# "Palladium-Catalyzed Diamination of Alkynes in Synthesis of Tetracycles" and "Copper-Catalyzed Cyanoalkylation of Unactivated Alkenes"

THÈSE N$^{O}$ 7553 (2017)

PRÉSENTÉE LE 27 JANVIER 2017

À LA FACULTÉ SCIENCES DE BASE
LABORATOIRE DE SYNTHÈSE ET PRODUITS NATURELS
PROGRAMME DOCTORAL EN CHIMIE ET GÉNIE CHIMIQUE

ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE

POUR L'OBTENTION DU GRADE DE DOCTEUR ÈS SCIENCES

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Suisse
2017

# Acknowledgment

This doctoral thesis was carried out from June 2012 to December 2016 in the Laboratory of Synthesis and Natural Products LSPN, Institute of Chemical Science and Engineering ISIC, École Polytechnique Fédérale de Lausanne EPFL. By that time, I have worked with a great number of people whose contribution in various ways to my thesis deserved special mention. It is a pleasure to convey my gratitude to them all in my humble acknowledgement.

First of all, I would like to thank Professor Jieping Zhu for giving me an opportunity to be a member of his group – a very competitive research environment. I am highly grateful for all the supervision, advices, experiences and knowledge he generously conveyed to me during this great time. His hardworking and dedication to chemistry is a great inspiration and motivation for me to keep pursuing and striving in research area. What I have learnt from you will be valuable experience coming along with me for whole life.

I would also like to thank Dr. Qian Wang, my PhD co-supervisor for all her help during four years of doctoral study. The knowledge, advice and experience in both theoretical and practical she shared with me are always valuable and helpful. All the discussion with her in or out of chemistry topics is really enjoyable and constructive. I appreciate Jieping and Qian's hospitality for invitations to home for party or special events with fantastic and delicious Chinese food.

I am grateful to all the jury members of my thesis defense: Professor Jerome Waser, Professor Nicolai Cramer, Professor Yannick Landais and Professor Markus Heinrich for accepting to serve on my committee and for taking time to evaluate this manuscript.

I would like to express my gratitude to all the staff of ISIC including our lab secretary, NMR and HRMS services, BCH-magasin's team, to EPFL and to National Centres of Competence in Research (NCCRs) for providing me with unique working conditions and necessary financial support throughout my doctoral work.

Collective and individual acknowledgments are also owed to all the present and group members in LSPN for nice and friendly working-atmosphere as well as fruitful discussion and memorable moments. Special thanks to Dr. Ala Bunescu for your kindness and warm-heartedness and particularly for being a good friend. Your hardworking, knowledge and passion in chemistry inspired me a lot for such a long and difficulty time of PhD. A warm thank goes to Dr. Tiffany Pou for all your help, encouragement at the beginning of my doctoral work. I would like to express my gratitude to all Chinese postdocs for creating really competitive working environment by their highly devoted working and attitude. Particularly, I have to mention Dr. Yao Bo who I collaborated in few projects;

he taught me many useful technique and experience when I did start working on methodologies. A word of thanks also goes to Dr. Wangqing Kong for the fruitful discussion in chemistry, for exchanging knowledge and culture. I would like to warmly thank to Jean-Baptiste, Thomas, Oliver, Antonin, Dylan, Cyril, Nicolas, Mathias and all other PhD students in LSPN for such nice working atmosphere. They took the most difficult duties for maintenance all the equipment and machines, giving our research a smooth run. It is my great pleasure to work with such nice, polite, humorous and smart people like them. Special thanks to all my labmates in BCH-5412 for sharing everