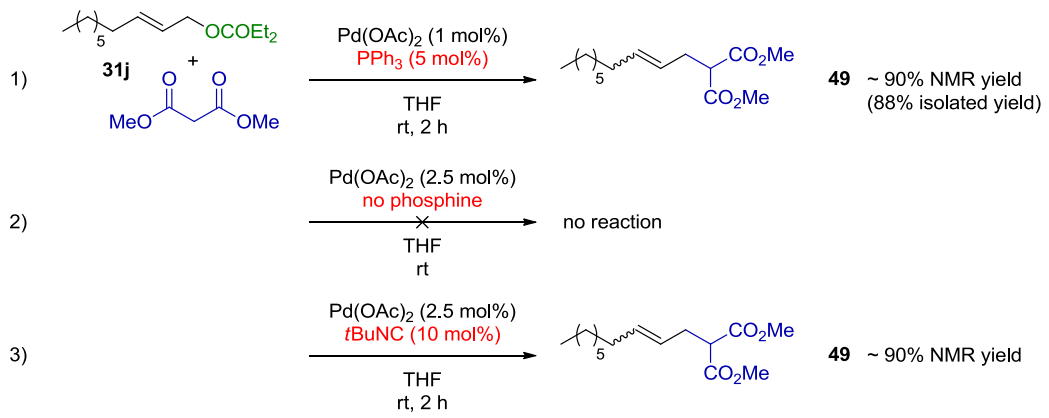
Standard conditions : Allyl carbonate **31j** (0.2 mmol), *t*BuNC (0.26 mmol), $Pd(OAc)_2$ (1 mol%), THF (1 mL), 50 °C, filtration through SiO_2 / [a] NMR yield of **32p**.

Table 3 : *Optimization of the reaction conditions for the synthesis of vinyl ketenimines from alkyl allyl carbonates*

Unable to improve the yield of product **32p**, further optimization was abandoned but additional experiments were carried out to study this undesired β–hydride elimination side-reaction. Interestingly, no side-products were formed in the classical Tsuji-Trost reaction from alkyl allyl carbonate **31j** (Scheme 32, equation 1). This suggested that no η^1-allyl Pd complex leading to unfortunate β–hydride elimination was part of the catalytic cycle. Indeed, it has been shown that only special ligands[42] or isocyanides[43] can force the monohapticity of the allyl moiety, which explains the limitation of our methodology for alkyl allyl carbonates. Also in line with the presentation of the multiple roles of *t*BuNC in chapter 1.2.1, no conversion was observed in absence of PPh_3 for the Tsuji-Trost reaction (equation 2) but adding 10 mol% *t*BuNC allowed the formation of product **49** (equation 3). As expected, *t*BuNC certainly allowed the reduction of Pd(II) to the active Pd(0)-species.

[42] a) Rülke, R. E.; Kliphuis, D.; Elsevier, C. J.; Fraanje, J.; Goubitz, K.; Leeuwen, P. W. N. M. van; Vrieze, K. *J. Chem. Soc., Chem. Commun.* **1994**, *0* (15), 1817–1819. b) Braunstein, P.; Naud, F.; Dedieu, A.; Rohmer, M.-M.; DeCian, A.; Rettig, S. J. *Organometallics* **2001**, *20* (14), 2966–2981. c) Kollmar, M.; Helmchen, G. *Organometallics* **2002**, *21* (22), 4771–4775.

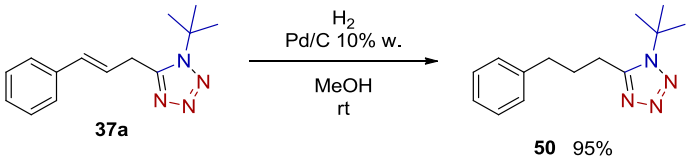
[43] Canovese, L.; Visentin, F.; Santo, C.; Bertolasi, V. *Organometallics* **2014**, *33* (7), 1700–1709.



Scheme 32 : *Tsuji-Trost reaction between non-conjugated allyl carbonates and dimethyl malonate*

1.2.6 Post-Modifications of 1,5-Disubstituted Tetrazoles

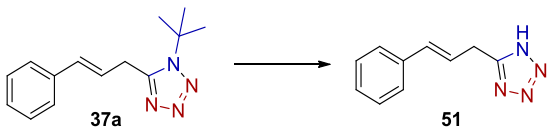
As first attempt at modifying model 1,5-disubstituted tetrazole **37a**, hydrogenation of the double bond was performed and delivered product **50** in excellent 95% yield (Scheme 33). It was known from previous reports that tetrazoles are stable under such hydrogenation conditions.[44]



Scheme 33 : *Stability of 1,5-disubstituted tetrazoles towards hydrogenation with Pd/C*

Of higher interest would be the cleavage of the *tert*-butyl group, as many unprotected tetrazoles are bioactive compounds. Unfortunately, this post-modification revealed troublesome, even under harsh conditions (Table 4). In the best case, only traces of the desired product **51** were observed in a complex reaction mixture (entry 4).

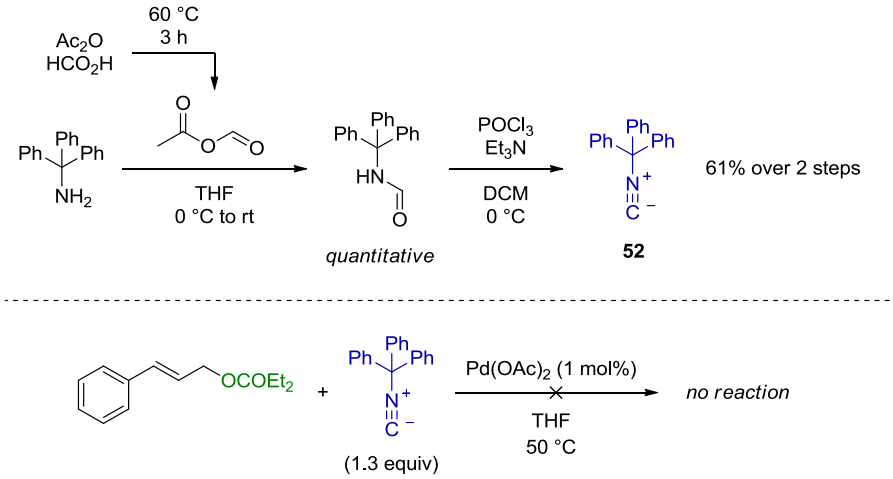
[44] Zhao, T.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Herdtweck, E.; Dömling, A. *Chem. Eur. J.* **2016**, *22* (9), 3009–3018.



	Conditions	Result
1	TFA (2 equiv), EtOH, 50 °C, 5 days	No reaction
2	HCl in EtOH (1.25 M), reflux, 4 days	Almost no reaction
3	Aq. HCl 33%, THF, 50 °C, 4 days	No reaction
4	TfOH (10 equiv.), EtOH, 70 °C, 1.5 days	Complex mixture

Table 4 : *Attempts at cleaving the* tert*-butyl group of* N-tert*-butyl tetrazoles*

A different strategy was thus envisaged to prepare unprotected tetrazole **51** : the use of an isocyanide bearing a cleavable group. Trityl isocyanide[45] **52** was chosen because the trityl group should be easily cleavable, as shown recently by Orru and coworkers.[46] Behloul and coworkers also published recently a detritylation method from tetrazoles using either Zn in MeOH/THF at reflux or HCl at rt.[47] Trityl isocyanide **52** was therefore synthesized in two steps from triphenylmethylamine (Scheme 34).[48] Unfortunately, this isocyanide was unsuitable for the preparation of the desired 1,5-disubstituted tetrazole.

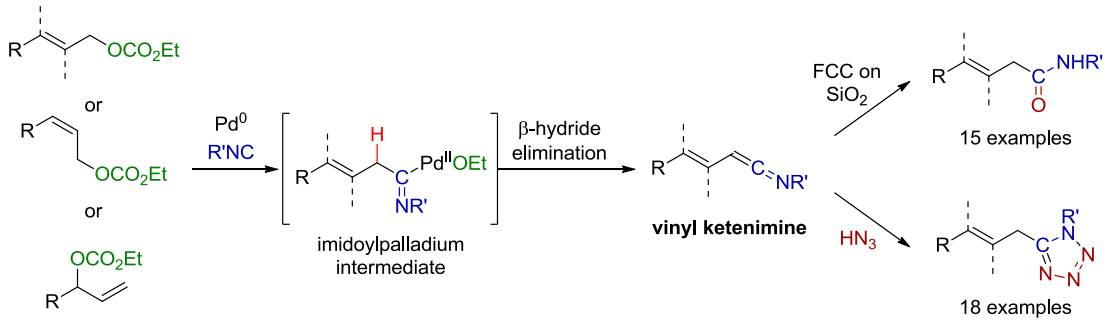


Scheme 34 : *Synthesis and reactivity of trityl isocyanide for the generation of vinyl ketenimines*

[45] Walborsky, H. M.; Topolski, M. *Triphenylmethyl isocyanide* in *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Ltd, 2001.
[46] Cioc, R. C.; Preschel, H. D.; van der Heijden, G.; Ruijter, E.; Orru, R. V. A. *Chem. Eur. J.* **2016**, *22* (23), 7837–7842.
[47] Behloul, C.; Bouchelouche, K.; Hadji, Y.; Benseghir, S.; Guijarro, D.; Nájera, C.; Yus, M. *Synthesis* **2016**, *48* (15), 2455–2460.
[48] a) Rong, J.; Deng, L.; Tan, P.; Ni, C.; Gu, Y.; Hu, J. *Angew. Chem. Int. Ed.* **2016**, *55* (8), 2743–2747. b) Wolstenhulme, J. R.; Cavell, A.; Gredičak, M.; Driver, R. W.; Smith, M. D. *Chem. Commun.* **2014**, *50* (88), 13585–13588.

1.2.7 Conclusion

A new method for the generation of vinyl ketenimines by a palladium-catalyzed reaction of isocyanides with allyl carbonates has been developed (Scheme 35). This work presents the first synthetically relevant β-hydride elimination from an imidoylpalladium intermediate. (*E*)-Allyl, (*Z*)-allyl and branched allyl carbonates could be used as starting materials. The vinyl ketenimines were readily hydrolyzed upon FCC purification on silica gel to give β,γ-unsaturated carboxamides. A novel three-component reaction was also developped for the synthesis of 1,5-disubstituted tetrazoles by reaction of the vinyl ketenimines with hydrazoic acid.

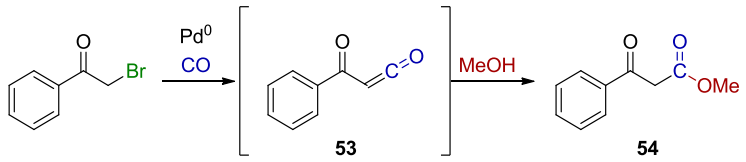


Scheme 35 : *Summarized synthesis and reactivity of vinyl ketenimines from allyl carbonates and isocyanides*

1.3 α-Oxo-Ketenimines

1.3.1 Introduction : Palladium Enolates

The palladium-catalyzed carbonylation of 2-bromoacetophenone reported by Stille and coworkers in 1975 is one of the first examples featuring a palladium enolate (Scheme 36).[49] No mechanism was proposed, but we may speculate the presence of a ketene intermediate **53** if the β-hydride elimination giving this ketene is faster than ligand exchange with MeOH and reductive elimination to give β-ketoester **54**. To date, many other insertions of carbon monoxide have been reported in α–position to carbonyl groups.[50]



Scheme 36 : *Palladium-catalyzed carboalkoxylation of α-bromoketones by Stille and coworkers*

Two major modes of generation of palladium enolates exist. The first is the direct oxidative addition of palladium(0)-species to α–halocarbonyl compounds, whose intermediates are then trapped by organometallic reagents such as cuprates,[51] tin-reagents,[52] or boronic acids,[53] for example (Scheme 37). Palladium enolates can also be generated by trapping of palladium(II)-species by enolates. α–Arylation of carbonyl compounds are based on this principle.[54] Palladium enolates can adopt two bonding modes, as demonstrated by the isolation of palladium enolate complexes by Hartwig and coworkers.[55] Furthermore, studies on the bonding modes have been carried out by Espinet and coworkers.[56]

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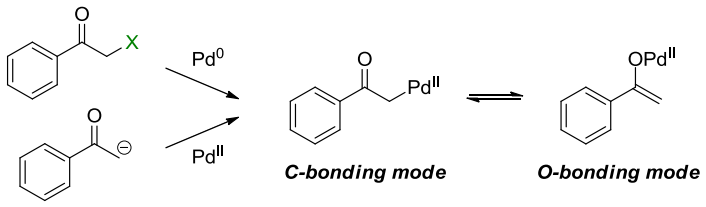
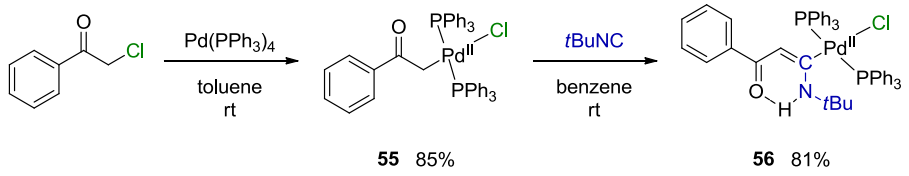
[49] Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40* (4), 532–534.
[50] For recent examples, see : a) Lapidus, A. L.; Eliseev, O. L.; Bondarenko, T. N.; Sizan, O. E.; Ostapenko, E. G.; Beletskaya, I. P. *Kinetics and Catalysis* **2004**, *45* (2), 234–238. b) Giboulot, S.; Liron, F.; Prestat, G.; Wahl, B.; Sauthier, M.; Castanet, Y.; Mortreux, A.; Poli, G. *Chem. Commun.* **2012**, *48* (47), 5889–5891. c) Wahl, B.; Bonin, H.; Mortreux, A.; Giboulot, S.; Liron, F.; Poli, G.; Sauthier, M. *Adv. Synth. Catal.* **2012**, *354* (16), 3105–3114. d) Perrone, S.; Capua, M.; Salomone, A.; Troisi, L. *J. Org. Chem.* **2015**.
[51] Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67* (6), 1969–1971.
[52] a) Lei, A.; Zhang, X. *Org. Lett.* **2002**, *4* (14), 2285–2288. b) Shi, W.; Liu, C.; Yu, Z.; Lei, A. *Chem. Commun.* **2007**, No. 23, 2342–2344. c) Kang, J. Y.; Connell, B. T. *J. Org. Chem.* **2011**, *76* (16), 6856–6859.
[53] Zimmermann, B.; Dzik, W. I.; Himmler, T.; Goossen, L. J. *J. Org. Chem.* **2011**, *76* (19), 8107–8112.
[54] Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36* (4), 234–245.
[55] See reference 35.
[56] Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18* (26), 5571–5576.



Scheme 37 : *Generation of palladium enolates and their bonding modes*

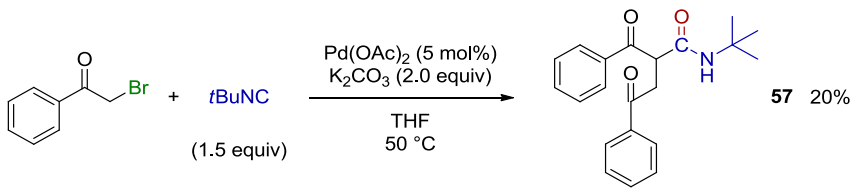
Of high interest for our research project is the stoichiometric oxidative addition of palladium(0) to 2-chloroacetophenone and the subsequent insertion of *t*BuNC, reported by Floriani and coworkers (Scheme 38).[57] The products could be isolated and studied by X-Ray christallography. They showed a C-bonding mode for palladium enolate **55** and a tautomerized form for complex **56**, stabilized by an intramolecular H-bond. The reactivity of complex **56** has not been studied further.



Scheme 38 : *Synthesis and characterization of an imidoylpalladium complex by Floriani and coworkers*

1.3.2 Discovery of a New Synthesis of α-Oxo-Ketenimines

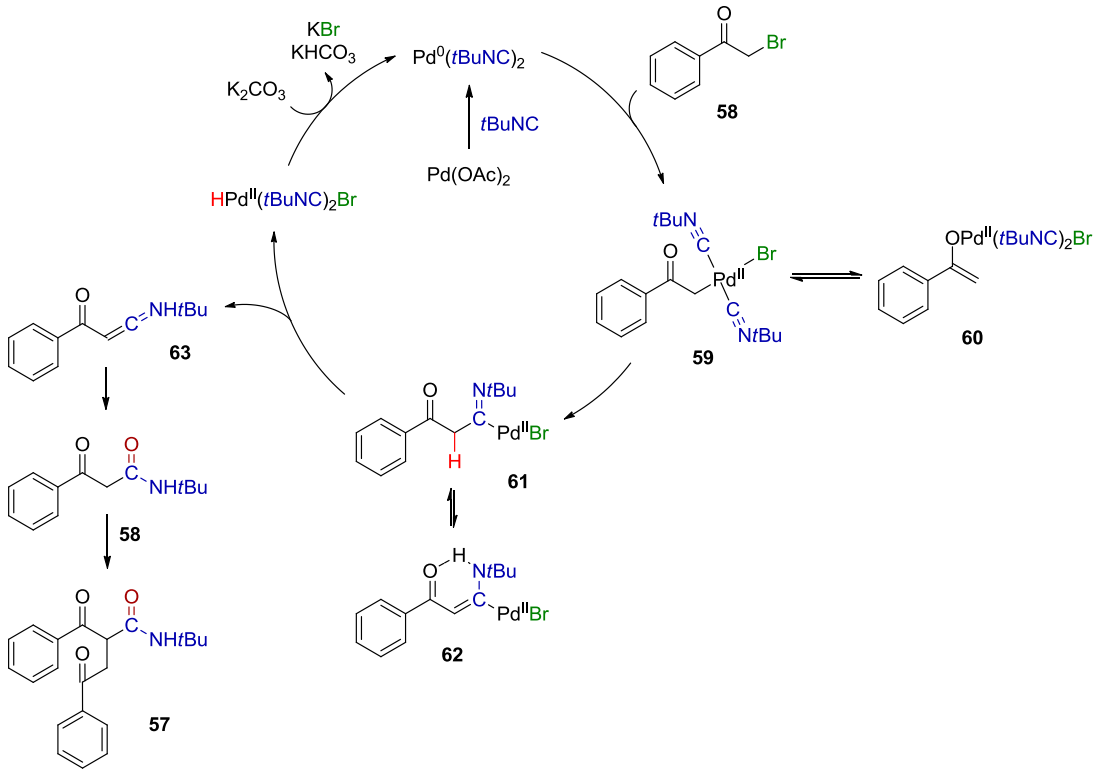
Inspired by Stille and coworkers' work on the carbonylation of 2-acetophenone, we combined this starting material with *t*BuNC, a palladium catalyst and a base (Scheme 39). To our delight, compound **57** was isolated in 20% yield.



Scheme 39 : *Discovery of a novel palladium-catalyzed insertion of isocyanide with an α-bromoketone*

[57] a) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *Organometallics* **1993**, *12* (2), 253–255. b) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12* (12), 4899–4907. c) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1994**, *13* (2), 441–450.

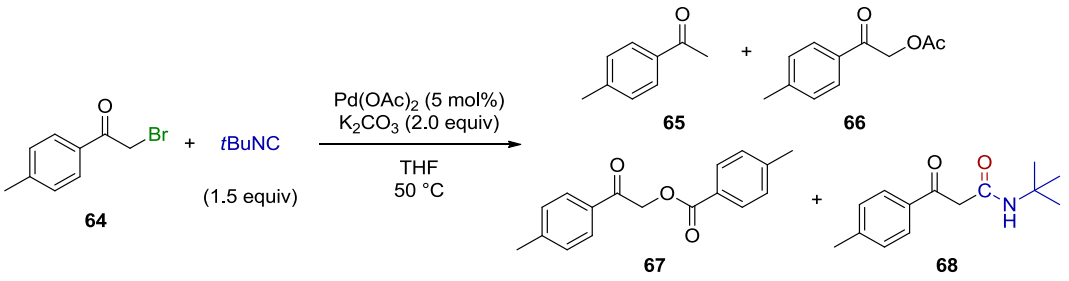
The following catalytic cycle is proposed for this transformation (Scheme 40) : after reduction of Pd(II) to Pd(0) by *t*BuNC, oxidative addition to 2-bromoacetophenone **58** would give *C*-bound palladium enolate **59**. For clarity purposes, isocyanide ligands may be omitted in the rest of the catalytic cycle. Complex **59** may be in equilibrium with *O*-bound tautomer **60**. Migratory insertion of isocyanide would then give imidoylpalladium complex **61**, that may be stabilized by a tautomeric form **62**. β-Hydride elimination from **61** would deliver α-oxo-ketenimine **63**. *In situ* hydrolysis of the ketenimine and reaction with 2-bromoacetophenone **58** would finally give product **57**.



Scheme 40 : *Proposed mechanism for the synthesis of* β*-ketoamides from* α*-bromoketones*

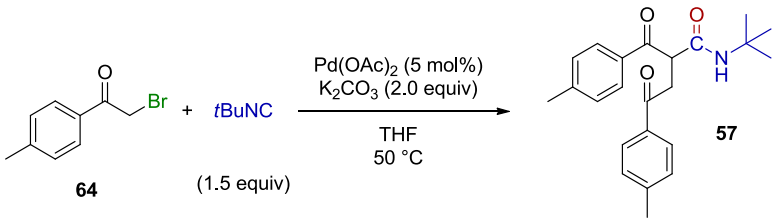
This reaction was carried out again using 2-bromo-4'-methylacetophenone **64** as model substrate and a complete analysis of the reaction mixture was performed (Scheme 41). Acetophenone **65**, α-acetoxyketone **66**, benzoate **67** and β-ketoamide **68** were isolated in similar yields. Notably, no trace of α-oxo-ketenimine **63** could be detected. Acetophenone **65** was certainly formed by protonation of *O*-bound palladium(II) enolate **60**.[58] α-Acetoxyketone **66** could be formed by direct S_N2 reaction of 2-bromoacetophenone with AcO^- released from $Pd(OAc)_2$. Benzoate **67** may have been formed by haloform reaction with an *in situ* formed 1,1,1-tribromoacetonphenone derivative.

[58] Urata, H.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *J. Organomet. Chem.* **1982**, *234* (3), 367–373.



Scheme 41 : *Side-products and intermediates isolated from the synthesis of β-ketoamides from α-bromoketones*

Extensive screening of the reaction conditions was then undertaken by varying the palladium catalysts, ligands, additives, bases and solvents. The influence of the temperature, the loadings and the concentration was also investigated (Table 5). To summarize, only $Pd(OAc)_2$, $Pd(TFA)_2$ and PdX_2 allowed the formation of some product, whereas the only bases that gave product were K_2CO_3 and K_3PO_4. It is worth mentionning that the use of Ag_2CO_3 as a base delivered new products that were not identified. Silver-catalysis is well known in the chemistry of isocyanides.[59] Ligands did not influence the outcome very much, probably due to the strong ligation of *t*BuNC on palladium. Furthermore, a loading of 5 equivalents of *t*BuNC completely blocked the reaction. The choice of the solvent seemed not crucial at this stage. Lowering the temperature to 35 °C led to similar results but increasing the temperature to 60 °C prevented the formation of the desired product. The role of some additives was also studied : TBABr and MS 4 Å were tolerated in the reaction mixture but LiBr, $AgNO_3$ and 18-crown-6 blocked the reaction.

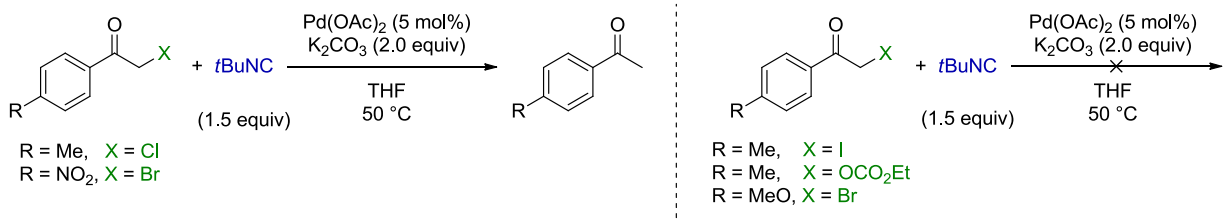


Pd-sources	Bases	Ligands	Solvents	Addidives
$Pd(OAc)_2$	K_2CO_3	PPh_3	THF	LiBr
$Pd(TFA)_2$	Na_2CO_3	PCy_3	1,4-Dioxane	$AgNO_3$
$PdCl_2$	Cs_2CO_3	P*t*Bu$_3$	Toluene	TBABr
$PdBr_2$	Ag_2CO_3	dppe	MeCN	18-Crown-6
PdI_2	K_3PO_4	dppp	DMF	MS 4 Å
$Pd(dppf)Cl_2$	Ag_3PO_4	Xphos	DCE	
$Pd(PPh_3)_4$	KF	DavePhos		
$Pd(dba)_2$	NaOAc	XantPhos		
PEPPSI-IPr	CsPiv	bipyridine		
	Et_3N	phenantroline		
	DABCO	4,4'-MeO-2,2'-bipyridine		
	DBU	6,6'-Me-2,2'-bipyridine		

Table 5 : *Screening of reagents for the optimization of the synthesis of β-ketoamides from α-haloketones*

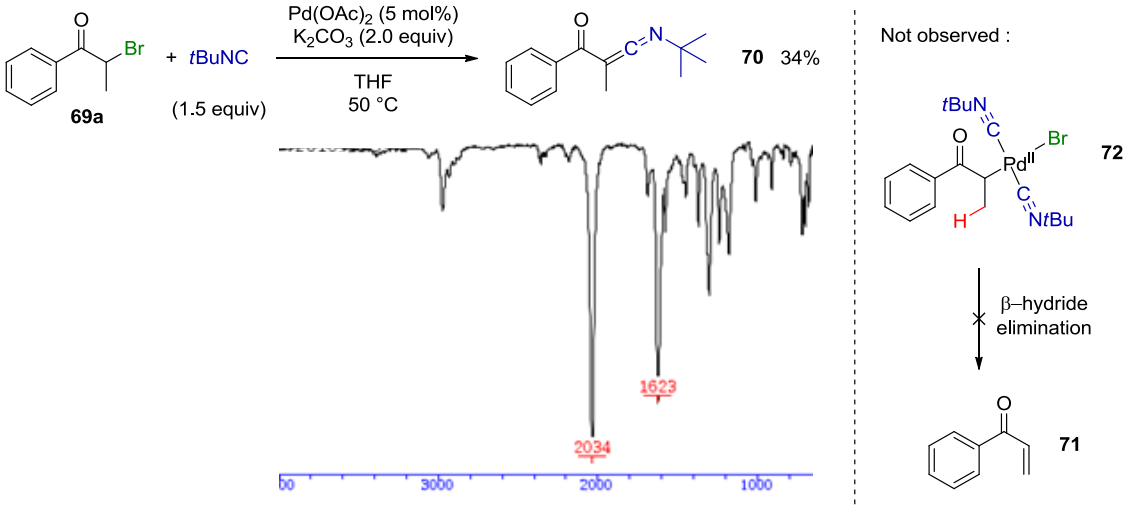
[59] Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115* (7), 2698–2779.

Faced with the difficult task to improve the yield of the desired product **57**, modification of the model substrate was envisaged (Scheme 42). In all cases, either acetophenones were obtained as major products or no reaction occured.



Scheme 42 : *Reactivity of 2-bromoacetophenone surrogates for the synthesis of* β*-ketoamides*

Then, a decisive modification of the starting material was designed and 2-bromopropiophenone **69a** was submitted to the standard reaction conditions (Scheme 43). In some cases, the substitution pattern at the α-position of the ketone was proven crucial by Hartwig and coworkers.[60] To our surprise, α-oxo-ketenimine **70** was identified as major product in 34% NMR yield after 2 days. IR spectroscopy showed a strong absorption band at 2034 cm^{-1} for the ketenimine group and another band at 1623 cm^{-1} for the conjugated ketone group. Interestingly, phenyl vinyl ketone **71** has never been observed, although its formation by β-hydride elimination from complex **72** could be feared. A fast migratory insertion from intermediate **72** may be responsible for this. While working on this research project, a related reaction for the synthesis of α-phosphonoketenimines from α-halophosphonates was published by Yang and coworkers.[61] A concurrent single example of α-oxo-ketenimine was also disclosed in this report.

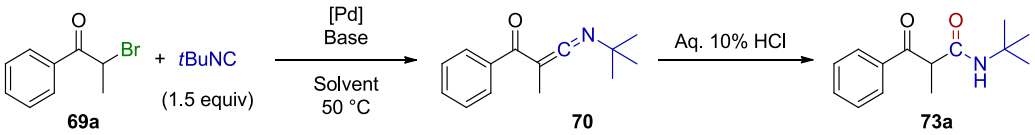


Scheme 43 : *Discovery of a novel palladium-catalyzed insertion of isocyanides for the synthesis of α-oxo-ketenimines*

[60] Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123* (24), 5816–5817.
[61] Yang, Q.; Li, C.; Cheng, M.-X.; Yang, S.-D. *ACS Catal.* **2016**, *6* (7), 4715–4719.

1.3.3 Optimization of the Reaction Conditions

Slight modifications of the standard reaction conditions were then performed (Table 6). Propiophenone was identified as the major side-product responsible for the low yields, as full conversion was obtained in most cases. The α-oxo-ketenimine could be hydrolyzed in one-pot with aqueous HCl to give β-ketoamide **73a**. In order to accelerate the reaction, the temperature was increased to 65 °C but no significant change of the yield was observed (entry 2). The use of K_3PO_4 accelerated the reaction, but with no improvement of the yield (entry 3). Na_2CO_3 and Cs_2CO_3 were inneficient bases, suggesting a strong counter-anion effect (entries 4 and 5). $PdCl_2$ as palladium precatalyst provided a higher yield of 47%, whereas PEPSSI-IPr was inneficient (entries 6 and 7). Surprisingly, lowering the catalyst loading to 1 mol% $Pd(OAc)_2$ increased the yield by 13% (entry 8). Finally, the choice of the solvent was crucial as the NMR yields of the α-oxo-ketenimine increased to 53% and 71% in 1,4-dioxane and toluene, respectively (entries 9 and 10). Hydrolysis of the α-oxo-ketenimine gave β-ketoamide in 68% yield. This promising initial survey of the reaction conditions prompted us to further optimize the yield of this novel reaction.



69a **70** **73a**

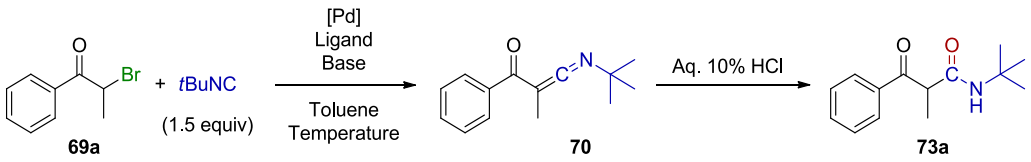
	Palladium	Base	Solvent	Time (days)	Yield[a]
1	$Pd(OAc)_2$	K_2CO_3	THF	2	34%
2	$Pd(OAc)_2$	K_2CO_3	THF	1.5	32%[b]
3	$Pd(OAc)_2$	K_3PO_4	THF	1	34%
4	$Pd(OAc)_2$	Na_2CO_3	THF	4	8%
5	$Pd(OAc)_2$	Cs_2CO_3	THF	4	13%
6	$PdCl_2$	K_2CO_3	THF	2.5	47%
7	PEPSSI-IPr	K_2CO_3	THF	4	25%
8	$Pd(OAc)_2$ 1 mol%	K_2CO_3	THF	1	47%
9	$Pd(OAc)_2$	K_2CO_3	1,4-Dioxane	4	53%
10	$Pd(OAc)_2$	K_2CO_3	Toluene	2	71%

Reaction conditions : 2-bromopropiophenone **69a** (0.4 mmol), *t*BuNC (0.6 mmol), palladium (5 mol%), base (0.8 mmol), solvent (2 mL), 50 °C / [a] NMR yield of **70** / [b] 65 °C

Table 6 : *Initial screening of reaction conditions for the synthesis of α-oxo-ketenimines from α-bromoketones*

The reaction conditions used in entry 10 (Table 6) with toluene (71% NMR yield of amide) were used as reference conditions for the screening of palladium catalysts, bases, additional ligands, loadings and

temperatures (Table 7). When $Pd(TFA)_2$ and $PdCl_2$ were used instead of $Pd(OAC)_2$, diminished yields were obtained (entries 2 and 3). Cs_2CO_3 and K_3PO_4 as bases also reduced the yields (entries 4 and 5). Full consumption of the starting material was not reached with KF, CsF, EtONa, Et_3N as bases (entry 6). *t*BuOK, DBU and DABCO decomposed the starting material (entries 7 and 8). The initial choice of K_2CO_3 remained the optimal base. The influence of additional ligands was then investigated : monophosphine ligands increased the rate of the reaction but without improvement of the yield (entries 9-11). The diphosphine ligands dppp and dppf strongly slowered the reaction to 4 days with decreased yields (entries 12 and 13). Finally, XantPhos and DavePhos lowered the yield by almost 30% (entries 14 and 15). Different loadings of the base provided yields below 60% (entries 16 and 17). A yield of 59% was obtained by doubling the concentration to 0.4 M (entry 18). The key parameter was found to be the temperature : 60 °C allowed the formation of α-oxo-ketenimine **70** in 84% NMR yield and 79% isolated yield of amide **73a** in only 12 h. However, further increasing the temperature to 70 °C led to incomplete conversion. A final optimisation of the $Pd(OAc)_2$, K_2CO_3 and *t*BuNC loadings at 60 °C did not improve the yield. Control experiments were finally run : the reaction was blocked with 34% of the starting material remaining under air. With additional water, full conversion was reached after longer reaction time and a low yield of 43% was obtained.

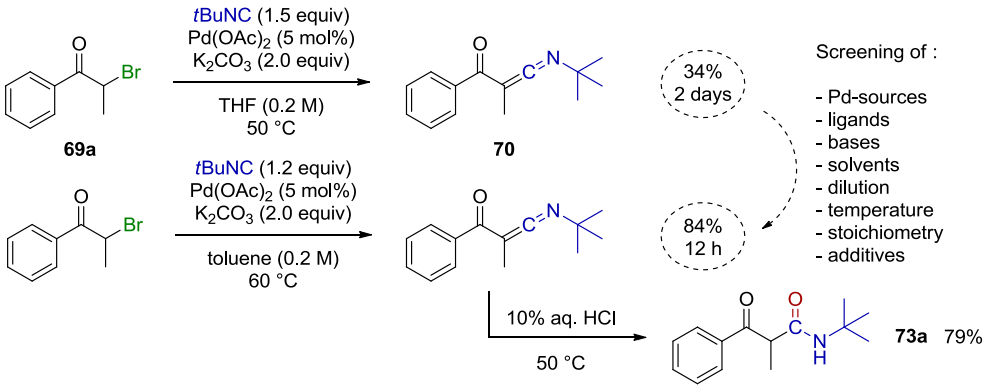


	Palladium	Base	Ligand	T (°C)	Time (days)	Yield[a]
1	$Pd(OAc)_2$	K_2CO_3	---	50 °C	2	71%
2	$Pd(TFA)_2$	K_2CO_3	---	50 °C	2	51%
3	$PdCl_2$	K_2CO_3	---	50 °C	2	49%
4	$Pd(OAc)_2$	K_3PO_4	---	50 °C	1.5	50%
5	$Pd(OAc)_2$	Cs_2CO_3	---	50 °C	1.5	50%
6	$Pd(OAc)_2$	K/CsF, EtONa, Et_3N	---	50 °C	1	no reaction
7	$Pd(OAc)_2$	*t*BuOK	---	50 °C	1	only SP
8	$Pd(OAc)_2$	DBU, DABCO	---	50 °C	< 1	decomposed
9	$Pd(OAc)_2$	K_2CO_3	PPh_3	50 °C	1	39%
10	$Pd(OAc)_2$	K_2CO_3	$[tBu_3PH]BF_4$	50 °C	1.5	60%
11	$Pd(OAc)_2$	K_2CO_3	XPhos	50 °C	1.5	70%
12	$Pd(OAc)_2$	K_2CO_3	dppp	50 °C	4	43%
13	$Pd(OAc)_2$	K_2CO_3	dppf	50 °C	4	31%
14	$Pd(OAc)_2$	K_2CO_3	XantPhos	50 °C	1.5	45%
15	$Pd(OAc)_2$	K_2CO_3	DavePhos	50 °C	4	49%
16	$Pd(OAc)_2$	K_2CO_3 (1.0 eq.)	---	50 °C	4	55%
17	$Pd(OAc)_2$	K_2CO_3 (3.0 eq.)	---	50 °C	1.5	59%
18	$Pd(OAc)_2$	K_2CO_3	---	50 °C	2	59%[b]
19	$Pd(OAc)_2$	K_2CO_3	---	60 °C	12 h	84%
20	$Pd(OAc)_2$	K_2CO_3	---	70 °C	blocked	18%
21	$Pd(OAc)_2$ (2.5 mol%)	K_2CO_3	---	60 °C	4	58%
22	$Pd(OAc)_2$ (7.5 mol%)	K_2CO_3	---	60 °C	12 h	73%
23	$Pd(OAc)_2$	K_2CO_3 (1.2 eq.)	---	60 °C	12 h	77%
24	$Pd(OAc)_2$	K_2CO_3 (3.0 eq.)	---	60 °C	12 h	75%
25	$Pd(OAc)_2$	K_2CO_3	---	60 °C	12 h	77%[c]
26	$Pd(OAc)_2$	K_2CO_3	---	60 °C	blocked	---[d]
27	$Pd(OAc)_2$	K_2CO_3	---	60 °C	1.5	43%[e]

Conditions : 2-bromopropiophenone **69a** (0.4 mmol), *t*BuNC (0.6 mmol), palladium (5 mol%), ligand (5 or 10 mol%), base (0.8 mmol), toluene (2 mL) / [a] NMR yield of **70** / [b] toluene (4 mL) / [c] *t*BuNC (0.8 mmol) / [d] under air / [e] + H_2O (1.0 mmol)

Table 7 : *Final screening of reaction conditions for the synthesis of α-oxo-ketenimines from α-bromoketones*

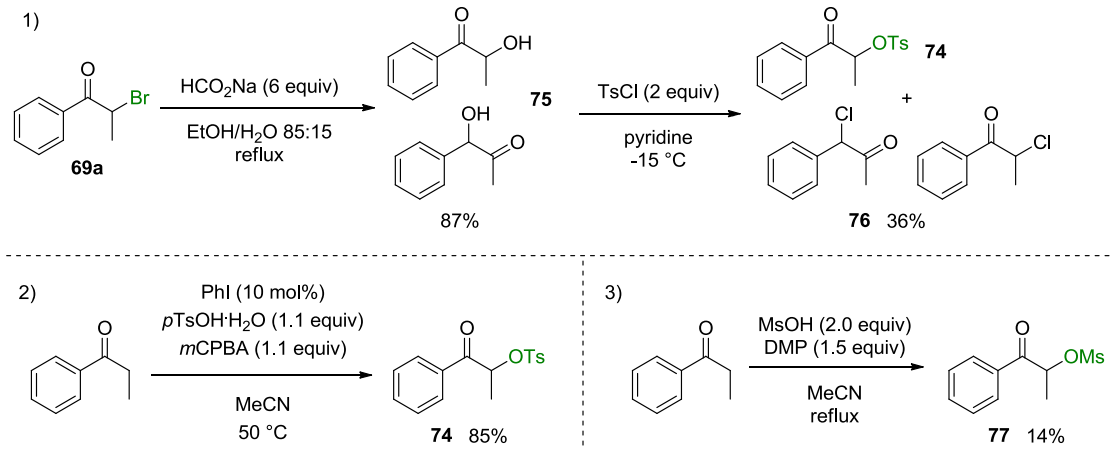
To summarize, the initial reaction conditions gave α-oxo-ketenime **70** in 34% NMR yield after 2 days. After extensive optimization, the same product was obtained in 84% NMR yield in only 12 h (Scheme 44). The latter was hydrolyzed with aqueous HCl 10% to obtain β–ketoamide **73a** in 79% isolated yield.



Scheme 44 : *Summary of the optimization of the synthesis of α-oxo-ketenimines from α-bromoketones*

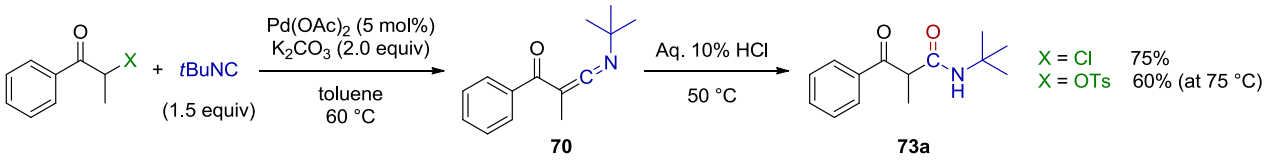
Replacement of the bromide group of 2-bromopropiophenone was then probed (Scheme 45). Synthesis of α-tosyloxyketone **74** was ineficient following the initial approach (equation 1) : S_N2 reaction of α-bromopropiophenone **69a** with sodium formate followed by hydrolysis gave an inseparable mixture of α-hydroxyketones **75**.[62] Nevertheless, these compounds were submitted to TsCl in pyridine and another unseparable mixture of the desired product **74** and α-chloroketones **76** was obtained, only in 36% overall yield. Fortunately, a direct procedure for the preparation of the desired product from propiophenone was found and delivered the product in 85% yield (equation 2).[63] The direct oxymesylation was low yieling and gave α-mesyloxyketone **77** in only 14% isolated yield, due to the poor conversion and formation of numerous side-products (equation 3).[64]

[62] For reaction conditions with a similar substrate, see : Pirkle, W. H.; Simmons, K. A. *J. Org. Chem.* **1983**, *48* (15), 2520–2527.
[63] Yamamoto, Y.; Kawano, Y.; Toy, P. H.; Togo, H. *Tetrahedron* **2007**, *63* (22), 4680–4687.
[64] Mahajan, U. S.; Akamanchi, K. G. *Synlett* **2008**, *2008* (7), 987–990.



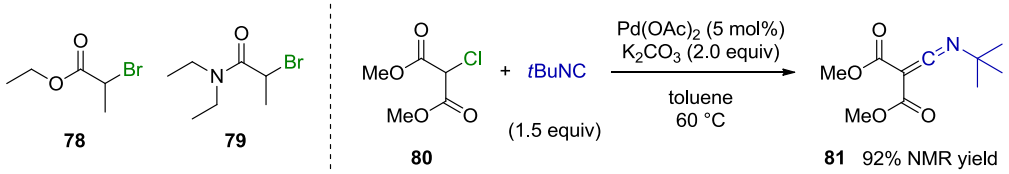
Scheme 45 : *Synthesis of an α-tosyloxyketone and an α-mesyloxyketone*

The reactivity of these starting materials and some other commercially available compounds was then probed (Scheme 46). To our pleasure, the reaction with α-chloroketone provided β–ketoamide **73a** in 75% yield. However, α-iodoketones were not suitable starting materials as the conversion was low. A higher temperature of 75 °C was necessary to reach full consumption of α-tosyloxyketone **74** and the product was obtained in 60% yield. Finally, the reaction was messy with α-mesyloxyketone **77**.



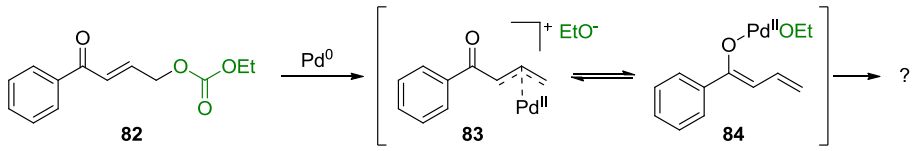
Scheme 46 : *Reactivity of 2-chloropropiophenone and 2-tosyloxypropiophenone*

Different α-halocarbonyl compounds were then submitted to the optimized reaction conditions (Scheme 47). With 2-bromopropionate **78** and 2-bromo-*N*,*N*-diethylpropanamide **79**, yields below 30% were obtained. Dehalogenation of 2-bromopropionate **78** was the major side-product, whereas low conversion of α-bromoamide **79** was observed. Interestingly, commercially available dimethyl chloromalonate **80** was converted in 92% NMR yield to the ketenimine **81**, which showed a strong absorbtion peak at 2171 cm^{-1} on its infrared spectrum.



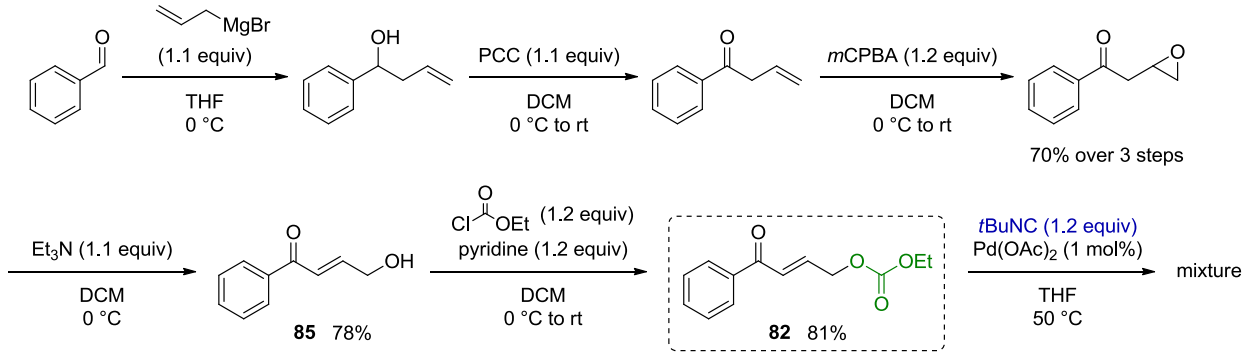
Scheme 47 : *Reactivity of ethyl 2-bromopropionate, 2-bromo-N,N-diethylpropanamide and dimethyl chloromalonate*

Allyl carbonate **82** was finally designed as electrophilic partner from which at least two types of Pd(II)-intermediates could be generated after oxidative addition of Pd(0) (Scheme 48) : either π-allyl Pd complex **83** (or η1-complex) or palladium enolate **84** may be in equilibrium and give rise to different isocyanide insertion products.



Scheme 48 : *Hypothetical α-oxo-π-allyl palladium complex and vinylogous palladium enolate*

Synthesis of allyl carbonate **82** was accomplished following a reported sequence for the synthesis of allyl alcohol **85** (Scheme 49).[65] As this alcohol was prone to cyclize to 2-phenylfuran with traces of acid, the work-up of the reaction had to be performed carefully and the NMR spectrum was recorded in CD_2Cl_2. When submitted to the reaction conditions for isocyanide insertion, allyl carbonate **82** was fully consumed but a very complex reaction mixture was generated.



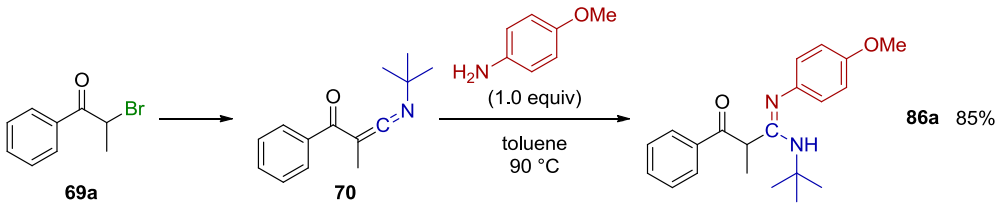
Scheme 49 : *Synthesis and reactivity of a carbonyl-conjugated allyl carbonate*

1.3.4 Reactivity Profile of the α-Oxo-Ketenimines

Having an efficient method for the preparation of α-oxo-ketenimines, their reactivity profile was then investigated. Simple nucleophilic additions were first attempted, starting with addition of 4-methoxyaniline to the crude α-oxo-ketenimine **70** in toluene (Scheme 50). The reaction was followed by infrared spectroscopy to monitor the consumption of the ketenimine group : a temperature of 90 °C was required for any reaction to proceed and β-ketoamidine **86a** was isolated in 85% yield as single product

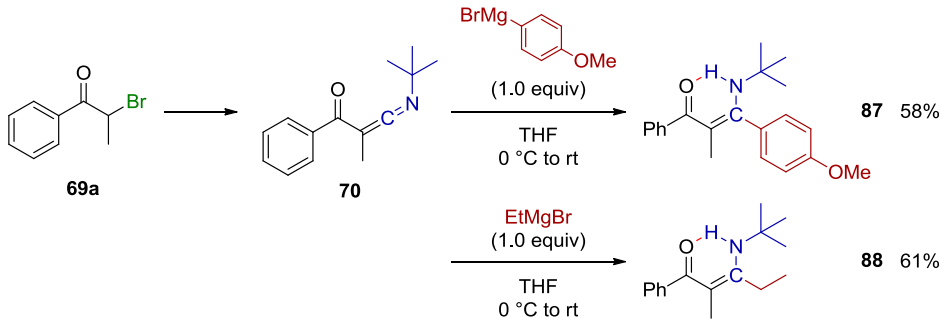
[65] Sada, M.; Ueno, S.; Asano, K.; Nomura, K.; Matsubara, S. *Synlett* **2009**, *2009* (5), 724–726.

from α-bromoketone, suggesting that the ketenimine was more electrophilic than the ketone moiety. This reaction is of synthetic interest, as very few methods allow the direct synthesis of β-ketoamidines. A sulfide contraction reaction is a notable example in this regard.[66]



Scheme 50 : *Nucleophilic addition of* p*-methoxyaniline to model α-oxo-ketenimine* ***70***

Also, crude α-oxo-ketenimine **70** was dissolved in THF and treated with aryl and alkyl Grignard reagents (Scheme 51). Enaminones **87** and **88** could be isolated in 58% and 61% yields from α-bromoketone **69a**. H-Bonds were clearly identified on the ^{1}H NMR spectra, thus allowing us to detemine the geometry of the enaminones. In the same way as 4-methoxyaniline, the Grignard reagents attacked exclusively at the ketenimine group. Small amounts of 1,3-diketones resulting from hydrolysis of the corresponding iminium tautomers were isolated after purification by column chromatography due to the relative instability of the enaminones on silica gel. To note, no reaction occurred with addition of 1 equivalent of $CeCl_3$ prior to the addition of ethyl magnesium bromide. It was hypothesised that the addition of an oxophilic Lewis acid may direct the nucleophilic addition at the ketone functionality.

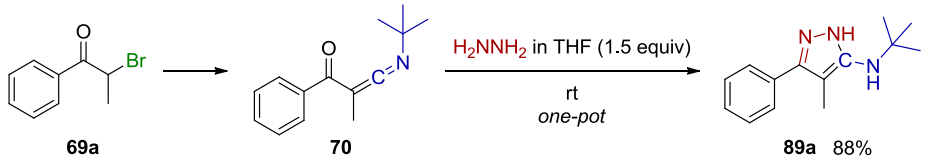


Scheme 51 : *Nucleophilic addition of Grignard reagents to model α-oxo-ketenimine* ***70***

Believing that α-oxo-ketenimines may react as "doubly electrophilic" partners, a "doubly nucleophilic" compound such as hydrazine was added to the crude reaction mixture of α-oxo-ketenimine **70** (Scheme 52). After 1 hour at room temperature, 5-aminopyrazole **89a** was isolated in 88% yield from α-

[66] Heffe, W.; Balsiger, R. W.; Thoma, K. *Helv. Chim. Acta* **1974**, *57* (4), 1242–1247.

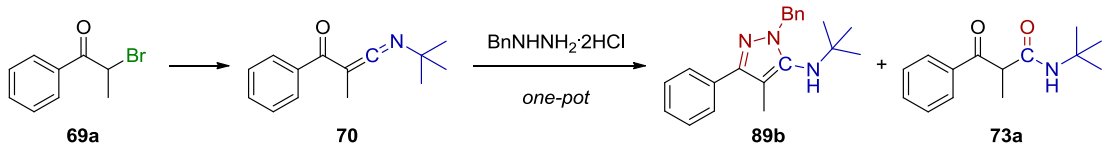
bromoketone **69a**. This efficient one-pot three-component reaction gives access to valuable products, as 5-aminopyrazoles are important classes of heterocycles in the pharmaceutical industry.[67]



69a **70** **89a** 88%

Scheme 52 : *Nucleophilic addition of hydrazine to model α-oxo-ketenimine **70***

The use of monosubstituted hydrazines was next considered for the synthesis of *N*-substituted 5-aminopyrazoles (Table 8). Addition of benzylhydrazine hydrochloride to the crude reaction mixture of **70** provided only traces of the desired *N*-benzylpyrazole **89b** along with β-ketoamide **73a** in 46% NMR (entry 1). Addition of K_2CO_3 before adding the hydrazine salt allowed the formation of 5-aminopyrazole **89b** in 50% NMR yield (entry 2). Attemps at neutralizing the hydrochloride salts with K_2CO_3 or $NaHCO_3$ were not successful (entries 3-6). Finally, addition of KOH to the reaction mixture of α-oxo-ketenimine **70** before adding the hydrazine salt gave access to 5-aminopyrazole **89b** in 81% NMR yield and 75% isolated yield.



69a **70** **89b** **73a**

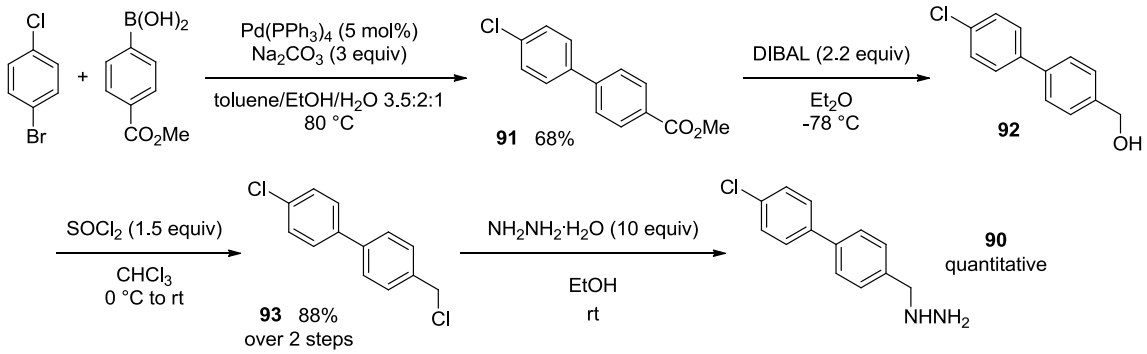
	$BnNHNH_2 \cdot 2HCl$ (loading)	**Reaction time**	**103 (NMR yield)**	**85 (NMR yield)**
1[1]	1.5 equiv	5 h	5%	46%
2[2]	1.0 equiv K_2CO_3 then 1.5 equiv	12 h	50%	10%
3	2.0 equiv (washed before use with $NaHCO_3$)	12 h	no reaction	
4	Premixed solution of 1.5 equiv + 3.0 equiv K_2CO_3 in toluene → insoluble	- - -	- - -	- - -
5	Premixed solution of 1.5 equiv + 3.0 equiv $NaHCO_3$ in toluene → insoluble	- - -	- - -	- - -
6[2]	Premixed solution of 1.5 equiv + 3.0 equiv $NaHCO_3$ in water (byphasic)	48 h	very slow	very slow
7	3.0 equiv KOH then 1.5 equiv	2 h	81%	8%

[1] Insoluble K_2CO_3 was filtered off before addition of $BnNHNH_2 \cdot 2HCl$.
[2] Release of CO_2 was observed.

Table 8 : *Optimization of the conditions for the reaction of model α-oxo-ketenimine **70** with a hydrazine hydrochloride*

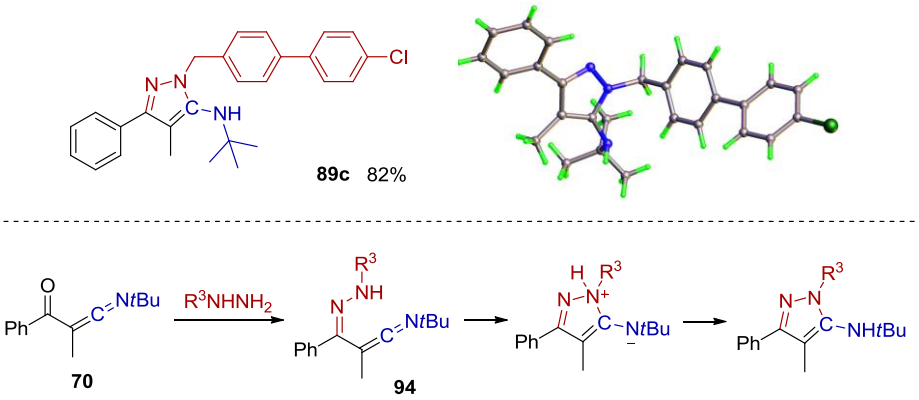
[67] For a recent review, see : Aggarwal, R.; Kumar, V.; Kumar, R.; Singh, S. P. *Beilstein Journal of Org. Chem.* **2011**, *7* (1), 179–197.

Having doubts regarding the substitution pattern of *N*-substituted 5-aminopyrazole **89b**, 4-arybenzyl hydrazine **90** was synthesized following a straightforward reaction sequence (Scheme 53). Suzuki coupling of 1-bromo-4-chlorobenzene with 4-(methoxycarbonyl)phenylboronic acid gave biaryl compound **91** in 68% yield.[68] The ester function was reduced to alcohol **92**, which was converted to chloride **93** in excellent 88% yield over 2 steps. Finally, nucleophilic displacement of chloride **93** with hydrazine delivered the desired 4-arylbenzyl hydrazine **90** in quantitative yield.[69]



Scheme 53 : *Synthesis of a 4-arylbenzyl hydrazine*

With this compound in hand, the synthesis of *N*-substituted 5-aminopyrazole **89c** was achieved in 82% yield (Scheme 54). Single crystals of this compound were grown and analyzed by X-ray diffraction to confirm the structure of the product. To note, a regioisomeric pyrazole was assigned by Capuano and coworkers (Scheme 11). Based on this X-ray structure, a cyclization mechanism is proposed : the reaction would be initiated by the nucleophilic attack of hydrazine at the ketone group to give hydrazone intermediate **94**, which would spontaneously cyclize to give 5-aminopyrazole **89c**.



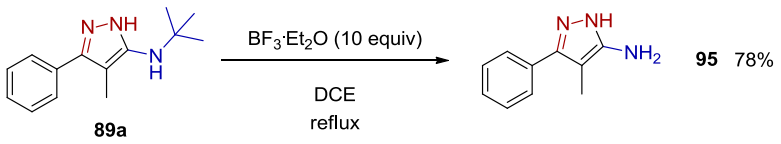
Scheme 54 : *X-ray structure of an* N*-substituted 5-aminopyrazole and proposed cyclization mechanism*

[68] For reaction conditions with a similar substrate, see : Hoveyda, H.; Schils, D.; Zoute, L.; Parcq, J. WO2011073376A1, June 23, 2011.

[69] For reaction conditions with a similar substrate, see : Zou, B.; Chan, W. L.; Ding, M.; Leong, S. Y.; Nilar, S.; Seah, P. G.; Liu, W.; Karuna, R.; Blasco, F.; Yip, A.; et al. *ACS Med. Chem. Lett.* **2015**, *6* (3), 344–348.

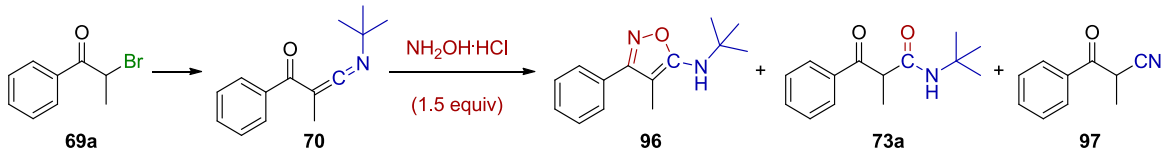
Surprisingly, reactions of α-oxo-ketenimine with 4-methoxyaniline and Grignard reagents delivered products resulting from nucleophilic attacks at the ketenimine function, whereas the reaction with hydrazine was initiated by an attack at the ketone group. A plausible explanation for this apparent divergency would be that reversible addition of anilines on the ketone may also occur, but would give rise to thermodynamically less stable intermediates or products than β-ketoamidines. Similarly, reversible addition of hydrazine on the ketenimine may also occur, although this seems less plausible as the addition product should directly undergo cyclization.

Removal of the *tert*-butyl group from 5-aminopyrazole **89a** was next performed with 10 equivalents of $BF_3{\cdot}Et_2O$ in DCE at reflux (Scheme 55). Heterocyle **95** was isolated in 78% yield and is a valuable building block for the synthesis of more complex heterocycles.



Scheme 55 : *Removal of the* tert*-butyl group from model 5-aminopyrazole* ***89a***

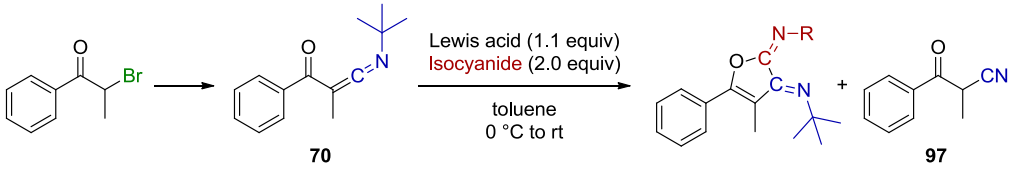
The successful synthesis of 5-aminopyrazoles with hydrazine prompted us to attempt the synthesis of 5-aminoisoxazoles with hydroxylamine (Table 9). No reaction occurred upon addition of hydroxylamine hydrochloride to the crude reaction mixture of α-oxo-ketenimine **70** and a temperature of 60 °C was necessary for the reaction to proceed (entry 1). A mixture of the desired isoxazole **96**, β-ketoamide **73a** and α-cyanoketone **97** was obtained. Addition of Et_3N at 60 °C of KOH at room temperature over 2 days did not allow the exclusive formation of isoxazole **96** (entries 2 et 3). Heating with KOH at 60 °C led to the formation of numerous products (entry 4). Based on these results, no further investigations were carried out.



	Base	Temperature	Reaction time	Result
1	- - -	60 °C	2 h	Mixture of **96**, **73a** and **97**
2	Et_3N (3.0 equiv)	60 °C	2 h	Mixture of **96** and **97**
3	KOH (1.5 equiv)	rt	2 days, then + 0.5 equiv KOH and $NH_2OH.HCl$)	Mixture of **96**, **73a** and **97**
4	KOH (2.0 equiv)	60 °C	- - -	Complex reaction mixture

Table 9 : *Attempted nucleophilic addition of hydroxylamine hydrochloride to model α-oxo-ketenimine* ***70***

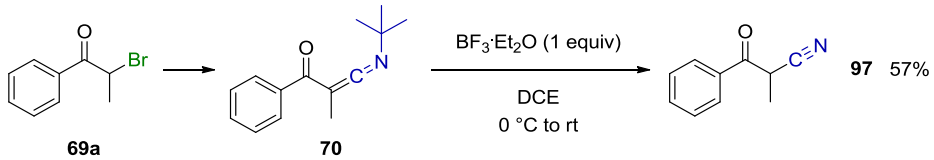
[4+1]-Cycloadditions between α-oxo-ketenimine **70** and different isocyanides were then attempted (Table 10), inspired by [4+1]-cycloadditions between enones and isocyanides reported by Saegusa and coworkers and by Chatani and coworkers.[70] In all cases, addition of Lewis acids led to removal of the *tert*-butyl group, giving α-cyanoketone **97** as major side-product.



	Isocyanide	Lewis acid	Result
1	*tert*-Butyl isocyanide	Et_2AlCl	Full conversion, mostly **97**
2	Benzyl isocyanide	Et_2AlCl	Full conversion, mostly **97**
3	2,6-dimethylphenyl isocyanide	Et_2AlCl	Full conversion, mostly **97**
4	*tert*-Butyl isocyanide	$GaCl_3$	Full conversion, mostly **97**
5	Benzyl isocyanide	$GaCl_3$	Full conversion, mostly **97**
6	2,6-dimethylphenyl isocyanide	$GaCl_3$	Full conversion, mostly **97**
7	- - -	Et_2AlCl	Full conversion, mostly **97**

Table 10 : *Attempted [4+1]-cycloaddition of model α-oxo-ketenimine **70** with isocyanides*

A clean synthesis of α-cyanoketone **97** was then performed on purpose and the product was isolated in 57% isolated yield with 10 equivalents of $BF_3{\cdot}Et_2O$ in DCE (Scheme 56).

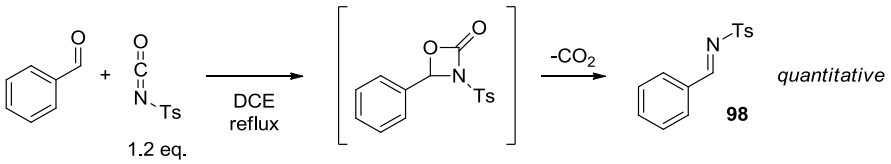


Scheme 56 : *Synthesis of an α-cyanoketone from model α-oxo-ketenimine **70***

Our attention was then focused on [2+2]-cycloadditions with imines to afford cyclic amidines that could be converted to β–lactams upon hydrolyzis. [2+2]-Cycloadditions between ketenes and imines were reported by Lectka and coworkers for the synthesis of enantiorich β–lactams catalyzed by cinchona-type

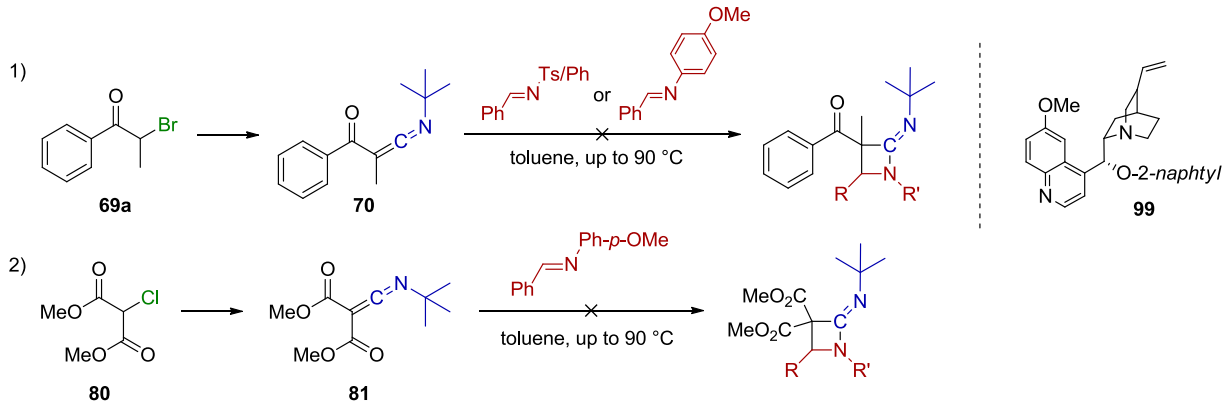
[70] a) Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47* (4), 741–743. b) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125* (26), 7812–7813.

catalysts.[71] *N*-Tosylimine **98** was synthesized by formal [2+2]-cycloaddition followed by extrusion of CO_2 (Scheme 57)[72] and the other amines were prepared by condensation of aldehydes with anilines.



Scheme 57 : *Synthesis of an* N*-tosylimine from aldehyde and isocyanate*

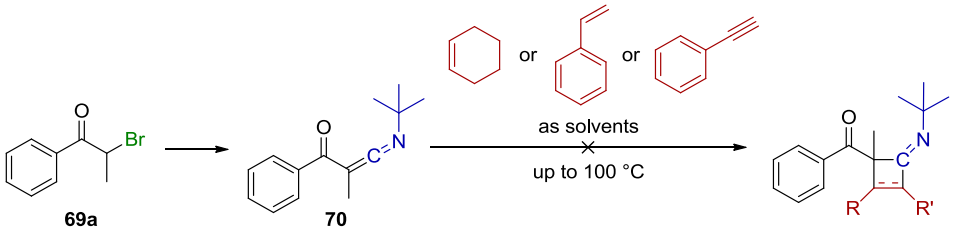
When the imines were added to the crude mixture of α-oxo-ketenimine **70**, no reaction was observed, even at 90 °C and in the presence of DABCO or cinchona derivative **99** as catalysts (Scheme 58, equation 1). α,α-Dioxo-ketenimine **81** did not exhibit a higher reactivity (equation 2).



Scheme 58 : *Attempted [2+2]-cycloaddition of α-oxo-ketenimines with imines*

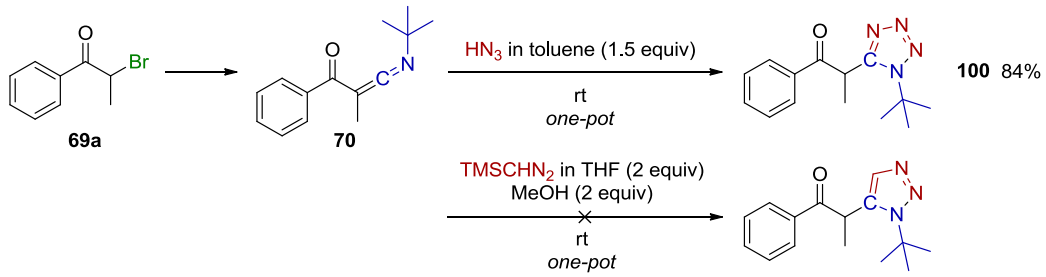
[2+2]-Cycloadditions with non-polarized unsaturations were then attempted (Scheme 59). α-Oxo-ketenimine **70** was heated up to 100 °C in cyclohexene, styrene or phenylacetylene but no reaction occurred.

[71] a) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2000**, *122* (32), 7831–7832. b) France, S.; Wack, H.; Hafez, A. M.; Taggi, A. E.; Witsil, D. R.; Lectka, T. *Org. Lett.* **2002**, *4* (9), 1603–1605. c) Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124* (23), 6626–6635.
[72] Huang, D.; Wang, X.; Wang, X.; Chen, W.; Wang, X.; Hu, Y. *Org. Lett.* **2016**, *18* (3), 604–607.



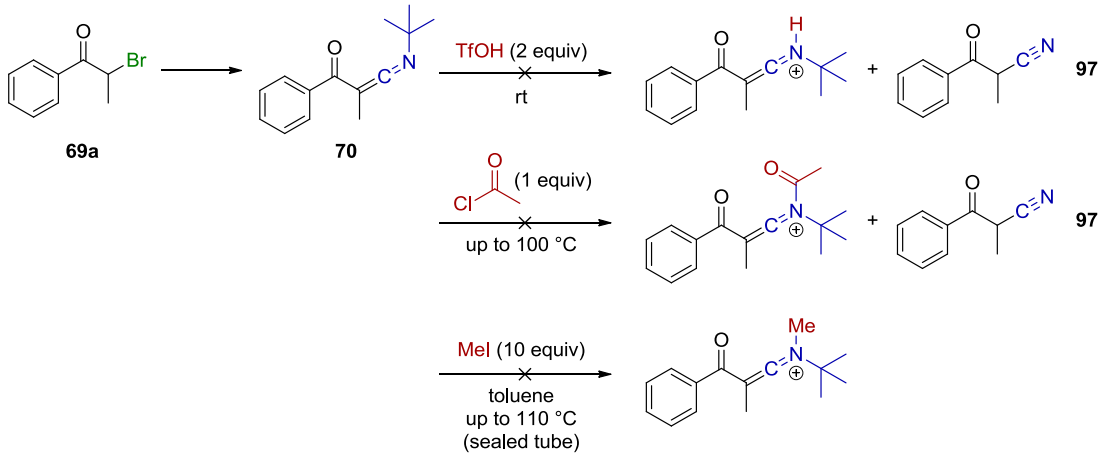
Scheme 59 : *Attempted [2+2]-cycloaddition of model α-oxo-ketenimine **70** with alkenes*

As was the case for vinyl ketenimines, α-oxo-ketenimine **70** reacted well to undergo formal [3+2]-cycloaddition with hydrazoic acid in one-pot to give 1,5-disubstituted tetrazole **100** in 84% isolated yield (Scheme 60). Unfortunately, trimethylsilyl diazomethane did not give the desired triazole product.



Scheme 60 : *Attempted [3+2]-cycloadditions of model α-oxo-ketenimine **70** with HN_3 and $TMSCHN_2$*

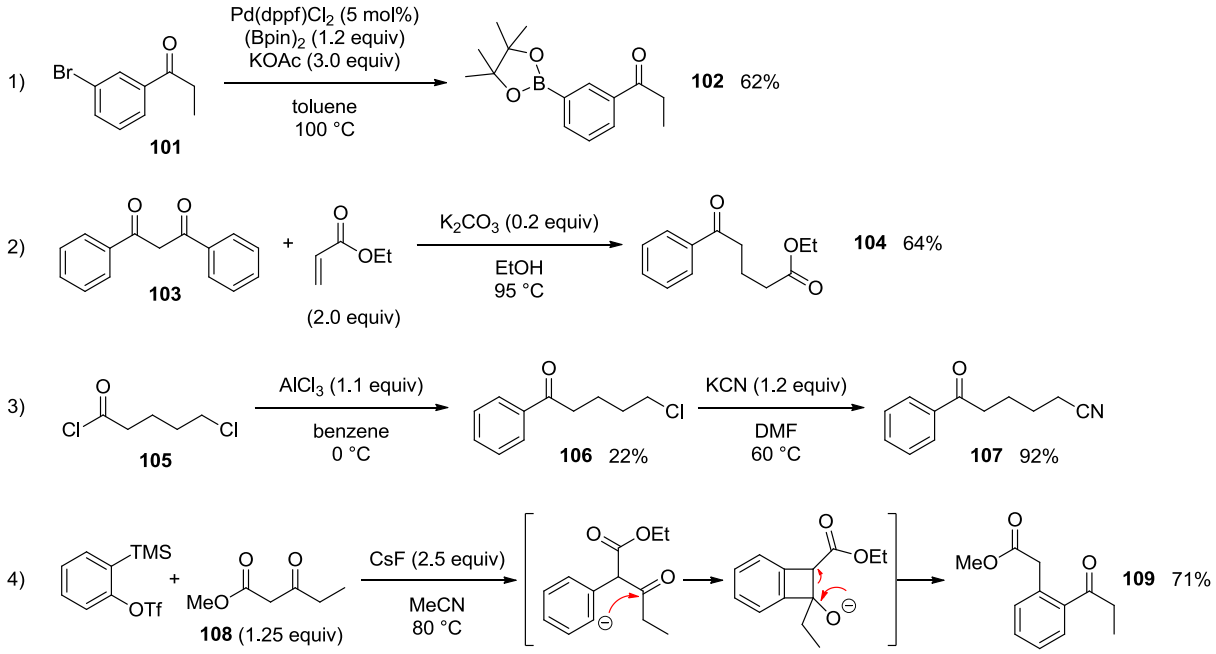
The conversion of α-oxo-ketenimine **70** to α-oxo-keteniminiums was then envisaged. As keteniminiums should be more reactive than ketenimines, we hypothesized that new transformations could be attempted with the keteniminiums. Protonation of **70** with triflic acid gave α-cyanoketone **97** as single product but with low conversion (Scheme 61). Acetylation gave a similar result. Finally, no reaction occurred when heating α-oxo-ketenimine **70** with MeI at high temperature in a sealed tube.



Scheme 61 : *Attempted activation of model α-oxo-ketenimine **70** to α-oxo-keteniminium*

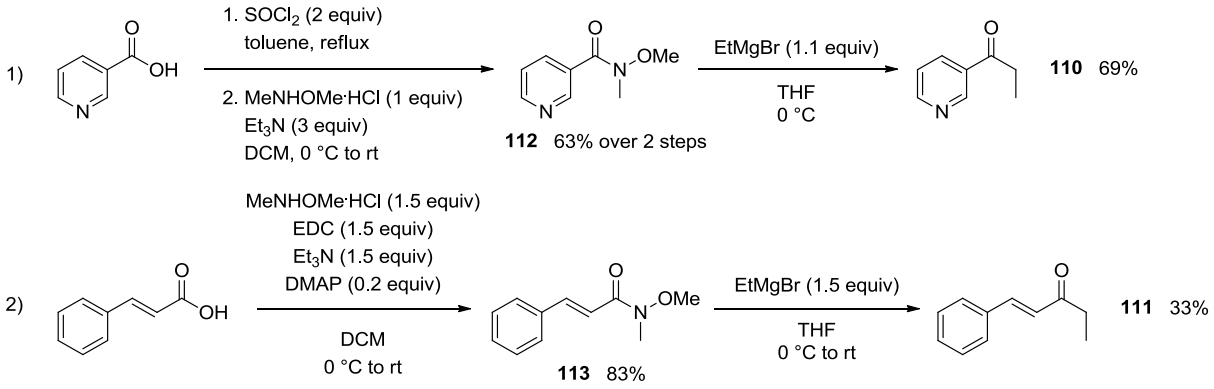
1.3.5 Synthesis of α-Bromoketones as Starting Materials

All non-commercially available α-bromoketones were synthesized by monobromination of their corresponding ketones using molecular bromine. In most cases, the ketones were prepared in a couple of steps without encountering major problems. Miyaura borylation of aryl bromide **101** gave boronate pinacol ester **102** in 62% yield (Scheme 62, equation 1).[73] Michael addition of dibenzoylmethane **103** to ethyl acrylate followed by fragmentation delivered δ–ketoester **104** in 64% yield (equation 2).[74] Friedel-Crafts acylation of benzene with 5-chlorovaleroyl chloride **105** allowed the preparation of valerophenone derivatives **106** and **107** in 22% and 92% yields (equation 3). A strong exotherm during the work-up of the Friedel-Crafts reaction unexpectedly converted most of the desired product to 1,5-diphenyl-1-pentanone, thus explaining the low 22% yield obtained. Following a procedure reported by Stoltz and coworkers (equation 4),[75] reaction of β-ketoester **108** with *in situ* generated benzyne as a strained intermediate, which underwent ring opening to release product **109** in 71% yield.



Scheme 62 : *Synthesis of propiophenones*

[73] Tong, S.; Xu, Z.; Mamboury, M.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54* (40), 11809–11812.
[74] For reaction conditions with a similar substrate, see : Cai, G.-X.; Wen, J.; Lai, T.-T.; Xie, D.; Zhou, C.-H. *Org. Biomol. Chem.* **2016**, *14* (8), 2390–2394.
[75] Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127* (15), 5340–5341.

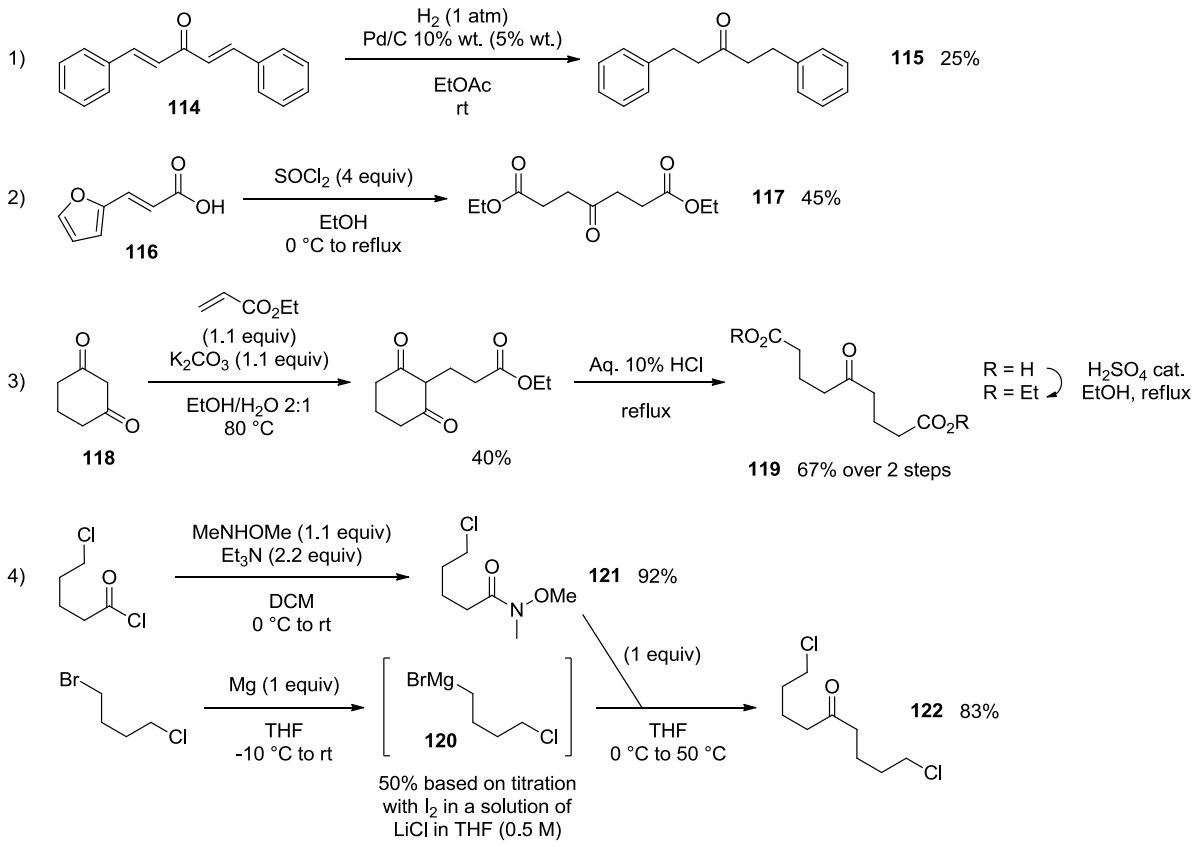


Scheme 63 : *Synthesis of ethyl ketones via Weinreb amides*

Ethyl ketones **110** and **111** (Scheme 63) were synthesized by nucleophilic addition of ethyl magnesium bromide to Weinreb amides **112** and **113**. The desired products were obtained in 69% and 33% yields, respectively. The second reaction was plagued by 1,4-addition side-products (equation 2).

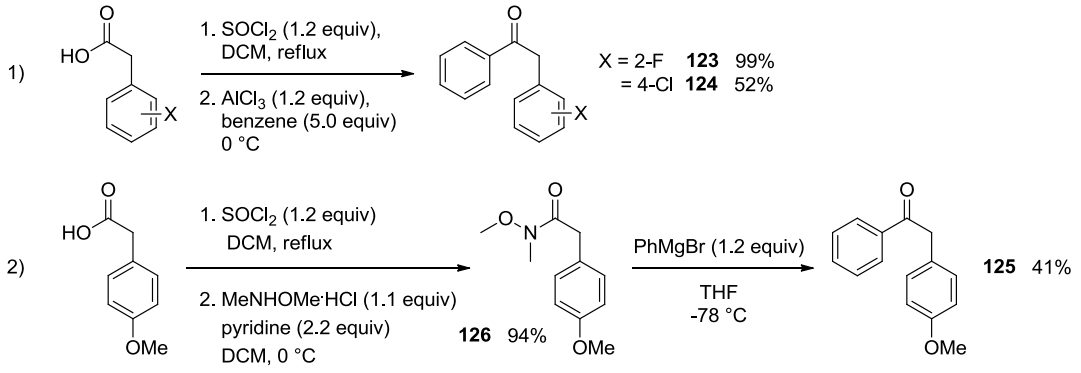
A couple of ketones bearing two alkyl substituents were then prepared (Scheme 64). Hydrogenation of dibenzylidenacetone **114** suffered from unexpected dimerization side-reactions but still provided the desired product **115** in 25% yield (equation 1). A reported rearrangement of 2-furanacrylic acid **116** in acidic ethanol gave access to diester **117** in 45% yield (equation 2).[76] Michael addition of 1,3-cyclohexanedione **118** to ethyl acrylate followed by retro-Dieckmann reaction and Fischer esterification furnished diester **119** in good yield (equation 3).[77] Finally, a solution of freshly prepared Grignard reagent **120**[78] was added to Weinreb amide **121**, which allowed the preparation of product **122** in 83% yield as single observed product.

[76] Marckowald, W. *Ber. Deutsch. Chem. Ges.* **1887**, *20* (2), 2811–2817.
[77] Stetter, H.; Rauhut, H. *Chem. Ber.* **1958**, *91* (11), 2543–2548.
[78] For reaction conditions with a similar substrate, see : Azuma, Y.; Newcomb, M. *Organometallics* **1984**, *3* (1), 9–14.



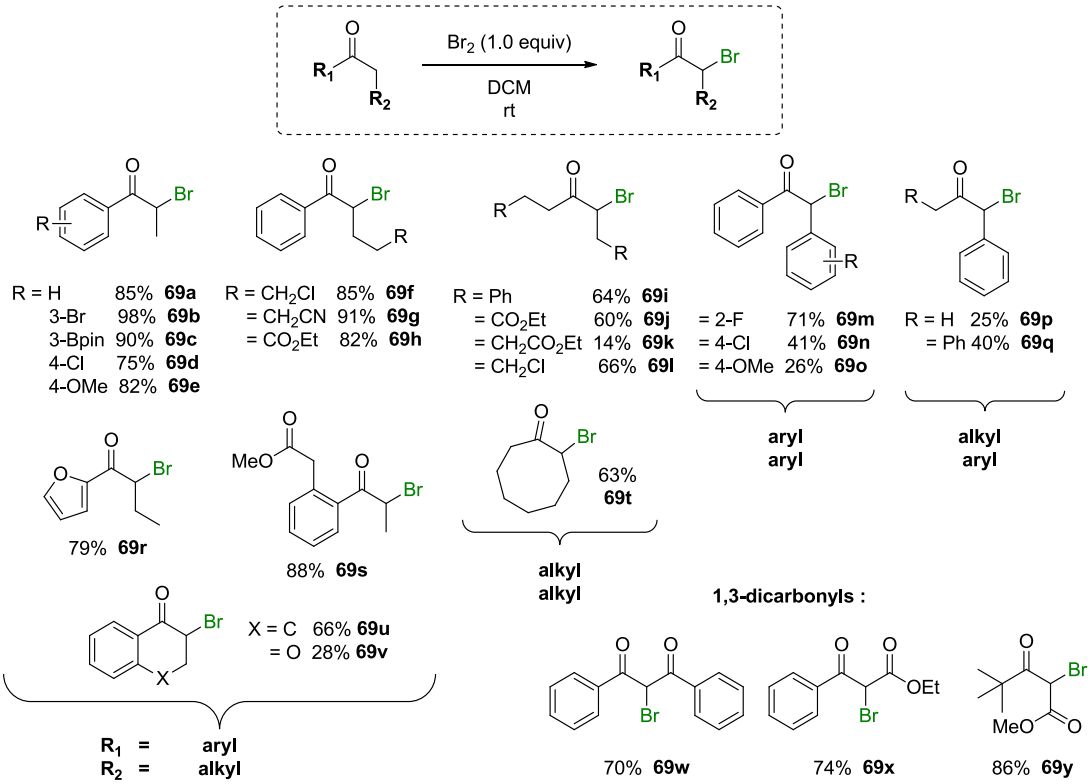
Scheme 64 : *Synthesis of dialkyl ketones*

The synthesis of α-aryl acetophenone derivatives also relied on Friedel-Crafts acylations and Weinreb amides (Scheme 65). Benzene was acylated with commercially available carboxylic acids to give compounds **123** and **124** in 99% and 52% yields (equation 1). α-Aryl acetophenone **125** was obtained in 41% yield by addition of phenyl magnesium bromide to Weinreb amide **126** (equation 2).



Scheme 65 : *Synthesis of α-aryl acetophenones*

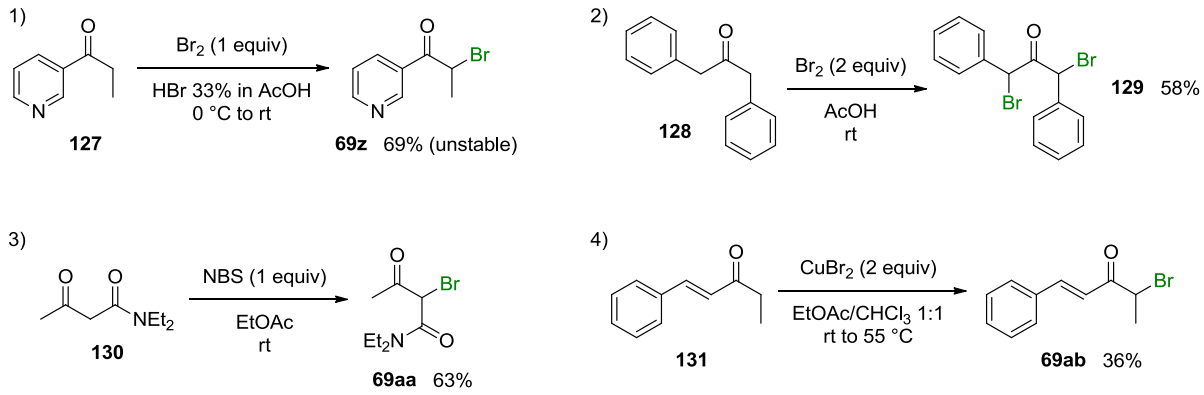
α-Bromination of the aforementioned and other commercially available ketones was then carried out with 1 equivalent of Br_2 in DCM (Scheme 66). Good to excellent yields were obtained, except for diester **69k** and α-bromoketone **69p**, which were isolated in only 14% and 25% yields among side-products. Unstable electron-rich α-bromoketone **69o** and bicycle **69v** were also isolated in low 26% and 28% yields.



Scheme 66 : *α-Bromination of ketones with Br_2 in DCM*

Several ketones required different reaction conditions for their monobromination (Scheme 67). Although no reaction was observed for 3-propionylpyridine **127** with an excess of Br_2 in DCM, replacement of the solvent by 33% HBr in AcOH delivered the desired α-bromoketone **69z** in 69% yield after purification by column chromatography (equation 1).[79] However, the product decomposed very quickly. A procedure for the α,α'-dibromination of dibenzyl ketone **128** in AcOH was followed and gave access to product **129** in 58% yield (equation 2).[80] Monobromination of β-ketoamide **130** was performed with NBS to give **69aa** in 63% yield (equation 3).[81] Specific reaction conditions for the α-bromination of ketones in the presence of unsaturations were found and applied for α,β-unsaturated ketone **131**. However, by heating substrate **131** with $CuBr_2$ in EtOAc/$CHCl_3$, the desired product **69ab** was isolated in only 36% yield among several side-products (equation 4).[82]

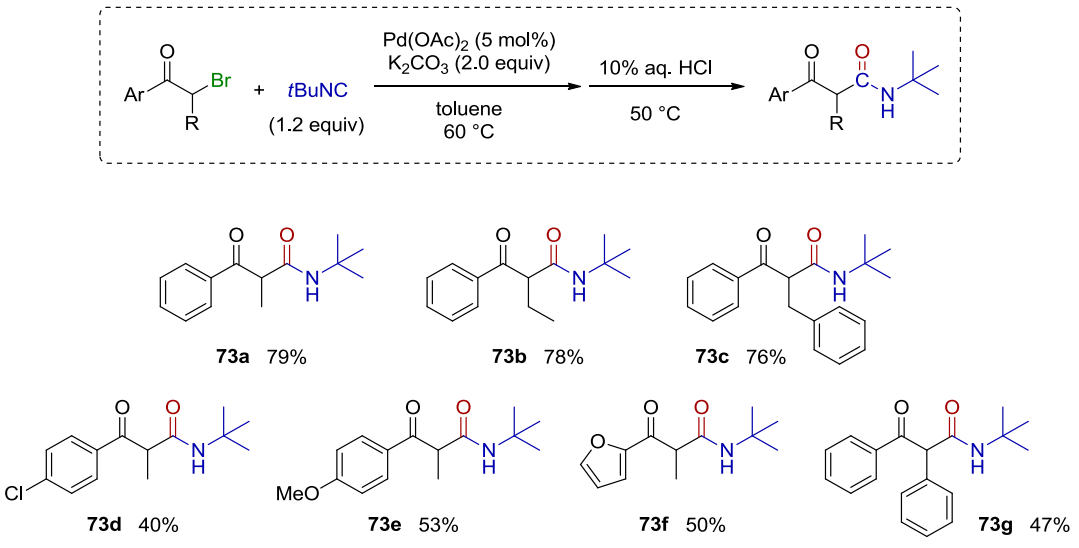
[79] For reaction conditions with a similar substrate, see : Jubian, V.; Packiarajan, M.; Reinhard, E. WO2007103295A2, September 13, 2007.
[80] For reaction conditions with a similar substrate, see : Nacsa, E. D.; Lambert, T. H. *Org. Lett.* **2013**, *15* (1), 38–41.
[81] For reaction conditions with a similar substrate, see : Yang, D.; Yan, Y.-L.; Law, K.-L.; Zhu, N.-Y. *Tetrahedron* **2003**, *59* (52), 10465–10475.
[82] Goud, P. M.; Sheri, A.; Desai, P. V.; Watkins, E. B.; Tekwani, B.; Sabnis, Y.; Gut, J.; Rosenthal, P. J.; Avery, M. A. *Med. Chem. Res.* **2005**, *14* (2), 74–105.



Scheme 67 : *α-Bromination of ketones with specific reaction conditions*

1.3.6 Scope of the Synthesis of β-Ketoamides

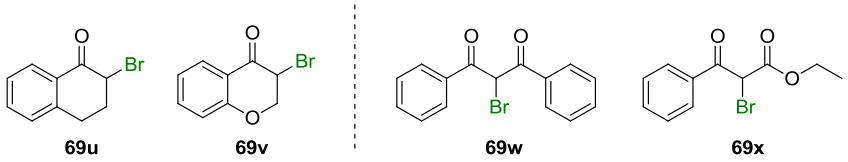
Before turning our attention to the synthesis of 5-aminopyrazoles and β-ketoamidines, a couple of β-ketoamides were synthesized to probe the generality of the α-oxo-ketenimine formation from α-haloketones (Scheme 68). Products **73a** to **73c** were obtained in good yields (76 to 79%). However, lower yields were observed with eletron-deficient and electron-rich aromatics **73d** and **73e** as well as with furyl derivative **73f** (40 to 53%). The α-aryl-β-ketoamide **73g** was also delivered in a modest 47% yield.



Scheme 68 : *Scope of the synthesis of* β*-ketoamides from α-bromoketones*

At this stage, five α-bromoketones did not react properly (Scheme 69). On one-hand, α-tetralone and chromanone derivatives **69u** and **69v** gave only traces of α–oxo-ketenimines. On the other hand, 1,3-

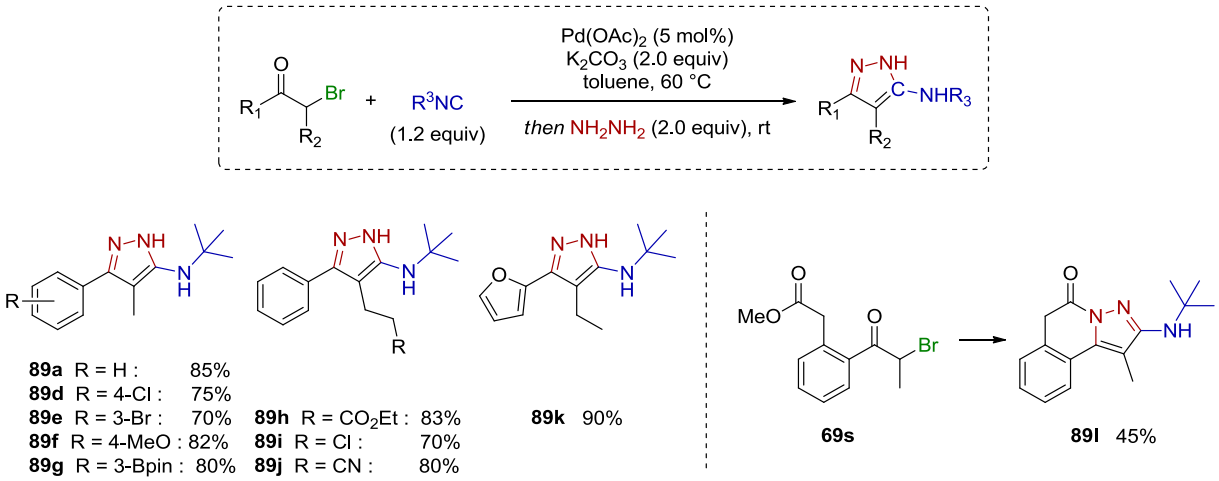
diketone **69w** and β–ketoester **69x** were efficiently converted to α-oxo-ketenimines, but the latter were then degraded under the harsh hydrolysis conditions.



Scheme 69 : *Unsuitable α-bromoketones for the synthesis of β-ketoamides under the optimized conditions*

1.3.7 Scope of the Synthesis of 5-Aminopyrazoles

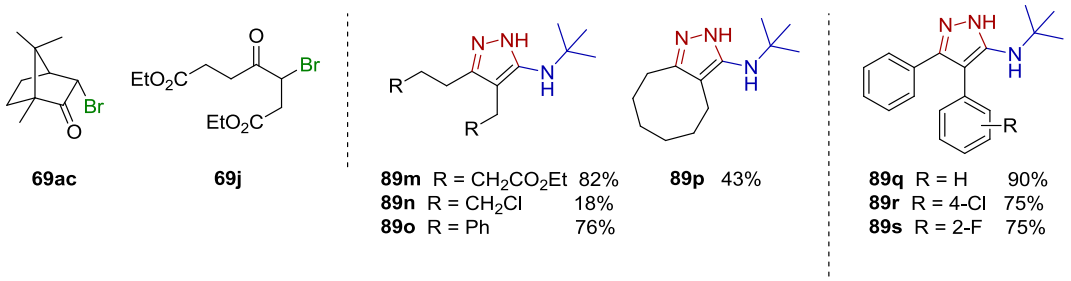
The scope of the one-pot three-component synthesis of 5-aminopyrazoles was next sought (Scheme 70). Both electron-withdrawing (**89d** and **89e**) and electron-donating groups (**89f**) on the aromatic moiety of 2-bromopropiophenone were tolerated and the products were isolated in high 75% to 82% yields. Notably, aryl bromide **89e** and aryl boronate **89g** were also compatible (70% and 80% yields), providing 5-aminopyrazoles that could be readily further functionalized. Electrophilic functionalities such as ester (**89h**, 83% yield), chloride (**89i**, 70% yield) and cyanide (**89j**, 80% yield), which are susceptible to nucleophilic attack by hydrazine, remained untouched to deliver the products in high yields. The highest yield was obtained for furyl derivative **89k** (90% yield). Of synthetic interest, tricyclic compound **89l** was directly formed in 45% yield under the standard optimized reaction conditions.



Scheme 70 : *Scope of the synthesis of 3-aryl-4-alkyl 5-aminopyrazoles from α-bromoketones*

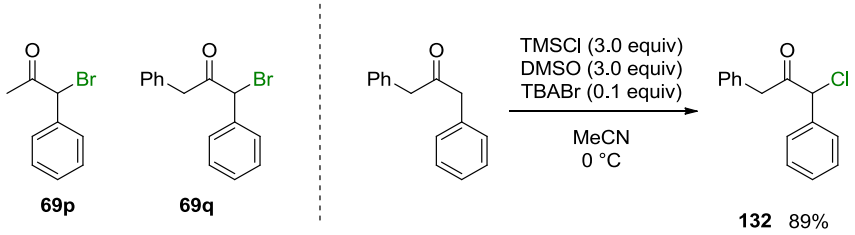
The potential of this methodoloy for the synthetis of 3,4-dialkyl and 3,4-diaryl 5-aminopyrazoles was then investigated (Scheme 71). Using the same standard reaction conditions, the conversion was low

with commercially available (+)-3-bromocamphor **69ac** and no desired product could be isolated. α-Bromoketone **69j** was almost instantaneously converted to its corresponding α,β-unsaturated ketone after β-elimination of bromide. However, diester with longer chains **89m** was isolated in 82% yield. Dichloride **89n** was isolated in small amount but diphenyl **89o** was obtained in 76% yields. Unfortunately, no further intramolecular cyclization of the electrophilic chains with both NH groups was observed upon heating. Surprisingly, cyclic product **89p** could only be synthesized in 43% yield, probably due to the lower stability of the palladium enolate intermediate. Also, 3,4-diaryl 5-aminopyrazoles **89q**, **89r** and **89s** could be readily synthesized in high yields (75% to 90%).



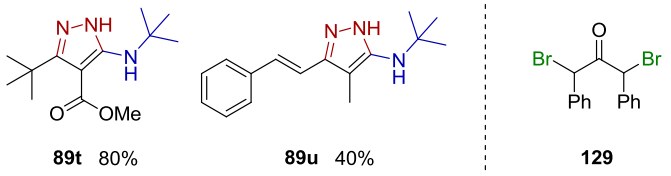
Scheme 71 : *Scope of the synthesis of 3,4-dialkyl and 3,4-diaryl 5-aminopyrazoles*

Following the successful application of this methodology for the preparation of 3-aryl-4-alkyl, 3,4-diakyl and 3,4-diaryl 5-aminopyrazoles, the synthesis of 3-alkyl-4-aryl 5-aminopyrazoles was attempted. Unfortunately, α-bromoketones **69p** and **69q** proved unsuitable for the generation of ketenimines (Scheme 72). Starting from the corresponding α-chloroketone **132**, which was be prepared in 89% yield, did not solve this issue.



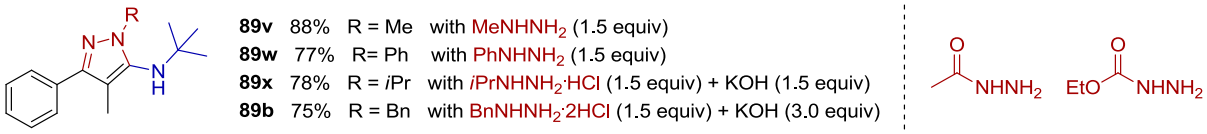
Scheme 72 : *Unsuccessfull synthesis of 3-alkyl-4-aryl 5-aminopyrazoles from α-bromoketones*

This methodology seems also applicable for the preparation of 5-aminopyrazoles bearing esters or alkenes, as suggested by the isolation of products **89t** and **89u** in a 80% and 40% yields (Scheme 73). Double ketenimine formation was attempted using dibromide **129**, but this substrate was degraded in the reaction mixture.



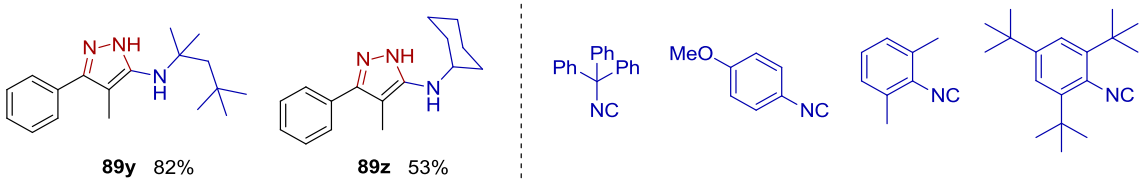
Scheme 73 : *Additional examples for the synthesis of 5-aminopyrazoles from α-bromoketones*

Screening of several *N*-substituted hydrazines was next performed (Scheme 74). Methylhydrazine and phenylhydrazine reacted well and delivered tetrasubstituted 5-aminopyrazoles **89v** and **89w** in 88% and 77% yields. As seen previously, the use of hydrazine hydrochloride salts required the addition of KOH to allow the synthesis of compounds **89x** and **89b** in 78% and 75% yields. Unfortunately, no reaction occurred with acetylhydrazine and ethyl carbazate at room temperature, and gradually heating up to 90 °C only generated complex reaction mixtures.



Scheme 74 : *Scope of the synthesis of* N*-substituted 5-aminopyrazoles from 2-bromopropiophenone*

Although *t*BuNC is often the best isocyanide for palladium-catalyzed insertions, sereral alkyl and aryl isocyanides were submitted to the standard reaction conditions (Scheme 75). As expected, 5-aminopyrazole **89y** was isolated in high 82% yield. However, the yield of the reaction dropped to 53% when using the less bulky cyclohexyl isocyanide (**89z**) and side-products were obtained in the course of this much slower reaction (2 days). No reaction occurred with trityl isocyanide, 4-methoxyphenyl isocyanide and the bulkier ortho-disubstituted aryl isocyanides.

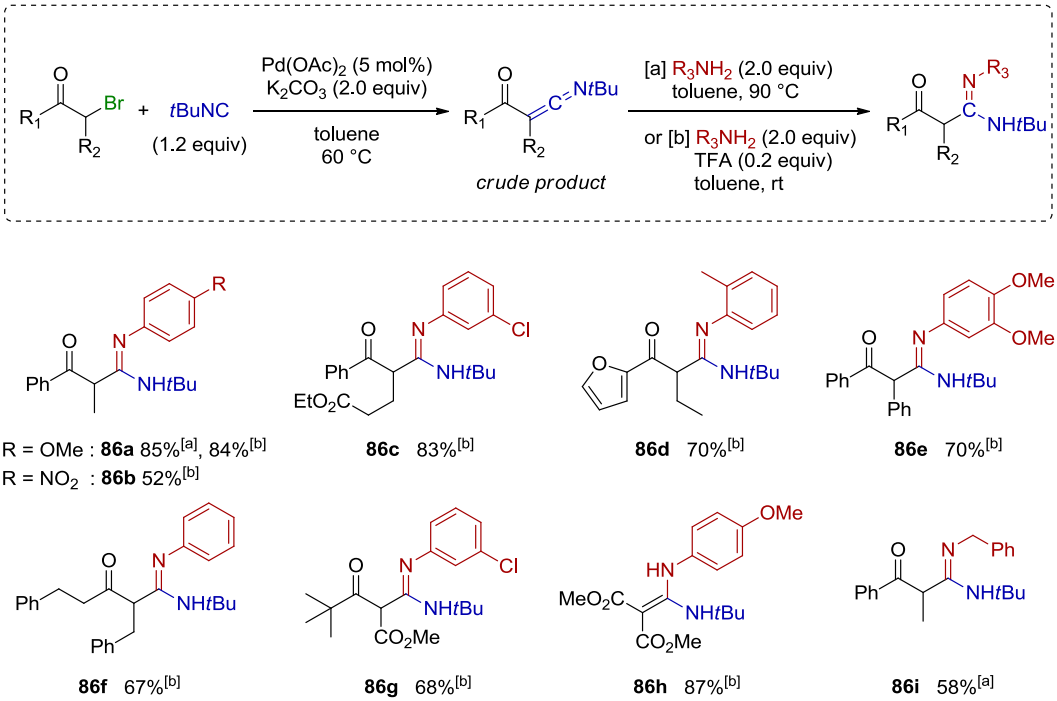


Scheme 75 : *Synthesis of 5-aminopyrazoles from 2-bromopropiophenone with various isocyanides*

1.3.8 Scope of the Synthesis of β-Ketoamidines

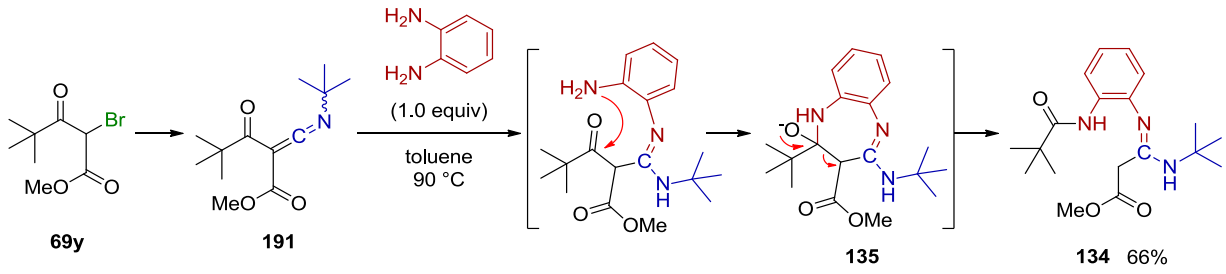
The generality of the methodology developed for the synthesis of β-ketoamidines was next investigated (Scheme 76). Product **86a** could be formed in almost identical yields at 90 °C or at room temperature

with a catalytic amount of TFA (85% and 84%, respectively). For the rest of the scope, the milder reaction conditions at room temperature with TFA were chosen. All α-bromoketones derived from aryl alkyl ketones (**86a** to **86d**), aryl aryl ketone (**86e**), alkyl alkyl ketone (**86f**), β-ketoester (**86g**) and malonate (**86h**) participated well in this reaction giving the products in 52% to 87% yields. To note, a lower yield of 52% for product **86b** was obtained with electron-poor *p*-nitroaniline. With benzylamine, a very low conversion was observed at room temperature with TFA. However, the desired β-ketoamidine **86i** could be isolated in 58% yield when the ketenimine and the amine were heated at 90 °C. Finally, no reaction occurred with morpholine, thus limiting the scope to anilines and primary amines.



Scheme 76 : *Scope of the synthesis of* β*-ketoamidines from* α*-bromocarbonyl compounds*

When α-oxo-ketenimine **133** was treated with 2-aminoaniline (Scheme 77), ester **134** was delivered in 66% yield after a proposed retro-Dieckmann-type opening of intermediate **135**. Performing the reaction at room temperature with TFA gave product **134** in 40% yield as major product. The presence of the bulky *tert*-butyl group may favor the retro-Dieckmann-type reaction from intermediate **135**.

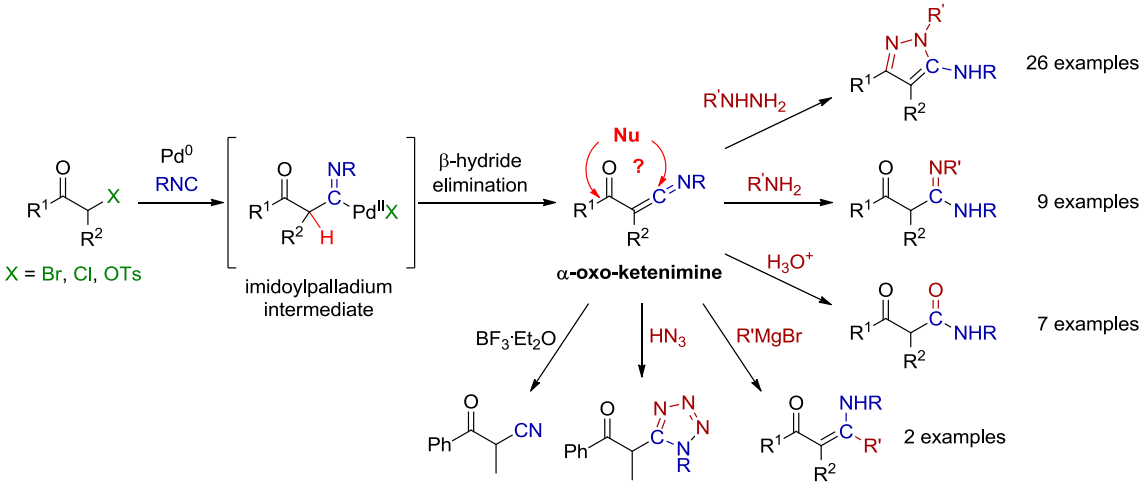


Scheme 77 : *Retro-Dieckmann-type side-reaction in the attempted synthesis of a 7-membered cyclic product*

1.3.9 Conclusion

Following our previous work on the palladium-catalyzed synthesis of vinyl ketenimines featuring an isocyanide insertion / β-hydride elimination sequence, we sucessfully exploited this sequence of elementary steps for the synthesis of α-oxo-ketenimines from α-haloketones (Scheme 78). The reactivity profile of the α-oxo-ketenimine group was then investigated. This led to the discovery of a divergent reactivity towards nucleophiles : hydrazines attacked at the ketone group whereas amines and other nucleophiles attacked at the ketenimine function.

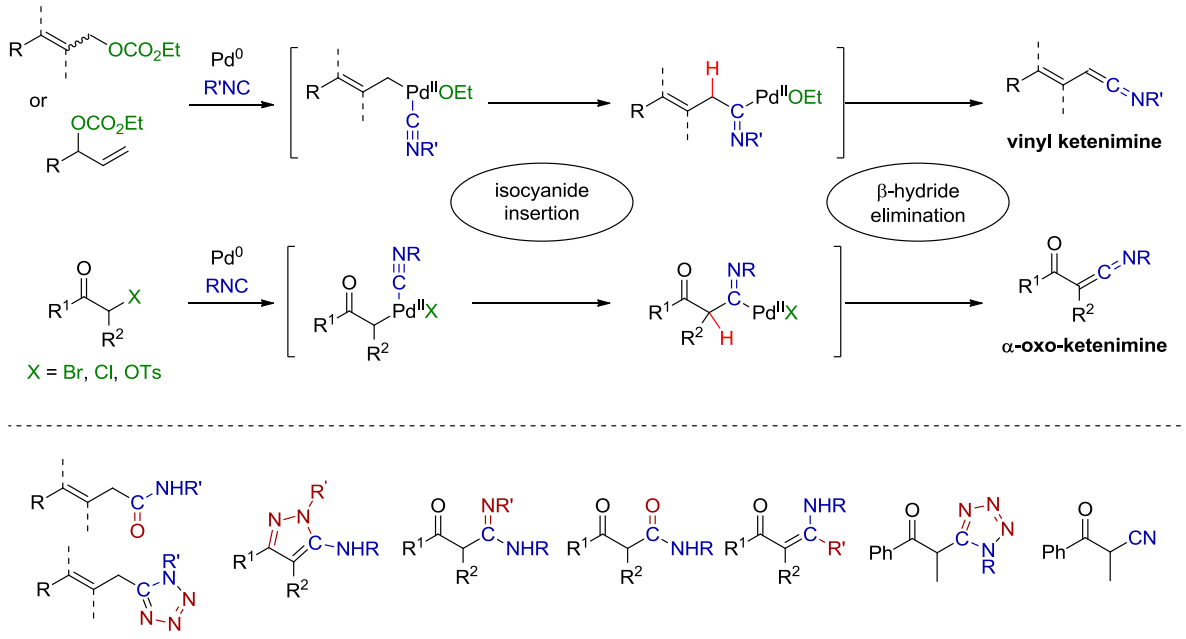
A one-pot three-component synthesis of tetrasubstituted 5-aminopyrazoles was subsequently developed and allowed the preparation of 26 pyrazoles with broad functional group variety. The α-oxo-ketenimine group was also a usefull precursor for the synthesis of β-ketoamidines and β-ketoamides. Finally, enaminones, tetrazole and α-cyanoketone could also be formed from the same precursor.



Scheme 78 : *Summarized synthesis and reactivity of α-oxo-ketenimines from allyl carbonates and isocyanides*

1.4 Conclusion

Two novel palladium-catalyzed methodologies were developed for the synthesis of ketenimines from isocyanides (Scheme 79). They both feature an isocyanide insertion / β-hydride elimination sequence for the generation of the ketenimines, which were further functionalized for the synthesis of valuable building blocks or pharmaceutically relevant products. This work was published in two articles.[83]



Scheme 79 : *Synthesis and derivatization of vinyl ketenimines and α-oxo-ketenimines*

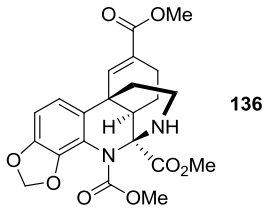
[83] a) Qiu, G.*; Mamboury, M.*; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55* (49), 15377–15381. b) Mamboury, M.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2017**, *23* (52), 12744–12748. (* These authors contributed equally)

CHAPTER 2 Synthetic Studies Towards the Total Synthesis of Mersilongine

2.1 Introduction

2.1.1 Isolation and Structure

Mersilongine **136** is a pentacyclic quinolinic alkaloid isolated in 2004 by Kam and coworkers from Malayan *Kopsia* species (Scheme 80).[84] Beside the quinolinic core, a bicyclic bridged aminal, an α,β-unsaturated ester and a 1,3-benzodioxole unit constitute the principal functionalities. It also features three contiguous chiral centers, two of them being quaternary. Mersilongine was obtained from the basic fraction derived from the ethanolic extract of the leaves.



136

Scheme 80 : *Structure of Mersilongine*

The structure of Mersilongine relates to other natural products isolated from *Kopsia* species, the Mersinine-type alkaloids.[85] Selected examples of this family are shown in Scheme 81. Mersinine B is a rearranged structure of the Mersilongine skeleton bearing three additional carbon atoms. Inversion of the chiral center at C(2) gives Mersinine A. For most of the other reported Mersinine-type alkaloids, both diastereomeric forms at C(2) were isolated. Mersidasine B and E are oxidized derivatives of Mersinine B.

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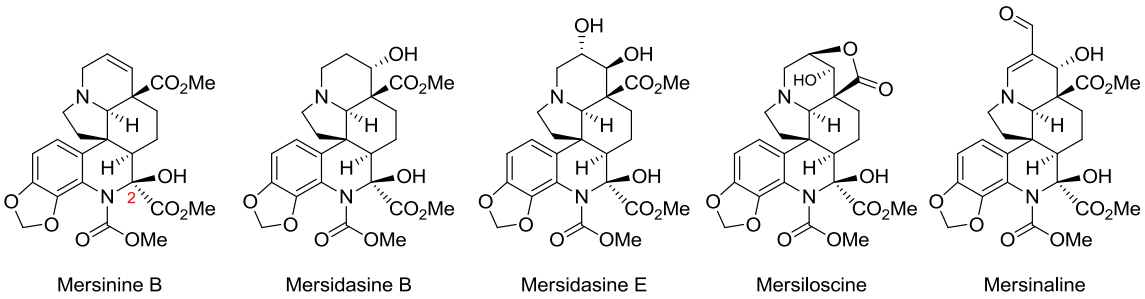
[84] Kam, T.-S.; Subramaniam, G. *Tet. Lett.* **2004**, *45* (17), 3521–3524.

[85] a) Kam, T.-S.; Subramaniam, G.; Lim, T.-M. *Tet. Lett.* **2001**, *42* (34), 5977–5980. b) Subramaniam, G.; Kam, T.-S. *Tet. Lett.* **2007**, *48* (38), 6677–6680. c) Subramaniam, G.; Choo, Y.-M.; Hiraku, O.; Komiyama, K.; Kam, T.-S. *Tetrahedron* **2008**, *64* (7), 1397–1408. d) Low, Y.-Y.; Subramaniam, G.; Lim, K.-H.; Wong, R. C. S.; Robinson, W. T.; Kam, T.-S. *Tetrahedron* **2009**, *65* (34), 6873–6876.

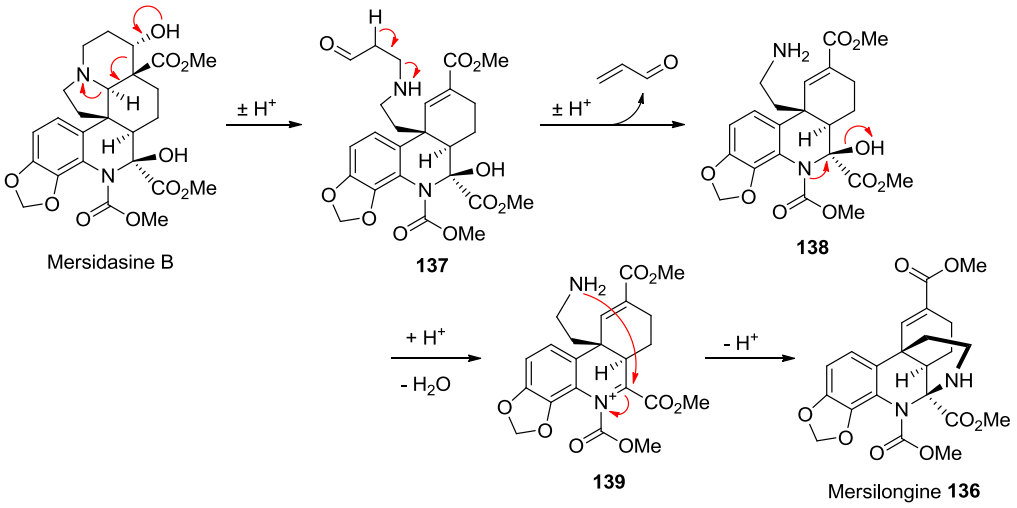
Mersiloscine probably arises from an isomer of Mersidasine E with inversion of the stereochemistry of the 1,2-diol group. Interestingly, Mersinaline possesses and additional formyl unit.



Scheme 81 : *Selected examples of Mersinine-type alkaloids*

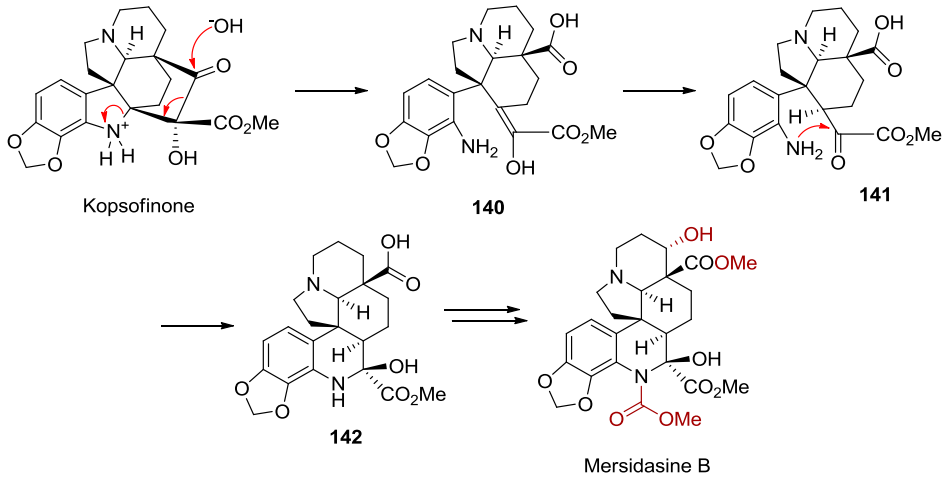
2.1.2 Proposed Biosynthesis from *Aspidosperma* Alkaloids

In the isolation report of Mersilongine, a possible rearrangement is proposed for the conversion of Mersinine-type alkaloids to Mersilongine (Scheme 82). Grob-fragmentation of Mersidasine B would give α,β-unsaturated ester **137**, which would undergo retro-Michael addition to release acrolein and deliver primary amine **138**. Alternatively and more likely, we propose that intermediate **138** could be formed from Mersidasine B by retro-aldol reaction, β-elimination and retro-aza-Michael addition. Elimination of H_2O from hemiaminal **138** would then form iminium intermediate **139**, that would be intramolecularly trapped to give Mersilongine **136**.



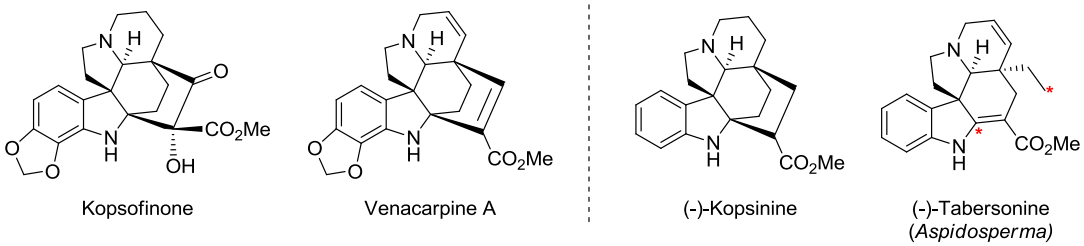
Scheme 82 : *Reported possible route for the biosynthesis of Mersilongine from Mersinine-type alkaloids*

Kam and coworkers reported a ring expansion of indoline scaffolds to quinoline skeletons *via* aziridium formation and fragmentation,[86] but instead we proposed that Mersidasine B may arise from Kopsofinone[87] or a similar natural product *via* a different mechanism (Scheme 83). First, fragmentation of protonated Kopsofinone would form enol **140**. This intermediate would tautomerize to α-ketoester **141**, which would finally be trapped by the amine to give hemiaminal **142**. From there, further functionalizations would give Mersidasine B.



Scheme 83 : *Proposed route for the biosynthesis of Mersidasine B from Kopsofinone*

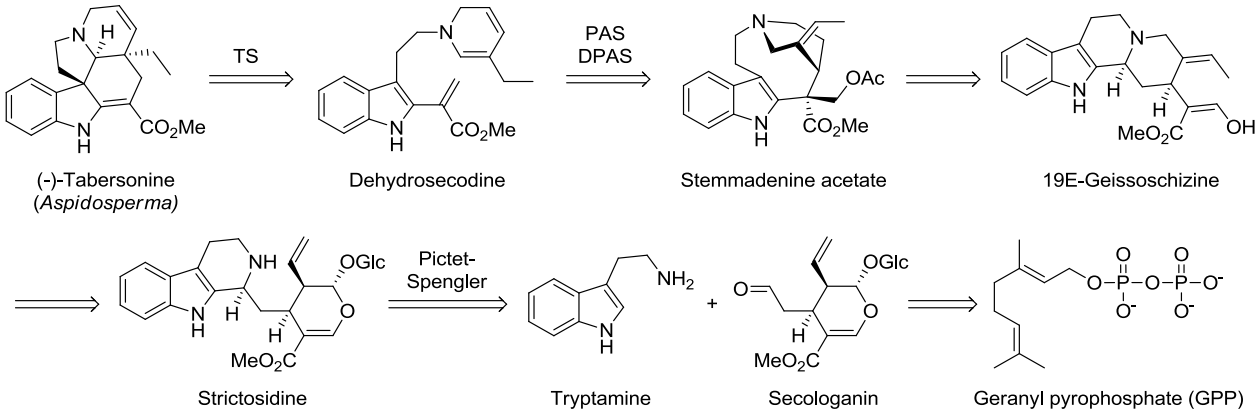
Kopsofinone is an oxidized form of Venacarpine A[88] and belongs to the family of Kopsinine-type alkaloids (Scheme 84).[89] These natural products are structurally closely related to the *Aspidosperma* alkaloids, for example (-)-Tabersonine.



Scheme 84 : *Selected examples of Kopsinine-type alkaloids and* Aspidosperma *alkaloids*

[86] See reference 85c.
[87] Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70* (11), 1783–1789.
[88] Kam, T.-S.; Choo, Y.-M. *Phytochemistry* **2004**, *65* (14), 2119–2122.
[89] a) Kam, T.-S.; Choo, Y.-M. *Tet. Lett.* **2003**, *44* (6), 1317–1319. b) Subramaniam, G.; Kam, T.-S. *Helv. Chim. Acta.* **2008**, *91* (5), 930–937.

The complete biosynthesis of (-)-Tabersonine is known and all the enzymes involved in the process have been identified (Scheme 85). (-)-Tabersonine would be formed by [4+2]-cycloaddition of Dehydrosecodine by an enzyme named Tabersonine Synthase (TS). This intermediate would arise from Stemmadenine acetate by reaction with Precondylocarpine Acetate Synthase (PAS) and Dehydrogenase Dihydroprecondylocarpine synthase (DPAS). These three enzymes were identified by Courdavault, O'Connor and coworkers and were reported in 2018.[90] The biosynthesis of Stemmadenine acetate was already known : it is the product of the conversion of 19E-Geissoschizine, which in turn comes from Strictosidine. This intermediate is formed by enantioselective Pictet-Spengler reaction of Tryptamine with Secologanin, which is derived from Geranyl pyrophosphate (GPP).[91]



Scheme 85 : *Biosynthesis of* Aspidosperma *alkaloids from tryptamine and Secologanin*

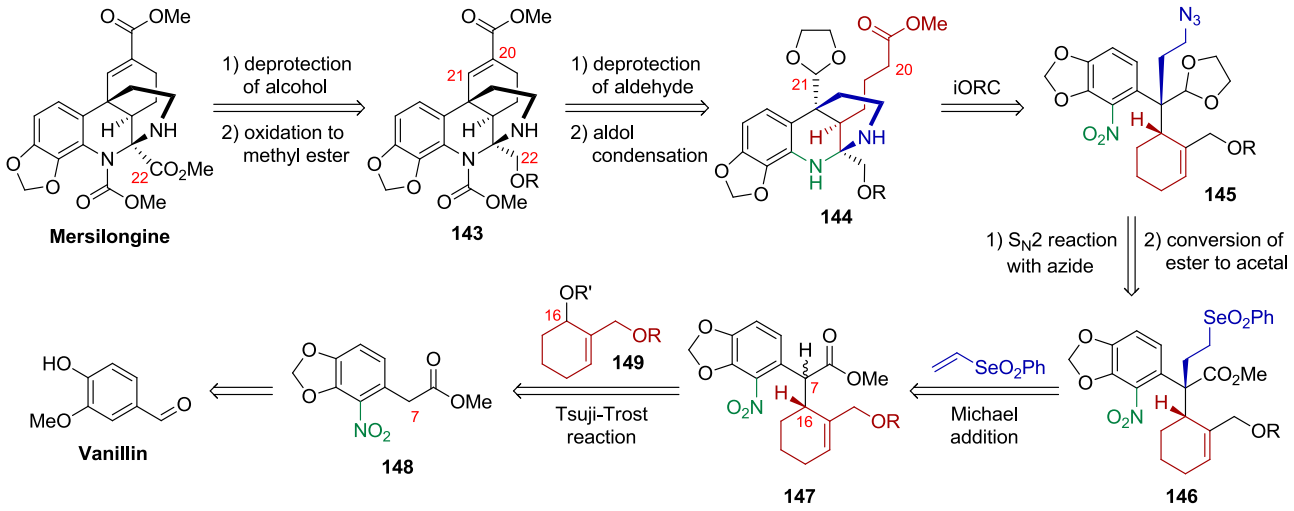
[90] Caputi, L.; Franke, J.; Farrow, S. C.; Chung, K.; Payne, R. M. E.; Nguyen, T.-D.; Dang, T.-T. T.; Carqueijeiro, I. S. T.; Koudounas, K.; Bernonville, T. D. de; et al. *Science* **2018**, *360* (6394), 1235–1239.

[91] Qu, Y.; Easson, M. E. A. M.; Simionescu, R.; Hajicek, J.; Thamm, A. M. K.; Salim, V.; Luca, V. D. *PNAS* **2018**, *115* (12), 3180–3185.

2.2 Retrosynthesis and Key Reactions

2.2.1 General Retrosynthetic Scheme

Our retrosynthesis of Mersilongine is depicted in Scheme 86. The methyl ester at C(22) would be formed by deprotection and oxidation of protected primary alcohol **143**. α,β-Unsaturated ester **143** would be synthesized by a last cyclization reaction from deprotected aldehyde **144** by aldol condensation. The C-C bond between C(20) and C(21) would be formed in this operation. Aminal **144** would be prepared by metamorphosis of intermediate **145** by applying an integrated Oxidation/Reduction/Cyclization one-pot sequence (iORC) developed in our group.[92] The mechanism for this transformation will be detailed in a next chapter. After the iORC sequence, protection of both NH of the aminal group will certainly be necessary. Azide **145** would be readily obtained from alkyl phenyl selenone **146**, which would be the product of diastereoselective Michael addition of α,α-disubstituted ester **147** to phenyl vinyl selenone. This strategy for the preparation of quaternary centers containing a CH_2-CH_2-N_3 chain was inspired by the total synthesis of (+)- and (-)-Trigonoliimine A reported by our group in 2013.[93] α,α-Disubstituted ester **147** would then be formed by enantioselective Tsuji-Trost reaction between α-arylester **148** and activated allyl alcohol **149** to forge the C-C bond between C(7) and C(16).[94] Finally, α-arylester **148** should be obtained in a couple of steps from commercially available vanilin.

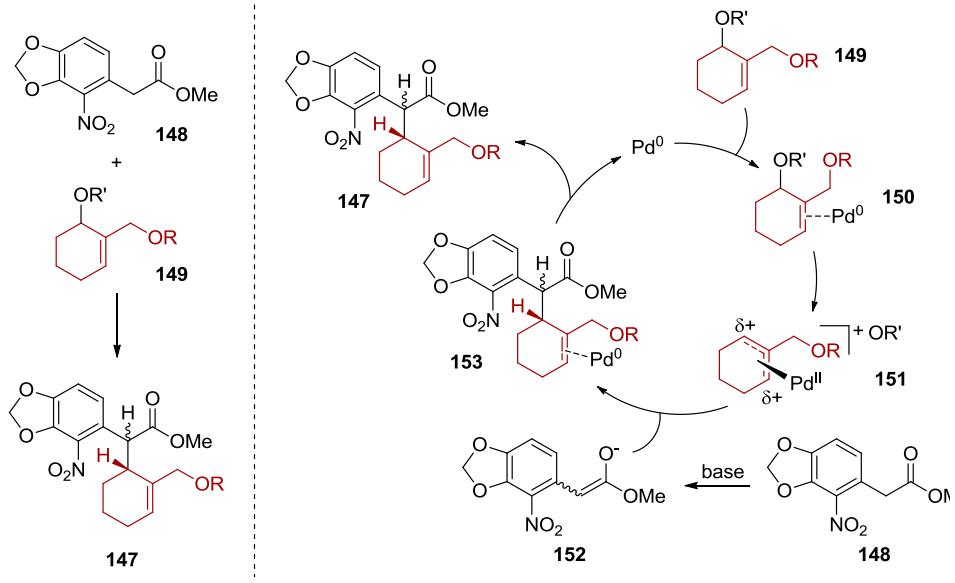


Scheme 86 : *General retrosynthetic scheme for the total synthesis of Mersilongine from vanillin*

[92] For a review, see : Xu, Z.; Wang, Q.; Zhu, J. *Chem. Soc. Rev.* **2018**, *47* (21), 7882–7898.
[93] Buyck, T.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52* (48), 12714–12718.
[94] Applications in total synthesis : Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103* (8), 2921–2944.

2.2.2 Tsuji-Trost Reaction

The Tsuji-Trost reaction between α-arylester **148** and activated allyl alcohol **149** is planned as a first key step in the total synthesis of Mersilongine (Scheme 87). The mechanism of this palladium-catalyzed allylic substitution would be the following, based on the well documented understanding of this reaction.[95] Pd(0) would first coordinate to cyclohexene **149** to form η^2-allyl Pd complex **150**. Oxidative addition, also called ionization, would then afford π-allyl Pd complex **151**. Racemic activated allyl alcohol **149** can be used as the chiral center would be lost in the π-allyl Pd complex. In absence of chiral ligand, enolate **152** could then attack at either terminal carbon atom of the allyl moiety ; soft nucleophiles such as enolates attack at the allyl moiety rather than at the metal center. However, if a chiral ligand is bound to the palladium, attack at one of both terminal carbon atoms will be favored to give η^2-allyl Pd complex **153** with the desired stereochemistry of the allylic proton. The stereochemistry of the center at the α-position of the ester should be determined by the geometry of the enolate **152**. As the next step in the total synthesis would be the deprotonation at this position, the stereochemistry of this proton does not need to be controlled. Finally, decoordination of Pd(0) would deliver the desired product **147** while regenerating the active catalyst.

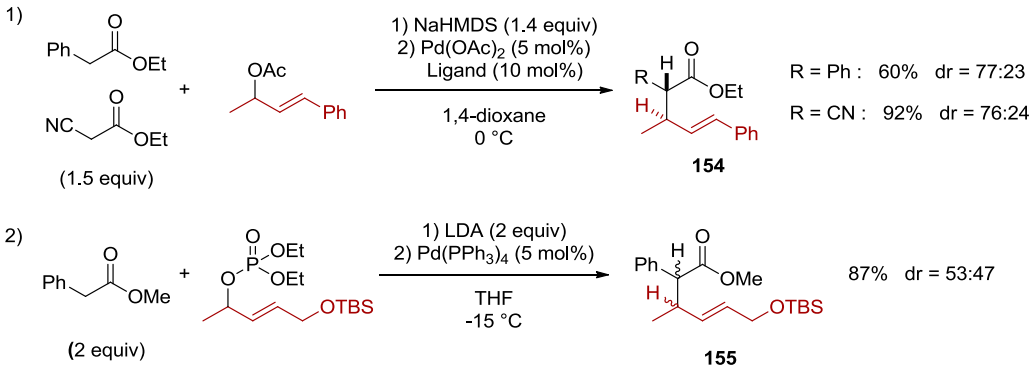


Scheme 87** : Tsuji-Trost reaction between α-arylester **148** and activated allyl alcohol **149

Although the Tsuji-Trost reaction was extensively developed for a wide range of substrates, only a few examples were reported for the reaction of esters with a single substituent at the α-position (other than 1,3-dicarbonyls) with activated *secondary* allyl alcohols, creating two adjacent tertiary centers. To the

[95] Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96* (1), 395–422.

best of our knowledge, there are only two reports, both without enantiocontrol (Scheme 88). In 2007, Kawatsura and coworkers published a reaction for the synthesis of products **154**, with moderate diastereoselectivities (equation 1).[96] In 2015, Kobayashi and coworkers published a similar example to make products **155** (equation 2), in this case without any diastereomeric ratio.[97] To note, reaction of α-aminoesters with activated secondary allyl alcohols has also been reported, giving racemic products or enantioenriched products.[98]



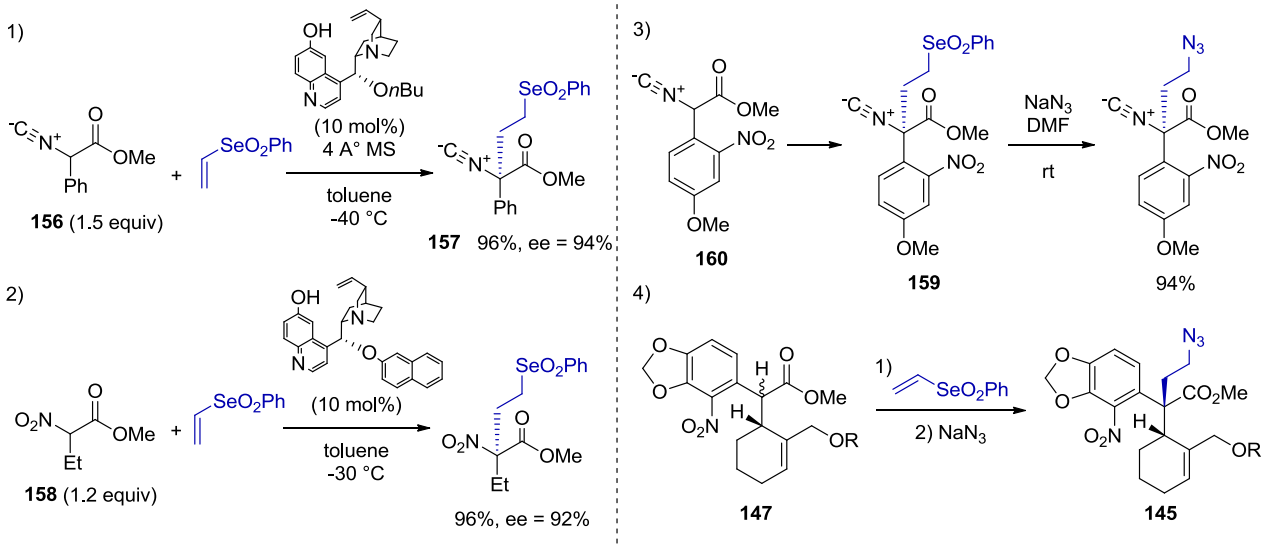
Scheme 88 : *Reported Tsuji-Trost reactions for the formation of two adjacent tertiary centers (not 1,3-dicarbonyls)*

2.2.3 Michael Addition to Phenyl Vinyl Selenone

In 2013, a catalytic enantioselective cinchona-catalyzed Michael addition between α-aryl-α-isocyanoacetate **156** and phenyl vinyl selenone was reported by our research group (Scheme 89, equation 1).[99] It allowed the synthesis of product **157** in excellent yield and enantiomeric excess. In 2016, the scope of this reaction was extended to α-alkyl-α-nitroacetates **158** using another cinchona-derived catalyst (equation 2).[100] The first methodology was successfully applied to the total synthesis of (+)- and (-)-Trigonoliimine A. The key step was the formation of the quaternary center of intermediate **159** from α-aryl-α-isocyanoacetate **160**, followed by S_N2 reaction of the phenylselenonyl group by an azide, demonstrating the excellent nucleofugality of the phenylselenonyl group (equation 3). A similar approach will be undertaken for the preparation of key intermediate **145** for the total synthesis of Mersilongine (equation 4). We expect that α-arylester **147** could be deprotonated by cinchona catalysts

[96] Kawatsura, M.; Ikeda, D.; Komatsu, Y.; Mitani, K.; Tanaka, T.; Uenishi, J. *Tetrahedron* **2007**, *63* (36), 8815–8824.
[97] Kinouchi, W.; Saeki, R.; Kawashima, H.; Kobayashi, Y. *Tet. Lett.* **2015**, *56* (17), 2265–2268.
[98] a) Soheili, A.; Tambar, U. K. *J. Am. Chem. Soc.* **2011**, *133* (33), 12956–12959. b) Spoehrle, S. S. M.; West, T. H.; Taylor, J. E.; Slawin, A. M. Z.; Smith, A. D. *J. Am. Chem. Soc.* **2017**, *139* (34), 11895–11902.
[99] See reference 93.
[100] Clemenceau, A.; Wang, Q.; Zhu, J. *Chemistry – A European Journal* **2016**, *22* (51), 18368–18372.

due to the presence of the electron-withdrawing *ortho*-nitroaryl group in place of the isocyano and nitro groups.

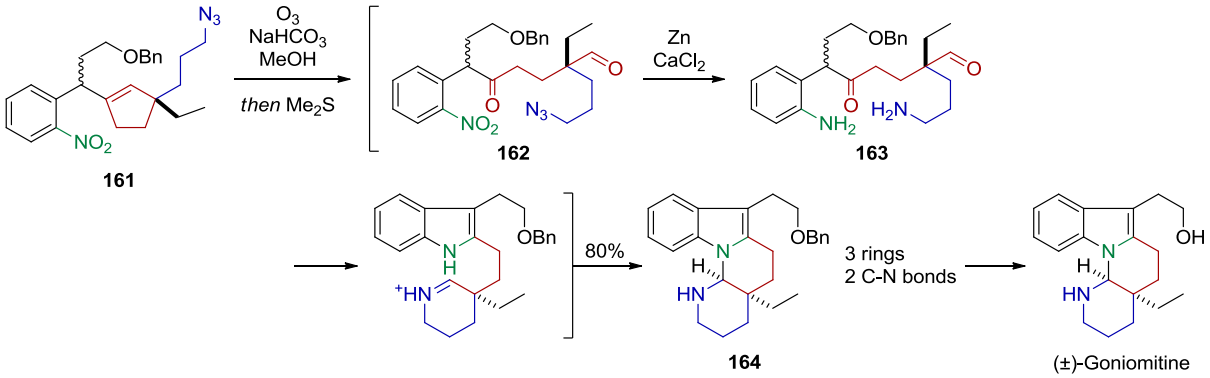


Scheme 89 : *Reported Michael additions to phenyl vinyl selenone and S_N2 substitution with NaN_3*

2.2.4 Integrated Oxidation/Reduction/Cyclization (iORC)

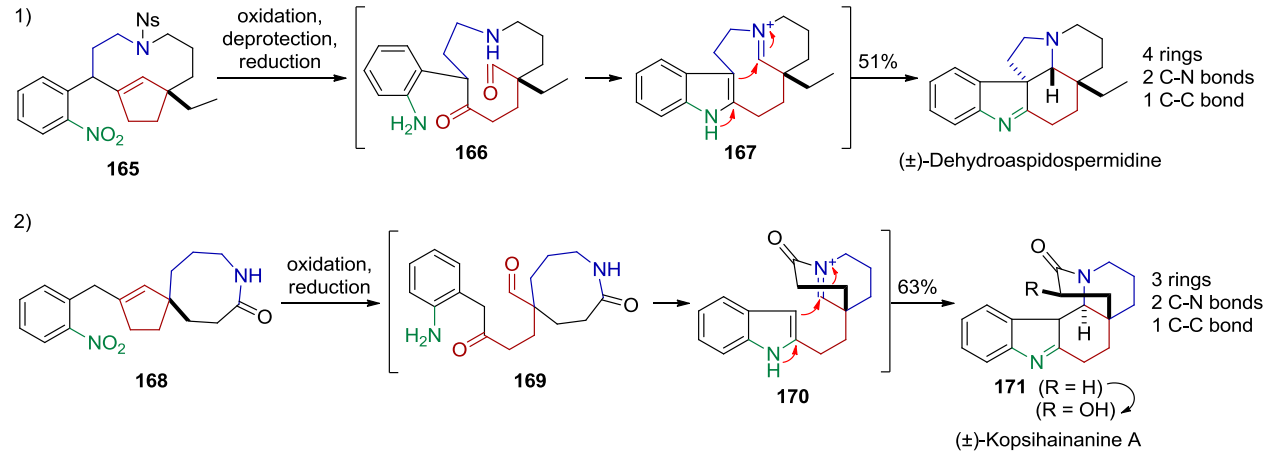
The integrated Oxidation/Reduction/Cyclization sequence (iORC) was developed in our research group for the transformation of cycloalkenes into structurally diverse nitrogen-containing natural products. This process was applied for the first time to the synthesis of (±)-Goniomitine as proof-of-concept (Scheme 90).[101] Cyclopentene **161** was cleaved oxidatively by ozonolyzis, generating ketoaldehyde **162** as intermediate. Then, Zn and $CaCl_2$ were added in one-pot to reduce both the nitro and the azide groups, giving diamine intermediate **163**, which spontaneously cyclized to polycyclic aminal **164**. This one-pot sequence delivered the product in 80% yield after forming 3 cycles and 2 C-N bonds, justifying the expression « metamorphosis of cyclopentene » often used in our recent publications to describe the iORC sequence. Removal of the benzyl group finally gave (±)-Goniomitine.

[101] See reference 40.



Scheme 90 : *Reported synthesis of (±)-Goniomitine by integrated Oxidation/Reduction/Cyclization (iORC)*

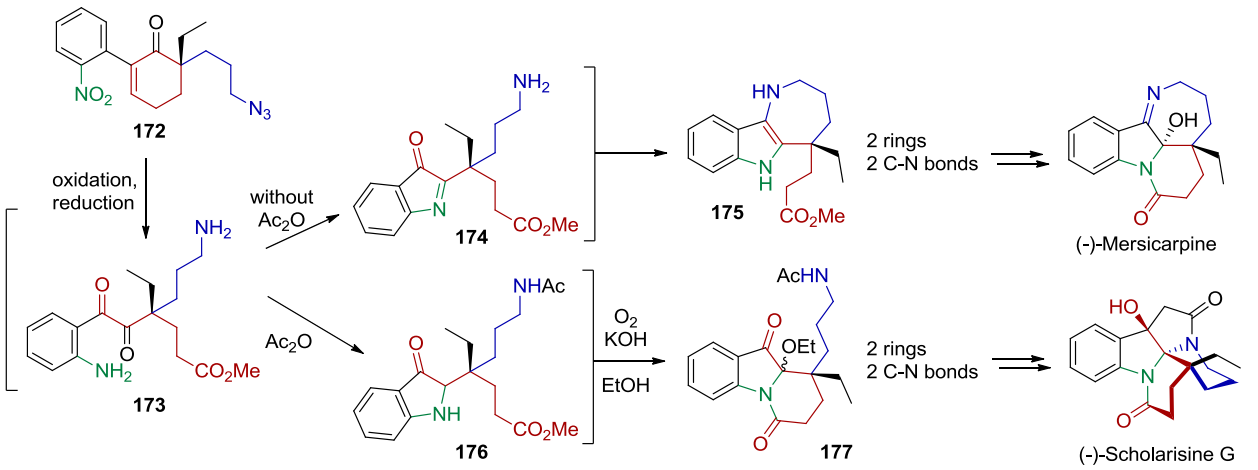
Inspired by the effiency of the iORC strategy for the synthesis of (±)-Goniomitine, it was hypothesized that the same approach could be applied for the synthesis of numerous structurally diverse indole alkaloids (Scheme 91).[102] Oxidative cleavage of cyclopentene **165** followed by deprotection of the nosyl group and reduction of the nitro group generated intermediate **166** (equation 1). Condensation of the aniline with the ketone afforded an indole **167**, which reacted transannularly with the cyclic iminium with remarkable stereocontrol to give (±)-Dehydroaspidospermidine in 51% yield. In this process, 4 rings, 2 C-N bonds and 1 C-C bond were formed. The iORC was also used as key step for the total synthesis of (±)-Kopsihainanine (equation 2) : oxidative cleavage of cyclopentene **168** and reduction of the nitro group generated intermediate **169**. Aniline then spontaneously condensed with the ketone and the amide condensed with the aldehyde to generate the indole/iminium couple **170**, which reacted intramolecularly to form the last C-C bond and deliver product **171** in excellent 63% yield. The latter was finally converted in one step to (±)-Kopsihainanine.



Scheme 91 : *Reported synthesis of (±)-Dehydroaspidospermidine and (±)-Kopsihainanine A by iORC sequences*

[102] See reference 40.

By carefully choosing the reaction conditions for the iORC process, different skeletons could be obtained from the same intermediate, as demonstrated by the total syntheses of (-)-Mersicarpine and (-)-Scholarisine G from cyclohexene **172** (Scheme 92).[103] After oxidative cleavage by ozonolysis and reduction of cyclohexene **172** by hydrogenation with Pd/C, giving aniline **173**, indolenine **174** was formed and primary amine could condense on the ketone to give 3-aminoindole **175**. This advanced intermediate was converted to (-)-Mersicarpine in two steps. On the other hand, if the reduction with Pd/C was carried out in the presence of Ac_2O, primary amine **173** was protected with an acetyl group, preventing any participation of this amine group in the iORC sequence. At the same time, aniline **173** condensed with the ketone and the resulting indolenine was reduced to indoline **176** under the hydrogenation conditions. To complete the iORC sequence, amidation and oxidation of intermediate **176** gave indoline **177**. Finally, (-)-Scholarisine G was obtained in a couple of steps from the product of the iORC.

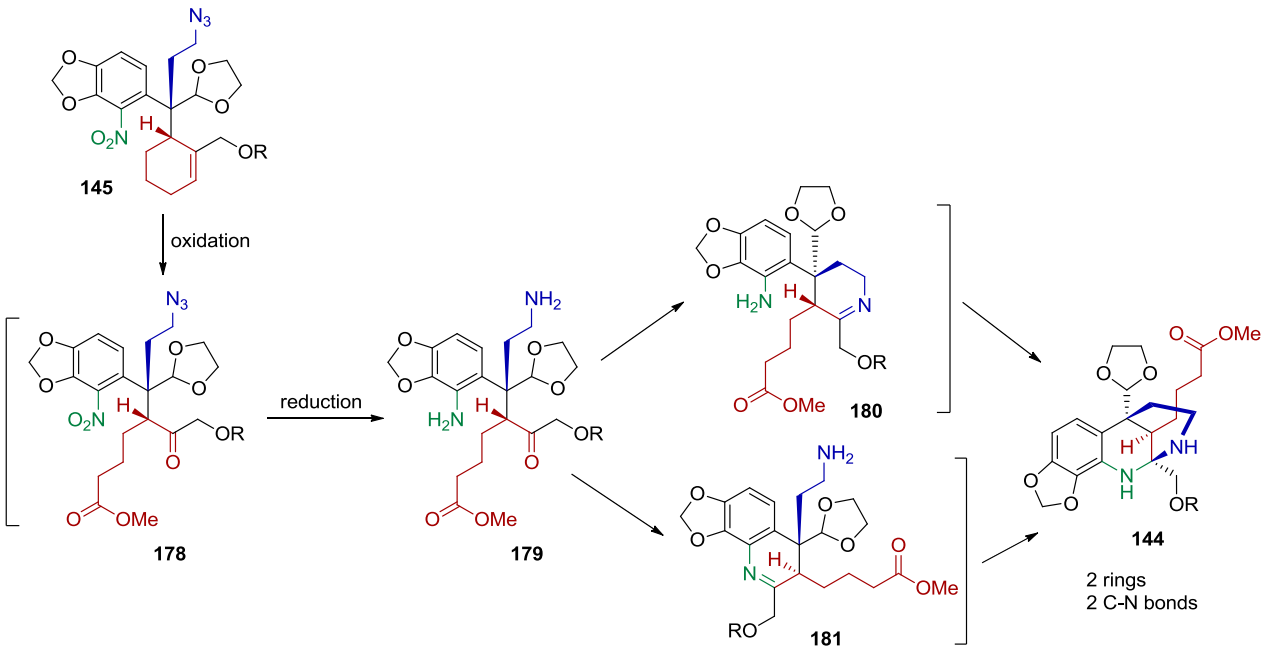


Scheme 92 : *Reported divergent synthesis of (-)-Mersicarpine and (-)-Scholarisine G by iORC sequences*

The iORC strategy has also been applied with interrupted sequences for the divergent total synthesis of (-)-Rhazinilam, (-)-Leucomidine B and (+)-Leucomidine F from a common intermediate.[104] So far, in all cases the iORC has been exploited for the synthesis of indoles, indolenines and indolins, *ie* 5-membered rings attached to the aromatic unit. The application of the iORC for the synthesis of Mersilongine featuring a tetrahydroquinoline core would be the first example of formation of a 6-membered ring attached to the aromatic unit. Starting from cyclohexene **145**, oxidative cleavage would give ketoester **178**, which would be reduced to diamine **179** (Scheme 93). From there, two cyclization sequences would be possible : the first would involve the condensation of the primary amine of **179** on the ketone, followed by trapping of imine **180** by the aniline. The second sequence would be initiated by

[103] Xu, Z.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc.* **2015**, *137* (20), 6712–6724.
[104] Dagoneau, D.; Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55* (2), 760–763.

condensation of aniline **179** on the ketone, followed by trapping of the imine **181** by the primary amine. In both cases, the 6-membered cyclic imines would be prone to isomerization to cyclic enamines. Such a process may lead to racemization or inversion of the chiral center at the α-position of the imine. Therefore, special attention will be paid to this chiral center during the optimization of the iORC sequence.

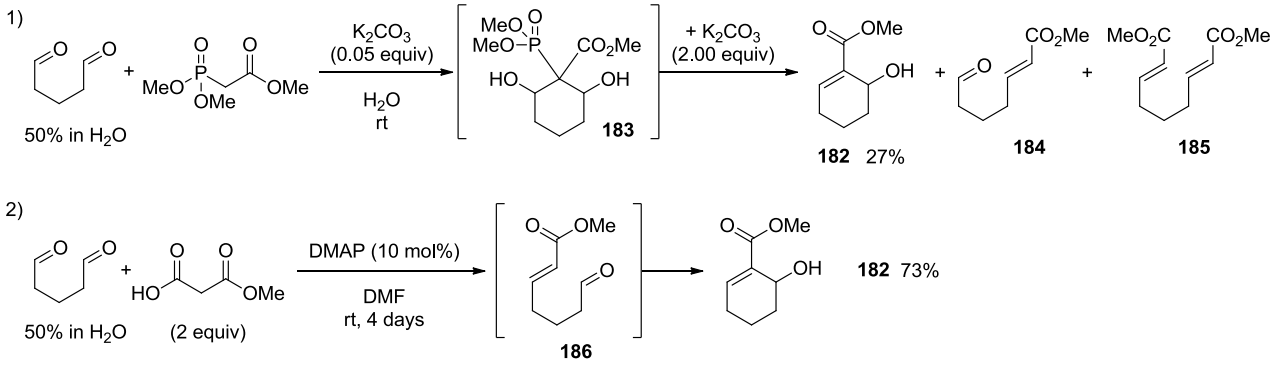


Scheme 93 : *Proposed iORC sequence for the synthesis of the quinolinic / bridged aminal core of Mersilongine*

2.3 Synthetic Studies

2.3.1 Synthesis of Activated Secondary Allyl Alcohols

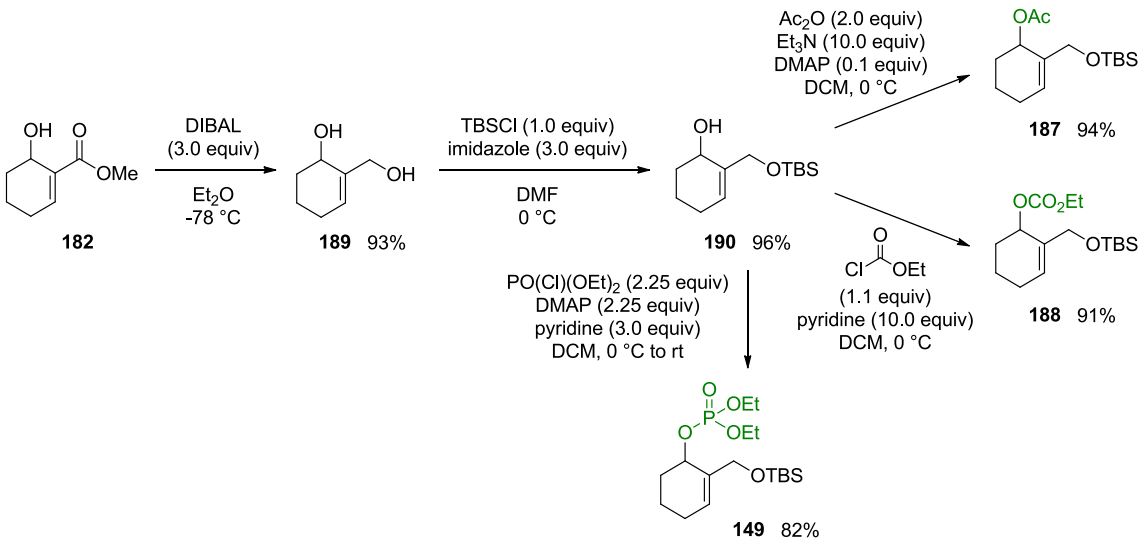
Two methods were found in the litterature for the direct synthesis of α,β-unsaturated ester **182** from commercially available starting materials. The first is a modified Horner-Wadsworth-Emmons reaction between glutaraldehyde and trimethyl phosphonoacetate, in which intermediate **183** has to be generated before the formation of the oxophosphetane intermediate (Scheme 94, equation 1).[105] The first attempt led to the isolation of the desired product in only 27% yield with side-products **184** and **185** in similar amounts. As influencing the reaction outcome by changing the reaction times and by delaying the addition of the base proved unsuccessful, our attention turned to another cascade reaction published by List and coworkers (equation 2).[106] They propose that reaction of glutaraldehyde with monomethyl malonate proceeds *via* Knoevenagel condensation followed by decarboxylation, delivering intermediate **186**, that would spontaneously undergo Morita-Baylis-Hillman reaction to give α,β-unsaturated ester **182** in one-pot. This protocol gave the desired product in 73% yield.



Scheme 94 : *Synthesis of α,β-unsaturated ester **182***

Conversion of α,β-unsaturated ester **182** to allyl alcohols **187**, **188** and **149** was then straightforward (Scheme 95). Reduction of the ester with DIBAL gave diol **189** in 93% yield. To note, the reaction was cleaner in Et_2O than in toluene. Selective monoprotection of the primary alcohol was accomplished in 96% yield to give **190** using typical reaction conditions. Functionalization of the remaining secondary alcohol was achieved in good yields. At this stage, acetate, ethylcarbonate and phosphonate were arbitrary chosen as activating groups for the subsequent Tsuji-Trost reaction.

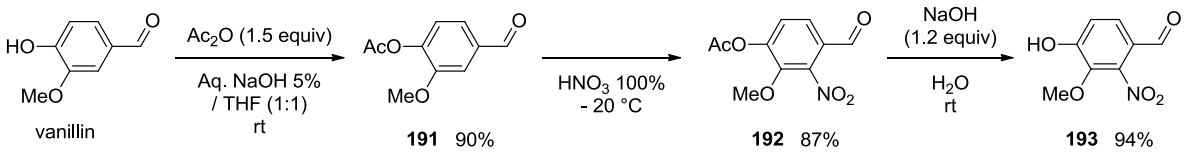
[105] Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villieras, J. *Tet. Lett.* **1986**, *27* (14), 1577–1578.
[106] List, B.; Doehring, A.; Hechavarria Fonseca, M. T.; Job, A.; Rios Torres, R. *Tetrahedron* **2006**, *62* (2–3), 476–482.



Scheme 95 : *Reduction of α,β-unsaturated ester* ***182*** *and synthesis of activated allyl alcohols* ***187***, ***188*** *and* ***149***

2.3.2 Synthesis of the α-Aryl Ester

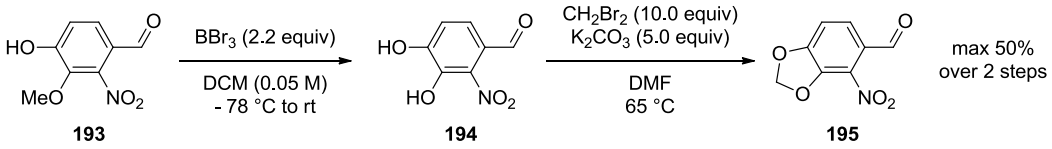
The preparation of the second coupling partner for the Tsuji-Trost reaction was then undertaken. As the direct nitration of vanillin would install the nitro group in *ortho*-position to the hydroxyl group, this position was deactivated by acylation of the phenol with Schotten-Baumann conditions, giving vanillin acetate **191** in 90% yield (Scheme 96).[107] This compound was then slowly dissolved in fuming nitric acid at -20 °C and the reaction mixture was then poured into cold water to recover product **192** by precipitation in 87% yield, containing trace amount of the undesired regioisomer resulting from nitration at the undesired position (ratio = 94:6).[108] Finally, removal of the acetyl group was achieved with NaOH and 2-nitrovanillin **193** was obtained by precipitation in 94% yield. Usually, the undesired regioisomer could be removed during the precipitation processes. 2-Nitrovanillin **193** is commercially available but could not be purchased at reasonable prices.



Scheme 96 : *Synthesis of 2-nitrovanillin* ***193*** *in 3 steps from vanillin*

[107] For example, see : Wang, T.; Wang, C.; Zhang, J.; He, H. *J. Heterocyclic Chem.* **2015**, *52* (5), 1406–1410.
[108] For example, see : a) Perez, R. A.; Fernandez-Alvarez, E.; Nieto, O.; Piedrafita, F. J. *J. Med. Chem.* **1992**, *35* (24), 4584–4588. b) Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125* (40), 12172–12178.

Demethylation of the methoxy group of 2-nitrovanillin with BBr_3 occurred amost quantitatively to give known compound **193** (Scheme 97),[109] despite the poor solubility of both the reactant and the product in DCM, which limited the scale of one batch to 20 g. Moreover, catechol **194** proved difficult to purifiy by column chromatography and was thus directly used in the next step without purification. Methylenation of this catechol was troublesome, as compound **194** tends to polymerize. Initially, 4 equivalents of CH_2Br_2 with 2 equivalents of K_2CO_3 in DMF at 80 °C gave product **195** in around 25% yield over 2 steps.[110] Finally, increasing the loading of the reagents and decreasing the temperature to 65 °C allowed the isolation of product **195** in 50% yield over 2 steps. Unfortunately, lower yields were often obtained and the work-up process was troublesome on large scales.



Scheme 97 : *Demethylation of 2-nitrovanillin **193** and methylenation of the resulting catechol **195***

Homologation of aldehyde **195** to α-aryl carboxylic acid **196** was then envisaged exploiting the transformation of trichloromethyl carbinols to carboxylic acids with a Jocic-type mechanism (Scheme 98, equation 1).[111] First, trichloromethyl carbinol **197** was easily synthesized in 80% yield following a procedure reported by Wyvratt and coworkers.[112] However, treatment of product **197** with NaOH and $NaBH_4$ did not deliver the desired carboxylic acid **196** (sequentially or in one-pot, at room temperature or at 50 °C and with various loadings). A more conventional approach involving a Wittig reaction was therefore selected for the homologation of aldehyde **195** (equation 2).[113] After optimization, vinyl ether **198** could be isolated in 84% yield. Then, its hydrolysis was achieved with HCl at 65 °C.[114] To note, no reaction occurred below 55 °C and aldehyde **199** was remarkably stable (no aldol reaction was observed). The product could be isolated in 96% yield.

[109] Sawada, Y.; Yanai, T.; Nakagawa, H.; Tsukamoto, Y.; Yokoi, S.; Yanagi, M.; Toya, T.; Sugizaki, H.; Kato, Y.; Shirakura, H.; et al. *Pest Management Science* **2003**, *59* (1), 36–48.

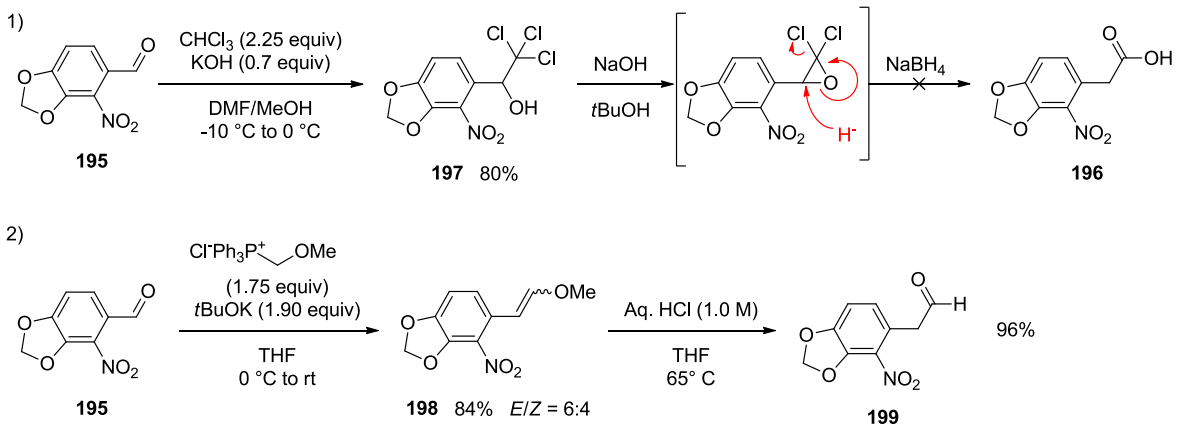
[110] For reaction conditions with a similar substrate, see : Li, D.-D.; Fang, F.; Li, J.-R.; Du, Q.-R.; Sun, J.; Gong, H.-B.; Zhu, H.-L. *Bioorg. Med. Chem. Lett.* **2012**, *22* (18), 5870–5875.

[111] Cafiero, L. R.; Snowden, T. S. *Org. Lett.* **2008**, *10* (17), 3853–3856.

[112] Wyvratt, J. M.; Hazen, G. G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52* (5), 944–945.

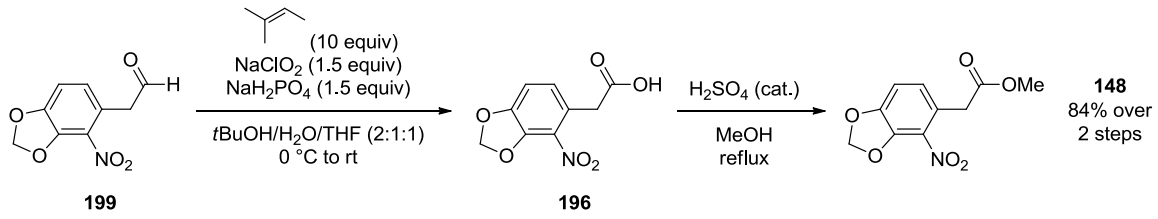
[113] For reaction conditions with a similar substrate, see : Tietze, L. F.; Hungerland, T.; Depken, C.; Maaß, C.; Stalke, D. *Synlett* **2012**, *23* (17), 2516–2520.

[114] For reaction conditions with a similar substrate, see : Tietze, L. F.; Duefert, S.-C.; Clerc, J.; Bischoff, M.; Maaß, C.; Stalke, D. *Angew. Chem. Int. Ed.* **2013**, *52* (11), 3191–3194.



Scheme 98 : *Homologation of aryl aldehyde **195** to α-aryl acetaldehyde **199***

Oxidation of α-aryl aldehyde **199** to α-aryl ester **148** was straightforward (Scheme 99). As the direct oxidation with Oxone did not meet the success,[115] Pinnick oxidation followed by Fischer esterification delivered the product in 84% yield over 2 steps. Addition of THF as co-solvent for the Pinnick oxidation was necessary to solubilize α-aryl aldehyde **199** in the reaction mixture.



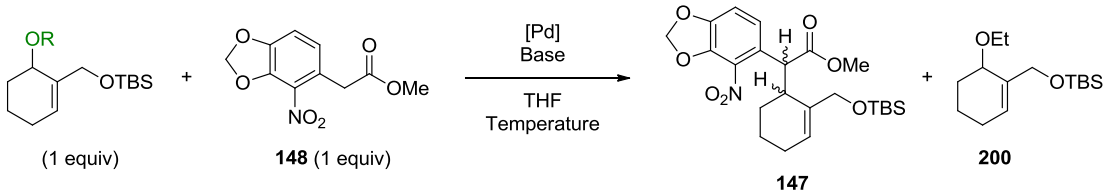
Scheme 99 : *Oxidation of α-aryl acetaldehyde **199** to α-aryl methyl acetate **148***

2.3.3 Tsuji-Trost Reaction

With activated allyl alcohols **187**, **188** and **149** and ester **148** in hand, the Tsuji-Trost reaction was then investigated (Table 11). Reactions were first set-up with $Pd(dba)_2$, $[Pd(allyl)Cl]_2$ or $Pd(PPh_3)_4$ as catalysts with –OAc or $–OCO_2Et$ as leaving groups (Table 11, entries 1-6). No reactions were observed in all cases, except with the use of $Pd(PPh_3)_4$ with $–OCO_2Et$, which produced side-product **200** in small amount, suggesting that the expected π-allyl Pd complex was generated. Interestingly, phosphonate **149** was totally consumed with $Pd(PPh_3)_4$ but unidentified products were formed and ester **148** remained untouched (entries 7-9). This encouraging result revealed the lack of intrinsic reactivity of ester **148** and several bases were thus added to the reaction mixture (entries 10-12). The use of LiHMDS allowed the isolation of the desired product **147** in 45% yield, whereas Et_3N and Cs_2CO_3 did not deprotonate ester

[115] Travis, B. R.; Sivakumar, M.; Hollist, G. O.; Borhan, B. *Org. Lett.* **2003**, *5* (7), 1031–1034.

148. As already reported in our group for α-aryl esters bearing a nitro group in *ortho*-position, a dark blue color is observed upon deprotonation. The order of addition was then investigated : deprotonation of ester **148** followed by addition of the remaining components gave only 10% yield of the desired product due to the dimerization of ester **148** (entry 13). To avoid this side-reaction, LiHMDS was added dropwise to a solution containing all the components, and the desired product was isolated in 71% yield (entry 14). Finally, decreasing the catalyst loading to 5 mol% and increasing the loading of phosphonate **149** gave product **147** in excellent 82% yield (entry 15). Later, on 5 mmol scale, 90% yield was obtained with 10:1 diastereomeric ratio. At this stage, it was not possible to determine the relative stereochemistry of the product by NMR and no single crystal could be obtained from this oil.



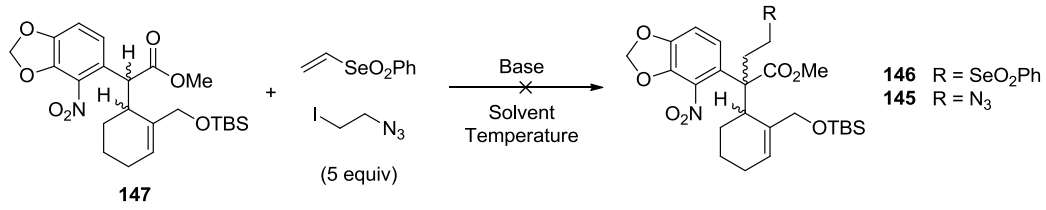
	R	Palladium (10 mol%)	Ligand (20 mol%)	Base (1.1 equiv)	Temp.	Result
1	Ac	$Pd(dba)_2$	PPh_3	---	rt to 40 °C	No reaction
2	Ac	$[Pd(allyl)Cl]_2$	PPh_3	---	rt to 40 °C	No reaction
3	Ac	$Pd(PPh_3)_4$	---	---	rt to 40 °C	No reaction
4	CO_2Et	$Pd(dba)_2$	PPh_3	---	rt to 40 °C	No reaction
5	CO_2Et	$[Pd(allyl)Cl]_2$	PPh_3	---	rt to 40 °C	No reaction
6	CO_2Et	$Pd(PPh_3)_4$	---	---	rt to 40 °C	Low conversion / some **200**
7	$PO(OEt)_2$	$Pd(dba)_2$	PPh_3	---	rt to 40 °C	No reaction
8	$PO(OEt)_2$	$[Pd(allyl)Cl]_2$	PPh_3	---	rt to 40 °C	No reaction
9	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	---	rt to 40 °C	Full conversion / decomposition of **149**
10[1]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	LiHMDS	-15 °C to rt	Full conversion, 45% **147**
11[1]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	Et_3N	rt	No reaction
12[1]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	Cs_3CO_3	rt	No reaction
13[2]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	LiHMDS	0 ° to rt	10% **147** / dimerization of **148**
14[3]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	LiHMDS	0 ° to rt	71% **147** (dr ~ 10:1)
15[3,4]	$PO(OEt)_2$	$Pd(PPh_3)_4$	---	LiHMDS	0 ° to rt	82% **147** (dr ~ 10:1)

[1] Base added last to the reaction mixture
[2] Deprotonation of **148**, then addition of a solution of $Pd(PPh_3)_4$ and **149**
[3] Addition of LiHMDS : 1 drop every 30 seconds to a solution of $Pd(PPh_3)_4$, **148** and **149**
[4] 5 mol% $Pd(PPh_3)_4$ and 1.3 equiv **149**

Table 11 : *Optimization of the Tsuji-Trost reaction between building blocks **148** and **149***

2.3.4 Formation of the Quaternary Center

After the Tsuji-Trost reaction, formation of the quaternary center was undertaken. Initially, a 1,4-addition on vinyl selenone was sought, which would allow the use of cinchona alkaloid to control the stereochemistry of the quaternary center. Unfortunately, no reaction was observed with vinyl selenone with various bases, solvents and temperatures (Table 12, entries 1-6). The direct alkylation with alkyl iodide was then attempted but again no reaction was observed (entries 7-10). The presence of the nitro group which would stabilize the anion may be part of the problem.

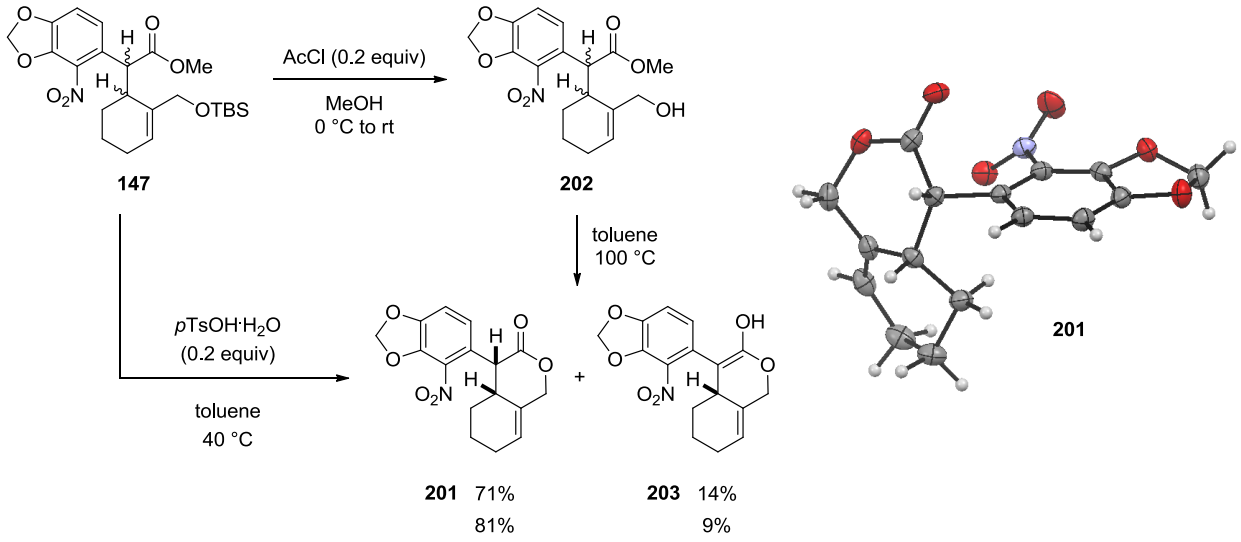


	Electrophile	Base	Solvent	Temperature	Result
1	Vinyl selenone	Et_3N	DCM	rt	No reaction
2	Vinyl selenone	DBU	Toluene	rt to 50 °C	No reaction
3	Vinyl selenone	*t*BuOK	THF	0 °C to 50 °C	No reaction
4	Vinyl selenone	*t*BuOK + 18-crown-6	THF	0 °C to 50 °C	Vinyl selenone decomposed
5	Vinyl selenone	NaH	DMF	0 °C to rt	No reaction
6	Vinyl selenone	LiHMDS	THF	-78 °C to rt	No reaction
7	Alkyl iodide	DBU	DCM	0 °C to rt	No reaction
8	Alkyl iodide	*t*BuOK	THF	0 °C to 50 °C	No reaction
9	Alkyl iodide	NaH	DMF	0 °C to 50 °C	Alkyl iodide decomposed
10	Alkyl iodide	LiHMDS	THF	-78 °C to rt	No reaction

Table 12 : *Attempted 1,4-addition of ester **147** with vinyl selenone or alkylation from ester **147***

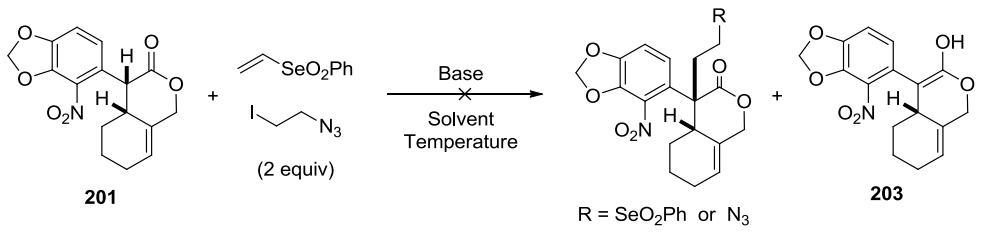
Assuming that δ-lactone **201** would have a different reactivity than ester **147** towards electrophiles such as phenyl vinyl selenone or alkyl iodide, δ-lactone **201** was synthesized (Scheme 100). First, silyl ether **147** was cleaved with *in situ* generated HCl in MeOH to give alcohol **202** quantitatively after evaporation of the solvent. Heating this compound to 100 °C in toluene gave a mixture of the desired δ-lactone **201** and its enol form **203** in excellent 85% overall yield. More efficiently, silyl ether **147** could be treated with *p*TsOH at room temperature to give δ-lactone **201** and its enol form in overall 90% yield. δ-Lactone **201** could be crystallized as single crystals and its relative stereochemistry was determined from its X-ray

structure. The formation of the δ-lactone could also be achieved in one-pot by addition of excess *p*TsOH after completion of the Tsuji-Trost reaction.



Scheme 100 : *Deprotection of protected allyl alcohol* ***147*** *and lactonization*

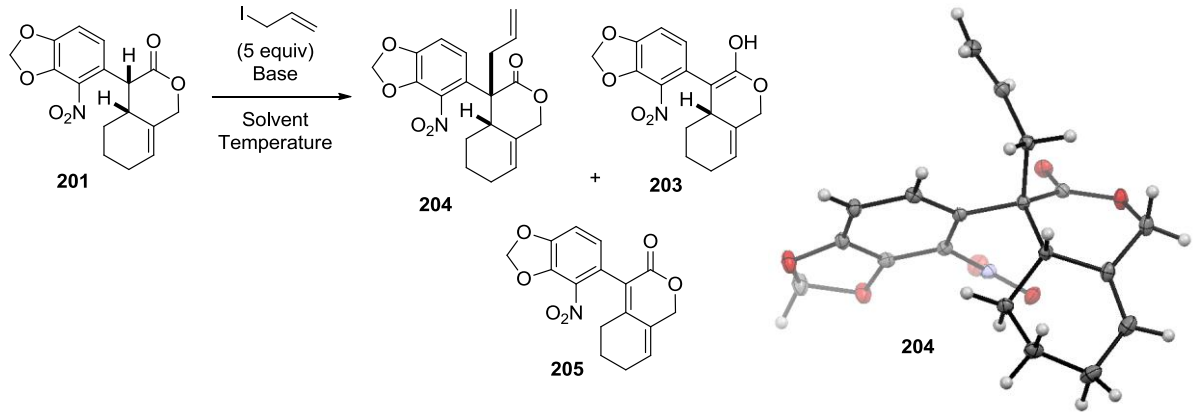
As planned, formation of the quaternary center in α-position of δ-lactone **201** was then attempted (Table 13). Unfortunately, no conditions were found to form the desired product.



	Electrophile	Base	Solvent	Temperature	Result
1	Vinyl selenone	K_2CO_3	DMF	0 °C to 90 °C	Formation of **203**
2	Vinyl selenone	DBU	Toluene	0 °C to 100 °C	Formation of **206**
3	Vinyl selenone	*t*BuOK	DMF	0 °C	Degradation
4	Vinyl selenone	NaH	DMF	0 °C to 50 °C	Degradation at 50 °C
5	Vinyl selenone	NaH	THF	0 °C to rt	Degradation at rt
7	Alkyl iodide	Cs_2CO_3	DMF	rt to 60 °C	Formation of **203**
8	Alkyl iodide	NaH	DMF	rt	Trace of *O*-alkylation ?

Table 13 : *Attempted 1,4-addition of δ-lactone* ***201*** *with vinyl selenone or alkylation from δ-lactone* ***201***

As the use of allyl iodide as very reactive electrophile has been reported in the litterature for the generation of quaternary centers in total synthesis at the α-position of carbonyls,[116] the reaction of δ-lactone **201** and allyl iodide was probed (Table 14). With weak bases such as K_2CO_3 or Cs_2CO_3, only enolization was observed (entries 1-3). Treatment of δ-lactone **201** with *t*BuOK in DMF also lead to enolization only, whereas instantaneous decomposition of **201** was observed in THF upon addition of base, suggesting that the anion is highly unstable in THF (entries 4-5). This was confirmed by the deprotonation in THF with LiHMDS, KHMDS or NaH (entries 6-8), even if traces amounts of the desired product **204** were observed with LiHMDS and KHMDS. Finally, NaH in DMF was the best combination and gave α-allyl δ-lactone **204** in 35% isolated yield with diene **205** as major side-product (entry 9). The highest 57% yield was obtained with portionwise addition of the base at 0 °C over 15 min before allowing the reaction to warm to room temperature, at which full conversion was directly observed (entry 10). Later on larger scale and with 10 equivalents of allyl iodide, α-allyl δ-lactone **204** was obtained in 65% yield. Single crystals of the product were obtained and the relative stereochemistry was confirmed by X-ray analysis. Remarkably, only the desired diastereomer was formed, with the allyl reacting exclusively at the least bulky face of the enolate. Regarding the mechanism, no *O*-allylated δ-lactone has ever been isolated or observed. Therefore, a proposed mechanism goes *via* direct *C*-allylation of the enolate rather than *via O*-allylation followed by Claisen rearrangement.



[116] a) Seo, J. H.; Artman, G. D.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71* (23), 8891–8900. b) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129* (45), 13794–13795. c) Liang, X.; Zhang, T.-Y.; Zeng, X.-Y.; Zheng, Y.; Wei, K.; Yang, Y.-R. *J. Am. Chem. Soc.* **2017**, *139* (9), 3364–3367. d) Han, S.-J.; Vogt, F.; Krishnan, S.; May, J. A.; Gatti, M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2014**, *16* (12), 3316–3319.

	Base	Solvent	Temperature	Result
1	K_2CO_3	Acetone	rt to 50 °C	Formation of **203**
2	K_2CO_3	DMF	rt to 100 °C	Formation of **203**
3	Cs_2CO_3	DMF	rt to 60 °C	Formation of **203**
4	*t*BuOK	DMF	0 °C to 50 °C	Formation of **203**
5	*t*BuOK	THF	0 °C	Decomposition
6	LiHMDS	THF	-78 °C to rt	Decomposition + trace of **204**
7	KHMDS	THF	-78 °C to rt	Decomposition + trace of **204**
8	NaH	THF	0 °C to rt	Decomposition
9	NaH	DMF	0 °C to 50 °C	35% isolated yield of **204**
10*	NaH	DMF	0 °C to rt quickly	57% isolated yield of **204**

* NaH added in 4 portions every 5 minutes

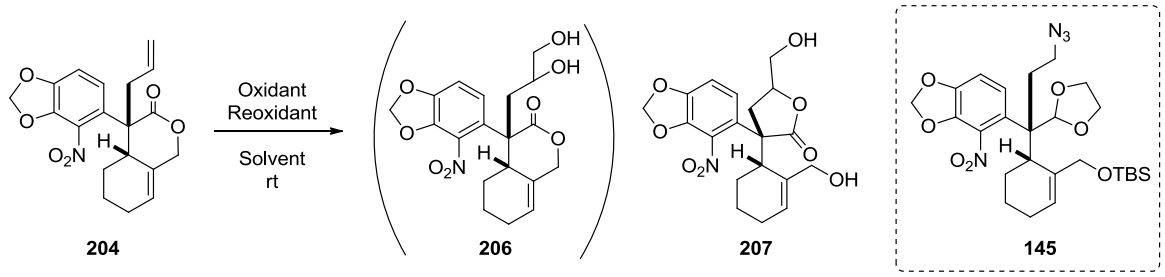
Table 14 : *Optimization of the C-allylation of δ-lactone* ***201***

2.3.5 Transformation of the α-Allyl Lactone : Dihydroxylation First

From α-allyl δ-lactone **204**, the allyl moiety had to be converted to $–CH_2CH_2N_3$ and the δ-lactone had to be opened to synthesize key intermediate **145** (Table 15). Functionalization of the allyl unit was arbitrary undertaken first by chemoselective oxidative cleavage of this terminal double bond leaving the trisubstituted double bond untouched. An ozonolysis was attempted, but a complex reaction mixture certainly resulting from non-selective cycloadditions was obtained. Our attention then turned to dihydroxylations with OsO_4 to form 1,2-diol **206**.[117] Only 30% of γ-lactone **207** was obtained among other unknown side-products in acetone/H_2O 2:1 with NMO as stoichiometric oxidant whereas very slow reactions were observed with $NaIO_4$ or NMO/K_2CO_3 in the same solvents (entries 1-3). Sharpless conditions did not work either.[118] The low solubility of α-allyl δ-lactone **204** was identified as the key problem and the starting material was then first dissolved in 1,4-dioxane/H_2O 6:1 at 50 °C, then cooled to room temperature before adding OsO_4 and NMO. Following this procedure, γ-lactone **207** was isolated in 82% yield. A similar result was obtained using the less toxic $K_2OsO_2(OH)_4$ as osmium precursor.

[117] For reaction conditions with a similar substrate, see : a) In acetone : a) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129* (45), 13794–13795. b) In THF : Liang, X.; Zhang, T.-Y.; Zeng, X.-Y.; Zheng, Y.; Wei, K.; Yang, Y.-R. *J. Am. Chem. Soc.* **2017**, *139* (9), 3364–3367.
[118] Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94* (8), 2483–2547.

Unfortunately, δ-lactone **206** has never been isolated, which would lead to a more direct route towards key intermediate **145**.



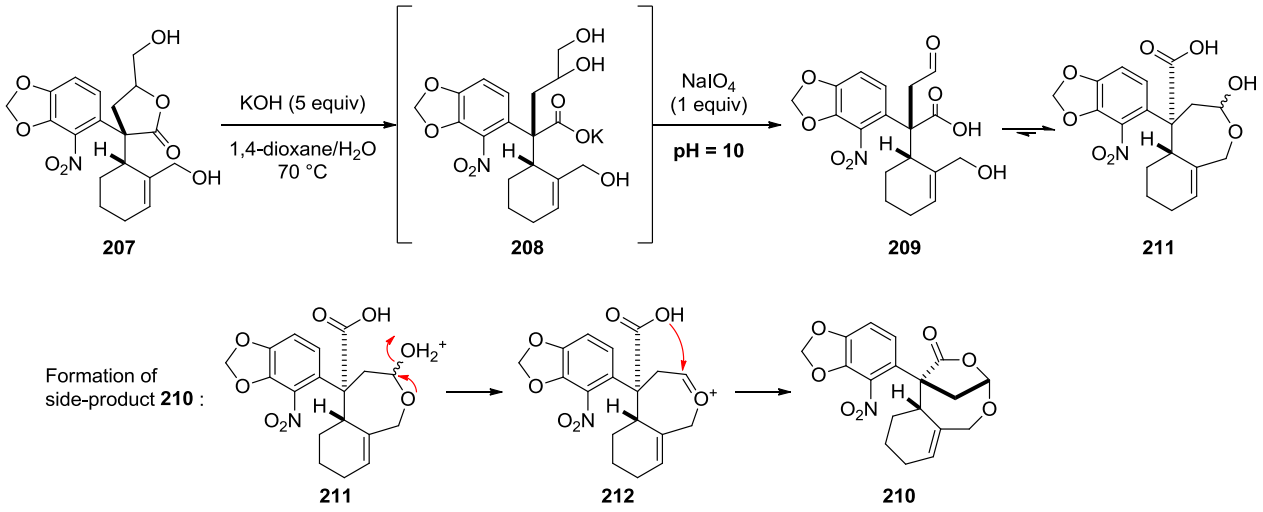
	Solvent	Oxidant (0.1 equiv)	Reoxidant (1.1 equiv)	Result
1	Acetone/H_2O 2:1	OsO_4	NMO	Full conversion, several products, **207** = 30%
2	Acetone/H_2O 2:1	OsO_4	$NaIO_4$	Viscous reaction mixture / slow reaction
3	Acetone/H_2O 2:1	OsO_4	NMO + K_2CO_3	Very slow reaction
4	*t*BuOH/H_2O 1:1	AD-mix β	---	No reaction
5	1,4-Dioxane/H_2O 6:1 *	OsO_4	NMO	82% isolated yield of **207** (dr=7:3)
6	1,4-Dioxane/H_2O 6:1 *	$K_2OsO_2(OH)_4$	NMO	Similar as above

* **204** dissolved at 50 °C, then cooled to rt

Table 15 : *Optimization of the chemoselective dihydroxylation of α-allyl δ-lactone* ***204***

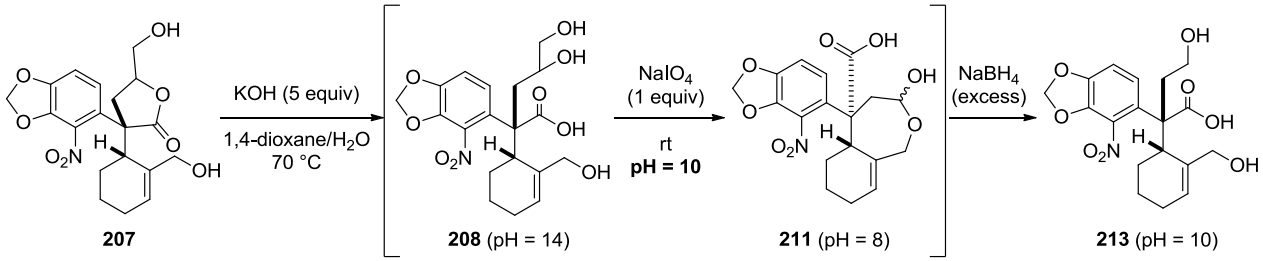
Direct oxidative cleavage of the masked 1,2-diol **207** with $NaIO_4$ was attempted, but no reaction occurred. Opening of γ-lactone **207** was thus necessary (Scheme 101). The reaction was slow with 5 equivalents of KOH in THF/H_2O at reflux but full conversion as obtained in 3 h in 1,4-dioxane/H_2O at 70 °C. As the isolation of triol **208** was envisaged troublesome, oxidative cleavage of the 1,2-diol was attempted in one-pot. When $NaIO_4$ was added, full decomposition of compound **208** was observed very quickly. The desired aldehyde **209** was probably formed but did not survive the strong basic environment (pH=14). The pH of the reaction mixture was therefore adjusted to pH=8 with HCl after opening the γ-lactone and $NaIO_4$ was added in one-pot : side-product **210** was formed exclusively and the measured pH at the end of the reaction was 6, showing the acidification effect of $NaIO_4$. The proposed mechanism for the formation of compound **210** is the following : the desired aldehyde was formed as cyclic acetal **211**, which was then converted to oxonium **212** in the presence of acid, which was intramolecularly trapped by the carboxylic acid to deliver bridged pentacycle **210**. With these two experiment showing both degradation of the desired product **209** at pH=14 and further side-reactions under acidic pH, the control of the pH was more carefully envisaged. Surprinsingly, addition of buffer solutions led to decomposition of the desired product (phosphate pH = 8.0, carbonate pH = 9.2, 9.9 or 10.8). Finally, adjusting the pH to

10 with HCl before adding $NaIO_4$ was the best approach, delivering cyclic acetal **211** in a final reaction mixture of pH = 8, at which the product seemed stable.



Scheme 101 : *Opening of γ-lactone **207** and oxidative cleavage of 1,2-diol **208***

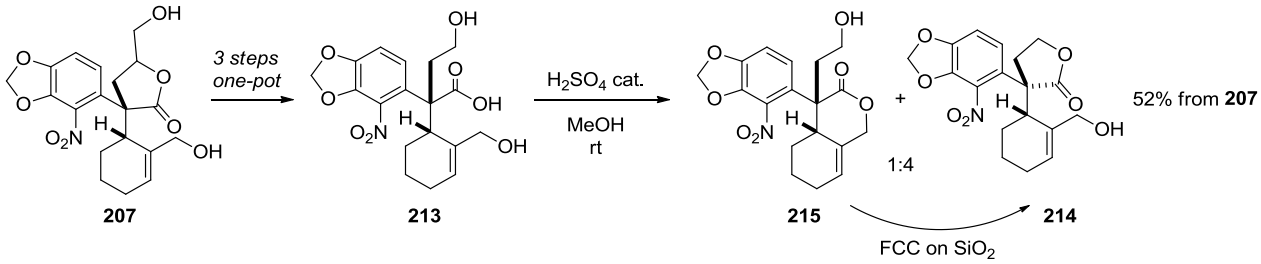
As acidification of the reaction mixture to extract acetal **211** from water was not possible, the direct reduction of this masked aldehyde was attempted in one-pot (Scheme 102). The half-life of $NaBH_4$ in water is 0.37 seconds at pH = 6, 36.8 seconds at pH = 8 and 61.4 minutes at pH = 10,[119] which should allow the reduction of acetal **211** in one-pot in our reaction, knowing that hydrolysis of $NaBH_4$ increases the pH. Indeed, when adding $NaBH_4$ in portions of 1 equivalent, no reaction was observed with the ~5 first portions, but an increase of the pH to 9-10 was observed. Then upon addition of more equivalents, full conversion was observed and diol **213** was isolated as single product from γ-lactone **207**. As the purification of this product by column chromatography did not seem possible, the crude product was direclty used in the next step.



Scheme 102 : *Opening of γ-lactone **207**, oxidative cleavage of 1,2-diol **208** and reduction of lactol **211** in one-pot*

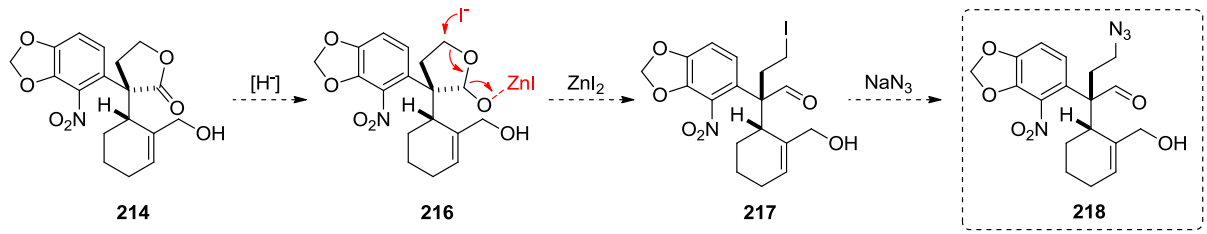
[119] https://www.dow.com/assets/attachments/industry/pharma_medical/chemical_reagents/reducing_agents/sodium_borohydride_digest.pdf (February 9, 2017)

Having diol **213** in hand, the objective was to protect the allyl alcohol and convert the primary alcohol to azide. However, diol **213** tends to lactonize spontaneously. It was thus forced to cyclize before being further functionalized. Treatment of diol **213** with a catlytic amount of H_2SO_4 in MeOH gave a mixture of γ-lactone **214** and δ-lactone **215**, which converged to γ-lactone **214** with time or upon purification by column chromatography (Scheme 103). γ-Lactone **214** could be isolated in 52% yield from starting diol **207**, after 4 chemical transformations.



Scheme 103 : *Size-selective lactonization of diol **213** to γ-lactone **214***

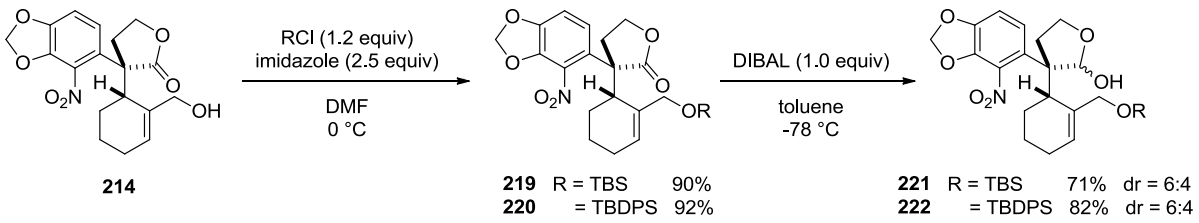
We were then inspired by a reaction sequence proposed by Nicolaou and coworkers for the opening of a lactol to alkyl iodide with ZnI_2. γ-Lactone **214** would first be converted to γ-lactol **216** (Scheme 104).[120] Treatment of this product with ZnI_2 would give iodide **217**, which should be easily converted to the desired key intermediate **218**.



Scheme 104 : *Envisaged transformation of γ-lactone **214** to key intermediate **218***

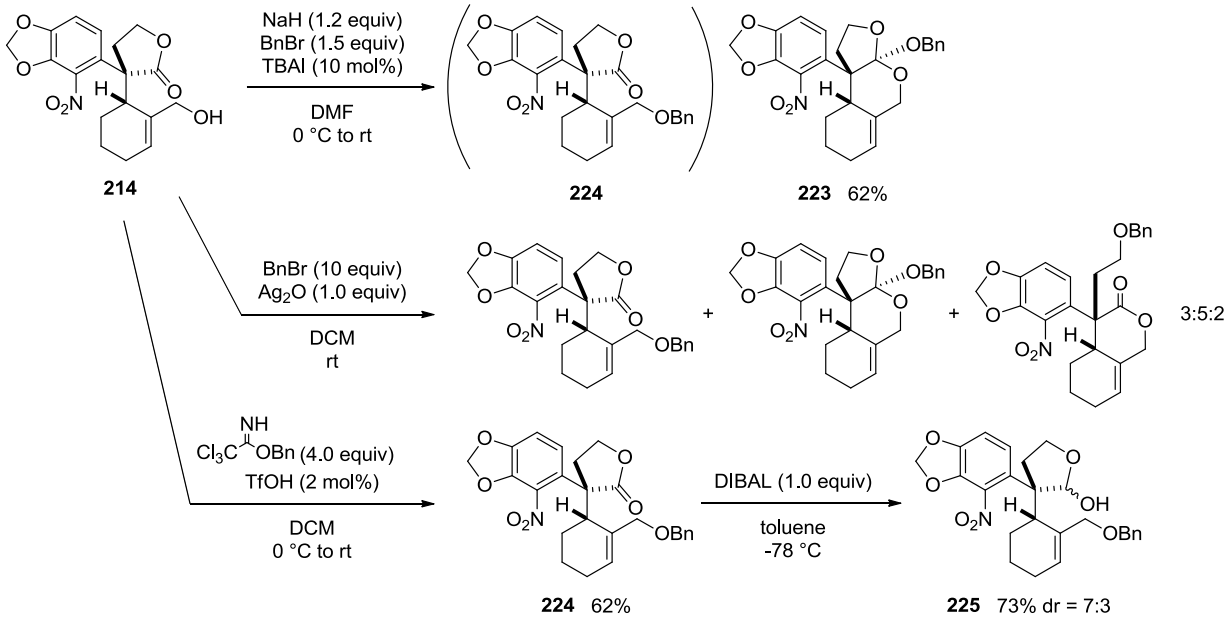
Towards this end, γ-lactone **214** was first protected with TBS and TBDPS in good 90% and 92% yields (Scheme 105). Reduction of the γ-lactones **219** and **220** with DIBAL delivered the desired γ-lactols **221** and **222** in good yields.

[120] Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem. Int. Ed.* **2009**, *48* (37), 6870–6874.



Scheme 105 : *Synthesis of γ-lacols **221** and **222** from the corresponding γ-lactones*

The protection of allyl alcohol **214** with a benzyl group was more troublesome (Scheme 106). Typical basic conditions (NaH, BnBr, TBAI) gave side-product **223** in 62% yield.[121] Neutral conditions (BnBr, Ag_2O) gave the desired benzyl alcohol **224**,[122] but as minor compound among side-products. Finally, acidic conditions (benzyl 2,2,2-trichloroacetamide, TfOH) allowed the synthesis of benzyl ether **224** in 62% yield,[123] which was reduced to the corresponding γ-lactol **225** in 73% yield.

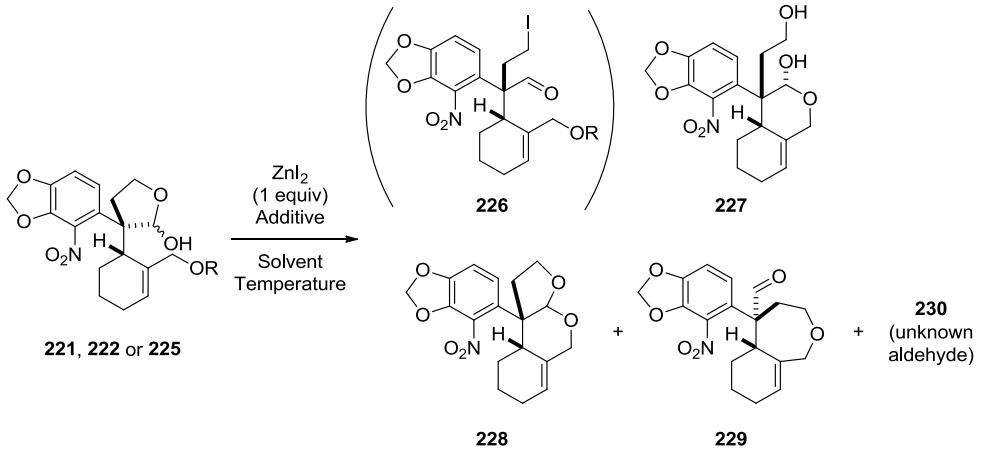


Scheme 106 : *Benzylation of allyl alcohol **214** and synthesis of γ-lacol **225***

The opening of the γ-lactols with ZnI_2 was then investigated (Table 16). Heating the starting material in THF or 1,4-dioxane with ZnI_2 in the presence of NaI did not furnish any new product (entry 1). In DCM or DCE, full conversion of the starting material was observed at room temperature with only 1 equivalent of ZnI_2. Unfortunately, the desired product **226** was not found and a mixture of side-products **227**, **228**, **229**

[121] For reaction conditions with TBAI with a similar substrate, see : Sridhar, C.; Vijaykumar, B. V. D.; Radhika, L.; Shin, D.-S.; Chandrasekhar, S. *Eur. J. Org. Chem.* **2014**, *2014* (30), 6707–6712.
[122] For reaction conditions with a similar substrate, see : Wang, L.; Hashidoko, Y.; Hashimoto, M. *J. Org. Chem.* **2016**, *81* (11), 4464–4474.
[123] For reaction conditions with a similar substrate, see : Eckenberg, P.; Groth, U.; Huhn, T.; Richter, N.; Schmeck, C. *Tetrahedron* **1993**, *49* (8), 1619–1624.

and **230** was obtained (entry 2). Cyclic ether **229** probably arised from an iodide intermediate which underwent intramolecular S_N2. On the other hand, the structure of **230** could never be detemined, but the TBS group was also removed. The same reaction was therefore run with TBDPS protection, expecting higher stability of this protecting group, but side-product **230** was obtained as major product (entry 3). Finally, benzyl ether **225** did not give the desired alkyl iodide **226**, but acetal **228** instead (entry 4).

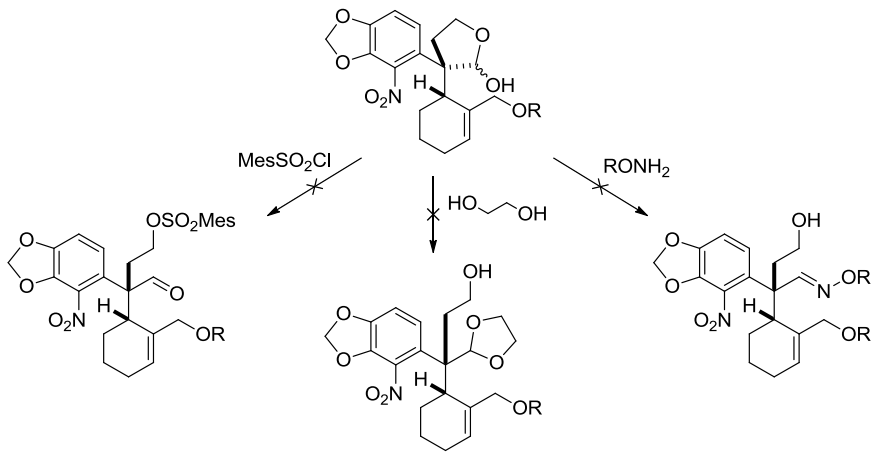


	R	Solvent	Additive	Temperature	Result
1	TBS	THF or 1,4-dioxane	NaI (5 equiv)	up to 90 °C	No reaction
2	TBS	DCM or DCE	- - -	0 °C to rt	**227** + **229** + **230** (ratio = 5:1:3)
3	TBDPS	DCM or DCE	- - -	0 °C to rt	**228** as major product
4	Bn	DCM or DCE	- - -	0 °C to rt	**228** as major product

Table 16 : *Attempted opening of γ-lactols with ZnI_2*

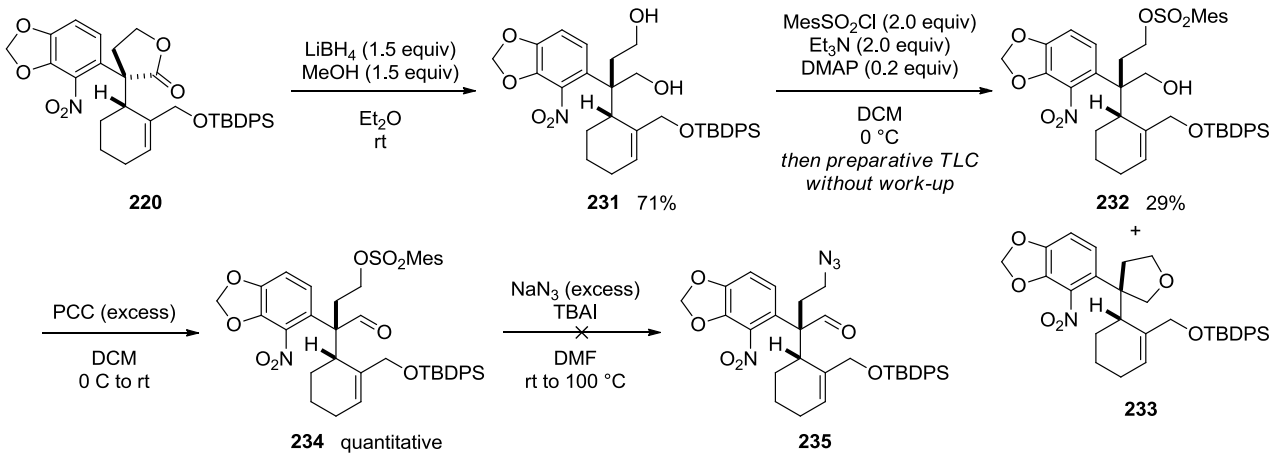
Several alternative approaches were also attempted for the opening of the γ-lactols (Scheme 107). Trapping the masked primary alcohol with mesitylenesulfonyl chloride did not work. Also, no reaction was observed when trying to protect the masked aldehyde with either ethylene glycol or *O*-substituted hydroxylamine.[124]

[124] For reaction conditions with a similar substrate, see : a) Malatinský, T.; Spišáková, M.; Babjak, M.; Doháňošová, J.; Marek, J.; Moncol, J.; Fischer, R. *Eur. J. Org. Chem.* **2017**, *2017* (6), 1086–1098. b) Rössler, S. L.; Schreib, B. S.; Ginterseder, M.; Hamilton, J. Y.; Carreira, E. M. *Org. Lett.* **2017**, *19* (20), 5533–5536.



Scheme 107 : *Attempted alternative methods for the opening of γ-lactols*

δ-Lactone **220** was then reduced to diol **231** in 71% yield with $LiBH_4$/MeOH in Et_2O (Scheme 108).[125] These conditions allow chemoselective reduction of carbonyl groups in the presence of nitro groups. Installation of a leaving group chemoselectively on the primary alcohol of diol **231** was then troublesome without touching the neopentyl alcohol. After several attempts, 29% yield of the desired product **232** could be isolated using bulky mesitylenesulfonyl chloride instead of tosyl chloride. The major side-reaction was the intramolecular S_N2 substitution of the product to give tetrahydrofuran **233**, which occurred both during the reaction and the work-up. Oxidation of neopentyl alcohol **232** to quaternary aldehyde **234** was then achieved quantitatively with PCC. However, S_N2 substitution of the sulfonyl group with azide did not proceed.

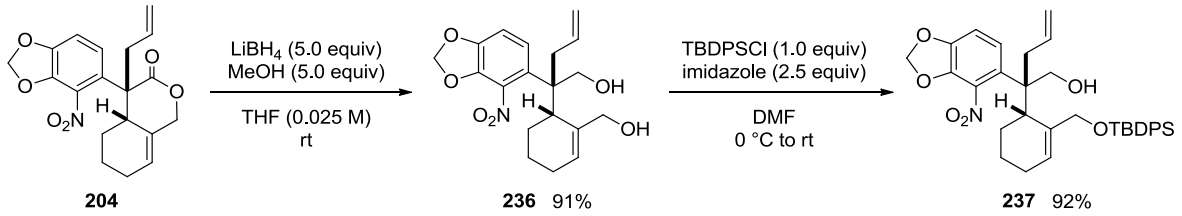


Scheme 108 : *Attempted conversion of γ-lactone **220** to key intermediate **235*** via *diol **231***

[125] Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51* (21), 4000–4005.

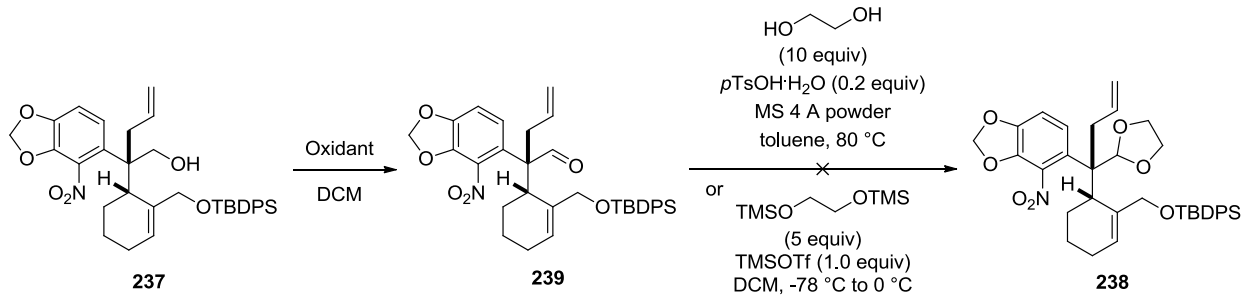
2.3.6 Transformation of the α-Allyl Lactone : Lactone Reduction First

At this stage, it was decided to come back to α-allyl δ-lactone **204** and focus on the opening of the δ-lactone before functionalizing the allyl moiety, as the opposite approach investigated so far led to synthetic impasses. α-Allyl δ-lactone **204** was direclty reduced to diol **236** in excellent yield (Scheme 109). Selective monoprotection of the allyl alcohol was also achieved in excellent 92% yield to give compound **237**.



Scheme 109 : *Reduction of δ-lactone **204** and selective monoprotection of allyl alcohol **236***

The reoxidation of neopentyl alcohol **237** was troublesome with PCC of PDC as oxidants, but proved very efficient with DMP or Swern conditions (Table 17). Probably due to steric hindrance, formation of cyclic acetal **238** from α-quaternary aldehyde **239** did not work with ethylene glycol or with the Noyori conditions.[126]

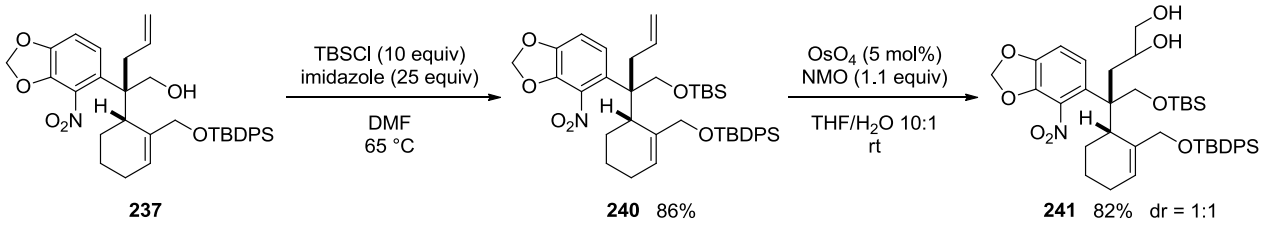


	Oxidant	Temperature	Result
1	PCC	0 °C	Some side-product as major product
2	PDC	0 °C to rt	No reaction
3	DMP	0 °C to rt	85% isolated yield
4	Swern	-78 °C to rt	Very clean reaction

Table 17 : *Oxidation of neopentyl alcohol **237** and attempted acetalization of the resulting aldehyde **239***

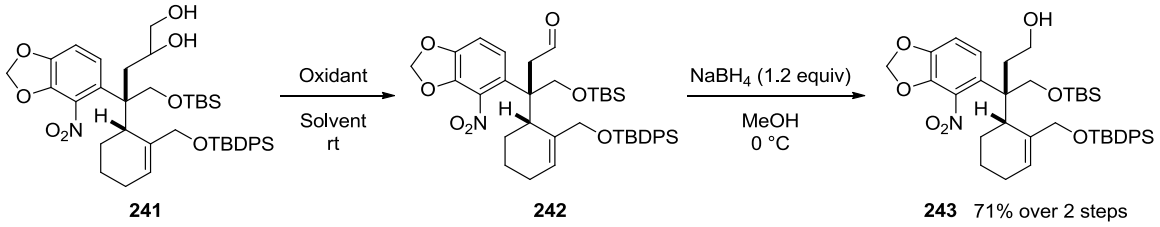
[126] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tet. Lett.* **1980**, *21* (14), 1357–1358.

Instead of oxidizing neopentyl alcohol **237**, it was directly protected with TBS. High loadings of the reagents and high temperature were necessary for the reaction to proceed and the desired product **240** was isolated in 86% yield. This product could also be obtained sequentially in one-pot from diol **236** in 85% yield. Chemoselective dihydroxylation of the allyl moiety was then performed under standard conditions to give 1,2-diol **241** in 82% yield. The reaction also proceeded well with 2 mol% of OsO_4.



Scheme 110 : *Protection of neopentyl alcohol **237** and chemoselective dihydroxylation of allyl **240***

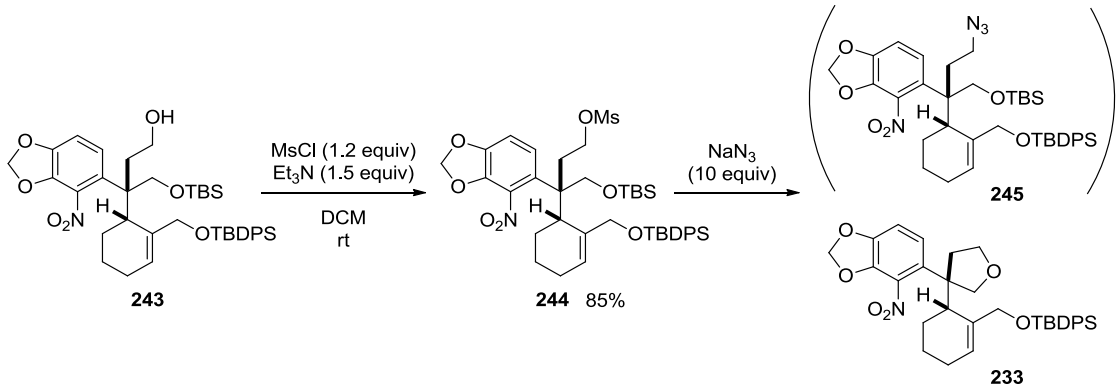
From there, oxidative cleavage of the 1,2-diol was investigated (Table 18). The starting material precipitated and formed aggregates when MeOH/H_2O and 1,4-dioxane/H_2O were used as solvents (entries 1 and 2). To avoid the use of H_2O, $Pb(OAc)_4$ in THF or MeCN was attempted and gave the product cleanly. Finally, reduction of the crude aldehyde **242** with $NaBH_4$ in MeOH provided alcohol **243** in 71% yield over 2 steps using $Pb(OAc)_4$ in THF.



	Oxidant	Solvent (0.05 M)	Result
1	$NaIO_4$	MeOH/H_2O 1:1 or 10:1	Formation of aggregates
2	$NaIO_4$	1,4-Dioxane/H_2O 1:1 or 10:1	Formation of aggregates
3	$Pb(OAc)_4$	THF	Very clean reaction
4	$Pb(OAc)_4$	MeCN	Very clean reaction

Table 18 : *Oxidative cleavage of 1,2-diol **241** and reduction of the resulting aldehyde **242***

Mesylation of primary alcohol **243** to mesylate **244** was completed in 85% yield. Unfortunately, S_N2 substitution reactions with azide to give key intermediate **245** always led to tetrahydrofuran side-product **233** (Table 19, entries 1-5). A control experiment without NaN_3 was run and also gave tetrahydrofuran **233** as exclusive product, showing the lability of the TBS group under these reaction conditions.

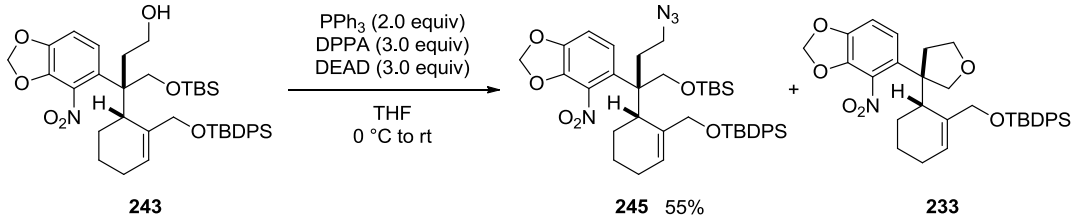


	Solvent	Additive	Temperature	Result
1	DMSO	- - -	rt to 40 °C	Formation of **233**
2	HMPA	- - -	rt to 40 °C	Formation of **233**
3	DMF	NaI	rt to 40 °C	Formation of **233**
4	DMF	TBAI	rt to 40 °C	Formation of **233**
5	DMSO	NaI	rt to 40 °C	Formation of **233**
6*	DMF	- - -	rt to 40 °C	Formation of **233**

* Without NaN_3 (control experiment)

Table 19 : *Attempted conversion of primary alchol **243** to alkyl azide **245*** via *mesylation/substitution*

As an alternative, Mitsunobu reaction of primary alcohol **243** with diphenylphosphoryl azide gave the desired alkyl azide **245** in 55% yield (Scheme 111).[127] Again, the yield of the reaction was plagued by the formation of tetrahydrofuran **233** as side-product.

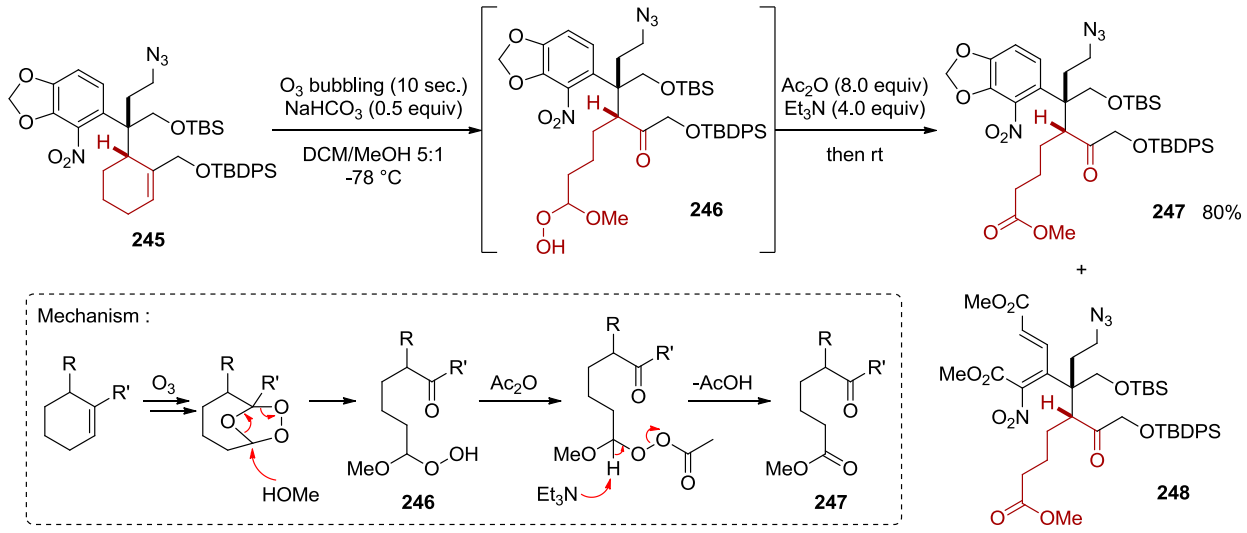


Scheme 111 : *Direct conversion of primary alchol **243** to alkyl azide **245** via Mitsunobu reaction*

[127] Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58* (22), 5886–5888.

2.3.7 Integrated Oxidation/Reduction/Cyclization (*i*ORC)

Having key intermediate **245** in hand, the key step of the total synthesis, *ie* the integrated Oxidation/Reduction/Cyclization (*i*ORC) was explored. Ozonolysis of the cyclohexene was attempted using conditions reported for the generation of ketoesters :[128] as shown in the mechanism, ozonolysis in MeOH gives a peroxyacetal **246**, which has to be treated with Ac_2O and Et_3N to be converted to methyl ester **247** (Scheme 112). Bubbling ozone during 5 minutes into a solution of **245** in DCM/MeOH in the presence of $NaHCO_3$, followed by addition of Ac_2O and Et_3N at room temperature afforded the desired product **247** in trace amounts among several side-products. One on them was identified as triester **248**, resulting from ozonolysis of the electron-rich aromatic ring. Ozonolysis of catechols to diesters is known in the litterature.[129] To avoid the reaction of ozone with the aromatic ring, ozone was bubbled during only 10 seconds and was directly replaced with argon after this short period of time. Following this procedure, selective ozonolysis of the cyclohexene could be achieved and the desired product **247** could be isolated in excellent 80% yield.

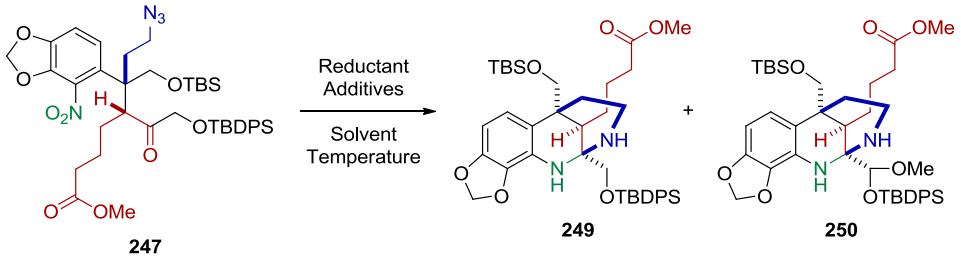


Scheme 112 : *Ozonolyzis of cyclohexene* ***245*** *to ketoester* ***247***

Reduction of the nitro and azide groups was first attempted by hydrogenation with Pd/C or PtO_2 (Table 20, entries 1-2). Only the nitro group was reduced at room temperature and increasing the temperature was necessary to reduce the azide group. However, several products were formed. With PtO_2, a product whose mass corresponds to [expected mass]+2 was found, which may result from hydrogenation of the aminal formed. Also, treatment of starting material **247** with $TiCl_3$ led to complete degradation (entry 3).

[128] Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tet. Lett.* **1982**, *23* (38), 3867–3870.
[129] Costa, P. R. R.; Pinheiro, S.; Lopes, C. C. *Tet. Lett.* **1985**, *26* (35), 4155–4158.

Then, reductions with zinc were attempted : reduction with aqueous NH_4Cl as additive gave the desired product **249** as major product (entry 4). With HCl, the conditions were too harsh and the products were degraded (entry 5). The reaction was slow with activated zinc at reflux in MeOH (entry 6), but addition of $CaCl_2$ allowed the formation of the product **249**, with side-product **250** resulting from an unexpected oxidation process (entry 7). In this case, zinc was activated with HCl. Then, similar conditions using iron were investigated : the reactions were very slow in anhydrous MeOH or *t*BuOH with NH_4Cl as additive, even at 50 °C (entries 8-9). With added H_2O, full conversion of the starting material was observed at 50 °C and the desired product was formed as major product (entries 10-11). To summarize, reductions with zinc or iron with NH_4Cl in alcohol/H_2O were the best conditions (entries 4 and 10).



	Reductant	Additive	Solvent	Temp.	Result
1	H_2 + Pd/C 10%	- - -	EtOH	up to 40 °C	Several products
2	H_2 + PtO_2	- - -	EtOH	up to reflux	Several products, major : expected mass +2
3	$TiCl_3$ in HCl (20 equiv)	NH_4OAc (50 equiv)	EtOH	rt	Complete degradation
4	Zn (100 equiv)	NH_4Cl (10 equiv)	EtOH/H_2O	rt	Desired product **249** as major product
5	Zn (100 equiv)	HCl 1.0 M (1 equiv)	EtOH/H_2O	rt	Several products then degradation
6	Activated Zn* (100 equiv)	- - -	MeOH	up to reflux	Slow reaction
7	Activated Zn* (100 equiv)	$CaCl_2$ (10 equiv)	MeOH	up to reflux	**249** and **250** as major products
8	Fe (50 equiv)	NH_4Cl (10 equiv)	MeOH	up to 50 °C	Very slow reaction
9	Fe (50 equiv)	NH_4Cl (10 equiv)	*t*BuOH	up to 50 °C	Very slow reaction
10	Fe (50 equiv)	NH_4Cl (10 equiv)	MeOH/H_2O	up to 50 °C	Desired product **249** as major product
11	Fe (50 equiv)	NH_4Cl (10 equiv)	*t*BuOH/H_2O	up to 50 °C	Desired product **249** as major product

* Zn powder was activated with HCl 10%.

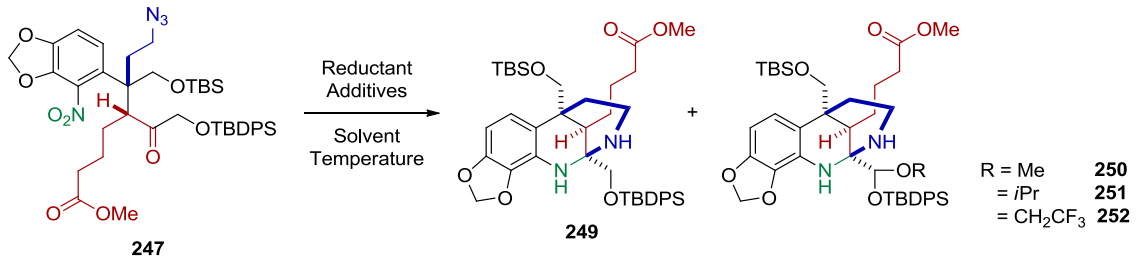
Table 20 : *Optimization of the reaction conditions for the Reduction/Cyclization of ketone* ***247*** *to aminal* ***249***

These reactions were set up on small scales (~1-2 mg). When the loading of the starting material was increased to 20 mg, a precipitate combining the starting material and the metal powder was quickly formed at the surface of the stirring bar and no reaction was observed. Higher dilutions or addition of co-organic solvents such as THF, 1,4-dioxane, toluene or DCM were probed, but did not solve this issue. As water was identified as the cause of the problem, the optimization of the reaction conditions was re-

investigated starting from activated zinc with $CaCl_2$ in MeOH at reflux, which delivered the desired product **249** (and the oxidized side-product **250**) in absence of water (entry 7).

The objective was therefore to modifiy the reaction conditions to avoid the formation of the oxidized side-product **250**, whose mechanism of formation remained unclear as no oxidant was added to the reaction (Table 21, entry 1). Setting up the reaction in the glovebox to avoid the presence of oxygen or running the reaction in absence of light did not prevent the formation of oxidized side-product **250** (entries 2-3). We therefore speculate that an intramolecular oxidation event takes place from an intermediate of the nitro or the azide reductions. Decreasing the temperature to 35 °C did not change the result (entry 4). Different solvents were then used : no reaction was obsevered in THF or HFIP (entries 5 and 8), whereas *i*PrOH and F_3CCH_2OH were incorporated in the oxidized side-product (the mass of **251** was confirmed by HRMS analysis). Finally, the use of highly active zinc, which had been activated with DCE and TMSCl,[130] gave the desired product with only traces of the oxidized side-product **250** (entry 9). Assuming that the oxidation process occurs intramolecularly, the more active zinc may reduce both nitro and azide groups fast enough to prevent the formation of side-product **250**. Interestingly, the reaction also worked without $CaCl_2$, but was slower and less clean (entry 10). Attempts at purifying aminal **249** by preparative TLC failed but the mass balance of the reaction is consistent and the ^{1}H NMR spectrum of the crude product is clean (Scheme 113).

[130] For the exact procedure, see : Tong, S.; Piemontesi, C.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed.* **2017**, *56* (27), 7958–7962.

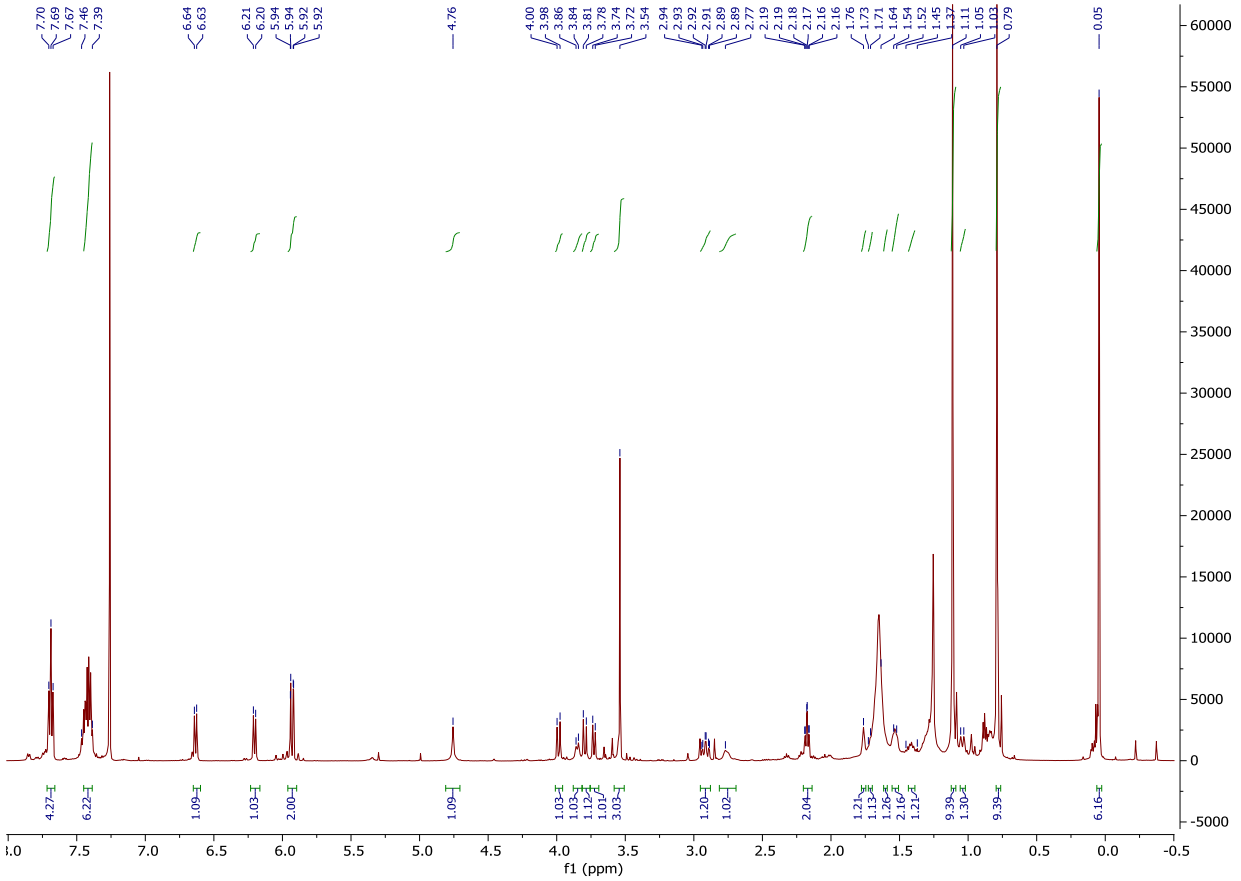


	Reductant (50 equiv)	Additive (10 equiv)	Solvent	Temperature	Result
1	Activated Zn[1]	$CaCl_2$	MeOH	50 °C	Mixture of **249** and **250**
2[2]	Activated Zn[1]	$CaCl_2$	MeOH	50 °C	Mixture of **249** and **250**
3[3]	Activated Zn[1]	$CaCl_2$	MeOH	50 °C	Mixture of **249** and **250**
4	Activated Zn[1]	$CaCl_2$	MeOH	35 °C	Slower reaction, mixture of **249** and **250**
5	Activated Zn[1]	$CaCl_2$	THF	50 °C	Very slow reaction
6	Activated Zn[1]	$CaCl_2$	*i*PrOH	up to 70 °C	Mixture of **249** and **251**
7	Activated Zn[1]	$CaCl_2$	F_3CCH_2OH	up to 70 °C	Mixture of **249** and **252** + side-products
8	Activated Zn[1]	$CaCl_2$	HFIP	up to 70 °C	No reaction
9	Activated Zn - type 2 [4]	$CaCl_2$	MeOH	50 °C	**249** and only traces of **250**
10	Activated Zn - type 2 [4]	- - -	MeOH	50 °C	**249** and only traces of **250** + traces of side-products

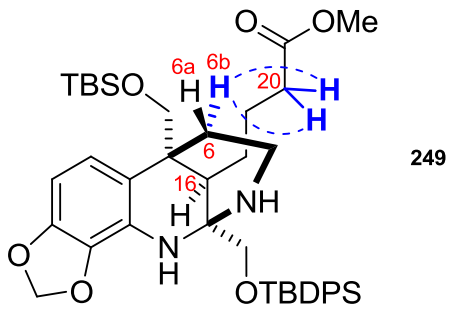
[1] Zn powder was activated with HCl 10%.
[2] The reaction was set up and run in the glovebox.
[3] The reaction was set up and run in absence of light.
[4] Zn powder was activated with DCE and TMSCl.

Table 21 : *Optimization of the reaction conditions for the Reduction/Cyclization of ketone* ***247*** *to aminal* ***249***

Aminal **249** was fully characterized by ^{1}H, ^{13}C, DEPT-135, HSQC, HMBC and NOESY NMR spectroscopy. The configuration of chiral center C(16) was a major concern, as its inversion could not be excluded in the course of the iORC process. No conclusive NOESY correlation was found for the proton at C(16) but an indirect proof confirmed the desired stereochemistry. To our delight, correlations between proton 6b at C(6) and both protons at C(20) were present on the spectrum (Scheme 114). Based on 3D and molecular models, these NOESY correlations would not exist if the stereochemistry was the opposite at C(16). No contradictory correlation was found.



Scheme 113 : *^{1}H NMR spectrum of the crude product* ***249***



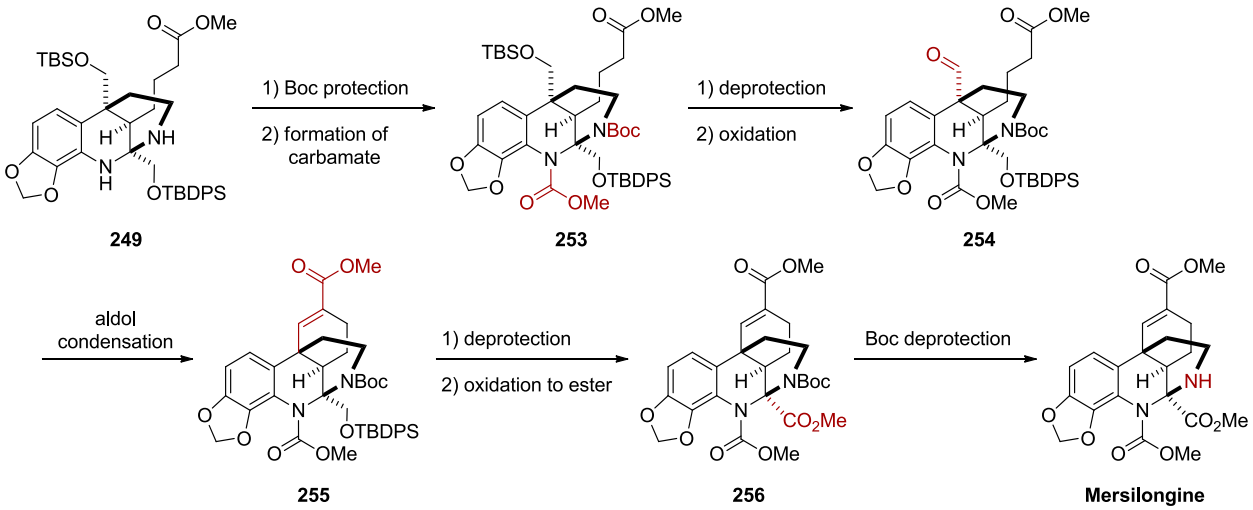
249

Scheme 114 : *Key NOESY correlations for the determination of the stereochemistry of aminal* ***249*** *at C(16)*

2.4 Outlook

2.4.1 Completion of the Total Synthesis of Mersilongine

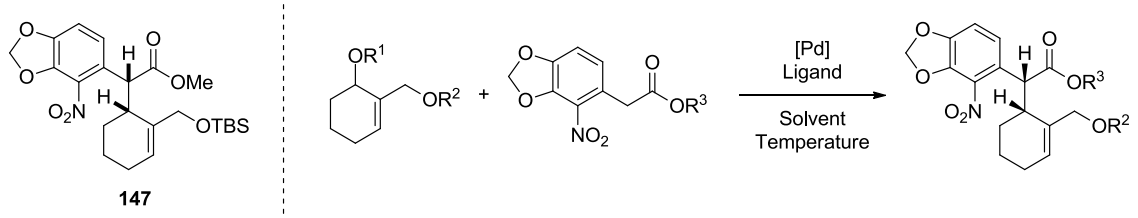
To complete the total synthesis of Mersilongine from key aminal **249**, the last ring has to be formed and several functional group modifications remain (Scheme 115). The aminal group would first be diprotected to avoid any issue assiociated with the sensitive amine functions : the secondary amine would be protected with Boc, followed by formation of carbamate on the aniline counterpart to give intermediate **253**. TBS-deprotection and oxidation of the neopentyl alcohol would then give aldehyde **254**. Aldol condensation would form α,β-unsaturated ester **255**, thus closing the last ring of the skeleton. The remaining protected primary alcohol would be converted to methyl ester **256**. Finally, removal of the Boc protecting group would give racemic Mersilongine.



Scheme 115 : *Planned sequence for the completion of Mersilongine from aminal* ***249***

2.4.2 Enantioselective Tsuji-Trost reaction

In the synthetic studies reported so far, intermediate **147** was obtained as a racemate (Scheme 116). In order to achieve the enantioselective total synthesis of Mersilongine, the Tsuji-Trost reaction must be enantioselective. As seen in the introduction, to date there is no report of such a reaction for the generation of two adjacent tertiary centers (other than 1,3-dicarbonyl products). A chiral ligand will be required and an obvious initial choice for the optimization of the reaction would be the DACH-phenyl Trost ligand.



Scheme 116 : *Planned enantioselective Tsuji-Trost reaction for the synthesis of enantioenriched product* ***147***

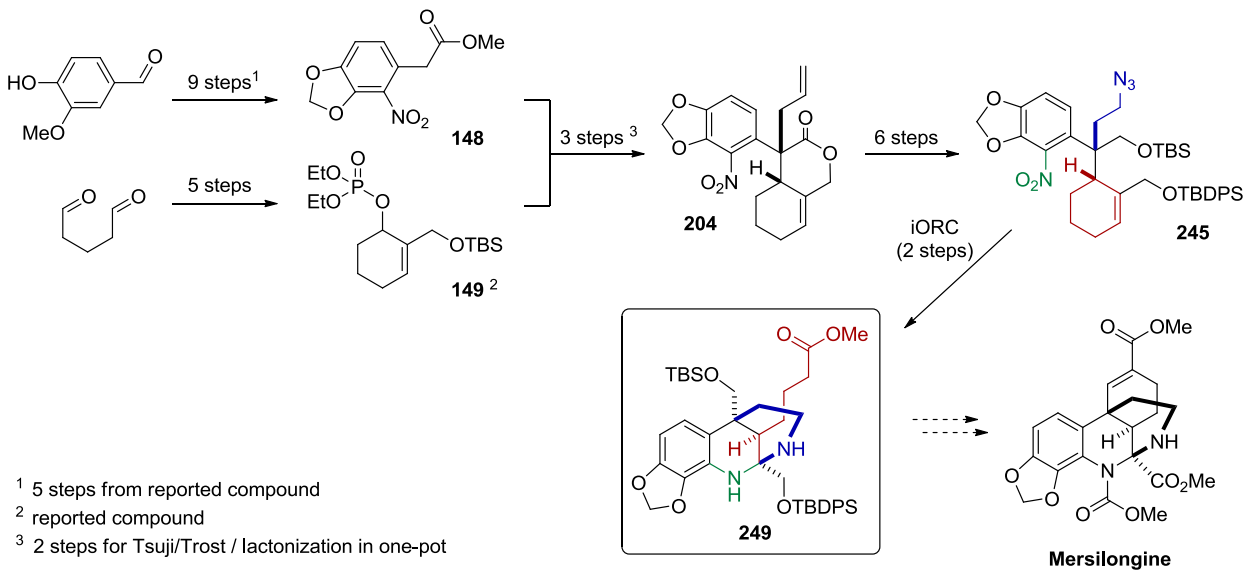
2.5 Conclusion

The synthesis of advanced key intermediate **245** towards the total synthesis of Mersilongine has been accomplished in 20 steps from vanilin (longest linear sequence) (Scheme 117). Three key transformations were successfully exploited or developed for the construction of the skeleton of Mersilongine :

- A high yielding Tsuji-Trost reaction between building blocks **148** and **149**. In this operation, two adjacent tertiary carbon centers were created with high diastereoselectivity.

- A substrate-controlled fully diastereoselective α-allylation of a lactone for the formation of the quaternary center of intermediate **204**.

- The first application of the iORC strategy for the synthesis of a quinolinic / bridged aminal core bearing three contiguous chiral centers.



Scheme 117 : *Summary of the synthesis of key intermediate aminal* ***249*** *from vanillin*

CHAPTER 3 Supporting Informations

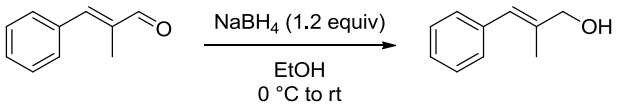
3.1 General Informations

Reagents and solvents were purchased from commercial sources and preserved under argon. Reagents were used without further purification unless otherwise noted. All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted.

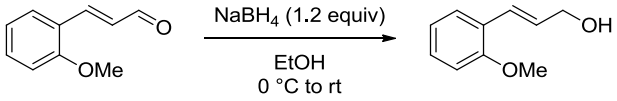
When solvents were indicated as dry they were either purchased as such, distilled prior to use or dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc., based on the Grubbs' design. Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 µm) silica. Reactions were monitored using Merck Kieselgel 60 F_{254} aluminium plates. TLC was visualized by UV fluorescence (254 nm) then one of the following: $KMnO_4$, phosphomolybdic acid, ninhydrin, p-anisaldehyde, vanillin. NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 or 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], 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), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. The spectra were reported in cm^{-1}. Mass spectra were determined with a Waters ACQUITY H-class UPLC/MS ACQ-SQD by electron ionisation (EI positive and negative) or a Finnigan TSQ7000 by electrospray ionization (ESI+). The accurate masses were measured by the mass spectrometry service of the EPFL by ESI-TOF using a QTOF Ultima from Waters or APPI-FT-ICR using a linear ion trap Fourier transform ion cyclotron resonance mass spectrometer from Thermo Scientific.

3.2 Vinyl Ketenimines

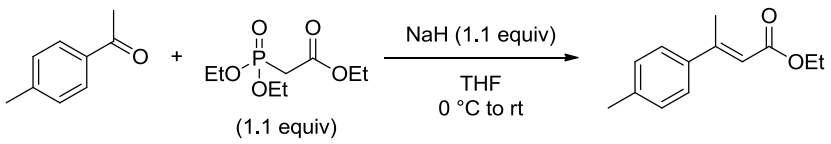
3.2.1 Synthesis of Precursors of Allyl Carbonates



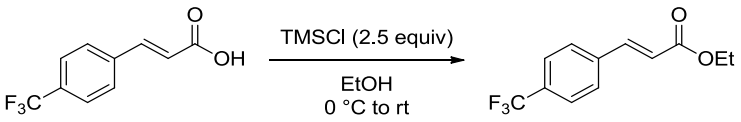
α-Methylcinnamyl alcohol (257) : To a solution of $NaBH_4$ (0.454 g, 12.0 mmol, 1.2 equiv) in EtOH (20 mL) at 0 °C was added α-methyl-*trans*-cinnamaldehyde (1.462 g, 10.0 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 1 h and was then quenched with sat. aqueous NH_4Cl. The aqueous layer was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford quantitatively α-methylcinnamyl alcohol **257** as a yellowish oil. The crude product was used in the next step without further purification.



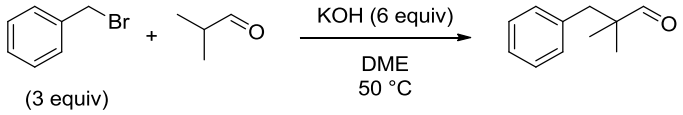
***o*-Methoxycinnamyl alcohol (258) :** To a solution of $NaBH_4$ (0.454 g, 12.0 mmol, 1.2 equiv) in EtOH (20 mL) at 0 °C was added 2-methoxycinnamaldehyde (1.622 g, 10.0 mmol, 1.0 equiv). The reaction mixture was stirred at rt for 1 h and was then quenched with sat. aqueous NH_4Cl. The aqueous layer was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford quantitatively *o*-methoxycinnamyl alcohol **258** as a yellow oil. The crude product was used in the next step without further purification.



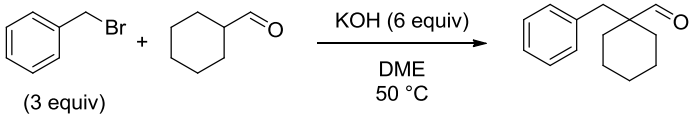
(*E*)-Ethyl 3-(*p*-tolyl)but-2-enoate (259) : To a suspsension of NaH (0.660 g of NaH 60% in mineral oil, 16.5 mmol, 1.1 equiv) in THF (20 mL) at 0 °C was added dropwise triethyl phosphonoacetate (3.28 mL, 16.5 mmol, 1.1 equiv) and the reaction mixture was stirred for 15 min. A solution of 4'-methylacetophenone (2.0 mL, 15.0 mmol, 1.0 equiv) in THF (10 mL) was then added. The reaction mixture was allowed to warm to rt and was stirred overnight. The reaction was quenched with sat. aqueous NH_4Cl, the aqueous layer was extracted with EtOAc (2x) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford α,β-unsaturated ester **259** as a colorless oil (1.354 g, 6.63 mmol, 44%). The crude product was used in the next step without further purification.



(*E*)-Ethyl 3-(4-(trifluoromethyl)phenyl)acrylate (260) : To a solution of 4-(trifluoromethyl)cinnamic acid (1.297 g, 6.0 mmol, 1.0 equiv) in EtOH (20 mL) at 0 °C was added TMSCl (1.9 mL, 15.0 mmol, 2.5 equiv). The reaction mixture was allowed to warm to rt and was stirred overnight. The reaction mixture was then partitioned between EtOAc and H_2O and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were washed with sat. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford quantitatively α,β-unsaturated ester **260** as a colorless solid. The crude product was used in the next step without further purification.

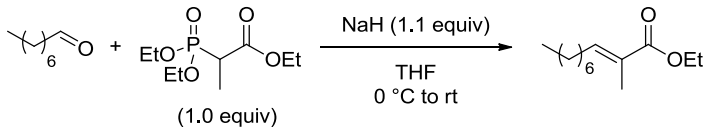


2,2-Dimethyl-3-phenylpropanal (43) : Benzyl bromide (7.14 mL, 60.0 mmol, 3.0 equiv) and isobutyraldehyde (1.83 mL, 20.0 mmol, 1.0 equiv) were added to a suspension of powdered KOH (6.733 g, 120.0 mmol, 6.0 equiv) in DME (200 mL). The reaction mixture was stirred at 50 °C for 2 h and allowed to cool to rt. The suspension was filtered and H_2O was added to the filtrate. The aqueous layer was acidified with aq. 10% HCl, extracted with Et_2O and the organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **43** as a colorless liquid (2.706 g, 16.7 mmol, 84% yield). The crude product was used in the next step without further purification.[131]



1-Benzylcyclohexanecarbaldehyde (261) : Benzyl bromide (3.57 mL, 30.0 mmol, 3.0 equiv) and cyclohexanecarboxaldehyde (1.83 mL, 10.0 mmol, 1.0 equiv) were added to a suspension of powdered KOH (3.367 g, 60.0 mmol, 6.0 equiv) in DME (100 mL). The reaction mixture was stirred at 50 °C for 2 h and allowed to cool to rt. The suspension was filtered and H_2O was added to the filtrate. The aqueous layer was acidified with aq. 10% HCl, extracted with Et_2O and the organic layers were washed with H_2O, brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **261** as a colorless liquid (1.802 g, 8.91 mmol, 89% yield). The crude product was used in the next step without further purification.[132]

[131] See reference 38.
[132] See reference 38.



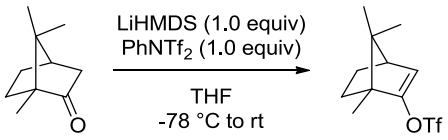
(*E*)-Ethyl 2-methyldec-2-enoate (262) : To a suspsension of NaH (0.440 g of NaH 60% in mineral oil, 11.0 mmol, 1.1 equiv) in THF (30 mL) at 0 °C was added dropwise triethyl 2-phosphonopropionate (2.14 mL, 10.0 mmol, 1.0 equiv) and the reaction mixture was stirred for 15 min. Octanal (1.56 mL, 10.0 mmol, 1.0 equiv) was then added dropwise. The reaction mixture was allowed to warm to rt and was stirred overnight. The reaction was quenched with sat. aqueous NH_4Cl, the aqueous layer was extracted with EtOAc (2x) and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 50:1 as eluent to afford α,β-unsaturated ester **262** as colorless oil (1.529 g, 7.20 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (tq, *J* = 7.7, 1.3 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.16 (q, *J* = 7.4 Hz, 2H), 1.82 (s, 3H), 1.48 – 1.38 (m, 2H), 1.35 – 1.21 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 142.8, 128.0, 60.7, 32.1, 29.7, 29.5, 29.0, 28.9, 23.0, 14.7, 14.4, 12.7.

IR υ (cm^{-1}) 2957 (w), 2927 (m), 2856 (w), 1711 (s), 1651 (w), 1464 (w), 1367 (w), 1269 (m), 1178 (w), 1142 (w), 1101 (m), 1040 (w), 746 (w).

HRMS (ESI) calcd for $C_{13}H_{25}O_2^+$ $[M+H]^+$ 213.1849; found 213.1857.

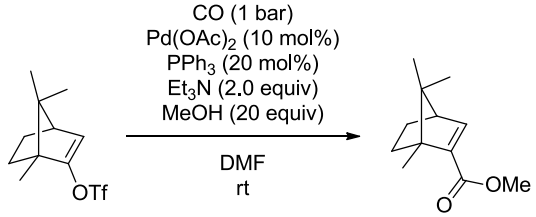


(1*S*,4*R*)-1,7,7-Trimethylbicyclo[2.2.1]hept-2-en-2-yl trifluoromethanesulfonate (44) : To a solution of camphor (3.045 g, 20.0 mmol, 1.0 equiv) in THF (40 mL) at -78 °C was added dropwise LiHMDS (20 mL of a 1.0 M solution in toluene, 20.0 mmol. 1.0 equiv) and the reaction mixture was stirred for 30 min. A solution of $PhNTf_2$ (7.145 g, 20.0 mmol, 1.0 equiv) in THF (40 mL) was then added dropwise over 15 min and the reaction mixture was stirred overnight while being allowed to warm to rt. The reaction was then quenched with sat. aqueous NH_4Cl and extracted with Et_2O. The organic layer was washed with sat. aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE as eluent to afford triflate **44** as a colorless oil (3.302 g, 11.6 mmol, 77% yield).[133] The spectroscopic data were consistent with those previously reported in the literature.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (d, *J* = 3.8 Hz, 1H), 2.45 (t, *J* = 3.7 Hz, 1H), 1.93 (ddt, *J* = 12.2, 8.5, 3.7 Hz, 1H), 1.65 (ddd, *J* = 12.1, 8.5, 3.6 Hz, 1H), 1.33 (ddd, *J* = 12.4, 9.1, 3.6 Hz, 1H), 1.15 (ddd, *J* = 12.5, 9.1, 3.6 Hz, 1H), 1.03 (s, 3H), 0.92 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 118.9 (q, *J* = 318.5 Hz), 118.0, 57.3, 54.2, 50.4, 31.2, 25.7, 20.1, 19.3, 9.8.

[133] See reference 40.



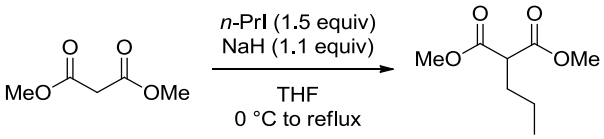
(1S,4R)-Methyl 1,7,7-trimethylbicyclo[2.2.1]hept-2-ene-2-carboxylate (45) : Triflate **44** (1.706 g, 6.0 mmol, 1.0 equiv), DMF (30 mL), MeOH (4.86 mL, 120.0 mmol, 20.0 equiv), Et_3N (1.68 mL, 12.0 mmol, 2.0 equiv), PPh_3 (315.0 mg, 1.2 mmol, 20 mol%) and $Pd(OAc)_2$ (135.0 mg, 0.6 mmol, 10 mol%) were loaded into a flask. The reaction mixture was purged with CO and stirred overnight under CO atmosphere (1 atm). The reaction mixture was concentrated under reduced pressure, diluted with EtOAc and washed with sat. aqueous NH_4Cl, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 30:1 as eluent to afford α,β-unsaturated ester **45** as yellowish oil (503.0 mg, 2.59 mmol, 43% yield).[134]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, *J* = 3.4 Hz, 1H), 3.70 (s, 3H), 2.43 (t, *J* = 3.7 Hz, 1H), 1.91 (ddt, *J* = 12.3, 8.3, 3.8 Hz, 1H), 1.61 (ddd, *J* = 12.0, 8.6, 3.6 Hz, 1H), 1.24 (s, 3H), 1.13 (ddd, *J* = 12.2, 9.2, 3.6 Hz, 1H), 0.97 (ddd, *J* = 12.4, 9.1, 3.5 Hz, 1H), 0.79 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 147.5, 141.0, 57.3, 54.3, 52.4, 51.3, 31.5, 24.9, 19.7, 19.5, 12.2.

IR υ (cm^{-1}) 2956 (m), 2875 (m), 1716 (s), 1589 (w), 1436 (w), 1337 (m), 1273 (m), 1237 (s), 1190 (w), 1077 (s), 760 (m).

HRMS (ESI) calcd for $C_{12}H_{19}O_2^+$ $[M+H]^+$ 195.1380; found 195.1380.



Dimethyl 2-propylmalonate (263) : Dimethylmalonate (5.71 mL, 50.0 mmol, 1.0 equiv) was added to a suspension of NaH (60% in mineral oil, 2.2 g, 55.0 mmol, 1.1 equiv) in THF (100 mL) at 0 °C. Propyl iodide (7.31 mL, 75.0 mmol, 1.5 equiv) was then added and the reaction mixture was stirred at 70 °C overnight. The reaction was then quenched with brine, extracted with Et_2O and the organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford malonate **263** as a colorless oil (5.678 g, 28.1 mmol, 56% yield). The spectroscopic data were consistent with those previously reported in the literature.[135]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 6H), 3.37 (t, *J* = 7.6 Hz, 1H), 1.92 – 1.84 (m, 2H), 1.40 – 1.29 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 52.8, 51.8, 31.2, 20.9, 14.0.

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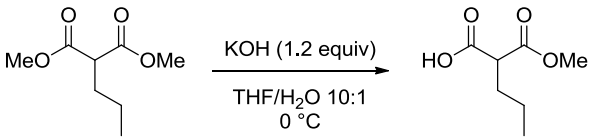
[134] For reaction conditions with a similar substrate, see : Findley, T. J. K.; Sucunza, D.; Miller, L. C.; Davies, D. T.; Procter, D. J. *Chem. Eur. J.* **2008**, *14* (23), 6862–6865.

[135] Campaña, A. G.; Estévez, R. E.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Buñuel, E.; Cárdenas, D.; Oltra, J. E. *Org. Lett.* **2007**, *9* (11), 2195–2198.



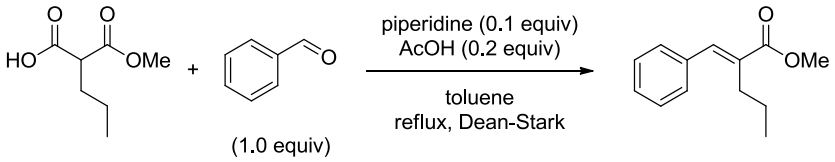
2-(Methoxycarbonyl)pentanoic acid (39) : To a solution of malonate **263** (2.023 g, 11.6 mmol, 1.0 equiv) in THF (16.7 mL) and H_2O (166.7 mL) at 0 °C was added dropwise a solution of KOH (0.673 g, 12 mmol, 1.05 equiv) in H_2O (48 mL) and the reaction mixture was stirred at 0 °C for 1 h, then acidified to pH=2 with aqueous HCl (10%, 4.5 mL). The reaction mixture was then partitioned between brine and EtOAc. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford mono-acid **39** as a colorless oil (1.449 g, 9.1 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.42 (t, *J* = 7.4 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.43 – 1.31 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 170.4, 53.0, 51.5, 31.3, 20.9, 14.0.

IR υ (cm^{-1}) 3229 (br), 2961 (m), 2877 (m), 2599 (br), 1710 (s), 1438 (m), 1243 (m), 1197 (s), 1165 (s), 1111 (m), 1061 (w), 1033 (w), 931 (w), 837 (w), 783 (w), 754 (w), 676 (w).

HRMS : not detected.

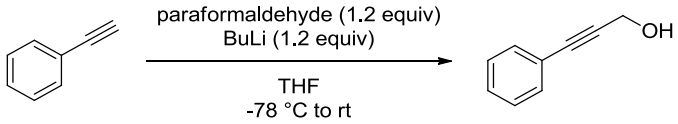


(*E*)-Methyl 2-benzylidenepentanoate (40) : To a solution of mono-acid **39** (1.602 g, 10.0 mmol, 1.0 equiv) in toluene (33 mL) in a 100 mL flask fitted with a Dean-Stark apparatus were added benzaldehyde (1.02 mL, 10.0 mmol, 1.0 equiv), piperidine (0.1 mL, 1.0 mmol, 10 mol%) and AcOH (0.12 mL, 1.0 mmol, 10 mol%). The reaction mixture was stirred under reflux overnight. The reaction mixture was then washed with sat. aqueous NH_4Cl, sat. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 30:1 as eluent to afford α,β-unsaturated ester **40** as a yellowish oil (1.418 g, 0.69 mmol, 69% yield).[136] The spectroscopic data were consistent with those previously reported in the literature.[137]

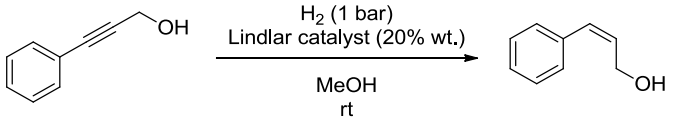
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.43 – 7.28 (m, 5H), 3.82 (s, 3H), 2.54 – 2.46 (m, 2H), 1.64 – 1.50 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 139.2, 136.2, 133.9, 129.5, 128.8, 128.6, 52.3, 29.9, 22.9, 14.5.

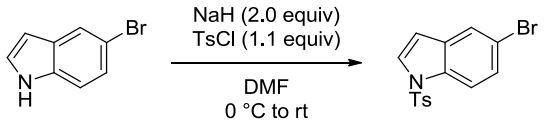
[136] For reaction conditions with a similar substrates, see : Leber, J.; Christensen, S.; Daines, R.; Li, M.; Weinstock, J.; Head, M. WO/2001/090099, November 30, 2001.
[137] Wolan, A.; Cadoret, F.; Six, Y. *Tetrahedron* **2009**, *65* (36), 7429–7439.



3-Phenylprop-2-yn-1-ol (264) : To a solution of phenylacetylene (1.1 mL, 10.0 mmol, 1.0 equiv) in THF (20 mL) at -78 °C was added dropwise BuLi (4.8 mL of a 2.5 M solution in hexane, 12.0 mmol, 1.2 equiv) and the reaction mixture was stirred for 30 min. Paraformaldehyde was then added and the reaction mixture was allowed to warm to rt over 2 h and stirred for 24 h. The reaction mixture was then washed with sat. aqueous NH_4Cl, brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford quantitatively alcohol **264** as a colorless oil. The crude product was used in the next step without further purification.[138]



(*Z*)-3-Phenylprop-2-en-1-ol (265) : To a suspension of Lindlar catalyst (112.0 mg, 20% wt.) in MeOH (20 mL) was added alcohol **264** (660.8 mg, 5.0 mmol, 1.0 equiv) and the reaction mixture was stirred under H_2 atmosphere (1 atm) for 2 days. The reaction mixture was filtered through Celite and concentrated under reduced pressure to afford alcohol **265** as a colorless oil. The crude product was used in the next step without further purification.

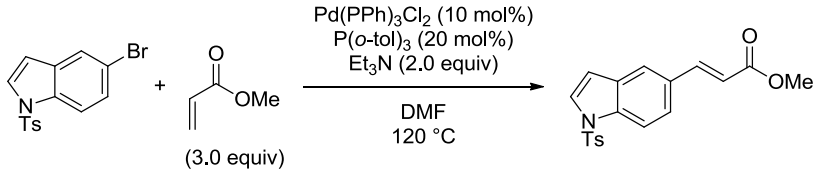


5-Bromo-1-tosyl-1*H*-indole (41) : NaH (60% in mineral oil, 0.49 g, 20.0 mmol, 2.0 eq.) was added to a solution of 5-bromoindole (1.96 g, 10.0 mmol, 1.0 eq.) in DMF (10 mL) and the reaction mixture was stirred stirred for 1 h. The reaction was then cooled to 0 °C and a solution of TsCl (2.14 g, 11.2 mmol, 1.12 eq.) in DMF (7 mL) was added. The reaction was allowed to warm to rt and concentrated under reduced pressure. The crude mixture was partitioned between H_2O and EtOAc, extracted and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 10:1 (Rf=0.30) as eluent to afford *N*-Ts-5-bromoindole **41** as a pale yellow solid (3.22 g, 9.2 mmol, 92% yield). The spectroscopic data were consistent with those previously reported in the literature.[139]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 1.8 Hz, 1H), 7.56 (d, *J* = 3.7 Hz, 1H), 7.39 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.59 (dd, *J* = 3.6, 0.5 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 135.3, 133.9, 132.8, 130.3, 127.9, 127.8, 127.1, 124.4, 117.1, 115.3, 108.6, 21.9.

[138] Zhu, N.; Wang, F.; Chen, P.; Ye, J.; Liu, G. *Org. Lett.* **2015**, *17* (14), 3580–3583.
[139] Garg, N. K.; Sarpong, R.; Stoltz, B. M. *J. Am. Chem. Soc.* **2002**, *124* (44), 13179–13184.



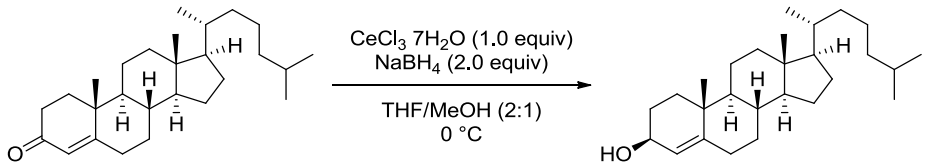
(*E*)-methyl 3-(1-tosyl-1*H*-indol-5-yl)acrylate (42) : 5-Bromoindole derivative **41** (2.102 g, 6.0 mmol, 1.0 eq.), $Pd(OAc)_2$ (135 mg, 0.6 mmol, 10 mol%), P(*o*-tol)$_3$ (365 mg, 1.2 mmol, 20 mol%), DMF (5 mL), methyl acrylate (1.62 mL, 18.0 mmol, 3.0 eq.) and Et_3N (1.67 mL, 12.0 mmol, 2 eq.) were loaded into a flask and the reaction mixture was heated at 120 °C for 12 h. The reaction mixture was concentrated under reduced pressure and the crude mixture was partitioned between sat. aqueous NH_4Cl and EtOAc. The aqueous phase was extracted with EtOAc and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 5:1 as eluent (Rf=0.27) to afford α,β-unsaturated ester **42** as viscous orange oil (845 mg, 2.38 mmol, 40% yield, 68% yield b.r.s.m.).[140]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 16.1 Hz, 1H), 7.67 (d, *J* = 1.2 Hz, 1H), 7.59 (d, *J* = 3.7 Hz, 1H), 7.50 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.67 (dd, *J* = 3.7, 0.6 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 3.80 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 145.6, 145.4, 136.1, 135.5, 131.5, 130.4, 130.1, 127.7, 127.2, 124.5, 122.3, 117.3, 114.3, 109.4, 52.1, 21.9.

IR υ (cm^{-1}) 2949 (w), 1711 (m), 1635 (m), 1608 (w), 1458 (m), 1442 (m), 1371 (m), 1308 (m), 1270 (m), 1251 (m), 1169 (s), 1124 (s), 1092 (m), 992 (m), 860 (w), 813 (m), 768 (w), 736 (m), 704 (m), 672 (s).

HRMS (ESI) calcd for $C_{19}H_{18}NO_4S^+$ $[M+H]^+$ 356.0951; found 356.0943.



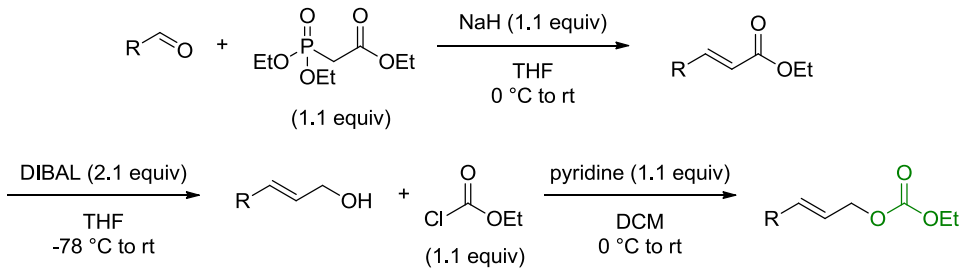
Cholest-4-en-3β-ol (266) : $NaBH_4$ (0.378 g, 10.0 mmol, 2.0 eq) was added portionwise to a solution of (+)-4-cholesten-3-one (1.923 g, 5.0 mmol, 1.0 eq.) and $CeCl_3 \cdot 7H_2O$ (1.863 g, 5.0 mmol, 1.0 eq.) in THF (30 mL) and MeOH (15 mL) at 0 °C. The reaction was stirred for 1 h and concentrated under reduced pressure. The crude reaction mixture was diluted with EtOAc, washed with aqueous HCl 5%, sat. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 6:1 as eluent (Rf=0.23) to afford cholest-4-en-3β-ol **266** as a colorless crystalline solid (1.657 g, 4.29 mmol, 86% yield).[141] The spectroscopic data were consistent with those previously reported in the literature.[142]

[140] For reaction conditions with a similar substrate, see : Tomoo, T.; Nakatsuka, T.; Katayama, T.; Hayashi, Y.; Fujieda, Y.; Terakawa, M.; Nagahira, K. *J. Med. Chem.* **2014**, *57* (17), 7244–7262.
[141] See reference 39.
[142] Carvalho, J. F. S.; Silva, M. M. C.; Sá e Melo, M. L. *Tetrahedron* **2009**, *65* (14), 2773–2781.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (d, *J* = 1.5 Hz, 1H), 4.20 – 4.09 (m, 1H), 2.25 – 2.12 (m, 1H), 2.04 – 1.91 (m, 3H), 1.86 – 1.77 (m, 1H), 1.76 – 1.66 (m, 2H), 1.60 – 1.20 (m, 13H), 1.16 – 1.06 (m, 5H), 1.05 (s, 3H), 1.01 – 0.93 (m, 2H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.77 – 0.69 (m, 1H), 0.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 123.6, 68.4, 56.5, 56.5, 54.8, 42.8, 40.2, 39.9, 37.7, 36.5, 36.3, 36.1, 35.7, 33.5, 32.6, 29.9, 28.6, 28.4, 24.6, 24.2, 23.2, 22.9, 21.4, 19.3, 19.0, 12.3.

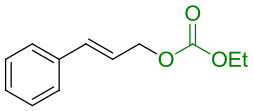
3.2.2 Synthesis of Allyl Carbonates



To a suspsension of NaH (60% in mineral oil, 1.1 equiv) in THF (0.2 M) at 0 °C was added dropwise triethyl phosphonoacetate (1.1 equiv) and the reaction mixture was stirred for 15 min. A solution of the aldehyde (1.0 equiv) in THF (1.0 M) was then added dropwise. The reaction mixture was allowed to warm to rt and stirred until complete consumption of the aldehyde (~4 h). The reaction was then quenched with sat. aqueous NH_4Cl, the aqueous layer was extracted with EtOAc (2x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude α,β-unsaturated ester was used in the next step without further purification.

To a solution of the above obtained α,β-unsaturated ester (1.0 equiv) in Et_2O (0.2 M) at -78 °C was added dropwise DIBAL (2.1 equiv) and the reaction mixture was stirred until complete consumption of the α,β-unsaturated ester (~2 h). The reaction was then allowed to warm to rt and a sat. aqueous solution of potassium sodium tartrate (Rochelle salt) was added and the reaction mixture was stirred for 1 h. The aqueous layer was then extracted with Et_2O (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude allyllic alcohol was used in the next step withtout further purification.

To a solution of the allyl alcohol (1.0 equiv) in DCM (0.4 M) at 0 °C was added pyridine (1.1 equiv) and the reaction mixture was stirred for 15 min. Ethyl chloroformate (1.1 equiv) was then added dropwise, the reaction mixture was allowed to warm to rt and stirred until complete consumption of the starting material (~1 h). The reaction mixture was washed with sat. aqueous NH_4Cl, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired allyl carbonate.

31a 

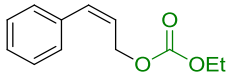
Cinnamyl ethyl carbonate

93% yield (from cinnamyl alcohol), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.79 (dd, *J* = 6.4, 1.3 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.4, 135.0, 128.9, 128.5, 127.0, 122.9, 68.5, 64.4, 14.6.

The spectroscopic data were consistent with those previously reported in the literature.[143]

31b 

(*Z*)-Ethyl (3-phenylallyl) carbonate

83% yield over 2 steps (from alcohol **265**), colorless liquid

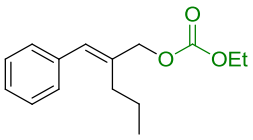
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.32 (m, 2H), 7.32 – 7.26 (m, 1H), 7.25 – 7.17 (m, 2H), 6.70 (d, *J* = 11.7 Hz, 1H), 5.85 (dt, *J* = 11.8, 6.6 Hz, 1H), 4.90 (dd, *J* = 6.6, 1.6 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.2, 133.7, 129.0, 128.7, 127.9, 125.6, 64.9, 64.5, 14.6.

IR υ (cm^{-1}) 2983 (w), 1741 (s), 1447 (w), 1373 (m), 1247 (s), 1003 (br), 919 (w), 875 (m), 792 (m), 773 (m), 699 (m).

HRMS (ESI) calcd for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$ 229.0835; found 229.0845.

[143] Wolstenhulme, J. R.; Cavell, A.; Gredičak, M.; Driver, R. W.; Smith, M. D. *Chem. Commun.* **2014**, *50* (88), 13585–13588.



31c

(*E*)-2-Benzylidenepentyl ethyl carbonate

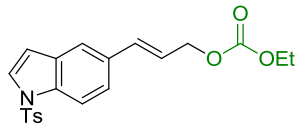
82% yield over 2 steps (from α,β-unsaturated ester **40**), colorless liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 2H), 7.27 – 7.21 (m, 3H), 6.58 (s, 1H), 4.72 (d, *J* = 1.1 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.31 – 2.24 (m, 2H), 1.60 – 1.49 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.3, 137.0, 129.6, 129.0, 128.6, 127.2, 71.8, 64.4, 31.2, 21.7, 14.7, 14.5.

IR υ (cm^{-1}) 2960 (w), 2933 (w), 2873 (w), 1734 (s), 1446 (w), 1377 (w), 1242 (s), 1088 (w), 994 (m), 920 (w), 880 (m), 791 (m), 745 (m), 698 (m).

HRMS (ESI) calcd for $C_{15}H_{20}NaO_3^+$ $[M+Na]^+$ 271.1305; found 271.1305.



31d

(*E*)-ethyl (3-(1-tosyl-1*H*-indol-5-yl)allyl) carbonate

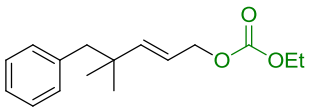
78% over 2 steps (from ester **42**), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 3.7 Hz, 1H), 7.51 (d, *J* = 1.4 Hz, 1H), 7.37 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.73 (d, *J* = 15.9 Hz, 1H), 6.62 (dd, *J* = 3.7, 0.7 Hz, 1H), 6.27 (dt, *J* = 15.8, 6.5 Hz, 1H), 4.77 (dd, *J* = 6.5, 1.2 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 145.4, 135.5, 135.1, 135.0, 131.9, 131.4, 130.2, 127.3, 127.1, 123.5, 122.2, 120.2, 114.0, 109.5, 68.6, 64.4, 21.9, 14.6.

IR υ (cm^{-1}) 2984 (br), 1741 (s), 1596 (w), 1459 (m), 1370 (m), 1251 (s), 1172 (s), 1144 (m), 1124 (s), 1090 (m), 994 (m), 969 (m), 874 (w), 813 (m), 791 (m), 767 (w), 726 (m), 704 (m), 676 (s).

HRMS (ESI) calcd for $C_{21}H_{21}AgNO_5S^+$ $[M+Ag]^+$ 506.0186; found 506.0188.

31e 

(*E*)-4,4-Dimethyl-5-phenylpent-2-en-1-yl ethyl carbonate

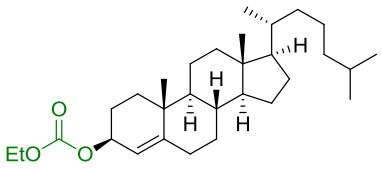
71% over 3 steps (from aldehyde **43**), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.18 (m, 3H), 7.11 – 7.04 (m, 2H), 5.83 (d, *J* = 15.7 Hz, 1H), 5.41 (dt, *J* = 15.7, 6.5 Hz, 1H), 4.58 (dd, *J* = 6.5, 1.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.00 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 146.3, 138.7, 130.9, 127.9, 126.3, 120.1, 69.0, 64.3, 49.3, 37.4, 26.9, 14.6.

IR υ (cm^{-1}) 2960 (br), 1742 (s), 1453 (w), 1380 (w), 1364 (w), 1248 (w), 1095 (w), 1012 (w), 979 (m), 921 (w), 874 (m), 792 (m), 734 (m), 702 (w).

HRMS (ESI) calcd for $C_{16}H_{22}NaO_3^+$ $[M+Na]^+$ 285.1461; found 285.1463.

31f 

Cholest-4-en-3β-yl ethyl carbonate

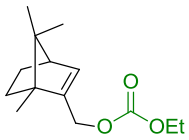
68% yield (from alcohol **266**), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (d, *J* = 1.4 Hz, 1H), 5.12 – 5.07 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.23 – 2.13 (m, 1H), 2.05 – 1.95 (m, 3H), 1.87 – 1.78 (m, 1H), 1.77 – 1.69 (m, 2H), 1.68 – 1.60 (m, 1H), 1.60 – 1.33 (m, 11H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27 – 1.19 (m, 1H), 1.18 – 1.05 (m, 5H), 1.05 (s, 3H), 1.02 – 0.92 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.80 – 0.70 (m, 1H), 0.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 150.4, 118.7, 74.8, 64.0, 56.5, 56.5, 54.5, 42.8, 40.2, 39.9, 37.7, 36.5, 36.2, 36.1, 35.1, 33.3, 32.6, 28.6, 28.4, 25.4, 24.6, 24.2, 23.2, 22.9, 21.3, 19.1, 19.0, 14.7, 12.3.

IR υ (cm^{-1}) 2934 (m), 2860 (m), 2850 (m), 1740 (s), 1466 (m), 1445 (m), 1374 (m), 1333 (w), 1253 (s), 1168 (w), 1114 (w), 1015 (m), 957 (w), 928 (w), 888 (w), 858 (m), 790 (m), 734 (w), 680 (w).

HRMS : not detected.

31g 

Ethyl (((1*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)methyl) carbonate

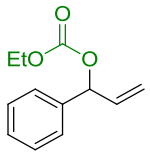
88% yield over 2 steps (from ester **45**), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (m, 1H), 4.70 – 4.56 (m, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.30 (t, *J* = 3.5 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.54 (ddd, *J* = 10.8, 8.7, 2.8 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 3H), 1.00 – 0.92 (m, 2H), 0.79 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 143.2, 133.6, 65.4, 64.2, 57.3, 54.1, 51.9, 31.9, 25.5, 19.8, 19.8, 14.7, 11.5.

IR υ (cm^{-1}) 2984 (w), 2953 (w), 2873 (w), 1744 (s), 1463 (w), 1378 (w), 1367 (w), 1248 (s), 1107 (w), 1010 (br), 876 (m), 793 (m).

HRMS (ESI) calcd for $C_{14}H_{22}NaO_3^+$ $[M+Na]^+$ 261.1461; found 261.1461.

31h 

Ethyl (1-phenylallyl) carbonate

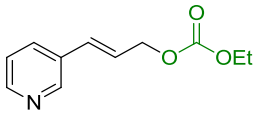
2 steps from benzaldehyde, colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 5H), 6.11 – 5.99 (m, 2H), 5.40 – 5.24 (m, 2H), 4.27 – 4.13 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 138.7, 136.2, 128.9, 128.7, 127.4, 117.7, 80.3, 64.4, 14.6.

IR υ (cm^{-1}) 2986 (w), 1742 (m), 1372 (w), 1246 (s), 1201 (w), 1090 (w), 1005 (m), 934 (w), 878 (w), 790 (w), 764 (w), 699 (m).

HRMS (ESI) calcd for $C_{12}H_{14}NaO_3^+$ $[M+Na]^+$ 229.0835; found 229.0834.

31i 

(*E*)-ethyl (3-(pyridin-3-yl)allyl) carbonate

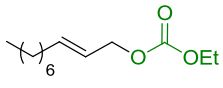
46% yield over 3 steps (from 3-pyridinecarboxaldehyde), brown oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.9 Hz, 1H), 8.49 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.71 (dt, *J* = 8.0, 1.7 Hz, 1H), 7.29 – 7.22 (m, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.37 (dt, *J* = 16.0, 6.1 Hz, 1H), 4.83 – 4.75 (m, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 149.4, 148.8, 133.5, 132.1, 131.0, 125.4, 123.9, 68.0, 64.6, 14.6.

IR υ (cm^{-1}) 2985 (w), 1739 (w), 1478 (w), 1381 (w), 1245 (s), 1097 (w), 970 (m), 921 (w), 875 (w), 842 (w), 790 (m), 708 (m).

HRMS (ESI) calcd for $C_{11}H_{14}NO_3^+$ $[M+H]^+$ 208.0968; found 208.0973.

31j 

(*E*)-Dec-2-en-1-yl ethyl carbonate

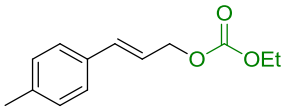
74% yield over 3 steps (from octanal), colorless liquid

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (dt, *J* = 15.1, 6.8 Hz, 1H), 5.58 (dt, *J* = 15.1, 7.0 Hz, 1H), 4.56 (d, *J* = 6.6 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.10 – 1.99 (m, 2H), 1.42 – 1.33 (m, 2H), 1.32 – 1.29 (m, 3H), 1.30 – 1.23 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 137.9, 123.5, 68.9, 64.2, 32.6, 32.1, 29.5, 29.4, 29.2, 23.0, 14.6, 14.4.

The spectroscopic data were consistent with those previously reported in the literature.[144]

[144] Katcher, M. H.; Norrby, P.-O.; Doyle, A. G. *Organometallics* **2014**, *33* (9), 2121–2133.

31k 

(*E*)-Ethyl (3-(*p*-tolyl)allyl) carbonate

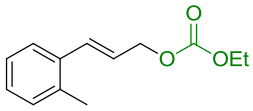
3 steps from *p*-tolualdehyde, colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 15.9 Hz, 1H), 6.25 (dt, *J* = 15.7, 6.2 Hz, 1H), 4.77 (dd, *J* = 6.5, 1.1 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 138.5, 135.1, 133.6, 129.7, 127.0, 121.8, 68.7, 64.4, 21.6, 14.6.

IR υ (cm^{-1}) 2983 (w), 1744 (s), 1515 (w), 1381 (w), 1300 (w), 1256 (s), 1011 (w), 972 (w), 792 (w).

HRMS (ESI) calcd for $C_{13}H_{16}NaO_3^+$ $[M+Na]^+$ 243.0992; found 243.0989.

31l 

(*E*)-Ethyl (3-(*o*-tolyl)allyl) carbonate

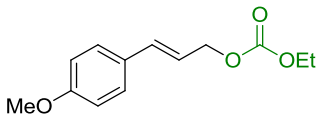
78% yield over 3 steps (from 2-methylbenzaldehyde), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.40 (m, 1H), 7.21 – 7.11 (m, 3H), 6.91 (d, *J* = 15.8 Hz, 1H), 6.19 (dt, *J* = 15.7, 6.5 Hz, 1H), 4.80 (dd, *J* = 6.5, 1.3 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 136.1, 135.6, 133.1, 130.7, 128.4, 126.5, 126.2, 124.2, 68.8, 64.4, 20.1, 14.6.

IR υ (cm^{-1}) 2983 (w), 1741 (s), 1462 (w), 1381 (w), 1247 (s), 1119 (w), 1008 (m), 968 (m), 919 (w), 875 (m), 791 (m), 748 (m).

HRMS (ESI) calcd for $C_{13}H_{16}AgO_3^+$ $[M+Ag]^+$ 327.0145; found 327.0140.

31m 

(*E*)-Ethyl (3-(4-methoxyphenyl)allyl) carbonate

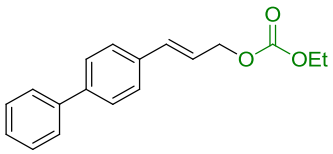
3 steps from *p*-anisaldehyde, yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.30 (m, 2H), 6.88 – 6.83 (m, 2H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.16 (dt, *J* = 15.8, 6.6 Hz, 1H), 4.76 (dd, *J* = 6.6, 1.1 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.4, 134.9, 129.2, 128.3, 120.5, 114.4, 68.8, 64.4, 55.6, 14.6.

IR υ (cm^{-1}) 2984 (w), 1742 (m), 1608 (w), 1513 (m), 1465 (w), 1382 (w), 1302 (w), 1247 (s), 1176 (w), 1102 (w), 1034 (w), 1010 (w), 972 (w), 848 (w), 792 (w).

HRMS (ESI) calcd for $C_{13}H_{16}O_4$ [M+] 236.1043; found 236.1042.

31n 

(*E*)-3-([1,1'-Biphenyl]-4-yl)allyl ethyl carbonate

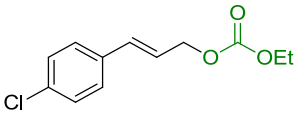
3 steps from biphenyl-4-carboxaldehyde, yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 4H), 7.50 – 7.42 (m, 4H), 7.38 – 7.34 (m, 1H), 6.74 (d, *J* = 15.9 Hz, 1H), 6.36 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.82 (dd, *J* = 6.5, 1.4 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 141.2, 140.8, 135.4, 134.5, 129.1, 127.7, 127.6, 127.4, 127.2, 122.9, 68.5, 64.4, 14.6.

IR υ (cm^{-1}) 2984 (w), 1743 (s), 1489 (w), 1383 (w), 1255 (s), 1103 (w), 1008 (w), 976 (w), 854 (w), 792 (w), 760 (m), 693 (w).

HRMS (ESI) calcd for $C_{18}H_{18}O_3$ [M+] 282.1250; found 282.1250.

31o 

(*E*)-3-(4-Chlorophenyl)allyl ethyl carbonate

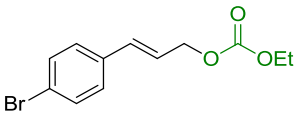
3 steps from 4-chlorobenzaldehyde, colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 6.64 (d, *J* = 15.9 Hz, 1H), 6.27 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.77 (d, *J* = 6.3 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 134.9, 134.2, 133.6, 129.1, 128.2, 123.6, 68.3, 64.5, 14.6.

IR υ (cm^{-1}) 2984 (w), 1741 (s), 1491 (w), 1409 (w), 1381 (w), 1302 (w), 1243 (s), 1091 (m), 1011 (m), 969 (m), 921 (w), 876 (w), 849 (m), 792 (m).

HRMS (ESI) calcd for $C_{12}H_{13}ClO_3$ [M+] 240.0548; found 240.0550.

31p 

(*E*)-3-(4-Bromophenyl)allyl ethyl carbonate

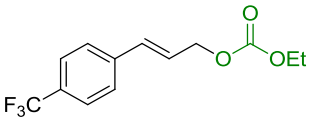
3 steps from 4-bromobenzaldehyde, yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 2H), 7.27 – 7.21 (m, 2H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.28 (dt, *J* = 15.9, 6.3 Hz, 1H), 4.76 (dd, *J* = 6.3, 1.3 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 135.3, 133.6, 132.1, 128.5, 123.7, 122.3, 68.2, 64.5, 14.6.

IR υ (cm^{-1}) 2983 (w), 1742 (s), 1489 (w), 1446 (w), 1403 (w), 1381 (w), 1365 (w), 1299 (w), 1253 (s), 1073 (w), 1009 (w), 970 (w), 849 (w), 791 (w).

HRMS (ESI) calcd for $C_{12}H_{13}BrO_3$ $[M]^+$ 284.0043, 286.0022; found 284.0039, 286.0017.

31q 

(*E*)-Ethyl (3-(4-(trifluoromethyl)phenyl)allyl) carbonate

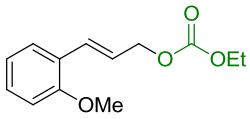
88% over 2 steps (from ester **260**), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 16.0 Hz, 1H), 6.39 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.81 (dd, *J* = 6.2, 1.3 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 139.9, 133.0, 130.2 (q, *J* = 33.1 Hz), 127.1, 125.9 (q, *J* = 3.7 Hz), 125.7, 124.4 (q, *J* = 272.7 Hz), 67.9, 64.5, 14.5.

IR υ (cm^{-1}) 2987 (w), 1744 (m), 1617 (w), 1383 (w), 1325 (s), 1303 (m), 1251 (s), 1165 (m), 1120 (s), 1067 (s), 1016 (m), 971 (m), 858 (m), 791 (m).

HRMS (ESI) calcd for $C_{13}H_{13}F_3NaO_3^+$ $[M+Na]^+$ 297.0709; found 297.0710.

31r 

(*E*)-Ethyl (3-(2-methoxyphenyl)allyl) carbonate

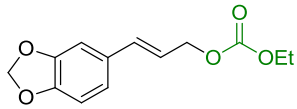
85% yield (from *o*-methoxycinnamyl alcohol **258**), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.28 – 7.22 (m, 1H), 7.01 (d, *J* = 16.0 Hz, 1H), 6.96 – 6.85 (m, 2H), 6.33 (dt, *J* = 16.0, 6.6 Hz, 1H), 4.79 (dd, *J* = 6.6, 1.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 155.4, 130.2, 129.6, 127.6, 125.4, 123.5, 121.0, 111.2, 69.2, 64.3, 55.8, 14.6.

IR υ (cm^{-1}) 2983 (w), 1741 (s), 1599 (w), 1489 (m), 1646 (m), 1381 (w), 1240 (s), 1177 (w), 1108 (w), 1027 (m), 979 (m), 920 (w), 875 (m), 791 (m), 751 (s).

HRMS (ESI) calcd for $C_{13}H_{16}NaO_4^+$ $[M+Na]^+$ 259.0941; found 259.0942.

31s 

(*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)allyl ethyl carbonate

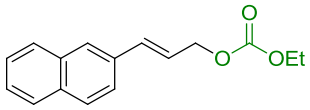
90% yield over 3 steps (from piperonal), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 1.6 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 6.59 (d, *J* = 15.8 Hz, 1H), 6.13 (dt, *J* = 15.8, 6.6 Hz, 1H), 5.96 (s, 2H), 4.75 (dd, *J* = 6.6, 1.2 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 148.4, 148.1, 134.9, 130.9, 122.0, 121.0, 108.6, 106.2, 101.5, 68.6, 64.4, 14.6.

IR υ (cm^{-1}) 2985 (w), 2895 (w), 1738 (s), 1504 (m), 1490 (m), 1446 (m), 1367 (w), 1242 (s), 1195 (m), 1125 (w), 1101 (w), 1037 (s), 1008 (m), 966 (m), 925 (m), 871 (m), 791 (m), 733 (m).

HRMS (ESI) calcd for $C_{13}H_{14}NaO_5^+$ $[M+Na]^+$ 273.0733; found 273.0729.

31t 

(*E*)-Ethyl (3-(naphthalen-2-yl)allyl) carbonate

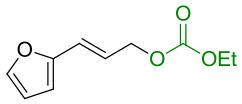
84% yield over 3 steps (from 2-naphtaldehyde), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 3H), 7.76 (s, 1H), 7.60 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.50 – 7.41 (m, 2H), 6.85 (d, *J* = 15.9 Hz, 1H), 6.43 (dt, *J* = 15.9, 6.4 Hz, 1H), 4.84 (dd, *J* = 6.4, 1.2 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 135.1, 133.9, 133.8, 133.6, 128.7, 128.4, 128.0, 127.4, 126.7, 126.5, 123.8, 123.2, 68.6, 64.5, 14.7.

IR υ (cm^{-1}) 3050 (w), 3001 (w), 1732 (s), 1447 (m), 1377 (m), 1305 (m), 1249 (s), 1112 (m), 1098 (m), 1001 (m), 975 (s), 915 (m), 903 (m), 869 (s), 838 (m), 817 (m), 794 (s), 753 (m), 741 (s).

HRMS (ESI) calcd for $C_{16}H_{16}NaO_3^+$ $[M+Na]^+$ 279.0992; found 279.0992.

31u 

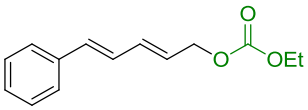
(*E*)-Ethyl (3-(furan-2-yl)allyl) carbonate

80% yield over 3 steps (from furfuraldehyde), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 1.6 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.37 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.29 (d, *J* = 3.3 Hz, 1H), 6.22 (dt, *J* = 15.8, 6.4 Hz, 1H), 4.75 (dd, *J* = 6.4, 1.3 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 152.1, 142.8, 122.9, 121.3, 111.7, 109.5, 68.1, 64.4, 14.6.

The spectroscopic data were consistent with those previously reported in the literature.[145]

31v 

Ethyl ((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl) carbonate

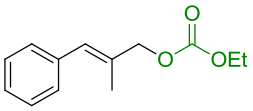
82% yield over 3 steps (from cinnamaldehyde), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 2H), 7.32 (td, *J* = 6.8, 1.6 Hz, 2H), 7.27 – 7.22 (m, 1H), 6.78 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.60 (d, *J* = 15.7 Hz, 1H), 6.49 (dd, *J* = 15.1, 10.6 Hz, 1H), 5.90 (dt, *J* = 15.2, 6.6 Hz, 1H), 4.71 (dd, *J* = 6.5, 1.0 Hz, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 137.2, 135.4, 134.5, 129.0, 128.2, 127.9, 126.9, 126.5, 68.2, 64.4, 14.6.

The spectroscopic data were consistent with those previously reported in the literature.[146]

[145] Knight, D. W.; Redfern, A. L.; Gilmore, J. *J. Chem. Soc., Perkin Trans. 1* **2001**, No. 21, 2874–2883.
[146] Ishii, Y.; Gao, C.; Xu, W. X.; Iwasaki, M.; Hidai, M. *J. Org. Chem.* **1993**, *58* (24), 6818–6825.

31w 

(*E*)-Ethyl (2-methyl-3-phenylallyl) carbonate

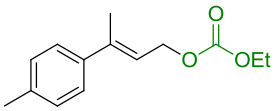
84% yield (from α-methylcinnamyl alcohol **257**), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.29 – 7.21 (m, 3H), 6.57 (s, 1H), 4.69 (s, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 1.92 (d, *J* = 1.2 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 137.2, 132.5, 129.3, 129.2, 128.5, 127.2, 73.8, 64.4, 15.8, 14.7.

IR υ (cm^{-1}) 2984 (w), 1742 (s), 1446 (w), 1377 (w), 1243 (s), 1007 (m), 919 (w), 880 (m), 851 (w), 791 (m), 747 (m), 699 (s).

HRMS (ESI) calcd for $C_{13}H_{16}NaO_3^+$ $[M+Na]^+$ 243.0992; found 243.0994.

31x 

(*E*)-Ethyl (3-(*p*-tolyl)but-2-en-1-yl) carbonate

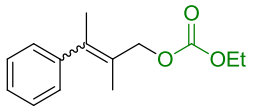
87% yield over 2 steps (from α,β-unsaturated ester **259**), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.91 (tq, *J* = 7.0, 1.3 Hz, 1H), 4.84 (d, *J* = 7.0 Hz, 2H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 2.11 (d, *J* = 1.3 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 141.2, 139.9, 137.8, 129.3, 126.1, 120.2, 65.1, 64.3, 21.4, 16.6, 14.6.

IR υ (cm^{-1}) 2983 (w), 1741 (s), 1445 (w), 1379 (w), 1247 (s), 1129 (w), 1010 (m), 990 (m), 918 (w), 875 (w), 812 (m), 791 (m).

HRMS (ESI) calcd for $C_{14}H_{18}AgO_3^+$ $[M+Ag]^+$ 341.0301; found 341.0304.

31y  ratio = 3:1

Ethyl (2-methyl-3-phenylbut-2-en-1-yl) carbonate

3 steps from acetophenone, colorless oil

Major isomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.17 – 7.13 (m, 2H), 4.84 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.08 (apparent q, *J* = 1.2 Hz, 3H), 1.67 (apparent q, *J* = 1.4 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 144.3, 137.7, 128.5, 128.2, 126.9, 125.8, 69.0, 64.4, 21.1, 18.5, 14.7.

Minor isomer:

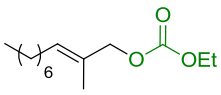
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.29 – 7.23 (m, 1H), 7.17 – 7.13 (m, 2H), 4.50 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.04 (s, 3H), 1.90 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 143.4, 138.4, 128.5, 128.3, 127.1, 125.8, 70.3, 64.2, 21.7, 16.7, 14.6.

Mixture of isomers:

IR υ (cm^{-1}) 2918 (w), 1741 (s), 1443 (w), 1375 (w), 1245 (s), 1116 (w), 1000 (m), 960 (w), 912 (w), 875 (w), 792 (w), 767 (m), 703 (m).

HRMS (ESI) calcd for $C_{14}H_{18}NaO_3^+$ $[M+Na]^+$ 257.1148; found 257.1151.

31z 

(*E*)-Ethyl (2-methyldec-2-en-1-yl) carbonate

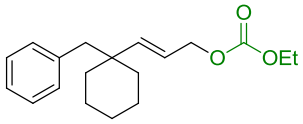
82% over 2 steps (from α,β-unsaturated ester **262**), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50 (t, *J* = 7.1 Hz, 1H), 4.50 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.02 (q, *J* = 7.1 Hz, 2H), 1.66 (s, 3H), 1.38 – 1.21 (m, 13H), 0.87 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 131.3, 129.7, 74.1, 64.2, 32.2, 29.6, 29.6, 29.5, 28.1, 23.0, 14.6, 14.4, 14.2.

IR υ (cm^{-1}) 2958 (w), 2925 (w), 2855 (w), 2361 (w), 1746 (s), 1464 (w), 1378 (w), 1249 (s), 1009 (w), 875 (w), 793 (w).

HRMS (ESI) calcd for $C_{14}H_{26}NaO_3^+$ $[M+Na]^+$ 265.1774; found 265.1778.



31aa

(*E*)-3-(1-Benzylcyclohexyl)allyl ethyl carbonate

77% yield over 3 steps (from aldehyde **261**), colorless oil

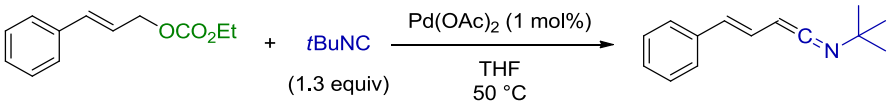
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 3H), 7.08 – 7.01 (m, 2H), 5.57 (d, *J* = 16.0 Hz, 1H), 5.34 (dt, *J* = 16.0, 6.4 Hz, 1H), 4.59 (dd, *J* = 6.4, 1.0 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.58 (s, 2H), 1.61 – 1.48 (m, 5H), 1.43 – 1.34 (m, 5H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 144.3, 138.2, 131.2, 127.8, 126.2, 122.8, 69.2, 64.2, 49.0, 40.6, 35.9, 26.7, 22.6, 14.7.

IR υ (cm^{-1}) 2929 (m), 2853 (w), 1744 (s), 1452 (w), 1381 (w), 1252 (s), 981 (w), 792 (w), 702 (m).

HRMS (ESI) calcd for $C_{19}H_{26}NaO_3^+$ $[M+Na]^+$ 325.1774; found 325.1770.

3.2.3 Synthesis of Vinyl Ketenimine **36**



To a solution of cinnamyl ethyl carbonate (41.2 mg, 0.2 mmol, 1.0 equiv) in THF (1 mL) was added $Pd(OAc)_2$ (0.45 mg, 0.002 mmol, 1 mol%). The reaction mixture was purged with argon and *t*BuNC (30 µL, 0.26 mmol, 1.3 equiv) was added. The reaction mixture was then stirred at 50 °C for 5 h. The reaction mixture was then allowed to cool to rt and the solvent was evaporated under reduced pressure to afford the crude ketenimine.

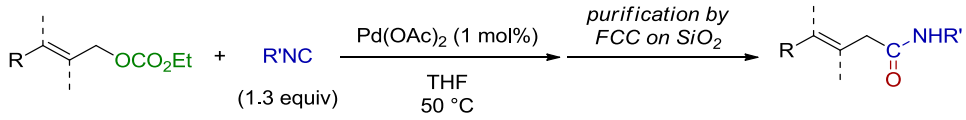
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (m, 5H), 6.60 (dd, *J* = 15.6, 10.7 Hz, 1H), 6.33 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 10.7 Hz, 1H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 184.4, 138.1, 128.5, 128.5, 126.2, 125.4, 123.9, 122.1, 59.8, 30.1.

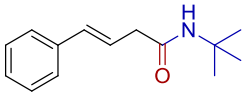
IR υ (cm^{-1}) 2971 (w), 2012 (s), 1671 (w), 1622 (w), 1596 (w), 1366 (w), 1238 (w), 1193 (w), 954 (w), 752 (w), 693 (w).

HRMS (ESI) calcd for $C_{14}H_{18}N^+$ $[M+H]^+$: 200.1434; found: 200.1443.

3.2.4 Synthesis of β,γ-Unsaturated Carboxamides



To a solution of the allyl carbonate (0.2 mmol, 1.0 equiv) in THF (1 mL) was added $Pd(OAc)_2$ (0.45 mg, 0.002 mmol, 1 mol%). The reaction mixture was purged with argon and *t*BuNC (29 µL, 0.26 mmol, 1.3 equiv) was added. The reaction mixture was then stirred at 50 °C until complete consumption of the starting material (~5 h). The reaction mixture was then allowed to cool to rt and deposited over SiO_2. Column chromatography with PE/EtOAc as eluent afforded the desired amide.

32a  87% (38 mg)

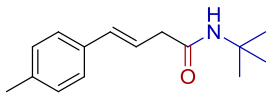
(*E*)-*N*-(*tert*-butyl)-4-phenylbut-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41-7.39 (m, 2H), 7.36-7.32 (m, 2H), 7.29 - 7.26 (m, 1H), 6.52 (d, *J* = 15.9 Hz, 1H), 6.31 (dt, *J* = 15.8, 7.2 Hz, 1H), 5.50 (s, 1H), 3.10 (dd, *J* = 7.3, 1.4 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 136.8, 134.1, 128.6, 127.7, 126.3, 123.0, 51.3, 41.9, 28.8.

IR υ (cm^{-1}) 3307, 2965, 1637, 1540, 1456, 1360, 1221, 963, 695.

HRMS (ESI) calcd for $C_{14}H_{20}NO^+$ $[M+H]^+$: 218.1539; found: 218.1544.

32b  88% (41 mg)

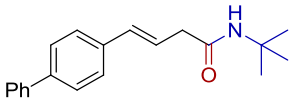
(*E*)-*N*-(*tert*-butyl)-4-(p-tolyl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.25 (dt, *J* = 15.8 Hz, 7.4 Hz, 1H), 5.43 (s, 1H), 3.08 (dd, *J* = 7.4, 1.4 Hz, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 137.9, 134.6, 134.3, 129.7, 126.2, 122.2, 51.7, 42.3, 29.2, 21.6.

IR υ (cm^{-1}) 3316, 2970, 1634, 1540, 1218, 960, 803, 679.

HRMS (ESI) calcd for $C_{15}H_{22}NO^+$ $[M+H]^+$: 232.1696; found: 232.1701.

32c 

(*E*)-4-([1,1'-Biphenyl]-4-yl)-*N*-(*tert*-butyl)but-3-enamide

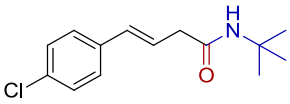
41% (24 mg)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61-7.55 (m, 4H), 7.46-7.42 (m, 4H), 7.36-7.34 (m, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.34 (dt, *J* = 15.8, 7.4 Hz, 1H), 5.42 (s, 1H), 3.10 (dd, *J* = 7.4, 1.4 Hz, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 140.6, 140.5, 135.8, 133.7, 128.8, 127.4, 127.3, 126.9, 126.7, 123.1, 51.4, 42.0, 28.8.

IR υ (cm^{-1}) 3283, 2965, 1634, 1553, 1354, 1227, 977, 746.

HRMS (ESI) calcd for $C_{20}H_{24}NO^+$ $[M+H]^+$: 294.1852; found: 294.1849.

32d  65% (33 mg)

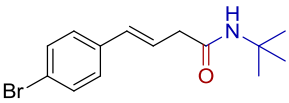
(*E*)-*N*-(*tert*-butyl)-4-(4-chlorophenyl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.18 (m, 4H), 6.37 (d, *J* = 15.9 Hz, 1H), 6.22 (dt, *J* = 15.9, 7.2 Hz, 1H), 5.33 (s, 1H), 2.99 (dd, *J* = 7.2, 1.7 Hz, 2H), 1.27 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 135.3, 133.2, 132.7, 128.7, 127.5, 123.8, 51.4, 41.8, 28.8.

IR υ (cm^{-1}) 3308, 2972, 1631, 1544, 1362, 1221, 1083, 964, 823, 796, 685.

HRMS (ESI) calcd for $C_{14}H_{19}ClNO^+$ $[M+H]^+$: 252.1150, 254.1120; found: 252.1148, 254.1118.

32e  66% (39 mg)

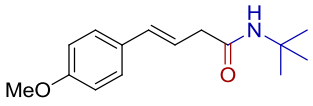
(*E*)-4-(4-Bromophenyl)-*N*-(*tert*-butyl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 6.42 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.8, 7.1 Hz, 1H), 5.40 (s, 1H), 3.05 (dd, *J* = 7.1, 1.3 Hz, 2H), 1.34 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 135.7, 132.8, 131.7, 127.8, 123.9, 121.4, 51.4, 41.8, 28.8.

IR υ (cm^{-1}) 3311, 2970, 1640, 1540, 1366, 1218, 1068, 969, 818, 791, 679.

HRMS (ESI) calcd for $C_{14}H_{19}BrNO^+$ $[M+H]^+$: 296.0645, 298.0624; found: 296.0642, 298.0621.

32f 

(*E*)-*N*-(*tert*-butyl)-4-(4-methoxyphenyl)but-3-enamide

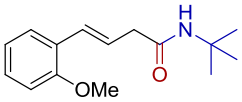
76% (38 mg)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.43 (d, *J* = 15.8 Hz, 1H), 7.27 (dt, *J* = 15.8, 7.3 Hz, 1H), 5.45 (s, 1H), 3.80 (s, 3H), 3.09 (dd, *J* = 7.3, 1.4 Hz, 2H), 1.35 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 159.2, 133.7, 129.5, 127.5, 120.6, 113.9, 55.3, 51.3, 41.9, 28.8.

IR υ (cm^{-1}) 3319, 2958, 1637, 1505, 1242, 1167, 960, 827, 722.

HRMS (ESI) calcd for $C_{15}H_{22}NO_2^+$ $[M+H]^+$: 248.1645; found: 248.1642.

32g  68% (34 mg)

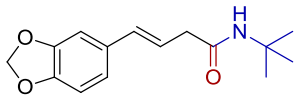
(*E*)-*N*-(*tert*-butyl)-4-(2-methoxyphenyl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, *J* = 6.2 Hz, 1H), 7.28-7.23 (m, 1H), 6.97– 6.93 (m, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.8, 7.3 Hz, 1H), 5.50 (s, 1H), 3.87 (s, 3H), 3.11 (dd, *J* = 7.3, 1.4 Hz, 2H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 156.5, 129.2, 128.7, 126.8, 125.8, 123.8, 120.7, 110.8, 55.4, 51.2, 42.5, 28.8.

IR υ (cm^{-1}) 3289, 2961, 1634, 1553, 1240, 969, 746.

HRMS (ESI) calcd for $C_{15}H_{22}NO_2^+$ $[M+H]^+$: 248.1645; found: 248.1651.

32h  62% (32 mg)

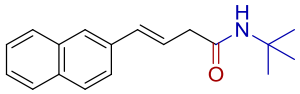
(*E*)-4-(Benzo[*d*][1,3]dioxol-5-yl)-*N*-(*tert*-butyl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (s, 1H), 6.80-6.73 (m, 2H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.11 (dt, *J* = 15.9, 7.3 Hz, 1H), 5.94 (s, 2H), 5.46 (s, 1H), 3.02 (dd, *J* = 7.4, 1.4 Hz, 2H), 1.33 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 148.0, 147.3, 133.8, 131.2, 126.8, 120.9, 108.3, 105.6, 101.1, 51.3, 41.8, 28.8.

IR υ (cm^{-1}) 3314, 2970, 1637, 1541, 1505, 1489, 1435, 1240, 1032, 963, 800, 673.

HRMS (ESI) calcd for $C_{15}H_{20}NO_3^+$ $[M+H]^+$: 262.1438; found: 262.1434.

32i  85% (45 mg)

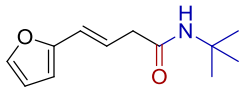
(*E*)-*N*-(*tert*-butyl)-4-(naphthalen-2-yl)but-3-enamide

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.80-7.77 (m, 3H), 7.71 (s, 1H), 7.61-7.58 (m, 1H), 7.48-7.41 (m, 2H), 6.65 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.9, 7.3 Hz, 1H), 5.50 (s, 1H), 3.13 (dd, *J* = 7.3, 1.4 Hz, 2H), 1.36 (s, 9H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 169.9, 134.3, 134.2, 133.6, 133.0, 128.3, 127.9, 127.7, 126.3, 126.2, 125.9, 123.5, 123.5, 51.4, 42.0, 28.8.

IR υ (cm^{-1}) 3316, 2972, 1641, 1544, 1356, 1218, 967, 799, 730, 685.

HRMS (ESI) calcd for $C_{18}H_{22}NO^+$ $[M+H]^+$: 268.1696; found: 268.1694.

32j  63% (26 mg)

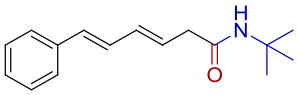
(*E*)-*N*-(*tert*-butyl)-4-(furan-2-yl)but-3-enamide

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.34 (d, *J* = 1.6 Hz, 1H), 6.36 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.32 (dt, *J* = 15.8 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 6.17 (dd, *J* = 15.8, 7.4 Hz, 1H), 5.40 (s, 1H), 3.03 (dd, *J* = 7.3, 1.2 Hz, 2H), 1.34 (s, 9H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 169.8, 152.2, 141.9, 122.6, 121.5, 111.3, 107.8, 51.4, 41.7, 28.8.

IR υ (cm^{-1}) 3322, 2967, 1648, 1540, 1363, 1218, 1011, 730.

HRMS (ESI) calcd for $C_{12}H_{18}NO_2^+$ $[M+H]^+$: 208.1332; found: 208.1330.

32k  53% yield (26 mg)

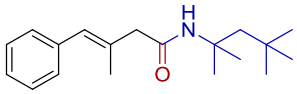
(3*E*,5*E*)-*N*-*tert*-butyl)-6-phenylhexa-3,5-dienamide

^{1}H NMR (CDCl$_3$, 400 MHz) δ 7.40 – 7.37 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 1H), 6.79 (dd, *J* = 15.6, 10.5 Hz, 1H), 6.53 (d, *J* = 15.7 Hz, 1H), 6.31 (dd, *J* = 15.4, 10.7 Hz, 1H), 5.87 (dt, *J* = 15.1, 7.4 Hz, 1H), 5.37 (s, 1H), 3.01 (dd, *J* = 7.4, 1.3 Hz, 2H), 1.35 (s, 9H).

^{13}C NMR (CDCl$_3$, 100 MHz) δ 169.9, 137.1, 134.8, 132.3, 128.6, 128.3, 127.6, 126.9, 126.4, 51.3, 41.8, 28.8.

IR υ (cm^{-1}) 3311, 2969, 1631, 1541, 1446, 1356 1248, 1221, 982, 749, 692.

HRMS (ESI) calcd for $C_{16}H_{22}NO^+$ $[M+H]^+$: 244.1696; found: 244.1694.

32l  75% (41 mg)

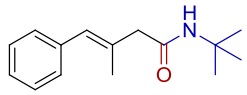
(*E*)-4-Phenyl-*N*-(2,4,4-trimethylpentan-2-yl)but-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.22 (m, 5H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.26 (dt, *J* = 15.8, 7.5 Hz, 1H), 5.50 (s, 1H), 3.06 (dd, *J* = 7.5, 1.3 Hz, 2H), 1.71 (s, 2H), 1.39 (s, 6H), 0.98 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 136.7, 134.5, 128.6, 127.7, 126.3, 122.9, 55.3, 51.7, 42.2, 31.7, 31.5, 29.2.

IR υ (cm^{-1}) 3298, 2949, 1628, 1549, 1354, 1218, 957, 689.

HRMS (ESI) calcd for $C_{18}H_{28}NO^+$ $[M+H]^+$: 274.2165; found: 274.2162.

32n-(*E*)  69% (32 mg)

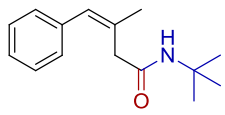
(*E*)-*N*-(*tert*-butyl)-3-methyl-4-phenylbut-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.27 (m, 5H), 6.43 (s, 1H), 5.58 (s, 1H), 3.04 (s, 2H), 1.94 (s, 3H), 1.37 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 137.5, 133.9, 129.5, 128.8, 128.3, 126.6, 51.1, 49.9, 28.7, 17.8.

IR υ (cm^{-1}) 3322, 2973, 1648, 1267, 727, 698.

HRMS (ESI) calcd for $C_{15}H_{22}NO_2^+$ $[M+H]^+$: 232.1696; found: 232.1701.

32n-(*Z*)  22% (10 mg)

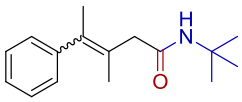
(*Z*)-*N*-(*tert*-butyl)-3-methyl-4-phenylbut-3-enamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.29 (m, 2H), 7.25 – 7.19 (m, 3H), 6.52 (s, 1H), 5.44 (*br* s, 1H), 3.06 (s, 2H), 1.96 (d, *J* = 1.2 Hz, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 137.6, 133.5, 129.6, 128.7, 128.7, 127.1, 51.5, 42.3, 29.0, 25.2.

IR υ (cm^{-1}) 3320, 2967, 2920, 1647, 1546, 1455, 1442, 1393, 1363, 1256, 1226, 1067, 1027, 702, 665.

HRMS (ESI) calcd for $C_{15}H_{21}NNaO^+$ $[M+Na]^+$ 254.1515; found 254.1523.

32o  50% (25 mg)

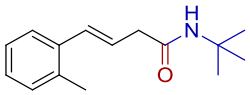
(*E*)-*N*-(*tert*-butyl)-3-methyl-4-phenylpent-3-enamide

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.70 (s, 1H), 3.07 (s, 2H), 2.00 (s, 3H), 1.62 (s, 3H), 1.37 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 143.9, 135.4, 128.3, 127.9, 126.7, 126.5, 50.9, 43.6, 28.8, 21.1, 20.9.

IR υ (cm^{-1}) 3307, 2967, 1645, 1543, 767, 743, 703.

HRMS (ESI) calcd for $C_{16}H_{24}NO^+$ $[M+H]^+$: 246.1852; found: 246.1858.

32q  58% (27 mg)

(*E*)-*N*-(*tert*-butyl)-4-(*o*-tolyl)but-3-enamide

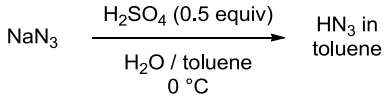
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.42 (m, 1H), 7.18-7.15 (m, 3H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.16 (dt, *J* = 15.8, 7.3 Hz, 1H), 5.44 (s, 1H), 3.10 (dd, *J* = 7.3, 1.4 Hz, 2H), 2.35 (s, 3H), 1.35 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 136.2, 135.6, 132.5, 130.6, 127.9, 126.5, 124.7; 51.6, 42.5, 29.1, 20.2.

IR υ (cm^{-1}) 3268, 2955, 1637, 1546, 1357, 1224, 960, 754.

HRMS (ESI) calcd for $C_{15}H_{22}NO^+$ $[M+H]^+$: 232.1696; found: 232.1693.

3.2.5 Preparation of Hydrazoic Acid in Toluene

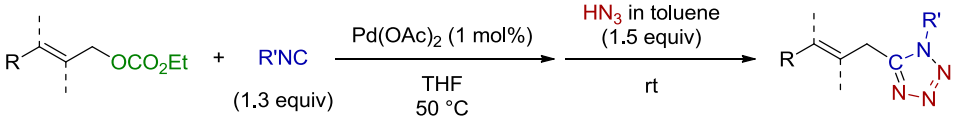


H_2O (5 mL) and toluene (20 mL) were added to NaN_3 (3.251 g, 50.0 mmol, 1.0 equiv) in a 50 mL three-necked flask containing a big stirring bar and fitted with 2 septums. To prevent overpressure and release of toxic HN_3, a cannula was connected from the reaction vessel to a bubbler filled with aqueous NaOH. The heterogeneous mixture was cooled to 0 °C and a solution of H_2SO_4 (1.33 mL, 25.0 mmol, 0.5 equiv) in H_2O (3 mL) was added very slowly from the addition funnel. The reaction mixture was then stirred at 0 °C for further 15 min. The organic layer was then withdrawn with a syringe and transfered into a flask containing 2 g of Na_2SO_4 in an ice bath and closed with a septum. After stirring for 5 min, the organic layer was withdrawn with a syringe and filtered with a big syringe filter directly into an empty bottle

closed with a septum. The resulting solution was finally titrated with aqueous NaOH 0.1 M using phenolphthalein as color indicator. The colorless solution of HN_3 in toluene (18 mL, 1.76 M) was kept in the fridge and used over weeks without noticeable degradation.[147]

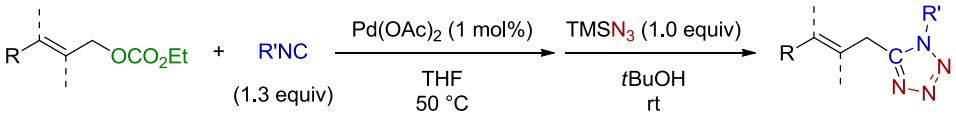
3.2.6 Synthesis of 1,5-Disubstituted Tetrazoles

Procedure [a] :



To a solution of the allyl carbonate (0.4 mmol, 1.0 equiv) in THF (2 mL) was added $Pd(OAc)_2$ (0.9 mg, 0.004 mmol, 1 mol%). The reaction mixture was purged with argon and *t*BuNC (59 µL, 0.52 mmol, 1.3 equiv) was added. The reaction mixture was then stirred at 50 °C until complete consumption of the starting material (~5 h). The reaction mixture was then allowed to cool to rt and a solution of HN_3 in toluene (1.76 M, 2.0 equiv) was added dropwise. The reaction mixture was stirred until complete consumption of the intermediate ketenimine and finally quenched with sat. aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired 1,5-disubstituted tetrazole.

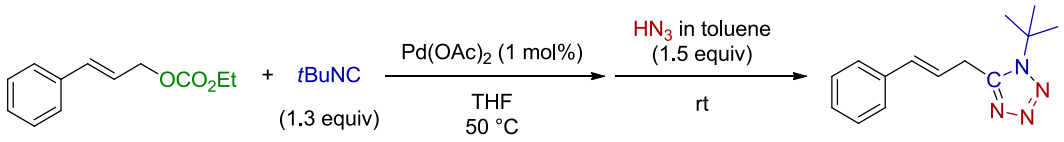
Procedure [b] :



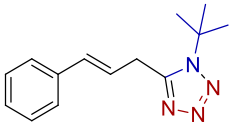
To a solution of the allyl carbonate (0.2 mmol, 1.0 equiv) in THF (1 mL) was added $Pd(OAc)_2$ (0.45 mg, 0.002 mmol, 1 mol%). The reaction mixture was purged with argon and *t*BuNC (29 µL, 0.26 mmol, 1.3 equiv) was added. The reaction mixture was then stirred at 50 °C until complete consumption of the starting material (~5 h). The reaction mixture was then allowed to cool to rt and the solvent was evaporated under reduced pressure. The residue was diluted with *t*BuOH (1 mL) and $TMSN_3$ (0.2 mmol) was added. The reaction mixture was stirred until complete consumption of the intermediate ketenimine. The volatiles were removed and the residue was purified by column chromatography with PE/EtOAc 15:1 as eluent to afford the desired 1,5-disubstituted tetrazole.

[147] See reference 32.

Gram-scale preparation of 37a according to procedure [a] :



To a solution of cinnamyl ethyl carbonate (1.031 g, 5.0 mmol, 1.0 equiv) in THF (25 mL) was added $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 1 mol%). The reaction mixture was purged with argon and *t*BuNC (0.74 mL, 6.5 mmol, 1.3 equiv) was added. The reaction mixture was then stirred at 50 °C until complete consumption of the starting material (~5 h). The reaction mixture was then allowed to cool to rt and a solution of HN_3 in toluene (1.76 M, 2.0 equiv) was added dropwise. The reaction mixture was stirred until complete consumption of the intermediate ketenimine and finally quenched with sat. aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 2:1 as eluent to afford 1,5-disubstituted tetrazole as a yellowish solid (0.973 g, 4.01 mmol, 80% yield).

37a 

1-(*tert*-butyl)-5-cinnamyl-1*H*-tetrazole

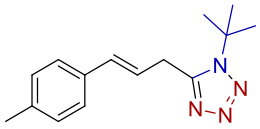
Conditions [b]: 58% yield (28.0 mg), yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 6.49 (d, *J* = 16.0 Hz, 1H), 6.41 (dt, *J* = 15.9, 5.8 Hz, 1H), 3.99 (dd, *J* = 5.6, 0.7 Hz, 2H), 1.77 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 136.6, 133.9, 128.9, 128.2, 126.7, 123.1, 61.3, 30.2, 29.6.

IR υ (cm^{-1}) 2986 (w), 1495 (m), 1463 (m), 1450 (m), 1397 (m), 1374 (m), 1319 (w), 1273 (m), 1244 (m), 1224 (m), 1204 (w), 1143 (m), 1115 (m), 1098 (m), 1082 (w), 1030 (w), 980 (s), 909 (m), 821 (m), 761 (s), 740 (s), 726 (s), 694 (s).

HRMS (ESI) calcd for $C_{14}H_{18}N_4Na^+$ $[M+Na]^+$ 265.1424; found 265.1429.

37b 

(*E*)-1-(*tert*-butyl)-5-(3-(p-tolyl)allyl)-1*H*-tetrazole

Conditions [a]: 69% yield (70.6 mg), yellowish solid

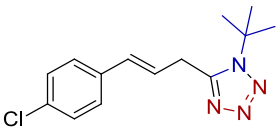
Conditions [b]: 66% yield (34.0 mg), yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.32 (dt, *J* = 15.9, 6.1 Hz, 1H), 3.96 (dd, *J* = 6.1, 1.2 Hz, 2H), 2.32 (s, 3H), 1.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 138.1, 133.8, 133.7, 129.6, 126.5, 122.0, 61.3, 30.2, 29.5, 21.5.

IR υ (cm^{-1}) 2986 (m), 2914 (w), 1514 (w), 1497 (m), 1464 (w), 1398 (m), 1372 (m), 1269 (w), 1240 (m), 1222 **(m), 1147 (m), 1117 (m), 1097 (m), 1032 (w), 972 (s), 939 (w), 836 (w), 799 (s), 771 (m), 732 (w).**

HRMS (ESI) calcd for $C_{15}H_{20}N_4Na^+$ $[M+Na]^+$ 279.1580; found 279.1586.

37c 

(*E*)-1-(*tert*-butyl)-5-(3-(4-chlorophenyl)allyl)-1*H*-tetrazole

Conditions [a]: 71% yield (78.6 mg), orange solid

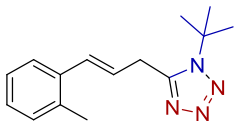
Conditions [b]: 57% yield (31.0 mg), orange solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 4H), 6.36 (d, *J* = 16.4 Hz, 1H), 6.31 (m, 1H), 3.89 (d, *J* = 4.7 Hz, 2H), 1.67 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 135.1, 133.8, 132.7, 129.1, 127.9, 123.7, 61.3, 30.1, 29.5.

IR υ (cm^{-1}) 2984 (m), 2920 (m), 2852 (m), 1721 (br), 1679 (br), 1595 (w), 1489 (s), 1463 (m), 1398 (m), 1372 (m), 1281 (m), 1224 (m), 1145 (m), 1115 (m), 1091 (s), 1028 (m), 1014 (m), 969 (s), 830 (s), 807 (s), 703 (w), 667 (w).

HRMS (ESI) calcd for $C_{14}H_{17}ClN_4Na^+$ $[M+Na]^+$ 299.1034, 301.1004; found 299.1043, 301.1017.

37d 

(*E*)-1-(*tert*-butyl)-5-(3-(o-tolyl)allyl)-1*H*-tetrazole

Conditions [a]: 74% yield (76.1 mg), yellowish solid

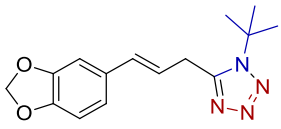
Conditions [b]: 49% yield (25.0 mg), yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.36 (m, 1H), 7.17 – 7.08 (m, 3H), 6.69 (d, *J* = 15.8 Hz, 1H), 6.25 (dt, *J* = 15.8, 6.4 Hz, 1H), 3.99 (dd, *J* = 6.4, 1.6 Hz, 2H), 2.29 (s, 3H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 135.8, 135.5, 131.8, 130.5, 128.0, 126.4, 126.1, 124.5, 61.2, 30.1, 29.8, 20.0.

IR υ (cm^{-1}) 2988 (w), 2936 (br), 1505 (w), 1483 (w), 1461 (m), 1415 (m), 1402 (m), 1376 (m), 1292 (w), 1231 (m), 1146 (m), 1121 (m), 1107 (m), 1075 (w), 1031 (w), 969 (s), 938 (w), 755 (s), 739 (s).

HRMS (ESI) calcd for $C_{15}H_{20}N_4Na^+$ $[M+Na]^+$ 279.1580 found 279.1584.

37e 

(*E*)-5-(3-(Benzo[*d*][1,3]dioxol-5-yl)allyl)-1-(*tert*-butyl)-1*H*-tetrazole

Conditions [a]: 78% yield (88.8 mg), orange solid

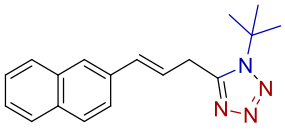
Conditions [b]: 53% yield (30.3 mg), orange solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.5 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.36 (d, *J* = 15.9 Hz, 1H), 6.20 (dt, *J* = 15.9, 6.3 Hz, 1H), 5.94 (s, 2H), 3.93 (dd, *J* = 6.3, 1.5 Hz, 2H), 1.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 148.4, 147.8, 133.5, 131.1, 121.4, 121.2, 108.6, 106.0, 101.5, 61.3, 30.2, 29.4.

IR υ (cm^{-1}) 2981 (w), 2899 (br), 1492 (s), 1447 (m), 1398 (m), 1370 (w), 1245 (s), 1194 (m), 1142 (m), 1116 (m), 1079 (w), 1038 (s), 974 (s), 937 (s), 864 (m), 823 (m), 803 (s), 786 (s), 620 (w), 610 (m).

HRMS (ESI) calcd for $C_{15}H_{18}N_4O_2Na^+$ $[M+Na]^+$ 309.1322; found 309.1333.

37f 

(*E*)-1-(*tert*-butyl)-5-(3-(naphthalen-2-yl)allyl)-1*H*-tetrazole

Conditions [a]: 66% yield (64.2 mg), brown solid

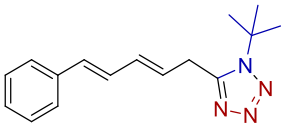
Conditions [b]: 72% yield (42.0 mg), brown solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 3H), 7.69 (s, 1H), 7.57 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.48 – 7.39 (m, 2H), 6.62 (d, *J* = 16.0 Hz, 1H), 6.52 (dt, *J* = 15.9, 6.1 Hz, 1H), 4.01 (dd, *J* = 6.0, 1.2 Hz, 2H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 134.0, 133.9, 133.8, 133.3, 128.6, 128.3, 127.9, 126.7, 126.7, 126.3, 123.6, 123.4, 61.3, 30.1, 29.6.

IR υ (cm^{-1}) 3056 (w), 2979 (w), 1598 (w), 1495 (w), 1398 (w), 1374 (m), 1279 (w), 1239 (m), 1143 (m), 1115 (m), 976 (s), 897 (w), 863 (m), 813 (s), 747 (s).

HRMS (ESI) calcd for $C_{18}H_{21}N_4^+$ $[M+H]^+$ 293.1761; found 293.1758.

37g 

1-(*tert*-butyl)-5-((2*E*,4*E*)-5-phenylpenta-2,4-dien-1-yl)-1*H*-tetrazole

Conditions [a]: 40% yield (92.9 mg), orange solid

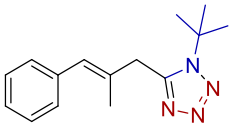
Conditions [b]: 43% yield (23.0 mg), orange solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2H), 7.32 – 7.25 (m, 2H), 7.25 – 7.18 (m, 1H), 6.77 (dd, *J* = 15.6, 10.4 Hz, 1H), 6.50 (d, *J* = 15.7 Hz, 1H), 6.25 (dd, *J* = 15.1, 10.6 Hz, 1H), 5.99 (dt, *J* = 15.2, 6.4 Hz, 1H), 3.90 (dd, *J* = 6.6, 1.0 Hz, 2H), 1.73 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 137.2, 134.3, 133.2, 128.9, 128.0, 128.0, 126.7, 126.6, 61.2, 30.1, 29.3.

IR υ (cm^{-1}) 2977 (w), 1491 (m), 1450 (m), 1395 (m), 1373 (m), 1280 (m), 1244 (m), 1141 (m), 1112 (m), 1094 (m), 1072 (w), 999 (s), 824 (m), 762 (s), 731 (m), 698 (w).

HRMS (ESI) calcd for $C_{16}H_{20}N_4Na^+$ $[M+Na]^+$ 291.1580; found 291.1586.

37h-(*E*) 

(*E*)-1-(*tert*-butyl)-5-(2-methyl-3-phenylallyl)-1*H*-tetrazole

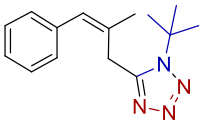
Conditions [a]: 70% yield (71.6 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.26 – 7.15 (m, 3H), 6.12 (s, 1H), 3.93 (d, *J* = 0.6 Hz, 2H), 1.91 (s, 3H), 1.76 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 137.4, 133.1, 129.1, 129.0, 128.5, 127.1, 61.5, 36.0, 30.1, 18.6.

IR υ (cm^{-1}) 2980 (m), 2940 (br), 1492 (m), 1465 (m), 1414 (m), 1373 (m), 1234 (s), 1144 (m), 1121 (m), 1101 (m), 1029 (w), 1003 (w), 935 (m), 842 (m), 751 (s), 706 (w).

HRMS (ESI) calcd for $C_{15}H_{20}N_4Na^+$ $[M+Na]^+$ 279.1580; found 279.1586.

37h-(*Z*) 

(*Z*)-1-(*tert*-butyl)-5-(2-methyl-3-phenylallyl)-1*H*-tetrazole

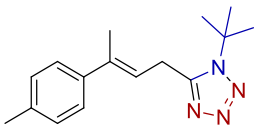
Conditions [a]: 20% yield (21.0 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.25 – 7.19 (m, 1H), 7.20 – 7.13 (m, 2H), 6.62 (s, 1H), 3.87 (d, *J* = 0.9 Hz, 2H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.59 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 137.6, 132.3, 129.6, 128.8, 128.7, 127.2, 61.1, 29.8, 29.8, 24.0.

IR υ (cm^{-1}) 2982 (w), 2934 (w), 1599 (w), 1491 (m), 1462 (m), 1441 (m), 1398 (m), 1376 (m), 1286 (w), 1239 (s), 1142 (m), 1112 (m), 1094 (m), 1026 (m), 924 (w), 850 (w), 824 (w), 744 (s), 703 (s).

HRMS (ESI) calcd for $C_{15}H_{20}N_4Na^+$ $[M+Na]^+$ 279.1580; found 279.1583.

37i 

(*E*)-1-(*tert*-butyl)-5-(3-(*p*-tolyl)but-2-en-1-yl)-1*H*-tetrazole

Conditions [a]: 38% yield (41.1 mg), colorless solid

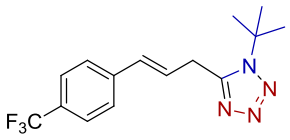
Conditions [b]: 46% yield (25.0 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.15 – 7.09 (m, 2H), 5.90 (tq, *J* = 6.5, 1.4 Hz, 1H), 3.94 (dd, *J* = 6.5, 0.9 Hz, 2H), 2.33 (s, 3H), 2.14 (d, *J* = 1.2 Hz, 3H), 1.75 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 139.9, 138.5, 137.5, 129.3, 126.0, 112.0, 61.1, 30.1, 26.0, 21.4, 16.8.

IR υ (cm^{-1}) 2986 (m), 2922 (m), 2856 (m), 1500 (m), 1460 (m), 1420 (m), 1374 (m), 1235 (s), 1174 (w), 1142 (m), 1116 (s), 1098 (m), 1016 (w), 924 (m), 814 (m), 800 (s), 728 (w), 693 (w), 624 (w).

HRMS (ESI) calcd for $C_{16}H_{22}N_4Na^+$ $[M+Na]^+$ 293.1737; found 293.1742.

37j 

(*E*)-1-(*tert*-butyl)-5-(3-(4-(trifluoromethyl)phenyl)allyl)-1*H*-tetrazole

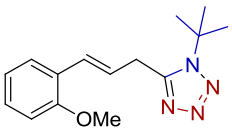
Conditions [a]: 60% yield (74.8 mg), yellowish solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 6.58 – 6.46 (m, 2H), 3.99 (d, *J* = 4.6 Hz, 2H), 1.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 140.0, 132.6, 130.0 (q, *J* = 32.6 Hz), 126.8, 125.9 (q, *J* = 3.9 Hz), 125.8, 124.4 (q, *J* = 271.6 Hz), 61.3, 30.1, 29.6.

IR υ (cm^{-1}) 2989 (w), 1616 (w), 1414 (w), 1397 (w), 1376 (w), 1326 (s), 1237 (w), 1164 (m), 1113 (s), 1067 (s), 1017 (w), 971 (w), 846 (br).

HRMS (ESI) calcd for $C_{15}H_{17}F_3N_4Na^+$ $[M+Na]^+$ 333.1297; found 333.1294.

37k 

(*E*)-1-(*tert*-butyl)-5-(3-(2-methoxyphenyl)allyl)-1*H*-tetrazole

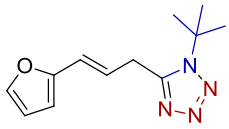
Conditions [a]: 68% yield (73.5 mg), yellow solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.25 – 7.18 (m, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 16.1 Hz, 1H), 6.38 (dt, *J* = 16.0, 6.4 Hz, 1H), 3.98 (dd, *J* = 6.4, 1.6 Hz, 2H), 3.81 (s, 3H), 1.74 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.1, 129.2, 128.9, 127.3, 125.7, 123.8, 121.0, 111.1, 61.3, 55.7, 30.1, 30.1.

IR υ (cm^{-1}) 2984 (br), 2939 (w), 2837 (w), 1598 (w), 1578 (w), 1489 (m), 1463 (m), 1398 (m), 1375 (m), 1293 (w), 1244 (s), 1143 (m), 1111 (m), 1052 (w), 1028 (m), 974 (m), 754 (s).

HRMS (ESI) calcd for $C_{15}H_{20}N_4NaO^+$ $[M+Na]^+$ 295.1529; found 295.1537.

37l 

(*E*)-1-(*tert*-butyl)-5-(3-(furan-2-yl)allyl)-1*H*-tetrazole

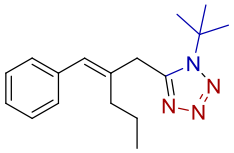
Conditions [a]: 61% yield (57.0 mg), brown oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.20 (m, 1H), 6.27 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.23 (dt, *J* = 16.1, 5.7 Hz, 1H), 6.19 (d, *J* = 16.3 Hz, 1H), 6.13 (d, *J* = 3.2 Hz, 1H), 3.87 (d, *J* = 5.8 Hz, 2H), 1.66 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 152.0, 142.4, 122.2, 121.5, 111.5, 108.5, 61.3, 30.1, 29.0.

IR υ (cm^{-1}) 2992 (m), 2926 (m), 2853 (w), 1721 (m), 1496 (m), 1464 (m), 1400 (m), 1376 (s), 1236 (s), 1114 (s), 1013 (m), 976 (m), 818 (w), 738 (s).

HRMS (ESI) calcd for $C_{12}H_{16}N_4NaO^+$ $[M+Na]^+$ 255.1216; found 255.1225.



37m-(*E*)

(*E*)-5-(2-Benzylidenepentyl)-1-(*tert*-butyl)-1*H*-tetrazole

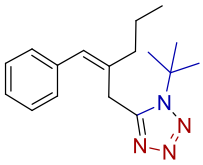
Conditions [a]: 43% yield (47.0 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.25 – 7.18 (m, 1H), 7.18 – 7.11 (m, 2H), 5.97 (s, 1H), 3.94 (d, *J* = 1.4 Hz, 2H), 2.30 – 2.21 (m, 2H), 1.76 (s, 9H), 1.59 – 1.50 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 137.8, 137.3, 129.0, 128.8, 128.5, 127.0, 61.6, 33.7, 33.2, 30.1, 21.6, 14.3.

IR υ (cm^{-1}) 2960 (s), 2933 (m), 2872 (m), 1494 (m), 1464 (m), 1398 (m), 1375 (m), 1237 (s), 1143 (m), 1112 (m), 1095 (m), 748 (m), 701 (s).

HRMS (ESI) calcd for $C_{17}H_{24}N_4Na^+$ $[M+Na]^+$ 307.1893; found 307.1901.



37m-(*Z*)

(*Z*)-5-(2-Benzylidenepentyl)-1-(*tert*-butyl)-1*H*-tetrazole

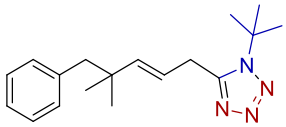
Conditions [a]: 31% yield (34.8 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.21 (m, 3H), 7.20 – 7.13 (m, 2H), 6.62 (s, 1H), 3.88 (s, 2H), 2.15 (td, *J* = 7.5, 1.0 Hz, 2H), 1.58 (s, 9H), 1.57 – 1.51 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 137.7, 136.3, 128.9, 128.9, 128.7, 127.2, 61.1, 39.0, 29.8, 28.2, 21.3, 14.1.

IR υ (cm^{-1}) 2960 (s), 2929 (s), 2872 (m), 2361 (m), 1492 (m), 1463 (m), 1397 (m), 1376 (m), 1287 (w), 1238 (m), 1142 (m), 1111 (m), 1093 (m), 1030 (w), 747 (m), 703 (s).

HRMS (ESI) calcd for $C_{17}H_{24}N_4Na^+$ $[M+Na]^+$ 307.1893; found 307.1902.

37o 

(*E*)-1-(*tert*-butyl)-5-(4,4-dimethyl-5-phenylpent-2-en-1-yl)-1*H*-tetrazole

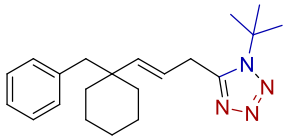
Conditions [a]: 73% yield (86.9 mg), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 3H), 7.10 – 7.00 (m, 2H), 5.59 (dt, *J* = 15.8, 1.3 Hz, 1H), 5.44 (dt, *J* = 15.8, 6.1 Hz, 1H), 3.75 (dd, *J* = 6.1, 1.3 Hz, 2H), 2.56 (s, 2H), 1.69 (s, 9H), 0.99 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 144.4, 138.7, 130.9, 128.0, 126.3, 112.0, 61.1, 49.4, 37.6, 30.2, 29.2, 27.1.

IR υ (cm^{-1}) 2964 (m), 1494 (m), 1465 (m), 1397 (m), 1376 (m), 1236 (m), 1144 (m), 1111 (m), 1031 (w), 975 (m), 736 (m), 703 (s).

HRMS (ESI) calcd for $C_{18}H_{26}N_4Na^+$ $[M+Na]^+$ 321.2050; found 321.2059.

37p 

(*E*)-5-(3-(1-Benzylcyclohexyl)allyl)-1-(*tert*-butyl)-1*H*-tetrazole

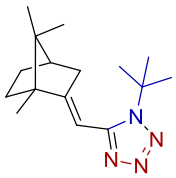
Conditions [a]: 76% yield (102.4 mg), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 – 7.09 (m, 3H), 7.03 – 6.96 (m, 2H), 5.39 – 5.31 (m, 2H), 3.80 – 3.72 (m, 2H), 2.55 (s, 2H), 1.68 (s, 9H), 1.56 – 1.48 (m, 4H), 1.39 – 1.31 (m, 4H), 1.31 – 1.16 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 142.2, 138.1, 131.1, 127.7, 126.1, 122.3, 61.0, 48.9, 40.7, 35.9, 30.1, 29.4, 26.6, 22.6.

IR υ (cm^{-1}) 2929 (m), 2853 (w), 1495 (w), 1453 (w), 1398 (w), 1376 (w), 1236 (w), 1144 (w), 977 (w), 909 (m), 730 (s), 703 (s).

HRMS (ESI) calcd for $C_{21}H_{32}NO^+$ $[M+H]^+$ 314.2478; found 314.2470.



37q-exo

1-(*tert*-butyl)-5-((*E*)-((1*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ylidene)methyl)-1*H*-tetrazole

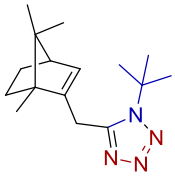
Conditions [a]: 65% yield (70.7 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (t, *J* = 2.3 Hz, 1H), 2.81 (ddt, *J* = 18.8, 4.8, 2.7 Hz, 1H), 2.46 (dd, *J* = 18.8, 2.2 Hz, 1H), 1.92 (t, *J* = 4.2 Hz, 1H), 1.89 – 1.79 (m, 1H), 1.73 (s, 9H), 1.38 – 1.19 (m, 3H), 1.08 (s, 3H), 0.96 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 152.0, 100.1, 60.4, 53.9, 48.7, 44.8, 38.8, 34.6, 30.0, 27.8, 19.9, 19.3, 13.1.

IR υ (cm^{-1}) 2953 (s), 2872 (m), 1657 (m), 1490 (m), 1462 (m), 1390 (s), 1375 (s), 1337 (m), 1303 (w), 1284 (w), 1231 (m), 1143 (m), 1115 (s), 827 (m).

HRMS (ESI) calcd for $C_{16}H_{26}N_4Na^+$ $[M+Na]^+$ 297.2050; found 297.2055.



37q-endo

1-(*tert*-butyl)-5-(((1*S*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl)methyl)-1*H*-tetrazole

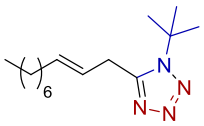
Conditions [a]: 23% yield (25.4 mg), colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (d, *J* = 2.5 Hz, 1H), 3.74 (dd, *J* = 17.7, 1.6 Hz, 1H), 3.64 (dd, *J* = 17.8, 1.4 Hz, 1H), 2.23 (t, *J* = 3.4 Hz, 1H), 1.82 (ddt, *J* = 12.2, 7.7, 3.4 Hz, 1H), 1.70 (s, 9H), 1.60 – 1.52 (m, 1H), 1.04 (s, 3H), 0.98 – 0.91 (m, 1H), 0.91 – 0.85 (m, 1H), 0.80 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 143.7, 131.0, 61.4, 57.0, 54.9, 51.8, 31.4, 30.2, 26.0, 25.2, 20.0, 19.8, 11.7.

IR υ (cm^{-1}) 2984 (m), 2952 (s), 2872 (m), 1502 (w), 1461 (m), 1398 (m), 1375 (s), 1237 (s), 1142 (m), 1108 (m), 877 (w), 824 (w), 796 (w).

HRMS (ESI) calcd for $C_{16}H_{26}N_4Na^+$ $[M+Na]^+$ 297.2065; found 297.2055.



37r-(*E*)

(*E*)-1-(*tert*-butyl)-5-(dec-2-en-1-yl)-1*H*-tetrazole

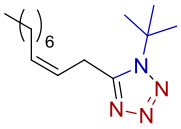
Conditions [a]: 28% yield (29.1 mg), colorless oil

^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.62 (dt, *J* = 15.1, 5.4 Hz, 1H), 5.53 (dt, *J* = 15.2, 6.9 Hz, 1H), 3.74 (d, *J* = 6.1 Hz, 2H), 2.03 (q, *J* = 6.6 Hz, 2H), 1.72 (s, 9H), 1.38 – 1.18 (m, 10H), 0.86 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.4, 135.5, 123.2, 61.1, 32.7, 32.1, 30.2, 29.4, 29.4, 29.3, 23.0, 14.4.

IR υ (cm^{-1}) 2926 (s), 2854 (m), 1498 (w), 1464 (w), 1398 (w), 1376 (w), 1238 (w), 1144 (w), 1111 (w), 972 (w).

HRMS (ESI) calcd for $C_{15}H_{28}N_4Na^+$ $[M+Na]^+$ 287.2206; found 287.2209.



37r-(*Z*)

(*Z*)-1-(*tert*-butyl)-5-(dec-2-en-1-yl)-1*H*-tetrazole

Conditions [a]: 9% yield (9.2 mg), colorless oil

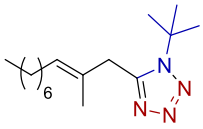
^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 – 5.51 (m, 2H), 3.77 (d, *J* = 5.5 Hz, 2H), 2.12 (q, *J* = 6.9 Hz, 2H), 1.73 (s, 9H), 1.48 – 1.35 (m, 2H), 1.35 – 1.18 (m, 8H), 0.88 (t, *J* = 6.1 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 134.1, 122.4, 61.0, 32.2, 30.1, 29.6, 29.5 28.0, 24.6, 23.0, 14.4.

IR υ (cm^{-1}) 2956 (m), 2926 (s), 2855 (m), 1732 (w), 1665 (w), 1497 (w), 1463 (m), 1396 (w), 1376 (m), 1286 (w), 1238 (m), 1144 (w), 1111 (w).

HRMS (ESI) calcd for $C_{15}H_{28}N_4Na^+$ $[M+Na]^+$ 287.2206; found 287.2211.

37s-(*E*)



(*E*)-1-(*tert*-butyl)-5-(2-methyldec-2-en-1-yl)-1*H*-tetrazole

Conditions [a]: 30% yield (32.9 mg), orange oil

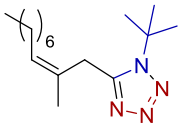
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (tq, *J* = 7.3, 1.2 Hz, 1H), 3.71 (s, 2H), 2.00 (q, *J* = 6.8 Hz, 2H), 1.69 (s, 9H), 1.65 (s, 3H), 1.32 – 1.18 (m, 10H), 0.85 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 129.6, 129.5, 61.3, 35.3, 32.1, 30.0, 29.7, 29.6, 29.5, 28.3, 23.0, 16.8, 14.4.

IR υ (cm^{-1}) 2956 (m), 2924 (s), 2857 (m), 1463 (m), 1398 (m), 1375 (m), 1288 (w), 1238 (s), 1144 (m), 1111 (m), 1094 (w), 1028 (w), 827 (w), 723 (w), 695 (w).

HRMS (ESI) calcd for $C_{16}H_{30}N_4Na^+$ $[M+Na]^+$ 301.2363; found 301.2367.

37s-(*Z*)



(*Z*)-1-(*tert*-butyl)-5-(2-methyldec-2-en-1-yl)-1*H*-tetrazole

Conditions [a]: 18% yield (19.5 mg), orange oil

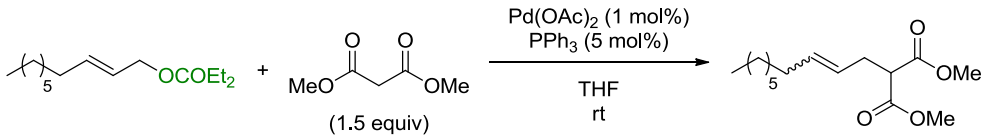
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (tq, *J* = 7.5, 1.0 Hz, 1H), 3.74 (s, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.72 (s, 9H), 1.66 – 1.63 (m, 3H), 1.40 – 1.33 (m, 2H), 1.32 – 1.20 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 129.7, 128.7, 61.0, 32.1, 29.9, 29.8, 29.7, 29.5, 28.6 (2 C), 23.6, 23.0, 14.4.

IR υ (cm^{-1}) 2956 (m), 2925 (s), 2854 (m), 1490 (w), 1462 (m), 1397 (m), 1376 (m), 1287 (w), 1238 (m), 1143 (w), 1111 (w), 1093 (w), 1027 (w), 913 (w), 855 (w), 725 (w), 692 (w).

HRMS (ESI) calcd for $C_{16}H_{30}N_4Na^+$ $[M+Na]^+$ 301.2363; found 301.2369.

3.2.7 Tsuji-Trost Reaction with a Non-Conjugated Allyl Carbonate



To a solution of the allyl carbonate **31j** (91.3 mg, 0.4 mmol, 1.0 equiv) and dimethyl malonate (69 µL, 0.6 mmol, 1.5 equiv) in THF (2 mL) was added $Pd(OAc)_2$ (0.9 mg, 0.004 mmol, 1 mol%) and PPh_3 (5.3 mg, 0.02 mmol, 5 mol%). The reaction mixture was purged with argon and was then stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure and the redisue was purified by column chromatography with PE/EtOAc 15:1 as eluent to afford the desired product **49** as a colorless oil (94.7 mg, 0.35 mmol, 88% yield).

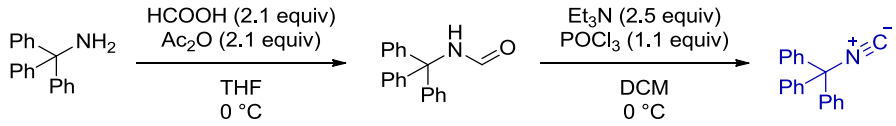
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (dt, *J* = 14.9, 6.7 Hz, 1H), 5.33 (dt, *J* = 15.0, 6.9 Hz, 1H), 3.71 (s, 6H), 3.40 (t, *J* = 7.6 Hz, 1H), 2.56 (t, *J* = 7.1 Hz, 2H), 1.94 (q, *J* = 6.5 Hz, 2H), 1.34 – 1.20 (m, 10H), 0.86 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 134.6, 125.3, 52.8, 52.4, 32.8, 32.3, 32.2, 29.7, 29.5, 29.4, 23.0, 14.5.

IR υ (cm^{-1}) 2955 (w), 2925 (w), 2854 (w), 1737 (s), 1436 (w), 1340 (w), 1270 (w), 1229 (m), 1196 (m), 1152 (m), 1028 (w), 970 (w).

HRMS (ESI) calcd for $C_{15}H_{26}NaO_4^+$ $[M+Na]^+$ 293.1723; found 293.1724.

3.2.8 Synthesis of Trityl Isocyanide



Formic acid (0.64 mL, 16.8 mmol, 2.1 eq.) and Ac_2O (1.59 mL, 16.8 mmol, 2.1 eq.) were stirred at 60 °C for 4 h before being cooled to 0 °C. This resulting mixture was then added to a solution of triphenylmethylamine (2.075 g, 8.0 mmol, 1.0 eq.) in THF (30 mL) at 0 °C. The reaction was allowed to warm to rt and stirred for 24 h. The reaction mixture was then partitioned between sat. aqueous Na_2CO_3 and EtOAc. The aqueous phase was extracted and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford trityl formamide as a yellowish crystalline solid. The crude product was used in the next step without further purification.[148]

[148] See reference 45.

Et_3N (2.45 mL, 17.5 mmol, 2.5 eq.) was added to a solution of trityl formamide (2.012 g mg, 7.0 mmol, 1.0 eq.) in DCM (30 mL). $POCl_3$ (0.70 mL, 7.7 mmol, 1.1 eq.) was then added dropwise and the reaction was stirred for 3 h. Sat. aqueous $NaHCO_3$ was then added and the aqueous layer was extracted with DCM (3x). The combined organic layers were washed with brin, dried over Na_2SO_4 and concentrated under reduced pressure to afford trityl isocyanide **52** as a yellowish solid (1.307 g, 4.85 mmol, 61% yield over 2 steps). The spectroscopic data were consistent with those previously reported in the literature.[149]

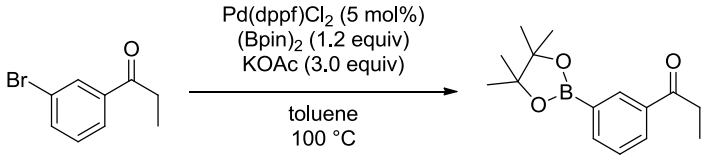
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 9H), 7.15 – 7.11 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 142.0, 128.7, 128.6, 128.5, 75.3.

[149] Bardsley, K.; Hagigeorgiou, M.; Lengyel, I.; Cesare, V. *Synthetic Communications* **2013**, *43* (12), 1727–1733.

3.3 α-Oxo-Ketenimines

3.3.1 Synthesis of Ketones



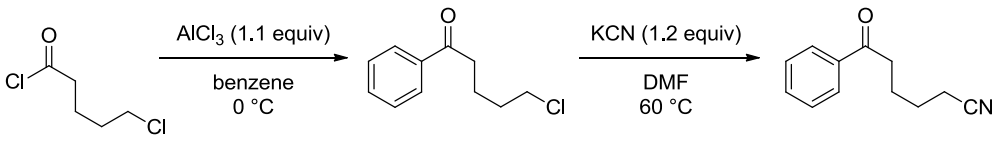
2-Bromo-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-one (102) : 3'-Bromopropiophenone **101** (2.131 g, 10.00 mmol, 1.0 equiv), bis(pinacolato)diboron (3.047 g, 12.00 mmol, 1.2 equiv), KOAc (2.940 g, 30.00 mmol, 3.0 equiv) and $Pd(dppf)Cl_2$ (127 mg, 0.50 mmol, 5 mol%) were dissolved in toluene (30 mL) and the reaction mixture was stirred under argon at 100 °C overnight. The reaction mixture was then filtered through Celite and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 15:1 as eluent to afford boronic acid pinacol ester **102** as a colorless crystalline solid (mp = 87-90 °C) (1.610 g, 6.18 mmol, 62% yield).[150]

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (*br* s, 1H), 8.06 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.98 (dt, *J* = 7.3, 1.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 3.05 (q, *J* = 7.2 Hz, 2H), 1.36 (s, 12H), 1.22 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.3, 139.3, 136.5, 134.5, 130.7, 128.2, 84.3, 32.1, 25.1, 8.4.

IR υ (cm^{-1}) 2978 (w), 2938 (w), 1688 (m), 1601 (w), 1485 (w), 1416 (w), 1359 (s), 1322 (m), 1274 (w), 1213 (s), 1143 (s), 959 (w), 862 (m), 791 (w), 702 (m), 675 (w).

HRMS (ESI) calcd for $C_{15}H_{22}BO_3^+$ $[M+H]^+$ 261.1657; found 261.1667.



5-Chloro-1-phenylpentan-1-one (106) : To a solution of 5-chlorovaleroyl chloride **105** (4.651 g, 30.0 mmol, 1.0 equiv) in benzene (15 mL) at 0 °C was added portionwise $AlCl_3$ (4.400 g, 33.0 mmol, 1.1 equiv) and the reaction mixture was stirred at 0 °C for 1 h. The reaction mixture was then carefully quenched with water, partitioned between sat. aqueous $NaHCO_3$ and EtOAc and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 25:1 to 10:1 as eluent to afford product **106** as a colorless solid (4.661 g, 23.7 mmol, 79% yield). The spectroscopic data were consistent with those previously reported in the literature.[151]

[150] For reaction conditions with a similar substrate, see reference 73.
[151] Wagner, P. J.; Lindstrom, M. J.; Sedon, J. H.; Ward, D. R. *J. Am. Chem. Soc.* **1981**, *103* (13), 3842–3849.

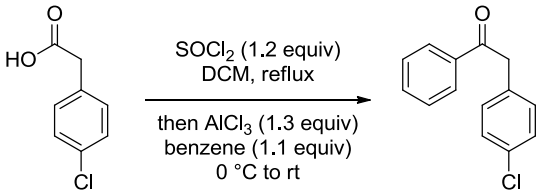
6-Oxo-6-phenylhexanenitrile (107) : KCN (195.4 mg, 3.00 mmol, 1.2 equiv) was added to a solution of alkyl chloride **106** (491.7 mg, 2.50 mmol, 1.0 equiv) in DMF (10 mL) and the reaction mixture was stirred at 60 °C for 24 h. The solvent was then evaporated under reduced pressure and the residue was partitioned between water and EtOAc and extracted with EtOAc. The combined organic layers were washed with brine dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 4:1 as eluent to afford nitrile **107** as a colorless oil (432.1 mg, 2.31 mmol, 92% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 – 7.92 (m, 2H), 7.61 – 7.54 (m, 1H), 7.51 – 7.44 (m, 2H), 3.05 (t, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 1.96 – 1.86 (m, 2H), 1.82 – 1.72 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 136.9, 133.4, 128.9, 128.2, 119.7, 37.5, 25.2, 23.3, 17.4.

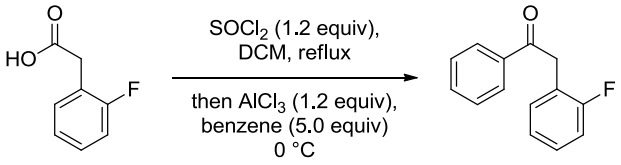
IR υ (cm^{-1}) 2948 (w), 2804 (w), 2245 (w), 1677 (s), 1596 (w), 1580 (w), 1449 (m), 1411 (w), 1376 (w), 1226 (w), 1204 (m), 1076 (w), 1002 (w), 760 (m), 732 (m), 692 (m).

HRMS (ESI) calcd for $C_{12}H_{14}NO^+$ $[M+H]^+$ 188.1070; found 188.1070.

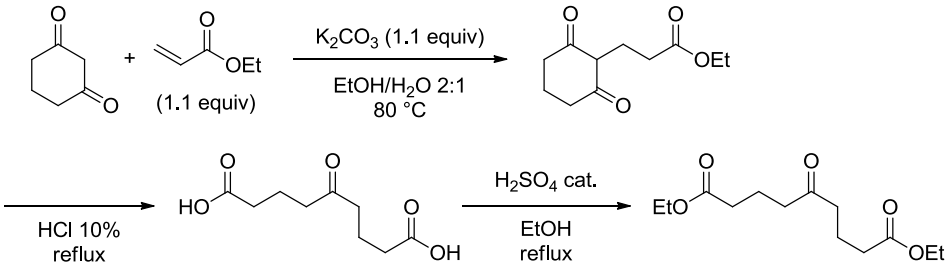


2-(4-Chlorophenyl)-1-phenylethanone (124) : A solution of 4-chlorophenylacetic acid (1.711 g, 10.0 mmol, 1.0 equiv) and $SOCl_2$ (0.88 mL, 12.0 mmol, 1.2 equiv) in DCM (15 mL) was refluxed overnight. Benzene (5.0 mL, 50.0 mmol, 5.0 equiv) and $AlCl_3$ (1.733 g, 13.0 mmol, 1.3 equiv) were then carefully added at 0 °C and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with H_2O and the reaction mixture was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 40:1 as eluent (Rf=0.25) to afford ketone **124** as a yellowish solid (1.190 g, 5.16 mmol, 52% yield). The spectroscopic data were consistent with those previously reported in the literature.[152]

[152] Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *Organometallics* **2008**, *27* (8), 1679–1682.



2-(2-Fluorophenyl)-1-phenylethanone (123) : A solution of 3-fluorophenylacetic acid (3.083 g, 20.0 mmol, 1.0 equiv) and $SOCl_2$ (1.75 mL, 24.0 mmol, 1.2 equiv) in DCM (40 mL) was refluxed overnight. Benzene (8.9 mL, 100.0 mmol, 5.0 equiv) and $AlCl_3$ (3.200 g, 24.0 mmol, 1.2 equiv) were then carefully added at 0 °C and the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with H_2O and the reaction mixture was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford ketone **123** as a yellow oil in quantitative yield, which was used without further purification.The spectroscopic data were consistent with those previously reported in the literature.[153]



Ethyl 3-(2,6-dioxocyclohexyl)propanoate (267) : To a solution of 1,3-cyclohexanedione **118** (6.728 g, 60.0 mmol, 1.0 equiv) in EtOH (100 mL) and water (50 mL) were added K_2CO_3 (8.292 g, 60.0 mmol, 1.0 equiv) and ethyl acrylate (7.2 mL, 66.0 mmol, 1.1 equiv) and the reaction mixture was stirred at 80 °C overnight. The reaction mixture was filtered and concentrated under reduced pressure. The residue was partitioned between water and EtOAc and the aqueous layer was extracted with EtOAc (8x). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 5:1 to 1:2 as eluent to afford product **267** as a crystalline colorless solid (4.850 g, 22.9 mmol, 38% yield). The spectroscopic data were consistent with those previously reported in the literature.[154]

5-Oxononanedioic acid (268) and diethyl 5-oxononanedioate (119) : A solution of the 1,3-diketone **267** (4.245 g, 20.0 mmol, 1.0 equiv) in aq. 10% HCl (100 mL) was stirred under reflux overnight. The reaction mixture was then extracted with EtOAc (8x) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford diacid **268**. The crude product was directly dissolved in EtOH (100 mL) containing H_2SO_4 (0.5 mL) and the reaction mixture was stirred under reflux overnight. The reaction mixture was then concentrated under reduced pressure and the residue was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude

[153] Desai, L. V.; Ren, D. T.; Rosner, T. *Org. Lett.* **2010**, *12* (5), 1032–1035.
[154] Asahi, K.; Nishino, H. *Tetrahedron* **2008**, *64* (8), 1620–1634.

product was purified by column chromatography with PE/EtOAc 1:3 as eluent to afford diester **119** as a yellowish liquid (3.470 g, 13.4 mmol, 67% yield over 2 steps).

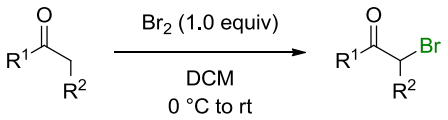
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, *J* = 7.1 Hz, 4H), 2.46 (t, *J* = 7.2 Hz, 4H), 2.31 (t, *J* = 7.2 Hz, 4H), 1.88 (p, *J* = 7.3 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 209.5, 173.3, 60.5, 41.7, 33.5, 19.1, 14.4.

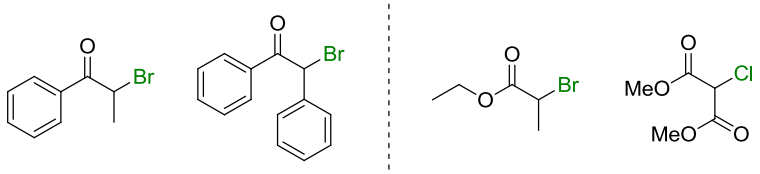
IR υ (cm^{-1}) 2983 (w), 2940 (w), 2928 (w), 1730 (s), 1452 (w), 1417 (w), 1373 (w), 1311 (w), 1249 (m), 1177 (s), 1099 (w), 1032 (m).

HRMS (ESI) calcd for $C_{13}H_{22}NaO_5^+$ $[M+Na]^+$ 281.1359; found 281.1369.

3.3.2 Synthesis of α-Bromoketones and Surrogates

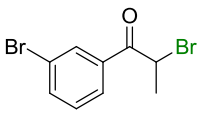


To a solution of the ketone (1.0 equiv) in DCM (0.2 M) at 0 °C was added dropwise Br_2 (1.0 equiv) and the reaction mixture was stirred at 0 °C. The reaction was monitored by TLC with PE/DCM as eluent and allowed to warm to room temperature until complete consumption of the starting material. A saturated aqueous solution of $Na_2S_2O_3$ was then added and the biphasic mixture was vigorously stirred for 30 min. The reaction mixture was then extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/DCM or PE/EtOAc as eluent to afford the desired α–bromoketone.

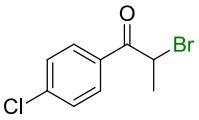


69a **69ad** **78** **80**

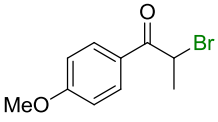
69a, **69ad**, **78** and **80** were commercially available and were quickly purified by column chromatography with PE/DCM as eluent before use.



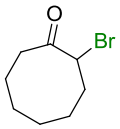
69b



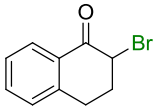
69d



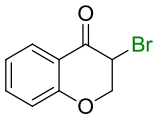
69e



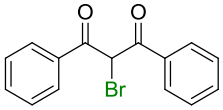
69t



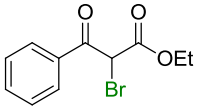
69u



69v

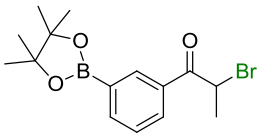


69w



69x

69b,[155] **69d**,[156] **69e**,[157] **69t**,[158] **69u**,[159] **69v**,[160] **69w**[161] and **69x**[162] were obtained by bromination of the corresponding commercially available ketones and the spectroscopic data were consistent with those previously reported in the literature.



69c

2-Bromo-1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-one

90% yield from 5.0 mmol of **101**, colorless oil

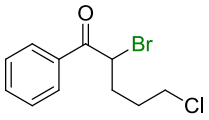
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.11 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.02 (d, *J* = 7.3 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 5.38 (q, *J* = 6.6 Hz, 1H), 1.90 (d, *J* = 6.6 Hz, 3H), 1.36 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 140.1, 135.1, 133.7, 131.8, 128.4, 84.4, 41.8, 25.1, 20.4.

IR υ (cm^{-1}) 2979 (w), 1688 (m), 1600 (w), 1420 (w), 1360 (s), 1326 (m), 1232 (m), 1143 (s), 1083 (w), 959 (w), 861 (w), 701 (m).

HRMS (ESI) calcd for $C_{15}H_{21}BBrO_3^+$ $[M+H]^+$ 339.0769, 341.0750; found 339.0770, 341.0751.

[155] See reference 154.
[156] Carroll, F. I.; Blough, B. E.; Abraham, P.; Mills, A. C.; Holleman, J. A.; Wolckenhauer, S. A.; Decker, A. M.; Landavazo, A.; McElroy, K. T.; Navarro, H. A.; et al. *J. Med. Chem.* **2009**, *52* (21), 6768–6781.
[157] Maji, T.; Karmakar, A.; Reiser, O. *J. Org. Chem.* **2011**, *76* (2), 736–739.
[158] Sims, E. A.; DeForest, C. A.; Anseth, K. S. *Tet. Lett.* **2011**, *52* (16), 1871–1873.
[159] See reference 157.
[160] Ankner, T.; Fridén-Saxin, M.; Pemberton, N.; Seifert, T.; Grøtli, M.; Luthman, K.; Hilmersson, G. *Org. Lett.* **2010**, *12* (10), 2210–2213.
[161] Khan, A. T.; Ali, M. A.; Goswami, P.; Choudhury, L. H. *J. Org. Chem.* **2006**, *71* (23), 8961–8963.
[162] See reference 161.

69f 

2-Bromo-5-chloro-1-phenylpentan-1-one

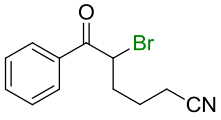
85% yield from 2.5 mmol of **106**, yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 7.99 (m, 2H), 7.64 – 7.58 (m, 1H), 7.52 – 7.48 (m, 2H), 5.18 (dd, *J* = 8.1, 6.1 Hz, 1H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.43 – 2.24 (m, 2H), 2.12 – 1.88 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 134.4, 134.0, 129.1, 129.0, 46.4, 44.3, 31.0, 30.5.

IR υ (cm^{-1}) 2958 (w), 2927 (w), 1685 (s), 1596 (w), 1580 (w), 1448 (m), 1356 (w), 1277 (m), 1243 (w), 1003 (w), 961 (w), 808 (w), 789 (w), 704 (m), 687 (m).

HRMS : not detected.

69g 

5-Bromo-6-oxo-6-phenylhexanenitrile

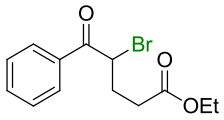
91% yield from 2.0 mmol of **107**, yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.2 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 5.15 (dd, *J* = 7.5, 6.9 Hz, 1H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.38 – 2.24 (m, 2H), 2.04 – 1.76 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 134.2, 129.1, 129.1, 119.2, 45.7, 32.4, 23.7, 17.1.

IR υ (cm^{-1}) 2928 (m), 2851 (w), 2364 (w), 1685 (s), 1450 (w), 1260 (m), 1101 (w), 799 (m), 774 (m), 750 (s), 707 (s), 667 (s).

HRMS : not detected.

69h 

Ethyl 4-bromo-5-oxo-5-phenylpentanoate

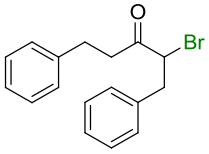
82% yield from 5.0 mmol of **104**, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.00 (m, 2H), 7.63 – 7.57 (m, 1H), 7.51 – 7.47 (m, 2H), 5.38 (dd, *J* = 8.4, 5.6 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.67 – 2.34 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 172.7, 134.4, 134.0, 129.1, 129.0, 60.9, 46.5, 31.7, 28.7, 14.4.

IR υ (cm^{-1}) 2982 (w), 1729 (s), 1685 (s), 1596 (w), 1580 (w), 1448 (m), 1376 (w), 1302 (w), 1270 (m), 1182 (s), 1097 (w), 1029 (m), 1002 (w), 965 (w), 881 (w), 854 (w), 801 (w), 705 (s), 687 (s).

HRMS (ESI) calcd for $C_{13}H_{16}BrO_3^+$ $[M+H]^+$ 299.0281, 301.0263; found 299.0283, 301.0264.

69i 

2-Bromo-1,5-diphenylpentan-3-one

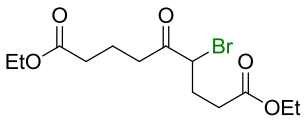
64% yield from 3.0 mmol of **115**, yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.24 (m, 5H), 7.24 – 7.13 (m, 5H), 4.43 (t, *J* = 7.4 Hz, 1H), 3.43 (dd, *J* = 14.3, 7.5 Hz, 1H), 3.16 (dd, *J* = 14.3, 7.3 Hz, 1H), 3.12 – 3.03 (m, 1H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.84 – 2.76 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 140.6, 137.2, 129.4, 128.8, 128.7, 128.5, 127.3, 126.4, 52.7, 41.8, 39.6, 30.1.

IR υ (cm^{-1}) 3028 (w), 1716 (m), 1604 (w), 1496 (w), 1455 (w), 1365 (w), 1068 (w), 1031 (w), 983 (w), 922 (w), 748 (m), 698 (s).

HRMS (ESI) calcd for $C_{17}H_{17}BrNaO^+$ $[M+Na]^+$ 339.0365, 341.0346; found 339.0360, 341.0341.



69k

Diethyl 4-bromo-5-oxononanedioate

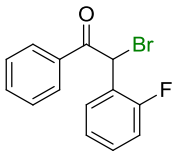
14% yield from 6.0 mmol of **119**, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.90 (dt, *J* = 17.7, 7.3 Hz, 1H), 2.66 (dt, *J* = 17.7, 7.0 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.37 – 2.27 (m, 3H), 2.24 – 2.13 (m, 1H), 1.95 (p, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 173.2, 172.5, 61.0, 60.7, 52.3, 38.6, 33.3, 31.8, 28.4, 19.3, 14.5, 14.4.

IR υ (cm^{-1}) 2981 (w), 1727 (s), 1446 (w), 1376 (w), 1301 (w), 1253 (m), 1183 (s), 1098 (w), 1028 (m), 859 (w), 791 (w).

HRMS (ESI) calcd for $C_{13}H_{21}BrNaO_5^+$ $[M+Na]^+$ 359.0468, 361.0449; found 359.0470, 361.0451.



69m

2-Bromo-2-(2-fluorophenyl)-1-phenylethanone

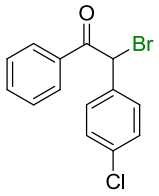
71% yield from 5.0 mmol of **123**, yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.97 (m, 2H), 7.63 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.35 – 7.30 (m, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.75 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 159.3 (d, *J* = 248.4 Hz), 134.1, 134.0, 131.7 (d, *J* = 1.9 Hz), 131.2 (d, *J* = 8.5 Hz), 129.2, 129.1, 125.2 (d, *J* = 3.6 Hz), 123.7 (d, *J* = 13.2 Hz), 115.8 (d, *J* = 21.9 Hz), 42.9 (d, *J* = 3.5 Hz).

IR υ (cm^{-1}) 3069 (w), 1696 (s), 1614 (w), 1596 (w), 1489 (s), 1449 (m), 1268 (w), 1235 (s), 1192 (w), 1092 (w), 991 (w), 860 (w), 801 (w), 754 (s), 688 (m).

HRMS : not detected.



69n

2-Bromo-2-(4-chlorophenyl)-1-phenylethanone

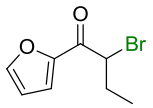
41% yield from 4.5 mmol of **124**, colorless solid (mp = 61-65 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 – 7.98 (m, 2H), 7.62 – 7.55 (m, 1H), 7.52 – 7.42 (m, 4H), 7.38 – 7.32 (m, 2H), 6.32 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 135.5, 134.6, 134.2, 134.2, 130.8, 129.4, 129.4, 129.2, 49.4.

IR υ (cm^{-1}) 1678 (s), 1594 (m), 1597 (w), 1491 (m), 1448 (m), 1413 (m), 1343 (m), 1299 (m), 1279 (m), 1219 (s), 1198 (m), 1186 (m), 1149 (m), 1089 (m), 1015 (m), 994 (m), 929 (w), 854 (w), 833 (m), 815 (m), 782 (w), 726 (s), 707 (m), 687 (s).

HRMS : not detected.



69r

2-Bromo-1-(furan-2-yl)butan-1-one

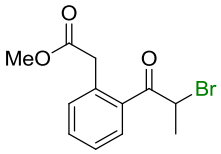
79% yield from 5.0 mmol of the corresponding commercially available ketone. Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.34 (dd, *J* = 3.6, 0.7 Hz, 1H), 6.59 (dd, *J* = 3.6, 1.7 Hz, 1H), 4.93 (dd, *J* = 7.6, 6.8 Hz, 1H), 2.27 – 2.04 (m, 2H), 1.07 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 150.7, 147.2, 119.2, 112.9, 49.4, 26.9, 12.3.

IR υ (cm^{-1}) 3133 (w), 2973 (w), 2935 (w), 2877 (w), 1677 (s), 1568 (w), 1464 (s), 1396 (w), 1305 (w), 1278 (w), 1239 (w), 1158 (w), 1041 (w), 1018 (w), 883 (w), 769 (m).

HRMS : not detected.



69s

Methyl 2-(2-(2-bromopropanoyl)phenyl)acetate

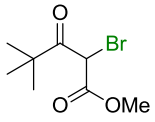
88% yield from 2.0 mmol of **109**, yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.8 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.6 Hz, 1H), 5.24 (q, *J* = 6.6 Hz, 1H), 4.00 (d, *J* = 16.7 Hz, 1H), 3.79 (d, *J* = 16.6 Hz, 1H), 3.70 (s, 3H), 1.87 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 172.0, 135.8, 135.0, 133.2, 132.7, 129.1, 127.6, 52.2, 44.0, 40.2, 20.6.

IR υ (cm^{-1}) 2951 (w), 1735 (s), 1685 (s), 1574 (w), 1436 (m), 1341 (m), 1240 (s), 1215 (s), 1165 (s), 1123 (w), 993 (m), 954 (w), 928 (w), 792 (w), 746 (w), 711 (w).

HRMS (ESI) : not detected.



69y

Methyl 2-bromo-4,4-dimethyl-3-oxopentanoate

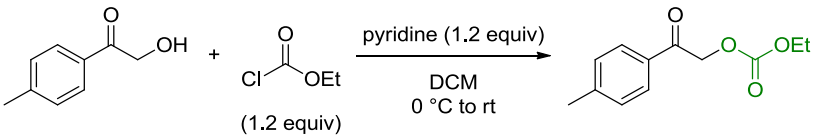
86% yield from 5.0 mmol of the corresponding commercially available ketone. Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (s, 1H), 3.80 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 165.8, 54.1, 45.5, 43.1, 26.8.

IR υ (cm^{-1}) 2972 (w), 1763 (s), 1759 (s), 1714 (s), 1478 (w), 1436 (w), 1370 (w), 1299 (m), 1268 (s), 1217 (s), 1148 (s), 1056 (m), 986 (s), 786 (w), 718 (w).

HRMS (ESI) calcd for $C_8H_{14}BrO_3^+$ $[M+H]^+$ 237.0121, 239.0107; found 237.0121, 239.0105.



Ethyl (2-oxo-2-(p-tolyl)ethyl) carbonate (270) : To a solution of 2-hydroxy-4'-methylacetophenone (130.2 mg, 0.62 mmol, 1.0 equiv) in DCM (1.25 mL) was added pyridine (62 µL, 0.77 mmol, 1.2 equiv) and ethyl chloroformate (73 µL, 0.77 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and then allowed to warm to rt. The reaction mixture was diluted with Et_2O, washed with H_2O, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 10:1 as eluent (Rf=0.34) to afford carbonate **270** as a yellow oil (78.0 mg, 0.33 mmol, 53% yield).

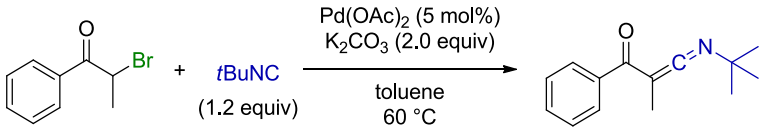
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 5.33 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 155.3, 145.3, 131.9, 129.9, 128.2, 68.8, 65.0, 22.1, 14.6.

IR υ (cm^{-1}) 2997 (w), 2957 (w), 2909 (w), 1742 (s), 1692 (s), 1606 (m), 1476 (w), 1427 (m), 1374 (m), 1290 (s), 1261 (s), 1235 (s), 1210 (m), 1185 (m), 1165 (w), 1134 (w), 1020 (m), 1016 (m), 979 (m), 939 (m), 876 (m), 814 (s), 791 (s), 720 (w).

HRMS (ESI) calcd for $C_{12}H_{15}O_4^+$ $[M+H]^+$ 223.0965; found 223.0968.

3.3.3 Synthesis and Diversification of α-Oxo-ketenimine **70**



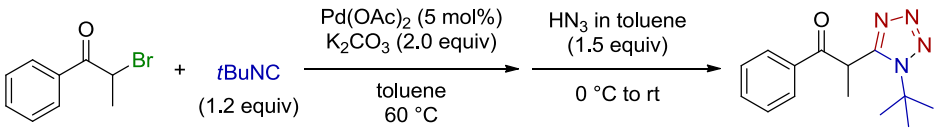
3-(*tert*-butylimino)-2-methyl-1-phenylprop-2-en-1-one (70) : To a solution of the α–bromoketone **69a** (85.2 mg, 0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and the isocyanide (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. The reaction mixture was filtered through a short pad of Celite and sat. aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford α–oxo-ketenimine **70** as a colorless oil (70.0 mg, 0.325 mmol, 81% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H), 7.45 – 7.39 (m, 1H), 7.38 – 7.33 (m, 2H), 1.90 (s, 3H), 1.15 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 175.1, 140.5, 130.8, 128.1, 127.6, 70.1, 61.7, 30.2, 10.5.

IR υ (cm^{-1}) 2974 (w), 2932 (w), 2032 (s)*, 1622 (s), 1576 (w), 1447 (w), 1368 (w), 1301 (m), 1238 (w), 1176 (m), 1008 (w), 908 (w), 716 (w), 699 (w), 678 (w). (*This peak corresponds to the ketenimine group).

HRMS (ESI) calcd for $C_{14}H_{17}NNaO^+$ $[M+Na]^+$ 238.1202; found 238.1205.



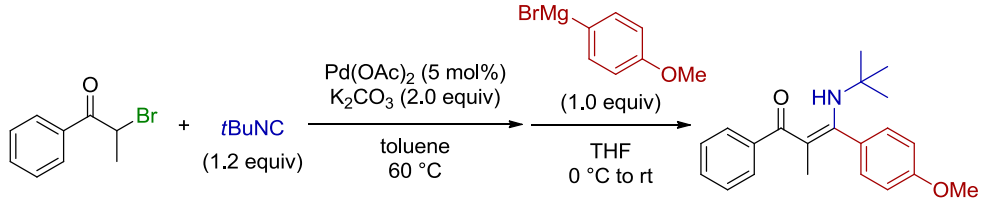
2-(1-(*tert*-butyl)-1*H*-tetrazol-5-yl)-1-phenylpropan-1-one (100) : To a solution of the α–bromoketone **69a** (85.2 mg, 0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and *t*BuNC (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. A solution of HN_3 in toluene (1.5 equiv), prepared according to a reported procedure,[11] was then added at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred until complete consumption of the α-oxo-ketenimine. The reaction mixture was then partitioned between sat. aqueous $NaHCO_3$ and EtOAc, extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford tetrazole **100** as a colorless solid (mp = 97-98 °C) (86.9 mg, 0.336 mmol, 84% yield from **69a**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 5.17 (q, *J* = 7.3 Hz, 1H), 1.83 (d, *J* = 7.3 Hz, 3H), 1.63 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 153.2, 134.5, 134.0, 129.2, 128.6, 61.5, 40.6, 30.1, 17.5.

IR υ (cm^{-1}) 2988 (w), 1674 (s), 1595 (w), 1578 (w), 1497 (w), 1453 (m), 1400 (w), 1378 (m), 1332 (w), 1282 (m), 1208 (s), 1148 (w), 1109 (m), 1054 (w), 970 (s), 791 (w), 744 (w), 703 (s), 685 (m).

HRMS (ESI) calcd for $C_{14}H_{18}N_4NaO^+$ $[M+Na]^+$ 281.1373; found 281.1379.



(*Z*)-3-(*tert*-butylamino)-3-(4-methoxyphenyl)-2-methyl-1-phenylprop-2-en-1-one (87) : To a solution of the α–bromoketone **69a** (85.2 mg, 0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and *t*BuNC (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone and allowed to cool to room temperature. The reaction mixture was filtered through a short pad of Celite and sat. aqueous $NaHCO_3$ was added. The aqueous

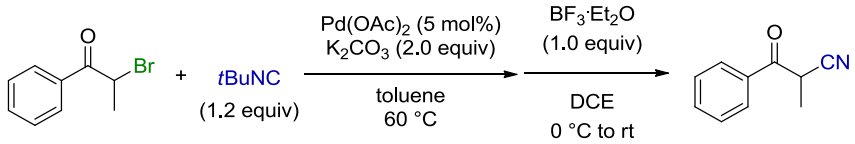
layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in THF (2 mL) and 4-methoxyphenylmagnesium bromide (0.8 mL of a 0.5 M solution in THF, 0.4 mmol, 1.0 equiv) was added at 0 °C. The reaction mixture was stirred at 0 °C until complete consumption of the α-oxo-ketenimine, quenched with sat. aqueous NH_4Cl, extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford enaminone **87** as a yellow solid (mp = 109-113 °C) (75.5 mg, 0.233 mmol, 58% yield from **69a**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1H), 7.50 – 7.44 (m, 2H), 7.38 – 7.30 (m, 3H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.7 Hz, 2H), 3.86 (s, 3H), 1.41 (s, 3H), 1.17 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0, 167.4, 160.0, 143.6, 130.3, 128.9, 128.8, 128.1, 127.5, 113.9, 99.7, 55.6, 54.1, 32.1, 17.8.

IR υ (cm^{-1}) 2931 (w), 1661 (w), 1607 (m), 1575 (m), 1546 (m), 1516 (m), 1466 (w), 1434 (w), 1322 (m), 1284 (m), 1241 (s), 1193 (m), 1164 (s), 1114 (m), 1027 (m), 1007 (s), 914 (w), 849 (m), 782 (w), 741 (w), 699 (s).

HRMS (ESI) calcd for $C_{21}H_{26}NO_2^+$ $[M+H]^+$ 324.1958; found 324.1958.



2-Methyl-3-oxo-3-phenylpropanenitrile (97) : To a solution of the α–bromoketone **69a** (85.2 mg, 0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and *t*BuNC (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone and allowed to cool to room temperature. The reaction mixture was filtered through a short pad of Celite and sat. aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was dissolved in DCE (2 mL) and $BF_3{\cdot}Et_2O$ (50 µL, 0.4 mmol, 1.0 equiv) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred until complete consumption of the α-oxo-ketenimine. The reaction mixture was quenched with sat. aqueous $NaHCO_3$, extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford α-cyanoketone **97** as a colorless oil (36.0 mg, 0.228 mmol, 57% yield from **69a**).

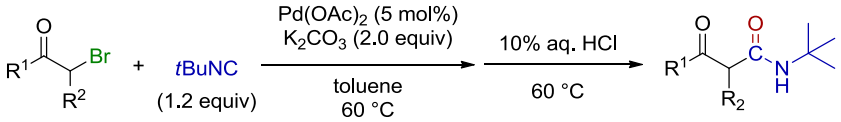
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.97 (m, 2H), 7.69 – 7.63 (m, 1H), 7.56 – 7.51 (m, 2H), 4.38 (q, *J* = 7.2 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.9, 134.7, 133.9, 129.3, 129.0, 118.3, 33.9, 15.1.

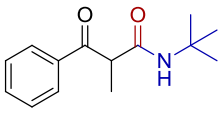
IR υ (cm^{-1}) 1693 (s), 1597 (w), 1451 (w), 1264 (m), 1214 (m), 1154 (w), 1000 (w), 971 (m), 792 (w), 743 (w), 694 (s).

HRMS (ESI) calcd for $C_{10}H_9NNaO^+$ $[M+Na]^+$ 182.0576; found 182.0569.

3.3.4 Synthesis of β-Ketoamides



To a solution of the α–bromoketone (85.2 mg, 0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and *t*BuNC (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. Aq. 10% HCl (1 mL) was then added and the reaction mixture was stirred at 60 °C until complete consumption of the α-oxo-ketenimine and allowed to cool to room temperature. The aqueous layer was extracted with EtOAc, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired β-ketoamide**.**

73a 

***N*-(*tert*-butyl)-2-methyl-3-oxo-3-phenylpropanamide**

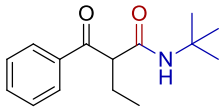
79%, colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.95 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 6.17 (*br* s, 1H), 4.24 (q, *J* = 7.2 Hz, 1H), 1.49 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 169.4, 136.3, 134.1, 129.1, 129.0, 51.6, 51.4, 28.9, 17.2.

IR υ (cm^{-1}) 3307 (br), 2971 (br), 2933 (w), 1692 (s), 1640 (s), 1545 (s), 1451 (m), 1364 (w), 1334 (w), 1252 (w), 1228 (m), 1203 (m), 963 (m), 730 (w), 690 (m).

HRMS (ESI) calcd for $C_{14}H_{20}NO_2^+$ $[M+H]^+$ 234.1489; found 234.1497.

73b 

2-Benzoyl-*N*-(*tert*-butyl)butanamide

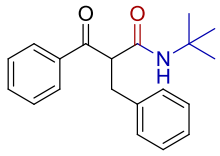
78% yield, colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 7.94 (m, 2H), 7.59 – 7.51 (m, 1H), 7.48 – 7.39 (m, 2H), 6.34 (*br* s, 1H), 4.12 (t, *J* = 7.3 Hz, 1H), 2.05 – 1.84 (m, 2H), 1.27 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 168.2, 136.9, 134.0, 129.0, 128.8, 58.6, 51.5, 28.8, 26.1, 12.2.

IR υ (cm^{-1}) 3282 (br), 3074 (br), 2966 (w), 2933 (w), 2876 (w), 1385 (m), 1638 (s), 1553 (m), 1451 (m), 1363 (w), 1348 (w), 1324 (w), 1265 (w), 1226 (m), 1200 (w).

HRMS (ESI) calcd for $C_{15}H_{21}NNaO_2^+$ $[M+Na]^+$ 270.1464; found 270.1470.

73c 

76% yield, colorless solid

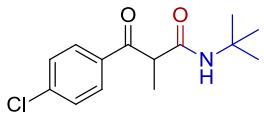
2-Benzyl-*N*-(*tert*-butyl)-3-oxo-3-phenylpropanamide

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.56 – 7.48 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.25 – 7.11 (m, 5H), 6.08 (*br* s, 1H), 4.45 (dd, *J* = 7.9, 6.8 Hz, 1H), 3.37 – 3.18 (m, 2H), 1.25 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 167.5, 138.4, 136.9, 133.9, 129.2, 128.9, 128.8, 128.7, 126.9, 59.1, 51.6, 37.8, 28.7.

IR υ (cm^{-1}) 3334 (br), 3064 (w), 3030 (w), 2969 (w), 2930 (w), 1687 (s), 1647 (s), 1541 (m), 1454 (m), 1364 (m), 1329 (w), 1281 (w), 1254 (w), 1228 (m), 1003 (w), 949 (w), 766 (w), 746 (m), 701 (m).

HRMS (ESI) calcd for $C_{20}H_{24}NO_2^+$ $[M+H]^+$ 310.1802; found 310.1812.

73d 

***N*-(*tert*-butyl)-3-(4-chlorophenyl)-2-methyl-3-oxopropanamide**

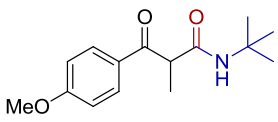
40% yield, colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.6 Hz, 2H), 6.05 (*br* s, 1H), 4.17 (q, *J* = 7.1 Hz, 1H), 1.47 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 168.8, 140.3, 134.3, 130.1, 129.1, 51.4, 51.3, 28.5, 16.5.

IR υ (cm^{-1}) 3293 (br), 3075 (br), 2972 (w), 2935 (w), 1694 (s), 1638 (s), 1592 (m), 1550 (s), 1455 (m), 1398 (w), 1366 (m), 1333 (m), 1251 (w), 1227 (m), 1204 (w), 1092 (m), 1014 (w), 964 (s), 850 (m), 781 (w).

HRMS (ESI) calcd for $C_{14}H_{19}ClNO_2^+$ $[M+H]^+$ 268.1099; found 268.1102.

73e 

***N*-(*tert*-butyl)-3-(4-methoxyphenyl)-2-methyl-3-oxopropanamide**

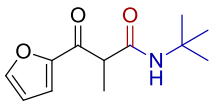
50% yield, colorless solid

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.2 Hz, 2H), 6.92 (d, *J* = 8.0 Hz, 2H), 6.27 (*br* s, 1H), 4.19 (q, *J* = 7.1 Hz, 1H), 3.85 (s, 3H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 169.8, 164.4, 131.4, 129.2, 114.3, 55.8, 51.5, 50.8, 28.8, 17.4.

IR υ (cm^{-1}) 3312 (br), 2970 (br), 2935 (w), 1682 (s), 1643 (s), 1600 (s), 1543 (b), 1513 (m), 1456 (m), 1365 (m), 1318 (m), 1252 (s), 1234 (s), 1172 (s), 1030 (m), 965 (m), 848 (m).

HRMS (ESI) calcd for $C_{15}H_{22}NO_3^+$ $[M+H]^+$ 264.1594; found 264.1596.

73f 

***N*-(*tert*-butyl)-3-(furan-2-yl)-2-methyl-3-oxopropanamide**

50% yield, orange solid

^{1}H NMR (400 MHz, CDCl) δ 7.62 (d, *J* = 1.2 Hz, 1H), 7.32 (d, *J* = 3.6 Hz, 1H), 6.54 (dd, *J* = 3.6, 1.7 Hz, 2H), 6.32 (s, 1H), 3.97 (q, *J* = 7.2 Hz, 1H), 1.45 (d, *J* = 7.2 Hz, 3H), 1.28 (s, 9H).

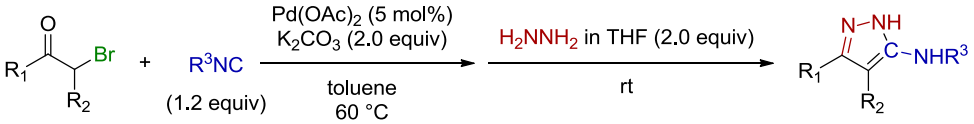
^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4, 168.8, 151.7, 147.7, 119.6, 112.9, 51.4, 50.9, 28.7, 16.8.

IR υ (cm^{-1}) 3321 (br), 2125 (w), 2971 (m), 2936 (w), 1683 (s), 1645 (s), 1542 (s), 1467 (s), 1393 (m), 1365 (m), 1328 (br), 1266 (m), 1226 (m), 1162 (w), 1038 (m), 1015 (m), 973 (m), 897 (m), 883 (m), 765 (br).

HRMS (ESI) calcd for $C_{12}H_{18}NO_3^+$ $[M+H]^+$ 224.1281; found 224.1284.

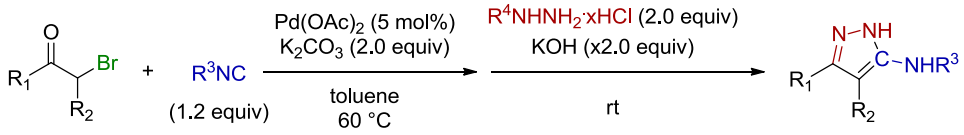
3.3.5 Synthesis of 5-Aminopyrazoles

Procedure [a] :



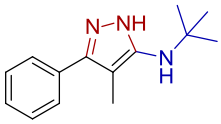
To a solution of the α–bromoketone (0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and the isocyanide (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. The reaction mixture was then allowed to cool to room temperature and a solution of NH_2NH_2 in THF (1.0 M, 0.8 mL, 2.0 equiv) was added dropwise. The reaction mixture was stirred at room temperature until complete consumption of the α–oxo-ketenimine. The reaction mixture was then partitioned between sat. aqueous NH_4Cl and EtOAc, extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired 5-aminopyrazole.

Procedure [b] :



To a solution of the α–bromoketone (0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and the isocyanide (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. The reaction mixture was then allowed to cool to room temperature and powedered KOH (1.0 equiv related to the HCl contained in $RNHNH_2{\cdot}HCl$) was added if necessary. The substituted hydrazine $RNHNH_2{\cdot}HCl$ (0.8 mmol, 2.0 equiv) was then added and the reaction mixture was stirred at room temperature until complete consumption of the α–oxo-ketenimine. The reaction mixture was then partitioned between sat. aqueous NH_4Cl and EtOAc, extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired 1-substituted 5-aminopyrazole.

89a



***N*-(*tert*-butyl)-4-methyl-5-phenyl-1*H*-pyrazol-3-amine**

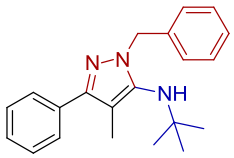
85% yield (78.0 mg), yellowish solid (mp = 79-80 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.48 (m, 2H), 7.44 – 7.38 (m, 2H), 7.36 – 7.31 (m, 1H), 2.03 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 141.9, 131.8, 128.8, 127.9, 127.3, 101.8, 52.5, 30.0, 8.5.

IR υ (cm^{-1}) 3209 (w), 3061 (w), 2965 (w), 2927 (w), 2866 (w), 1570 (m), 1513 (m), 1463 (w), 1389 (w), 1363 (m), 1223 (m), 1139 (w), 1074 (w), 1013 (w), 936 (w), 911 (w), 767 (m), 732 (m), 696 (s).

HRMS (ESI) calcd for $C_{14}H_{20}N_3^+$ $[M+H]^+$ 230.1652; found 230.1660.

89b 

1-Benzyl-*N*-(*tert*-butyl)-4-methyl-5-phenyl-1*H*-pyrazol-3-amine

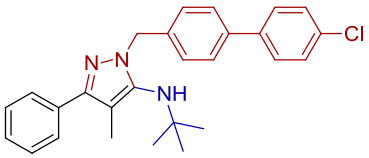
75% yield (95.5 mg), yellowish solid (mp = 80-82 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.43 – 7.37 (m, 2H), 7.32 – 7.21 (m, 4H), 7.18 – 7.14 (m, 2H), 5.39 (s, 2H), 2.16 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 143.2, 138.0, 128.7, 128.5, 127.6, 127.5, 127.3, 127.3, 108.7, 55.4, 52.0, 30.8, 11.3.

IR υ (cm^{-1}) 3263 (w), 2966 (w), 2918 (w), 2866 (w), 1553 (w), 1494 (w), 1456 (w), 1361 (w), 1321 (w), 1203 (w), 1075 (w), 1024 (w), 814 (w), 746 (m), 693 (s).

HRMS (ESI) calcd for $C_{21}H_{26}N_3^+$ $[M+H]^+$ 320.2121; found 320.2124.

89c 

***N*-(*tert*-butyl)-1-((4'-chloro-[1,1'-biphenyl]-4-yl)methyl)-4-methyl-3-phenyl-1*H*-pyrazol-5-amine**

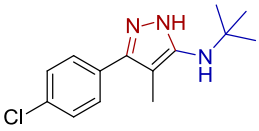
82% yield (136.9 mg), yellow solid (mp = 91-94 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.75 (m, 2H), 7.52 – 7.49 (m, 4H), 7.47 – 7.39 (m, 4H), 7.36 – 7.31 (m, 1H), 7.28 (d, *J* = 8.2 Hz, 2H), 5.46 (s, 2H), 2.59 (*br* s, 1H), 2.21 (s, 3H), 1.27 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 143.1, 139.4, 139.0, 137.6, 135.0, 133.4, 129.0, 128.5, 128.4, 127.8, 127.5, 127.2 (2 C), 108.6, 55.4, 51.6, 30.8, 11.3.

IR υ (cm^{-1}) 2970 (w), 1605 (w), 1550 (w), 1482 (m), 1478 (m), 1388 (w), 1361 (m), 1326 (m), 1312 (w), 1205 (m), 1096 (m), 1005 (m), 798 (s), 777 (s), 771 (m), 700 (s).

HRMS (ESI) calcd for $C_{27}H_{29}ClN_3^+$ $[M+H]^+$ 430.2045; found 430.2037.

89d 

***N*-(*tert*-butyl)-5-(4-chlorophenyl)-4-methyl-1*H*-pyrazol-3-amine**

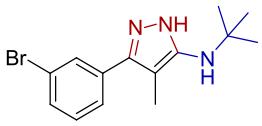
75% yield (78.8 mg), colorless solid (mp = 102-106 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.38 – 7.34 (m, 2H), 2.00 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.0, 133.9, 130.4, 129.1, 128.6, 102.2, 52.7, 30.0, 8.5.

IR υ (cm^{-1}) 2964 (w), 1567 (w), 1491 (w), 1364 (w), 1216 (w), 1093 (w), 1009 (w), 833 (w), 752 (s).

HRMS (ESI) calcd for $C_{14}H_{19}ClN_3^+$ $[M+H]^+$ 264.1262; found 264.1265.

89e 

5-(3-Bromophenyl)-*N*-(*tert*-butyl)-4-methyl-1*H*-pyrazol-3-amine

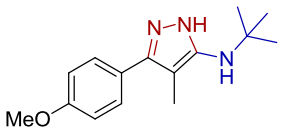
70% yield (86.3 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 1.5 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.29 (d, *J* = 7.9 Hz, 1H), 2.02 (s, 3H), 1.34 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 141.7, 134.2, 130.9, 130.4, 130.2, 125.9, 122.9, 102.6, 52.7, 30.1, 8.5.

IR υ (cm^{-1}) 3198 (w), 2964 (m), 1585 (w), 1559 (m), 1520 (m), 1479 (m), 1390 (w), 1363 (m), 1224 (m), 1141 (w), 1075 (w), 1026 (w), 909 (w), 787 (s), 734 (s), 692 (m).

HRMS (ESI) calcd for $C_{14}H_{19}BrN_3^+$ $[M+H]^+$ 308.0761, 310.0739; found 308.0762, 310.0743.

89f 

***N*-(*tert*-butyl)-5-(4-methoxyphenyl)-4-methyl-1*H*-pyrazol-3-amine**

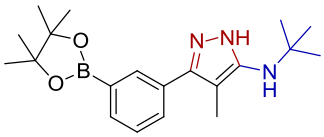
82% yield (85.5 mg), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 6.97 – 6.92 (m, 2H), 3.83 (s, 3H), 1.99 (s, 3H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.0, 141.7, 128.6, 124.3, 114.3, 101.3, 55.5, 52.4, 30.0, 8.4.

IR υ (cm^{-1}) 2950 (w), 2241 (w), 1676 (s), 1596 (w), 1580 (w), 1449 (m), 1412 (w), 1375 (w), 1225 (w), 1203 (m), 1002 (w), 759 (s), 732 (s), 691 (s).

HRMS : not detected.

89g 

***N*-(*tert*-butyl)-4-methyl-5-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-1*H*-pyrazol-3-amine**

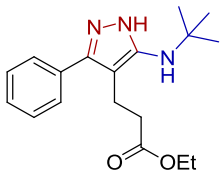
80% yield (113.2 mg), yellowish solid (mp = 157-158 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.78 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.57 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 2.02 (s, 3H), 1.35 (s, 9H), 1.34 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 141.7, 134.3, 133.6, 131.1, 130.3, 128.2, 102.2, 84.1, 52.5, 30.0, 25.0, 8.4.

IR υ (cm^{-1}) 2975 (w), 1519 (w), 1478 (w), 1353 (s), 1316 (m), 1226 (w), 1142 (s), 1079 (w), 964 (w), 910 (w), 863 (w), 733 (s), 708 (m).

HRMS (ESI) calcd for $C_{20}H_{31}BN_3O_2^+$ $[M+H]^+$ 356.2504; found 356.2505.



89h

Ethyl 3-(3-(*tert*-butylamino)-5-phenyl-1*H*-pyrazol-4-yl)propanoate

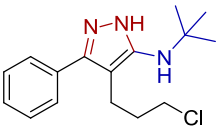
83% yield (104.8 mg), yellowish solid (mp = 121-123 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.40 (m, 4H), 7.39 – 7.34 (m, 1H), 4.43 (*br* s, 2H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.77 (t, *J* = 7.1 Hz, 2H), 2.48 (t, *J* = 7.1 Hz, 2H), 1.39 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 152.8, 142.5, 131.6, 129.0, 128.3, 127.5, 104.8, 60.8, 52.0, 34.9, 29.9, 18.0, 14.3.

IR υ (cm^{-1}) 3376 (w), 3261 (w), 2954 (w), 1720 (s), 1530 (m), 1510 (m), 1376 (w), 1296 (m), 1228 (m), 1177 (s), 1058 (w), 936 (w), 763 (w), 694 (s), 628 (m).

HRMS (ESI) calcd for $C_{18}H_{26}N_3O_2^+$ $[M+H]^+$ 316.2020; found 316.2020.



89i

***N*-(*tert*-butyl)-4-(3-chloropropyl)-5-phenyl-1*H*-pyrazol-3-amine**

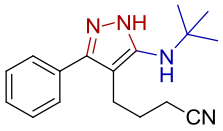
70% yield (81.3 mg), yellowish solid (mp = 99-100 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.45 (m, 2H), 7.43 – 7.38 (m, 2H), 7.37 – 7.32 (m, 1H), 3.52 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.92 (p, *J* = 6.5 Hz, 2H), 1.37 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 141.9, 131.5, 128.9, 128.2, 127.5, 104.2, 52.2, 44.9, 32.9, 30.0, 19.5.

IR υ (cm^{-1}) 3217 (w), 2960 (w), 1571 (w), 1510 (m), 1457 (w), 1389 (w), 1364 (w), 1226 (w), 910 (w), 767 (m), 734 (s), 697 (s).

HRMS (ESI) calcd for $C_{16}H_{23}ClN_3^+$ $[M+H]^+$ 292.1575; found 292.1578.

89j 

4-(3-(*tert*-butylamino)-5-phenyl-1*H*-pyrazol-4-yl)butanenitrile

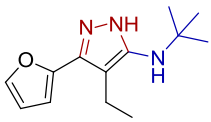
80% yield (90.5 mg), yellow solid (mp = 114-117 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 5H), 4.12 (*br* s, 2H), 2.62 (t, *J* = 7.1 Hz, 2H), 2.26 (t, *J* = 6.9 Hz, 2H), 1.78 (p, *J* = 7.1 Hz, 2H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 142.2, 131.2, 129.2, 128.7, 127.5, 119.9, 103.9, 52.4, 29.9, 25.7, 21.6, 16.8.

IR υ (cm^{-1}) 3246 (w), 2962 (m), 2933 (w), 2869 (w), 2245 (w), 1679 (w), 1589 (w), 1510 (s), 1459 (m), 1363 (m), 1228 (m), 1122 (w), 968 (w), 913 (w), 768 (m), 733 (s), 699 (s), 643 (w).

HRMS (ESI) calcd for $C_{17}H_{23}N_4^+$ $[M+H]^+$ 283.1917; found 283.1922.

89k 

***N*-(*tert*-butyl)-4-ethyl-5-(furan-2-yl)-1*H*-pyrazol-3-amine**

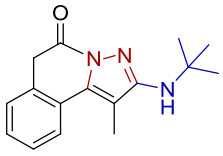
90% yield (84.2 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, *J* = 1.7, 0.5 Hz, 1H), 6.51 (d, *J* = 3.4 Hz, 1H), 6.47 (dd, *J* = 3.3, 1.8 Hz, 1H), 2.50 (q, *J* = 7.6 Hz, 2H), 1.36 (s, 9H), 1.13 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.4, 141.7, 133.2, 111.5, 107.9, 106.1, 52.4, 30.1, 16.2, 14.5.

IR υ (cm^{-1}) 3199 (w), 2964 (s), 2933 (m), 2870 (m), 1574 (w), 1518 (s), 1462 (s), 1391 (w), 1363 (m), 1268 (w), 1227 (m), 1137 (w), 1014 (m), 985 (w), 897 (w), 799 (w), 738 (s).

HRMS (ESI) calcd for $C_{13}H_{20}N_3O^+$ $[M+H]^+$ 234.1601; found 234.1599.



89l

2-(*tert*-butylamino)-1-methylpyrazolo[5,1-*a*]isoquinolin-5(6*H*)-one

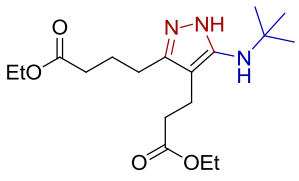
45% yield (48.7 mg), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.28 – 7.25 (m, 1H), 4.06 (s, 2H), 2.23 (s, 3H), 1.51 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 158.3, 137.9, 131.4, 128.5, 128.4, 127.5, 125.1, 124.3, 106.5, 52.3, 37.4, 29.3, 9.5.

IR υ (cm^{-1}) 3364 (w), 3194 (w), 2968 (w), 2926 (w), 2870 (w), 1692 (s), 1620 (m), 1538 (s), 1458 (w), 1395 (m), 1361 (s), 1237 (m), 1212 (m), 957 (w), 921 (w), 765 (w), 727 (s).

HRMS (ESI) calcd for $C_{16}H_{20}N_3O^+$ $[M+H]^+$ 270.1601; found 270.1601.



89m

Diethyl 3,3'-(3-(*tert*-butylamino)-1*H*-pyrazole-4,5-diyl)dipropanoate

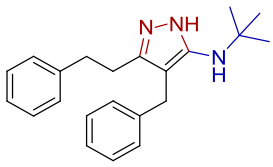
82% yield (58.2 mg) on 0.2 mmol scale, yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 6.9 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 2.61 – 2.51 (m, 2H), 2.44 (t, *J* = 6.8 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.91 (p, *J* = 7.0 Hz, 2H), 1.32 (s, 9H), 1.25 (t, *J* = 7.3 Hz, 3H), 1.25 – 1.21 (m, 2H), 1.22 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 173.4, 151.8, 142.4, 104.5, 60.8, 60.6, 52.0, 34.9, 33.7, 30.0, 24.6, 24.5, 17.6, 14.4, 14.4.

IR υ (cm^{-1}) 2964 (w), 2934 (w), 1730 (s), 1524 (w), 1458 (w), 1374 (w), 1178 (s), 1041 (w).

HRMS (ESI) calcd for $C_{18}H_{32}N_3O_4^+$ $[M+H]^+$ 354.2387; found 354.2387.



89o

4-Benzyl-*N*-(*tert*-butyl)-5-phenethyl-1*H*-pyrazol-3-amine

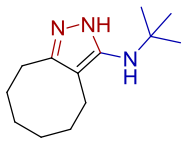
76% yield (101.4 mg), yellowish solid (mp = 98-102 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 4H), 7.21 – 7.16 (m, 2H), 7.13 – 7.08 (m, 4H), 3.57 (s, 2H), 2.85 – 2.79 (m, 4H), 1.20 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 142.2, 141.1, 140.3, 128.7, 128.7, 128.6, 128.4, 126.4, 126.4, 104.3, 52.2, 35.6, 29.9, 28.6, 27.4.

IR υ (cm^{-1}) 3228 (w), 3027 (w), 2959 (w), 2925 (w), 1602 (w), 1522 (m), 1494 (m), 1454 (m), 1388 (w), 1362 (w), 1226 (w), 1075 (w), 1031 (w), 729 (m), 699 (s).

HRMS (ESI) calcd for $C_{22}H_{28}N_3^+$ $[M+H]^+$ 334.2278; found 334.2276.



89p

***N*-(*tert*-butyl)-4,5,6,7,8,9-hexahydro-1*H*-cycloocta[c]pyrazol-3-amine**

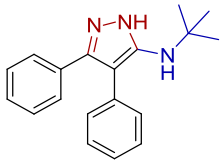
43% yield (38.3 mg), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.65 (t, *J* = 5.9 Hz, 2H), 2.37 (t, *J* = 6.2 Hz, 2H), 1.69 – 1.57 (m, 4H), 1.49 – 1.41 (m, 4H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 142.7, 106.0, 52.3, 30.2, 29.0, 28.6, 26.0, 25.4, 25.0, 21.1.

IR υ (cm^{-1}) 3212 (w), 2960 (w), 2925 (m), 2853 (w), 1589 (w), 1519 (w), 1458 (w), 1388 (w), 1362 (w), 1229 (w), 908 (w), 731 (s).

HRMS (ESI) calcd for $C_{13}H_{24}N_3^+$ $[M+H]^+$ 222.1965; found 222.1971.



89q

***N*-(*tert*-butyl)-4,5-diphenyl-1*H*-pyrazol-3-amine**

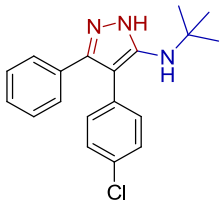
90% yield (104.5 mg), colorless solid (mp = 173-175 °C)

^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.37 – 7.18 (m, 10H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, CD_2Cl_2) δ 152.9, 141.4, 133.5, 131.1, 130.3, 129.3, 128.9, 128.4, 127.8, 126.9, 107.7, 52.2, 29.8.

IR υ (cm^{-1}) 3229 (w), 2964 (w), 2209 (w), 1665 (w), 1513 (m), 1445 (w), 1361 (w), 1284 (w), 1229 (m), 1135 (w), 1073 (w), 1020 (w), 940 (w), 761 (m), 735 (m), 697 (s), 637 (w).

HRMS (ESI) calcd for $C_{19}H_{22}N_3^+$ $[M+H]^+$ 292.1808; found 292.1814.



89r

***N*-(*tert*-Butyl)-4-(4-chlorophenyl)-5-phenyl-1*H*-pyrazol-3-amine**

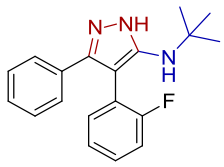
77% yield (100.0 mg), yellowish solid (mp = 186-188 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.27 (m, 5H), 7.17 (d, *J* = 8.5 Hz, 2H), 4.13 (*br* s, 2H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 141.5, 132.7, 131.6, 131.4, 130.3, 129.4, 128.9, 128.5, 127.6, 106.5, 52.2, 29.9.

IR υ (cm^{-1}) 3271 (w), 2956 (w), 1513 (s), 1498 (m), 1459 (w), 1361 (w), 1285 (w), 1230 (m), 1089 (w), 1013 (m), 939 (w), 829 (s), 768 (m), 739 (m), 723 (m), 693 (s).

HRMS (ESI) calcd for $C_{19}H_{21}ClN_3^+$ $[M+H]^+$ 326.1419; found 326.1416.



89s

***N*-(*tert*-butyl)-4-(2-fluorophenyl)-5-phenyl-1*H*-pyrazol-3-amine**

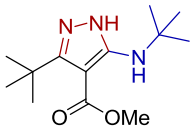
75% yield (92.2 mg), yellow solid (mp = 199-200 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 6H), 7.21 – 7.10 (m, 1H), 7.16 – 7.09 (m, 2H), 1.33 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (d, *J* = 245.9 Hz), 152.7, 142.8, 132.9 (d, *J* = 3.4 Hz), 130.9, 129.1 (d, *J* = 8.0 Hz), 128.8, 128.3, 127.1, 124.7 (d, *J* = 3.4 Hz), 120.7 (d, *J* = 15.9 Hz), 116.3 (d, *J* = 22.3 Hz), 101.8, 52.3, 29.9.

IR υ (cm^{-1}) 3226 (w), 2960 (w), 1684 (w), 1511 (s), 1448 (m), 1362 (w), 1258 (w), 1212 (m), 1102 (w), 1018 (w), 939 (w), 759 (s), 696 (s).

HRMS (ESI) calcd for $C_{19}H_{21}FN_3^+$ $[M+H]^+$ 310.1714; found 310.1720.



89t

Methyl 3-(*tert*-butyl)-5-(*tert*-butylamino)-1*H*-pyrazole-4-carboxylate

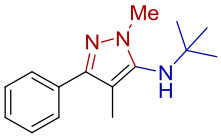
80% yield (80.6 mg), yellowish solid (mp = 142-144 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (*br* s, 1H), 6.12 (*br* s, 1H), 3.80 (s, 3H), 1.38 (s, 18H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 157.4, 155.5, 94.5, 51.1, 50.7, 33.1, 29.6, 28.4.

IR υ (cm^{-1}) 3349 (w), 2960 (w), 1646 (s), 1541 (m), 1506 (m), 1445 (s), 1365 (m), 1314 (m), 1220 (m), 1208 (m), 1102 (s), 797 (m), 735 (w), 700 (w), 663 (w).

HRMS (ESI) calcd for $C_{13}H_{24}N_3O_2^+$ $[M+H]^+$ 254.1863; found 254.1870.



89v

***N*-(*tert*-butyl)-1,4-dimethyl-5-phenyl-1*H*-pyrazol-3-amine**

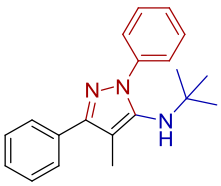
88% yield (85.5 mg), colorless solid (mp = 79-80 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.66 (m, 2H), 7.43 – 7.37 (m, 2H), 7.32 – 7.26 (m, 1H), 3.79 (s, 3H), 2.13 (s, 3H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 142.9, 134.8, 128.3, 127.3, 127.0, 107.5, 55.5, 35.7, 30.5, 10.9.

IR υ (cm^{-1}) 2972 (w), 2870 (w), 1684 (w), 1554 (w), 1479 (w), 1466 (w), 1447 (w), 1388 (w), 1361 (m), 1205 (m), 1024 (w), 754 (m), 698 (s), 677 (m).

HRMS (ESI) calcd for $C_{15}H_{22}N_3^+$ $[M+H]^+$ 244.1808; found 244.1811.



89w

***N*-(*tert*-butyl)-4-methyl-1,5-diphenyl-1*H*-pyrazol-3-amine**

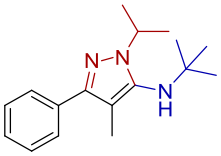
77% yield (94.5 mg), colorless solid (mp = 98-99 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.76 (m, 2H), 7.71 – 7.67 (m, 2H), 7.46 – 7.40 (m, 4H), 7.36 – 7.28 (m, 2H), 2.22 (s, 3H), 0.97 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 143.3, 140.7, 134.4, 128.9, 128.6, 127.8, 127.7, 127.1, 125.4, 109.2, 56.0, 30.4, 11.0.

IR υ (cm^{-1}) 3063 (w), 2967 (w), 2928 (w), 2867 (w), 1597 (m), 1562 (w), 1499 (s), 1465 (m), 1417 (w), 1389 (w), 1358 (s), 1220 (w), 1202 (w), 1164 (w), 1073 (w), 1013 (w), 976 (w), 773 (m), 761 (m), 698 (s), 684 (m).

HRMS (ESI) calcd for $C_{20}H_{24}N_3^+$ $[M+H]^+$ 306.1965; found 306.1970.

89x 

***N*-(*tert*-butyl)-1-isopropyl-4-methyl-5-phenyl-1*H*-pyrazol-3-amine**

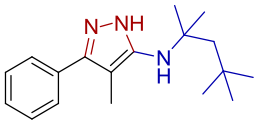
78% yield (84.7 mg), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.42 – 7.36 (m, 2H), 7.30 – 7.25 (m, 1H), 4.80 (hept, *J* = 6.6 Hz, 1H), 2.12 (s, 3H), 1.45 (d, *J* = 6.7 Hz, 6H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.3, 135.2, 128.3, 127.5, 126.9, 107.4, 54.9, 47.7, 30.4, 22.5, 10.9.

IR υ (cm^{-1}) 2972 (w), 1554 (w), 1468 (w), 1450 (w), 1389 (w), 1364 (w), 1270 (w), 1222 (w), 1204 (w), 1157 (w), 1018 (w), 911 (w), 774 (m), 734 (s), 698 (s), 614 (w).

HRMS (ESI) calcd for $C_{17}H_{26}N_3^+$ $[M+H]^+$ 272.2121; found 272.2121.

89y 

4-Methyl-3-phenyl-*N*-(2,4,4-trimethylpentan-2-yl)-1*H*-pyrazol-5-amine

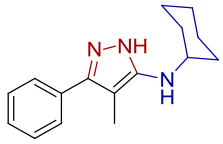
82% yield (93.2 mg), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.2 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.37 – 7.32 (m, 1H), 2.00 (s, 3H), 1.75 (s, 2H), 1.44 (s, 6H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 141.5, 131.6, 128.9, 128.0, 127.3, 100.9, 56.0, 53.6, 32.0, 31.9, 29.9, 8.3.

IR υ (cm^{-1}) 3228 (w), 2952 (s), 1593 (w), 1514 (s), 1478 (m), 1384 (w), 1365 (m), 1228 (m), 1146 (w), 1012 (w), 767 (m), 698 (s).

HRMS (ESI) calcd for $C_{18}H_{28}N_3^+$ $[M+H]^+$ 286.2278; found 286.2280.

89z 

***N*-Cyclohexyl-4-methyl-3-phenyl-1*H*-pyrazol-5-amine**

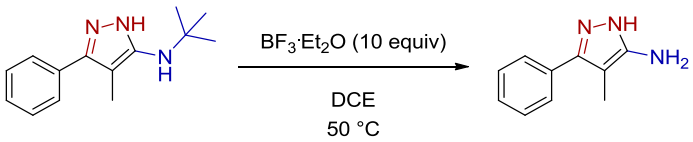
53% yield (46.0 mg), yellowish oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.32 (m, 4H), 7.28 (t, *J* = 6.8 Hz, 1H), 3.44 – 3.32 (m, 1H), 2.12 – 2.10 (m, 2H), 1.94 (s, 3H), 1.77 – 1.62 (m, 2H), 1.66 – 1.60 (m, 1H), 1.41 – 1.32 (m, 2H), 1.20 – 1.05 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 141.5, 131.1, 129.0, 128.2, 127.3, 98.9, 52.9, 34.3, 26.1, 25.3, 8.0.

IR υ (cm^{-1}) 3167 (w), 2926 (s), 2853 (m), 1524 (s), 1450 (m), 1169 (w), 1012 (w), 945 (w), 911 (w), 768 (m), 734 (m), 697 (s).

HRMS (ESI) calcd for $C_{16}H_{22}N_3^+$ $[M+H]^+$ 256.1808; found 256.1814.



4-Methyl-3-phenyl-1*H*-pyrazol-5-amine (95) : To a solution of the 5-aminopyrazole **89a** (23.0 mg, 0.1 mmol, 1.0 equiv) in DCE (2 mL) at 0 °C was added $BF_3{\cdot}Et_2O$ (124 µL, 1.0 mmol, 10.0 equiv) and the reaction mixture was stirred at 50 °C for 2 h. Water was then added at rt, the crude product was extracted in the aqueous layer (pH=0) and the organic layer was discarded. The aqueous layer was then basified with sat. aqueous $NaHCO_3$ and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with DCM/MeOH 10:1 as eluent to afford the desired 5-aminopyrazole **95** as a yellowish oil (13.5 mg, 0.078 mmol, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.46 (m, 2H), 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 1H), 6.23 (*br* s, 3H), 2.03 (s, 3H).

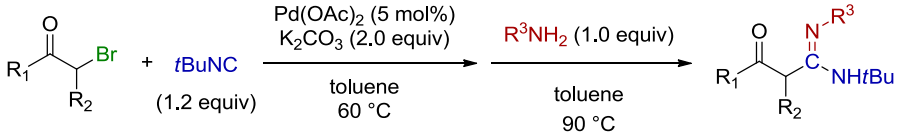
^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 142.1, 130.6, 129.1, 128.5, 127.4, 99.3, 7.9.

IR υ (cm^{-1}) 2921 (w), 1606 (w), 1501 (s), 1074 (w), 768 (m), 697 (s).

HRMS (ESI) calcd for $C_{10}H_{12}N_3^+$ $[M+H]^+$ 174.1026; found 174.1029.

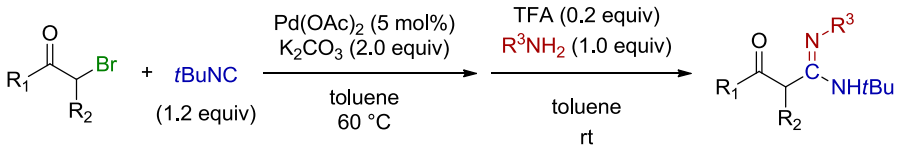
3.3.6 Synthesis of β-Ketoamidines

Procedure [a] :

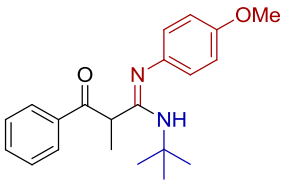


To a solution of the α–bromoketone (0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and the isocyanide (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. The reaction mixture was filtered through a short pad of Celite and sat. aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude ketenimine was dissolved in toluene, the amine (1.0 equiv) was added and the reaction mixture was stirred at 90 °C until complete consumption of the α–oxo-ketenimine. The reaction mixture was partitioned between sat. aqueous NH_4Cl and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under recuced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired β–ketoamidine.

Procedure [b] :



To a solution of the α–bromoketone (0.4 mmol, 1.0 equiv) in toluene (2 mL) were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 5 mol%) and K_2CO_3 (110.6 mg, 0.8 mmol, 2.0 equiv). The reaction mixture was purged with argon and the isocyanide (0.48 mmol, 1.2 equiv) was added. The reaction mixture was then stirred at 60 °C until complete consumption of the α–bromoketone. The reaction mixture was filtered through a short pad of Celite and sat. aqueous $NaHCO_3$ was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude ketenimine was dissolved in toluene, the amine (1.0 equiv) and TFA (6 µL, 0.08 mmol, 0.2 equiv) were added and the reaction mixture was stirred at room temperature until complete consumption of the α–oxo-ketenimine. The reaction mixture was partitioned between sat. aqueous NH_4Cl and EtOAc and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under recuced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford the desired β–ketoamidine.



86a

***N*-(*tert*-butyl)-*N*'-(4-methoxyphenyl)-2-methyl-3-oxo-3-phenylpropanimidamide**

Conditions [a] : 85% yield (114.8 mg), yellow solid (mp = 106-107 °C)

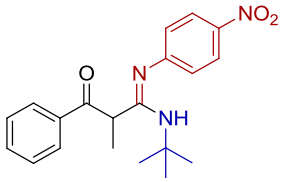
Conditions [b] : 84% yield (113.2 mg)

^{1}H NMR (400 MHz, $CDCl_3$) δ.74 (d, *J* = 7.5 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 4.55 (q, *J* = 6.9 Hz, 1H), 4.52 (s, 1H), 3.81 (s, 3H), 1.44 (d, *J* = 6.9 Hz, 3H), 1.31 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 155.0, 153.6, 144.2, 136.0, 133.7, 128.6, 128.6, 123.0, 114.6, 55.7, 51.3, 42.9, 28.6, 17.4.

IR υ (cm^{-1}) 2960 (w), 1676 (w), 1632 (s), 1502 (s), 1450 (w), 1361 (w), 1239 (s), 1189 (m), 1101 (w), 1035 (w), 962 (w), 839 (w), 719 (w), 689 (w).

HRMS (ESI) calcd for $C_{21}H_{27}N_2O_2^+$ $[M+H]^+$ 339.2067; found 339.2066.



86b

***N*'-(*tert*-butyl)-2-methyl-*N*-(4-nitrophenyl)-3-oxo-3-phenylpropanimidamide**

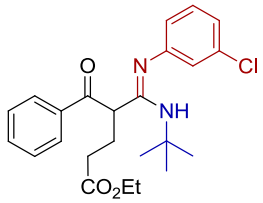
Conditions [b] : 52% yield (73.2 mg), yellow solid (mp = 119-120 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.17 (m, 2H), 7.71 – 7.66 (m, 2H), 7.63 – 7.57 (m, 1H), 7.45 – 7.39 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.21 (*br* s, 1H), 4.45 (q, *J* = 6.9 Hz, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.36 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.3, 157.1, 153.2, 142.6, 135.6, 134.3, 129.0, 128.5, 125.5, 122.5, 52.0, 42.9, 28.5, 18.3.

IR υ (cm^{-1}) 3391 (w), 1681 (w), 1621 (m), 1582 (m), 1530 (m), 1500 (s), 1332 (s), 1259 (m), 1222 (m), 1197 (m), 1102 (w), 961 (w), 864 (m), 851 (m), 769 (w), 748 (w), 710 (m), 694 (s), 667 (w), 611 (w).

HRMS (ESI) calcd for $C_{20}H_{24}N_3O_3^+$ $[M+H]^+$ 354.1812; found 354.1812.



86c

Ethyl 4-benzoyl-5-(*tert*-butylamino)-5-((3-chlorophenyl)imino)pentanoate

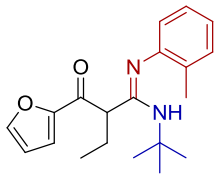
Conditions [b] : 83% yield (141.8 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 8.1 Hz, 1H), 6.64 (s, 1H), 6.54 (d, *J* = 7.6 Hz, 1H), 5.14 (s, 1H), 4.64 (t, *J* = 6.8 Hz, 1H), 4.04 (q, *J* = 7.1 Hz, 1H), 4.03 (q, *J* = 7.1 Hz, 1H), 2.32 – 2.22 (m, 3H), 2.15 – 2.02 (m, 1H), 1.36 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 172.5, 151.9, 151.3, 135.9, 134.6, 134.3, 130.1, 129.0, 128.8, 122.5, 122.0, 120.7, 60.9, 51.6, 46.7, 31.8, 28.6, 28.4, 14.3.

IR υ (cm^{-1}) 3393 (w), 2962 (w), 1732 (m), 1671 (m), 1632 (s), 1587 (s), 1525 (s), 1471 (m), 1449 (m), 1361 (w), 1251 (m), 1211 (s), 1186 (s), 1159 (m), 1071 (w), 1029 (w), 782 (m), 724 (w), 687 (m).

HRMS (ESI) calcd for $C_{24}H_{30}ClN_2O_3^+$ $[M+H]^+$ 429.1939; found 429.1943.



86d

***N*'-(*tert*-butyl)-2-(furan-2-carbonyl)-*N*-(*o*-tolyl)butanimidamide**

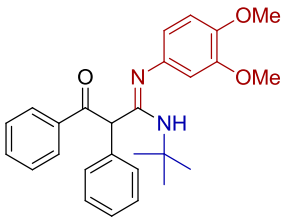
Conditions [b] : 70% yield (91.2 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 0.7 Hz, 1H), 7.19 – 7.08 (m, 2H), 6.93 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 3.4 Hz, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.45 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.14 (s, 1H), 4.18 (dd, *J* = 8.8, 6.2 Hz, 1H), 2.05 – 1.92 (m, 4H), 1.86 – 1.72 (m, 1H), 1.41 (s, 9H), 0.85 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 152.1, 150.6, 149.5, 148.0, 130.5, 130.4, 126.3, 121.9, 121.6, 119.9, 112.5, 51.2, 49.5, 28.8, 26.8, 18.7, 12.3.

IR υ (cm^{-1}) 3398 (w), 2964 (w), 1663 (m), 1634 (s), 1595 (m), 1525 (m), 1485 (m), 1463 (s), 1390 (w), 1360 (w), 1254 (m), 1225 (m), 1201 (w), 1183 (m), 1113 (w), 1041 (w), 1021 (w), 998 (w), 769 (m), 741 (w).

HRMS (ESI) calcd for $C_{20}H_{27}N_2O_2^+$ $[M+H]^+$ 327.2067; found 327.2071.



86e

***N*-(*tert*-butyl)-*N*'-(3,4-dimethoxyphenyl)-3-oxo-2,3-diphenylpropanimidamide**

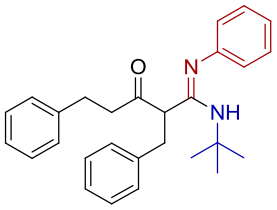
Conditions [b] : 70% yield (119.7 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 7.1 Hz, 2H), 7.27 (t, *J* = 7.1 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 8.3 Hz, 1H), 6.16 (s, 1H), 5.91 (s, 1H), 4.90 (s, 1H), 3.80 (s, 3H), 3.55 (s, 3H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 151.2, 149.3, 144.8, 144.4, 136.6, 136.4, 133.8, 129.1, 128.8, 128.7, 128.7, 127.7, 113.3, 112.2, 106.8, 56.4, 55.5, 54.5, 51.7, 28.6.

IR υ (cm^{-1}) 2975 (w), 1675 (w), 1633 (s), 1598 (w), 1504 (s), 1450 (w), 1264 (w), 1222 (m), 1189 (w), 1129 (w), 1029 (w).

HRMS (ESI) calcd for $C_{27}H_{31}N_2O_3^+$ $[M+H]^+$ 431.2329; found 431.2333.



86f

2-Benzyl-*N*'-(*tert*-butyl)-3-oxo-*N*,5-diphenylpentanimidamide

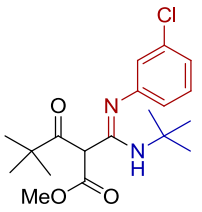
Conditions [b] : 67% yield (110.1 mg), orange oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 6.97 (m, 8H), 6.92 – 6.87 (m, 2H), 6.84 – 6.76 (m, 3H), 6.24 (d, *J* = 7.4 Hz, 2H), 4.35 (s, 1H), 3.74 (dd, *J* = 8.2, 6.6 Hz, 1H), 2.88 (dd, *J* = 13.6, 8.3 Hz, 1H), 2.73 (dd, *J* = 13.5, 6.5 Hz, 1H), 2.67 – 2.49 (m, 3H), 2.26 – 2.15 (m, 1H), 1.22 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 150.8, 150.3, 140.7, 138.4, 129.1, 129.1, 128.6, 128.4, 126.8, 126.3, 122.0, 121.8, 55.2, 51.4, 44.5, 37.0, 29.4, 28.6.

IR υ (cm^{-1}) 3388 (w), 3027 (w), 2964 (w), 1707 (w), 1629 (s), 1592 (m), 1524 (m), 1487 (m), 1451 (w), 1363 (w), 1252 (w), 1225 (w), 1192 (m), 1072 (w), 773 (w), 754 (m), 696 (s).

HRMS (ESI) calcd for $C_{28}H_{33}N_2O^+$ $[M+H]^+$ 413.2587; found 413.2596.



86g

Methyl 2-(*N*'-(*tert*-butyl)-N-(3-chlorophenyl)carbamimidoyl)-4,4-dimethyl-3-oxopentanoate

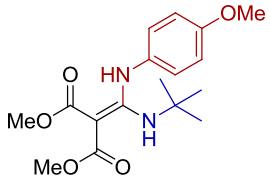
Conditions [b] : 68% yield (99.8 mg), colorless oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, *J* = 7.9 Hz, 1H), 6.95 (ddd, *J* = 8.0, 2.0, 0.9 Hz, 1H), 6.69 (t, *J* = 2.0 Hz, 1H), 6.57 (ddd, *J* = 7.9, 1.9, 0.9 Hz, 1H), 5.09 (s, 1H), 4.92 (s, 1H), 3.73 (s, 3H), 1.40 (s, 9H), 1.02 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 167.2, 151.5, 146.2, 134.7, 130.2, 122.3, 122.2, 120.2, 54.3, 53.3, 52.0, 46.2, 28.4, 26.1.

IR υ (cm^{-1}) 3415 (w), 2967 (w), 1750 (m), 1703 (w), 1639 (s), 1588 (s), 1533 (s), 1466 (m), 1363 (w), 1260 (m), 1222 (m), 1191 (m), 1166 (s), 1061 (m), 1010 (w), 844 (w), 782 (m), 684 (w).

HRMS (ESI) calcd for $C_{19}H_{28}ClN_2O_3^+$ $[M+H]^+$ 367.1783; found 367.1797.



86h

Dimethyl 2-(*N*'-(*tert*-butyl)-*N*-(4-methoxyphenyl)carbamimidoyl)malonate

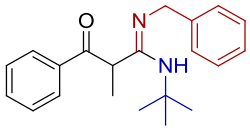
Conditions [b] : 87% yield (117.1 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (*br* s, 1H), 8.79 (*br* s, 1H), 7.07 – 7.03 (m, 2H), 6.83 – 6.79 (m, 2H), 3.77 (s, 3H), 3.62 (s, 6H), 1.18 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 164.1, 157.0, 134.7, 124.7, 114.5, 81.6, 55.7, 55.4, 51.4, 30.7.

IR υ (cm^{-1}) 2950 (w), 1697 (w), 1637 (s), 1511 (s), 1436 (m), 1360 (m), 1286 (m), 1238 (s), 1217 (s), 1084 (s), 1034 (w), 829 (w), 808 (w), 732 (w).

HRMS (ESI) calcd for $C_{17}H_{25}N_2O_5^+$ $[M+H]^+$ 337.1758; found 337.1758.



86i

***N*-Benzyl-*N*'-(*tert*-butyl)-2-methyl-3-oxo-3-phenylpropanimidamide**

Conditions [a] : 58% yield (74.7 mg), yellow oil

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (*br* s, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.45 (m, 2H), 7.40 – 7.26 (m, 7H), 5.13 (d, *J* = 16.2 Hz, 1H), 5.07 (q, *J* = 6.1 Hz, 1H), 4.62 (d, *J* = 16.2 Hz, 1H), 1.62 (s, 9H), 1.45 (d, *J* = 6.4 Hz, 3H).

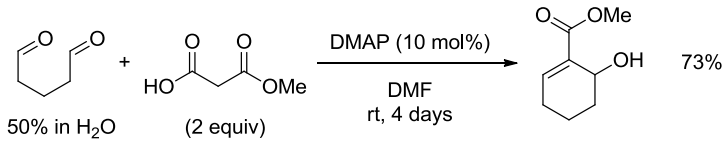
^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 162.8, 136.9, 135.1, 134.7, 129.5, 129.3, 128.7, 128.4, 127.3, 54.8, 47.8, 41.1, 28.4, 17.9.

IR υ (cm^{-1}) 3204 (w), 3029 (w), 2931 (w), 1688 (m), 1637 (s), 1596 (m), 1450 (w), 1379 (w), 1230 (w), 1206 (w), 967 (w), 927 (w), 728 (m), 696 (w).

HRMS (ESI) calcd for $C_{21}H_{27}N_2O^+$ $[M+H]^+$ 323.2118; found 323.2122.

3.4 Mersilongine

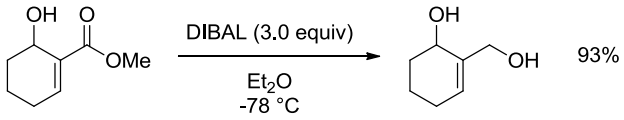
3.4.1 Synthesis of Building Blocks **148** and **149**



Methyl 6-hydroxycyclohex-1-enecarboxylate (182) : To a solution of glutaraldehyde (9.81 mL of a 50% solution in H_2O, 55.0 mmol, 1 equiv) and monomethyl malonate (12.99 g, 110.0 mmol, 2 equiv) in DMF (110 mL, 0.5 M) was added DMAP (0.67 g, 5.5 mmol, 10 mol%) and the reaction mixture was stirred at room temperature for 4 days. The crude reaction mixture was then partitioned between H_2O and EtOAc and extracted many times with EtOAc. The combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 5:1 as eluent to afford α,β-unsaturated ester **182** as colorless oil (5.69 g, 36.5 mmol, 73% yield). The spectroscopic data were consistent with those reported in the literature.[163]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 4.0 Hz, 1H), 4.55 – 4.50 (m, 1H), 3.77 (s, 3H), 2.33 – 2.22 (m, 1H), 2.19 – 2.07 (m, 1H), 1.88 – 1.70 (m, 3H), 1.64 – 1.55 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 143.4, 132.4, 63.6, 51.9, 30.1, 26.3, 17.6.

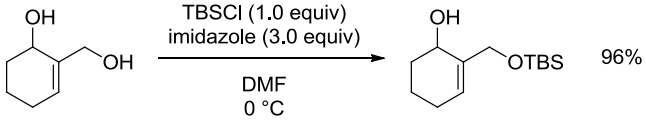


2-(Hydroxymethyl)cyclohex-2-enol (189) : To a solution of ester **182** (1.87 g, 11 mmol, 1 equiv) in Et_2O (55 mL, 0.2 M) at -78 °C was added dropwise DIBAL (27.5 mL of a 1.2 M solution in toluene, 33 mmol, 3 equiv) and the reaction mixture was stirred at -78 °C for 2 h. The crude reaction mixture was then allowed to warm to 0 °C and a saturated solution of Rochelle salt (25 mL) was added. The biphasic mixture was stirred for 1 h and extracted many times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford diol **189** as a colorless oil (1.31 g, 10.2 mmol, 93% yield). The crude product was used in the next step without further purification. The spectroscopic data were consistent with those reported in the literature.[164]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (t, *J* = 3.6 Hz, 1H), 4.32 (t, *J* = 4.7 Hz, 1H), 4.20 (dd, *J* = 21.4, 12.6 Hz, 2H), 2.16 – 2.07 (m, 1H), 2.03 – 1.94 (m, 1H), 1.81 – 1.74 (m, 2H), 1.74 – 1.67 (m, 1H), 1.63 – 1.54 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 128.8, 67.3, 67.2, 31.9, 25.4, 18.3.

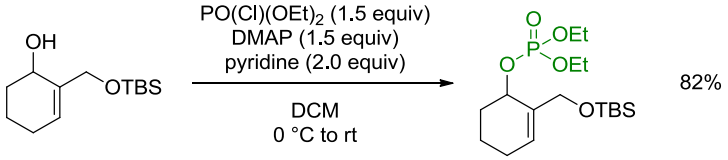
[163] See reference 106.
[164] Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125* (32), 9801–9807.



2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-2-enol (190) : Diol **189** (9.48 g, 74.0 mmol, 1.00 equiv), TBSCl (11.71 g, 77.7 mmol, 1.05 equiv) and imidazole (15.11 g, 222.0 mmol, 3.0 equiv) were dissolved in DMF (148 mL, 0.5 M) at 0 °C and the reaction mixture was stirred at 0 °C for 1 h. The crude reaction mixture was partitioned between H_2O and Et_2O and extracted with Et_2O. The combined organic layers were washed many times with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford alcohol **190** as a colorless oil (17.3 g, 71.0 mmol, 96% yield). The crude product was used in the next step without further purification. The spectroscopic data were consistent with those reported in the literature.[165]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.95 (m, 1H), 5.33 (t, *J* = 3.9 Hz, 1H), 4.06 (dd, *J* = 34.6, 13.3 Hz, 2H), 2.18 – 2.08 (m, 1H), 2.04 (s, 1H), 1.90 – 1.82 (m, 1H), 1.79 – 1.69 (m, 1H), 1.69 – 1.57 (m, 2H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 135.2, 128.1, 67.2, 64.4, 26.1, 25.0, 21.6, 18.6, 18.2, -5.3.

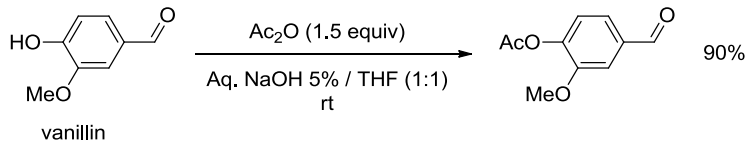


2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-yl diethyl phosphate (149) : To a solution of alcohol **190** (2.91 g, 12 mmol, 1 equiv) in DCM (60 mL, 0.2 M) at 0 °C were added diethyl chlorophosphate (2.60 mL, 18.00 mmol, 1.5 equiv), pyridine (1.94 mL, 24 mmol, 2.0 mmol) and DMAP (2.20 g, 18 mmol, 1.5 equiv) and the reaction mixture was stirred at room temperature for 5 h. The combined organic layers were washed with saturated aqueous NH_4Cl and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc as eluent to afford phosphonate **149** as a colorless oil (3.72 g, 9.84 mmol, 82% yield). The spectroscopic data were consistent with those reported in the literature.[166]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.95 (s, 1H), 4.87 – 4.80 (m, 1H), 4.17 (d, *J* = 1.9 Hz, 2H), 4.15 – 4.05 (m, 4H), 2.18 – 2.07 (m, 2H), 2.05 – 1.94 (m, 1H), 1.81 – 1.69 (m, 2H), 1.66 – 1.57 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 6H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4 (d), 127.5, 72.0 (d), 64.0, 63.7 (t), 30.1, 26.1, 24.9, 18.6, 17.7, 16.3 (dd), -5.2 (d).

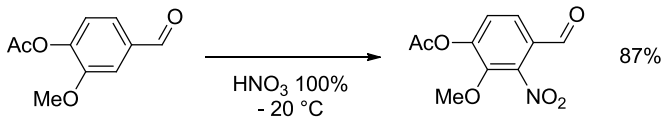
[165] See reference 164.
[166] See reference 164.



4-Formyl-2-methoxyphenyl acetate (191) : Vanillin (15.22 g, 100 mmol, 1 equiv) was dissolved in a 5% aqueous NaOH solution (100 mL, 1 M) and a solution of Ac_2O (10.40 mL, 150 mmol, 1.5 equiv) in THF (100 mL, 1.0 M) was added dropwise over 30 min and the reaction mixture was stirred at room temperature for 1 h. The crude reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure until complete removal of excess Ac_2O to afford vanillin acetate **191** as a grey solid (17.4 g, 89.8 mmol, 90% yield). The crude product was used in the next step without further purification and the spectroscopic data were consistent with those reported in the literature.[167]

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.50 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 168.5, 152.2, 145.1, 135.4, 125.0, 123.6, 111.0, 56.3, 20.8.

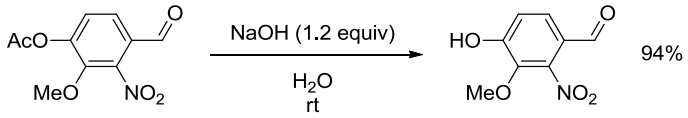


4-Formyl-2-methoxy-3-nitrophenyl acetate (192) : Vanillin acetate **191** (11.65 g, 60 mmol, 1 equiv) was extremely carefully added portionwise over 2 h to fuming nitric acid (60 mL, 1 M) at -20 °C (strongly exothermic). At the end of the addition, the crude reaction mixture was poured extremely carefully to H_2O (50 mL) at 0 °C under vigorous stirring (strongly exothermic). The precipitate was filtered, washed with H_2O until and H_2O/EtOH 5:1 until neutralization to afford 2-nitrovanillin acetate **192** as a yellow solid (12.4 g, 51.9 mmol, 87% yield). The crude product was used in the next step without further purification and the spectroscopic data were consistent with those reported in the literature.[168]

^{1}H NMR (400 MHz, Acetone-d6) δ 9.97 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 3.96 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 149.7, 144.2, 125.4, 122.5, 111.9, 103.6, 52.4, 38.9.

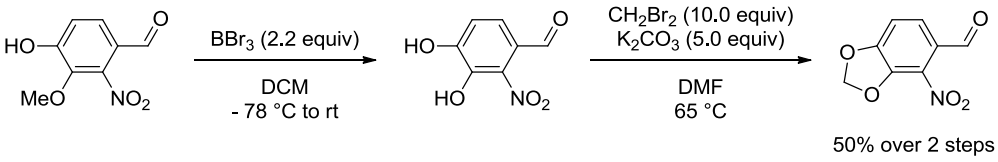
[167] See reference 107.
[168] See reference 107.



4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (193) : 2-Nitrovanillin acetate **192** (11.96 g, 50 mmol, 1.0 equiv) was added portionwise to a solution of NaOH (2.4 g, 60 mmol, 1.2 equiv) in H_2O (50 mL, 1 M) at room temperature and the reaction mixture was stirred for 1 h. The crude reaction mixture was then cooled to 0 °C and 10% aqueous HCl was carefully added until pH = 1. The precipitate was filtered and washed with cold water until neutralization to afford 2-nitrovanillin **193** as a yellow solid (9.30 g, 47.2 mmol, 94% yield). The crude product was used in the next step without further purification and the spectroscopic data were consistent with those reported in the literature.[169]

^{1}H NMR (400 MHz, Acetone-d6) δ 9.80 (s, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.9, 155.4, 146.4, 139.3, 128.5, 121.1, 117.8, 63.2.



4-Nitrobenzo[*d*][1,3]dioxole-5-carbaldehyde (195) : BBr_3 (6.36 mL, 66 mmol, 2.2 equiv) was added dropwise to a suspension of 2-nitrovanillin **193** (5.91 g, 39 mmol, 1.0 equiv) in DCM (300 mL, 0.1 M) at -78 °C and the reaction was allowed to warm to room temperature over 5 h. DCM (300 mL) and brine (300 mL) were then added[170] and the layers were separated.[171] The organic layer was partially concentrated under reduced pressure while the aqueous layer was extracted with Et_2O. The combined organic layers (DCM and Et_2O) were then washed with brine until neutralization, dried over Na_2SO_4 and concentrated under reduced pressure to afford catechol **194** as a dark brown solid. The crude product was used in the next step without further purification. Catechol **194**, K_2CO_3 (45.60 g, 330 mmol, 5.0 equiv) and CH_2Br_2 (46.31 mL, 660 mmol, 10.0 equiv) were stirred in DMF (264 mL, 0.25 M) at 65 °C for 8 h and the crude reaction mixture was concentrated to dryness under reduced pressure. H_2O (300 mL) was then added and the crude reaction mixture was stirred for 1 h to until almost complete solubilization. This aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was passed through a column of silica and recrystallized from EtOH at 70 °C and washed with cold petroleum ether to afford benzodioxole derivative **195** as an orange solid (m.p. = 99-100 °C) (6.44 g, 32.9 mmol, 50% yield over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.30 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 154.4, 143.2, 126.1, 124.8, 111.5, 104.7.

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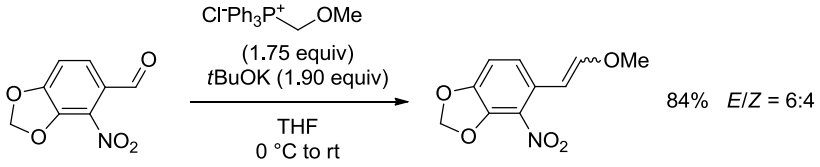
[169] See reference 107.
[170] The solid sticking on the walls of the flask was scratched with a spatula to dissolve it.
[171] The product is not fully soluble in DCM.

IR υ (cm^{-1}) 721 (s), 786 (s), 815 (s), 841 (s), 906 (s), 1042 (s), 1140 (w), 1172 (w), 1228 (s), 1263 (s), 1335 (s), 1455 (w), 1471 (s), 1523 (s), 1685 (s), 2160 (s).

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_8H_6NO_5^+$ 196.0240; Found 196.0233.



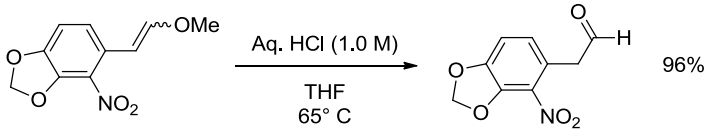
5-(2-Methoxyvinyl)-4-nitrobenzo[*d*][1,3]dioxole (198) : *t*BuOK (5.97 g, 53.2 mmol, 1.90 equiv) was added portionwise to a suspension of the phosphonium salt[172] (16.80 g, 49.0 mmol, 1.75 equiv) in THF (260 mL, 0.2 M) at 0 °C. A solution of aldehyde **195** (5.46 g, 28.0 mmol, 1.00 equiv) in THF (100 mL) was then added dropwise over 30 min at 0 °C and the reaction mixture was allowed to warm to room temperature and stirred for 4 h. Saturated aqueous NH_4Cl was then adden and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was redissolved in a minimum volume of Et_2O and stored in the freezer overnight. The precipitate (triphenyl phosphine oxide and excess phosphonium salt) was filtered and discarded. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography with PE/EtOAc 10:1 as eluent to afford vinyl ether **198** as dark orange solid (m.p. = 75-77 °C) (5.30 g, 23.7 mmol, 84% yield, *E*/*Z* = 6:4). Major isomer :

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.79 (d, *J* = 12.8 Hz, 1H), 6.07 (s, 2H), 6.05 (d, *J* = 12.8 Hz, 1H), 3.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.1, 147.7, 142.9, 132.2, 125.3, 119.7, 111.9, 103.2, 99.6, 56.6.

IR υ (cm^{-1}) 721 (s), 810 (s), 829 (s), 910 (s), 988 (m), 1042 (s), 1091 (m), 1137 (m), 1237 (s), 1302 (w), 1345 (s), 1477 (s), 1527 (s), 1655 (s).

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_5^+$ 224.0553; Found 224.0546.



2-(4-Nitrobenzo[*d*][1,3]dioxol-5-yl)acetaldehyde (199) : To a solution of vinyl ether **198** (4.46 g, 20 mmol, 1 equiv) in THF (80 mL, 0.25 M) was added 1.0 M aqueous HCl (80 mL) and the reaction mixture was stirred at 65 °C for 5 h. The crude reaction mixture was allowed to cool to room temperature and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine until neutralization, dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **199** as a

[172] This reagent was purchased from Sigma-Aldrich.

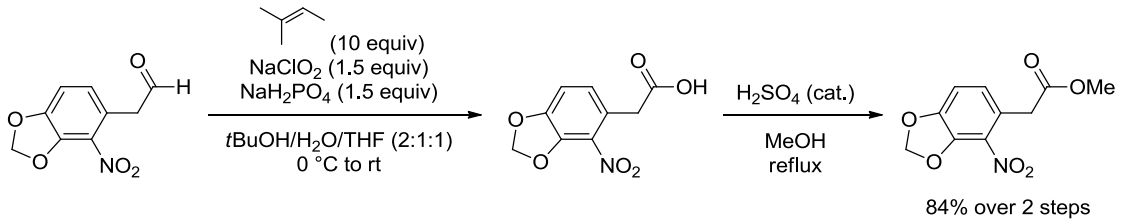
pale yellow solid (m.p. = 111-113 °C) (3.99 g, 19.1 mmol, 96% yield).The crude product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 2H), 3.98 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 149.9, 144.4, 133.5, 125.6, 121.1, 112.3, 103.7, 47.9.

IR υ (cm^{-1}) 722 (s), 811 (s), 835 (m), 908 (s), 1027 (s), 1056 (s), 1199 (w), 1259 (s), 1347 (s), 1471 (s), 1530 (s), 1616 (s), 1725 (s).

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_9H_8NO_5^+$ 210.0397; Found 210.0391.



Methyl 2-(4-nitrobenzo[d][1,3]dioxol-5-yl)acetate (148) : Aldehyde **199** (5.23 g, 25.0 mmol, 1.0 equiv) and 2-methyl-2-butene (26.5 mL) were dissolved in THF (125 mL, 0.2 M) before adding *t*BuOH (250 mL). The reaction mixture was cooled to 0 °C and a solution of $NaClO_2$ (3.39 g, 37.5 mmol, 1.5 equiv) and NaH_2PO_4 (4.50 g g, 37.5 mmol, 1.5 equiv) in H_2O (125 mL) was slowly added. The reaction mixture was then stirred at room temperature for 1 h and 1 M aqueous HCl was added. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford carboxylic acid **196** as a yellow solid. The crude product was used in the next step without further purification. Carboxylic acid **196** was dissolved in MeOH (250 mL, 0.1 M) with a few drops of 100% H_2SO_4 and the reaction mixture was reflux for 5 h. The crude reaction mixture was then partially concentrated under reduced pressure and stored in the freezer overnight. The precipitate was filtered and washed with cold MeOH until neutralization to afford methyl ester **148** as a pale yellow solid (m.p. = 111-112 °C) (5.00 g, 20.9 mmol, 84% yield over 2 steps).

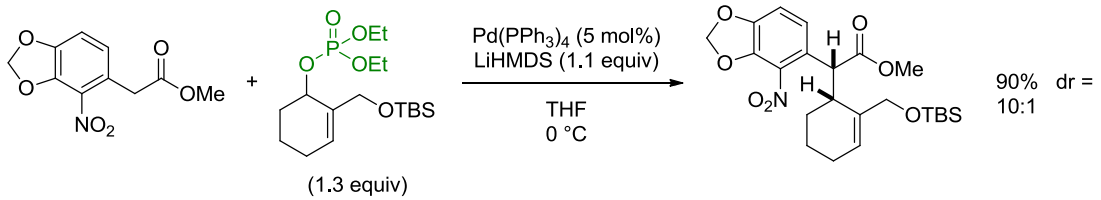
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 2H), 3.93 (s, 2H), 3.73 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 185.8, 167.7, 149.3, 144.6, 126.3, 126.2, 126.1, 125.7, 63.1, 21.0.

IR υ (cm^{-1}) 721 (s), 794 (w), 816 (s), 840 (m), 899 (m), 915 (s), 977 (m), 1050 (s), 1123 (m), 1165 (m), 1203 (s), 1244 (s), 1340 (s), 1449 (w), 1534 (s), 1722 (s).

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_9NNaO_6^+$ 262.0322; Found 262.0325.

3.4.2 From Tsuji-Trost Reaction to Aminal **249**



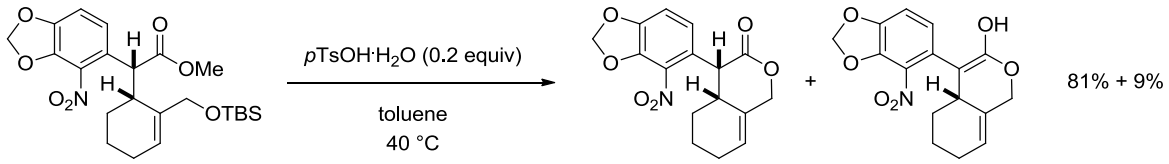
(*R*)-methyl-2-((*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-yl)-2-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)acetate (147) : To a solution of α-aryl ester **148** (1.196 g, 5 mmol, 1.0 equiv) and phosphonate **149** (2.272 g, 6 mmol, 1.2 equiv) in THF (50 mL, 0.1 M) at 0 °C was added $Pd(PPh_3)_4$ (288 mg, 5 mol%). LiHMDS (5 mL of a 1 M solution in THF, 5 mmol, 1.0 equiv) was then added dropwise (10 drops every 20 seconds) and the reaction mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 10:1 to afford α,α-disubstituted ester **147** as a pale yellow oil (2.10 g, 4.53 mmol, 90% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.3 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 1H), 6.25 (d, *J* = 5.3 Hz, 2H), 5.85 (s, 1H), 4.45 (d, *J* = 9.4 Hz, 1H), 3.79 (s, 3H), 3.51 (s, 2H), 3.03 – 2.95 (m, 1H), 2.27 – 2.10 (m, 2H), 1.88 – 1.76 (m, 2H), 1.76 – 1.65 (m, 1H), 1.60 – 1.48 (m, 1H), 0.96 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 148.9, 142.3, 137.1, 127.1, 125.6, 125.1, 123.2, 111.2, 103.5, 68.1, 66.6, 52.3, 47.6, 38.8, 31.1, 26.9, 26.1, 24.7, 18.5, -5.2.

IR υ (cm^{-1}) 721 (s), 760 (s), 1247 (s), 1534 (m), 1740 (m), 1769 (m), 1805 (w), 2024 (m), 2163 (w), 2922 (s).

HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{33}NO_7SiNa^+$ 486.1924; Found 486.1927.



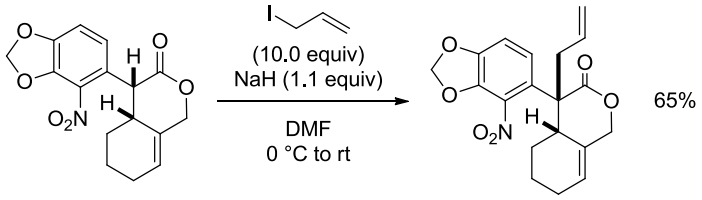
(4*R*,4a*R*)-4-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)-4a,5,6,7-tetrahydro-1*H*-isochromen-3(4*H*)-one (201) : To a solution of α,α-disubstituted ester **147** (1.81 g, 3.90 mmol, 1.0 equiv) in toluene (39 mL, 0.1 M) was added *p*TsOH·H_2O (0.15 g, 0.78 mmol, 0.2 equiv) and the reaction mixture was stirred at 40 °C for 1 h. The crude reaction mixture was partially concentrated under reduced pressure and the crude product was purified by column chromatography with PE/EtOAc 5:3 as eluent to afford lactone **201** as a yellow solid (m.p. = 143-146 °C) (1.11 g, 3.51 mmol, 90% yield, ratio = 9:1). Major tautomer :

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, *J* = 8.3 Hz, 1H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.17 (dd, *J* = 13.2, 1.2 Hz, 2H), 5.89 (d, *J* = 2.8 Hz, 1H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.67 – 4.57 (m, 2H), 3.21 – 3.10 (m, 1H), 2.18 – 2.01 (m, 2H), 1.78 – 1.69 (m, 1H), 1.52 – 1.37 (m, 2H), 1.16 – 1.04 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 149.0, 142.8, 134.4, 131.2, 128.4, 126.0, 122.2, 111.4, 103.5, 72.3, 44.6, 37.8, 26.5, 24.8, 21.8.

IR υ (cm^{-1}) 809 (s), 915 (m), 1046 (s), 1234 (s), 1353 (m), 1472 (m), 1534 (s), 1728 (s), 2866 (w), 2917 (w).

HRMS (ESI/TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{15}NO_6Na^+$ 340.0797; Found 340.0798.



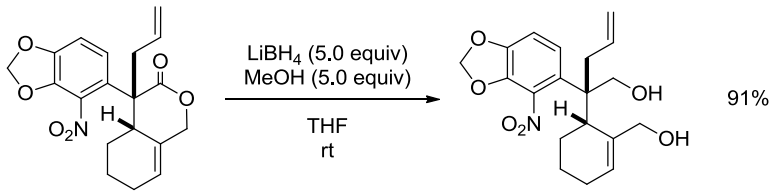
(4*R*,4a*S*)-4-allyl-4-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)-4a,5,6,7-tetrahydro-1*H*-isochromen-3(4*H*)-one (204) **:** To a solution of lactone **201** (2.28 g, 7.2 mmol, 1.0 equiv) and freshly distilled allyl iodide (5.34 mL, 72.0 mmol, 10.0 equiv) in DMF (72 mL, 0.1 M) at 0 °C was added NaH (0.53 g, 1.1 equiv) in 4 portions (1 portion every 5 min) and the reaction mixture was allowed to warm to room temperature. H_2O (15 mL) was then added and the crude reaction mixture was stored in the freezer overnight. The precipitate was filtered and washed with cold pentane to afford α-allyl lactone **204** as a yellow solid (m.p. = 207-208 °C) (1.676 g, 4.69 mmol, 65% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (s, 2H), 6.15 (d, *J* = 23.3 Hz, 2H), 5.87 (s, 1H), 5.78 – 5.66 (m, 1H), 5.24 (d, *J* = 30.0 Hz, 1H), 5.19 (s, 1H), 4.96 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 12.5 Hz, 1H), 3.08 (dd, *J* = 14.3, 6.1 Hz, 1H), 2.87 (dd, *J* = 14.3, 7.8 Hz, 1H), 2.77 (s, 1H), 2.12 – 1.96 (m, 2H), 1.69 – 1.59 (m, 1H), 1.45 – 1.30 (m, 2H), 1.19 – 1.06 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 148.8, 143.7, 134.2, 132.6, 129.3, 128.5, 126.4, 122.5, 120.5, 110.2, 103.5, 72.6, 54.8, 46.7, 44.7, 27.4, 24.8, 22.4.

IR υ (cm^{-1}) 760 (m), 781 (m), 817 (s), 892 (m), 917 (s), 1021 (s), 1042 (s), 1190 (s), 1243 (s), 1309 (w), 1351 (s), 1391 (m), 1450 (m), 1471 (m), 1534 (s), 1703 (s), 2935 (w).

HRMS (APCI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_6^+$ 358.1285; Found 358.1275.



(*R*)-2-((*S*)-2-(hydroxymethyl)cyclohex-2-en-1-yl)-2-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)pent-4-en-1-ol (236) **:** To a solution of α-allyl lactone **204** (2.15 g, 6 mmol, 1 equiv) in THF (240 mL, 0.025 M) were added MeOH (1.2 mL, 30 mmol, 5 equiv) and $LiBH_4$ (0.65 g, 30 mmol, 5 equiv) portionwise at room temperature and the reaction mixture was stirred for 2 h. The reaction was quenched with H_2O and the crude reaction mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over

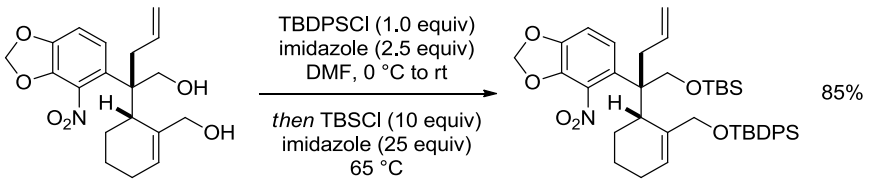
Na_2SO_4 and concentrated under reduced pressure to afford diol **236** as a pale yellow oil (1.97 g, 5.45 mmol, 91% yield). The crude product was used in the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.6 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 1H), 6.11 (dd, *J* = 12.3, 1.3 Hz, 2H), 6.03 (d, *J* = 3.6 Hz, 1H), 5.74 – 5.61 (m, 1H), 5.14 (d, *J* = 17.0 Hz, 1H), 4.99 (d, *J* = 9.9 Hz, 1H), 4.07 (s, 2H), 3.97 (dd, *J* = 43.8, 11.9 Hz, 2H), 2.87 (t, 1H), 2.88 – 2.77 (m, 1H), 2.69 – 2.61 (m, 1H), 2.11 – 2.00 (m, 2H), 1.70 – 1.48 (m, 3H), 1.44 – 1.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 141.7, 139.4, 135.6, 129.3, 128.9, 123.0, 118.0, 109.5, 103.1, 67.8, 51.6, 44.6, 42.5, 40.8, 26.7, 24.6, 20.0.

IR υ (cm^{-1}) 688 (s), 725 (s), 815 (s), 912 (s), 1045 (s), 1224 (s), 1247 (s), 1359 (s), 1477 (s), 1536 (s), 2935 (s).

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{23}NNaO_6^+$ 384.1418; Found 384.1410.



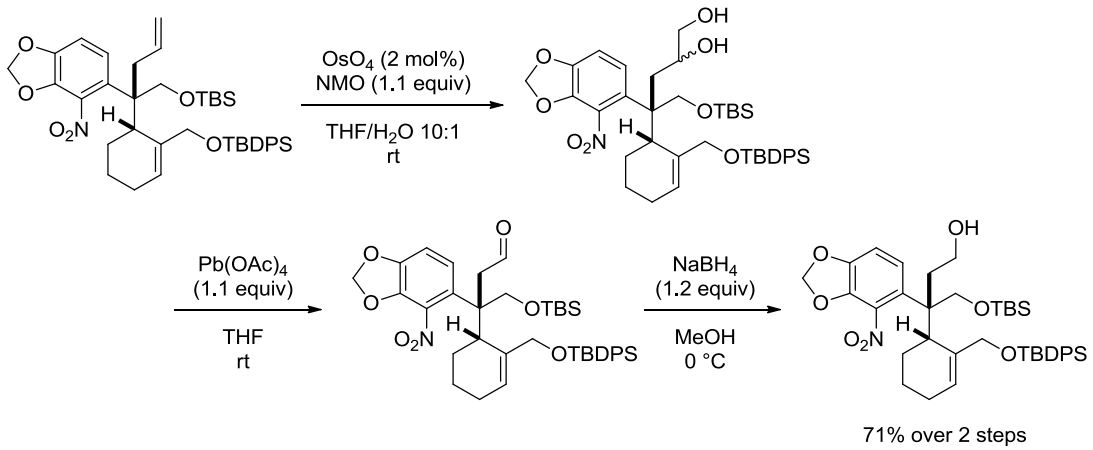
***tert*-Butyl(((*S*)-6-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)-2-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)pent-4-en-2-yl)cyclohex-1-en-1-yl)methoxy)diphenylsilane (240) :** To a solution of diol **236** (1.80 g, 5.0 mmol, 1.0 equiv) in DMF (50 mL, 0.1 M) at 0 °C were added imidazole (0.95 g, 12.5 mmol, 2.5 equiv) and TBDPSCl (1.36 mL, 5.0 mmol, 1.0 equiv) and the reaction mixture was allowed to warm to room temperature. After full consumption of the starting material (1 h), imidazole (8.51 g, 125.0 mmol, 25.0 equiv) and TBSCl (7.54 g, 50.0 mmol, 10.0 equiv) were added and the reaction mixture was stirred at 65 °C for 3 h. The crude reaction mixture was allowed to cool to room temperature and partitioned between H_2O and Et_2O. The aqueous layer was extracted with Et_2O, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 20:1 as eluent to afford diprotected diol **240** as a black oil (3.04 g, 4.26 mmol, 85% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.64 (m, 4H), 7.47 – 7.37 (m, 6H), 6.82 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 6.00 (dd, *J* = 11.8, 1.2 Hz, 2H), 5.97 (s, 1H), 5.78 – 5.67 (m, 1H), 5.01 (dd, *J* = 17.1, 1.8 Hz, 1H), 4.93 (dd, *J* = 10.2, 1.8 Hz, 1H), 4.01 (dd, *J* = 23.4, 13.5 Hz, 2H), 3.91 (dd, *J* = 31.7, 10.2 Hz, 2H), 2.97 – 2.92 (m, 1H), 2.75 – 2.60 (m, 2H), 2.00 (d, *J* = 50.7 Hz, 2H), 1.73 – 1.65 (m, 1H), 1.63 – 1.49 (m, 2H), 1.45 – 1.35 (m, 1H), 1.09 (s, 9H), 0.81 (s, 9H), -0.01 (s, 3H), -0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 141.4, 137.5, 136.3, 135.7, 135.7, 133.9, 133.9, 130.6, 129.7, 127.7, 127.7, 126.8, 123.5, 116.8, 109.0, 102.8, 68.5, 67.1, 51.4, 42.2, 39.4, 27.0, 26.4, 25.9, 24.8, 21.0, 19.4, 18.2, -5.6, -5.7.

IR υ (cm^{-1}) 703 (s), 741 (w), 777 (m), 811 (s), 835 (s), 1053 (s), 1104 (s), 1251 (m), 1474 (m), 1535 (m), 2855 (w), 2930 (w).

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{41}H_{55}NNaO_6Si_2^+$ 736.3460; Found 736.3437.



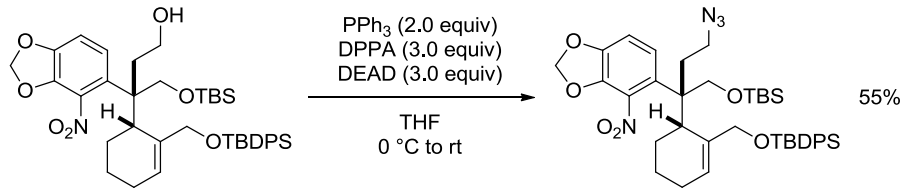
(*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((*S*)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)cyclohex-2-en-1-yl)-3-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)butan-1-ol (243) :: To a solution of allyl **240** (1.32 g, 1.85 mmol, 1.0 equiv) in THF/H_2O 10:1 (37 mL + 3.7 mL, 0.05 M) were added NMO (0.24 g, 2.04 mmol, 1.1 equiv) and OsO_4 (0.22 mL of a 4% wt solution of OsO_4 in H_2O, 2 mmol%) and the reaction mixture was stirred for 2 h at room temperature. Brine was then added and the crude reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was passed through silica gel to afford an inseparable mixture of diastereomers of diol **241** as a yellow oil (1.13 g, 1.51 mmol, 82% yield, dr = 1:1). To a solution of diol **241** (0.45 g, 0.60 mmol, 1.0 equiv) in THF (12 mL, 0.05 mL) at room temperature was added $Pb(OAc)_4$ (0.27 g, 0.66 mmol, 1.1 equiv) portionwise. Saturated aqueous $NaHCO_3$ was then added and the crude reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to afford aldehyde **242**. The crude product was used in the next step without further purification. Aldehyde **242** was then dissolved in MeOH (12 mL, 0.05 mL) at 0 °C and $NaBH_4$ (0.027 mg, 0.72 mmol, 1.2 equiv) was added portionwise. The reaction was quenched with saturated aqueous $NaHCO_3$ and the crude reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 5:1 as eluent to afford alcohol **243** as a blue/grey solid (m.p. = 69-71 °C) (0.28 g, 0.39 mmol, 71% over 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.61 (m, 4H), 7.46 – 7.34 (m, 6H), 6.87 (d, *J* = 8.6 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 6.04 (dd, *J* = 12.4, 1.2 Hz, 2H), 5.90 (s, 1H), 4.08 (d, *J* = 10.9 Hz, 1H), 3.98 (dd, *J* = 40.0, 13.0 Hz, 2H), 3.69 (d, *J* = 10.8 Hz, 1H), 3.56 – 3.45 (m, 2H), 2.80 (s, 1H), 2.12 (t, *J* = 6.3 Hz, 2H), 2.05 – 1.87 (m, 2H), 1.54 – 1.45 (m, 1H), 1.44 – 1.32 (m, 3H), 1.06 (s, 9H), 0.83 (s, 9H), 0.05 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 141.6, 136.7, 135.8, 135.8, 135.2, 133.9, 133.8, 129.8, 128.9, 127.8, 127.7, 123.4, 109.2, 103.1, 68.6, 68.5, 60.7, 51.6, 43.2, 27.0, 26.0, 24.6, 20.6, 19.4, 18.3, -5.5, -5.7.

IR υ (cm^{-1}) 701 (s), 741 (w), 778 (m), 816 (s), 836 (s), 1043 (s), 1080 (s), 1110 (s), 1255 (s), 1359 (w), 1474 (s), 1539 (s), 2861 (w), 2936 (w).

HRMS (APCI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{40}H_{55}NNaO_7Si_2^+$ 740.3409; Found 740.3407.



(((*S*)-6-((*R*)-4-azido-1-((*tert*-butyldimethylsilyl)oxy)-2-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)butan-2-yl)cyclohex-1-en-1-yl)methoxy)(*tert*-butyl)diphenylsilane (245) : To a solution alcohol **243** (0.319 g, 0.4 mmol, 1.0 equiv) in THF (4 mL, 0.1 M) at 0 °C were added PPh_3 (0.210 g, 0.8 mmol, 2 equiv), DPPA (0.26 mL, 1.2 mmol, 3 equiv) and DEAD (0.52 mL, 1.2 mmol, 3 equiv) and the reaction mixture was stirred at room temperature for 2 h. The crude reaction mixture was quickly evaporated under reduced pressure at room temperature and the crude product was purified by column chromatography with PE/EtOAc 20:1 as eluent to afford azide **245** as a yellow oil (177 mg, 0.22 mmol, 55% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 4H), 7.45 – 7.35 (m, 6H), 6.85 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.06 (d, *J* = 15.9 Hz, 2H), 5.85 (s, 1H), 4.12 (dd, *J* = 60.6, 12.7 Hz, 2H), 4.02 (d, *J* = 10.8 Hz, 1H), 3.74 (d, *J* = 10.8 Hz, 1H), 3.31 (td, *J* = 11.4, 6.2 Hz, 1H), 3.04 (td, *J* = 11.6, 5.7 Hz, 1H), 2.84 (s, 1H), 2.28 – 2.14 (m, 2H), 1.99 – 1.83 (m, 2H), 1.49 – 1.32 (m, 4H), 1.07 (s, 9H), 0.83 (s, 9H), 0.02 (s, 3H), -0.00 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 141.6, 136.8, 135.8, 135.8, 135.1, 133.8, 129.8, 128.6, 128.2, 127.8, 127.8, 123.0, 109.3, 103.2, 69.0, 68.4, 50.5, 50.0, 42.4, 37.5, 29.9, 27.0, 26.0, 24.6, 20.8, 19.4, 18.3, -5.5, -5.7.

IR υ (cm^{-1}) 741 (s), 776 (s), 1049 (s), 1079 (s), 1253 (s), 1473 (s), 1538 (s), 2088 (s), 2162 (s), 2864 (w), 2929 (m).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{40}H_{54}N_4NaO_6Si_2^+$ 765.3474; Found 765.3462

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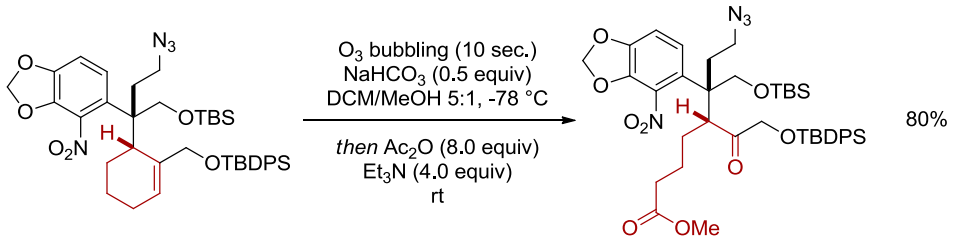


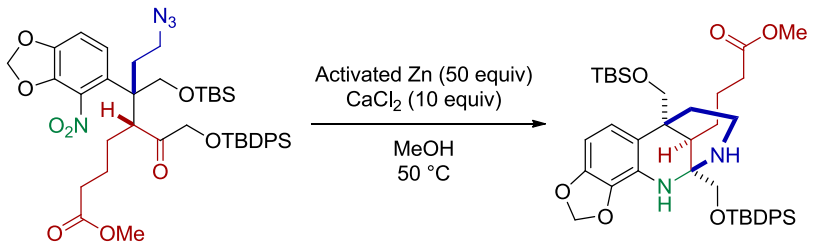
(5*R*,6*R*)-methyl-8-azido-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-(2-((*tert*-butyldiphenylsilyl)oxy)acetyl)-6-(4-nitrobenzo[*d*][1,3]dioxol-5-yl)octanoate (247) : Ozone was bubbled during 10 seconds into a solution of cyclohexene **245** (0.104 g, 0.14 mmol, 1.0 equiv) and $NaHCO_3$ (0.006 g, 0.07 mmol, 0.5 equiv) in DCM/MeOH (4.5 mL + 0.75 mL, 0.03 M) at -78 °C and argon was bubbled directly after to expel ozone. The reaction mixture was then allowed to warm to 0 °C and Ac_2O (0.11 mL, 1.12 mmol, 8.0 equiv) and Et_3N (0.08 mL, 0.56 mmol, 4.0 equiv) were added. The reaction mixture was then stirred at room temperature for 2 h and concentrated under reduced pressure. The crude product was purified by column chromatography with PE/EtOAc 7:1 as eluent to afford ketoester **247** as a pale yellow oil (90.2 mg, 0.11 mmol, 80% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.60 (m, 4H), 7.46 – 7.33 (m, 6H), 6.78 (d, *J* = 8.6 Hz, 1H), 6.74 (d, *J* = 8.6 Hz, 1H), 6.08 (dd, *J* = 18.6, 1.3 Hz, 2H), 4.08 – 3.88 (m, 4H), 3.60 (s, 3H), 3.28 (td, *J* = 11.8, 5.8 Hz, 1H), 3.20 (d, *J* = 10.7 Hz, 1H), 2.96 (td, *J* = 11.8, 4.4 Hz, 1H), 2.20 – 2.04 (m, 3H), 1.93 – 1.81 (m, 1H), 1.71 – 1.60 (m, 1H), 1.23 (s, 3H), 1.07 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 173.3, 148.2, 142.1, 135.8, 135.8, 135.1, 132.9, 132.8, 130.0, 128.0, 127.9, 125.8, 124.0, 109.8, 103.4, 72.7, 66.4, 54.0, 51.7, 49.1, 48.7, 34.7, 34.1, 29.9, 28.2, 26.9, 26.0, 23.7, 19.4, 18.2, 1.2, -5.5, -5.7.

IR υ (cm^{-1}) 703 (s), 737 (s), 780 (s), 814 (s), 837 (s), 907 (m), 1041 (s), 1081 (s), 1108 (s), 1158 (m), 1235 (s), 1255 (s), 1362 (w), 1476 (s), 1536 (s), 1737 (s), 2091 (s), 2161 (w), 2855 (w), 2930 (w).

HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{41}H_{56}N_4NaO_9Si_2^+$ 827.3478; Found 827.3486.



Methyl 4-((6R,10R,12R)-6-(((tert-butyldimethylsilyl)oxy)methyl)-10-(((tert-butyldiphenylsilyl)oxy)methyl)-6,7,8,9,10,11-hexahydro-6,10-methano[1,3]dioxolo[4',5':5,6]benzo[1,2-d][1,3]diazocin-12-yl)butanoate (249) : To a solution of ketoester **247** (20.1 mg, 0.025 mmol, 1 equiv) in MeOH (2.5 mL, 0.01 mL) were added activated Zn[173] (82.7 mg, 1.25 mmol, 50 equiv) and $CaCl_2$ (27.7 mg, 0.25 mmol, 10 equiv) and the reaction mixture was stirred at 50 °C for 1 h. The crude reaction mixture was then allowed to cool to room temperature. The solids were filtered and discarded and the organic layer was concentrated under reduced pressure to afford aminal as a pale yellow oil **249**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (t, *J* = 7.9 Hz, 4H), 7.47 – 7.38 (m, 6H), 6.63 (d, *J* = 8.3 Hz, 1H), 6.20 (d, *J* = 8.3 Hz, 1H), 5.93 (dd, *J* = 10.4, 1.3 Hz, 2H), 4.76 (s, 1H), 3.99 (d, *J* = 10.9 Hz, 1H), 3.85 (d, *J* = 8.7 Hz, 1H), 3.79 (d, *J* = 10.9 Hz, 1H), 3.73 (d, *J* = 8.7 Hz, 1H), 3.54 (s, 3H), 2.91 (td, *J* = 12.2, 3.3 Hz, 1H), 2.81 – 2.72 (m, 1H), 2.18 (t, *J* = 7.1 Hz, 2H), 1.76 (s, 1H), 1.72 – 1.69 (m, 1H), 1.64 – 1.59 (m, 1H), 1.56 – 1.50 (m, 2H), 1.47 – 1.35 (m, 1H), 1.11 (s, 9H), 1.06 – 0.99 (m, 1H), 0.79 (s, 6H), 0.05 (s, 6H).

IR υ (cm^{-1}) 723 (s), 758 (s), 1085 (m), 1112 (m), 1738 (s), 2162 (s), 2359 (w), 2529 (s), 2858 (s), 2928 (s).

HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{41}H_{59}N_2O_6Si_2^+$ 731.3906; Found 731.3916.

[173] See reference 130.

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Curriculum Vitae

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Personal informations

Nationality : Swiss / Date of birth : March 18, 1990

Employment history

2015-2019 (4 years) : **Doctoral Assistant** (École Polytechnique Fédérale de Lausanne EPFL, Switzerland)

- PhD in organic chemistry
- Thesis director : Prof. Jieping Zhu
- Research in homogeneous catalysis and total synthesis

Teaching activities :

- Exercises sessions in organic chemistry (1 h per week for 3 semesters / ~50 students each time)
- Laboratory sessions in organic chemistry (1 d per week for 2 semesters / 8 students each time)
- Supervision of 2 internship students in the laboratory

"Teaching Excellence Award 2018" of the Section of Chemistry and Chemical Engineering

Presentations :

- 3x Poster presentations at the Swiss Chemical Society Fall Meetings (2015, 2016 and 2017)
- Oral presentation at the Swiss Chemical Society Fall Meeting 2018
- 2x Poster presentations at the Swiss Summer School in Villars-sur-Ollon (2015 and 2017)
- Oral presentation at the Swiss Summer School in Villars-sur-Ollon (2015)

2014-2015 (6 months) : **Intern in R&D** (Firmenich SA, La Plaine, Geneva, Switzerland)

- Development of catalytic processes and synthetic routes on large scales
- Participation to common laboratory tasks (maintenance of equipment)
- Supervisor : Dr. Philippe Dupau

2013-2014 (6 months) : **Research student** (Imperial College London, United-Kingdom)

- Research in total synthesis
- Supervisor : Prof. Alan C. Spivey

Education

2012-2014 (1.5 years) : **École Polytechnique Fédérale de Lausanne EPFL**, Switzerland

- Master of Science in Molecular and Biological Chemistry (MSc)
- Organic, inorganic and computational chemistry

2009-2012 (3 years) : **University of Fribourg**, Switzerland

- Bachelor of Science in Chemistry (BSc) with Minor in Physics
- Languages of the teaching : French and German

2005-2009 (4 years) : **Collège Saint-Michel**, Fribourg, Switzerland

- Maturité gymnasiale (Baccalauréat)
- Major topics : latin and sciences

Qualifications

Languages : - French : Native
- English : Full professional proficiency
- German : Limited working proficiency

Informatics : - Microsoft Windows, Mac OS, Linux (Debian-based)
- Microsoft Office, Libre/Open Office, LaTex, Zotero, Origin
- SciFinder, Reaxys, Scopus, Google Scholar
- Bash, C++, Python, basics of web development

Publications

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5) M. Mamboury, Q. Wang, J. Zhu, *Chem. Eur. J.* **2017**, *17*, 12744-12748

4) H. Abas, S. M. Linsdall, M. Mamboury, H. S. Rzepa, A. C. Spivey, *Synfacts* **2017**, *13*, 780

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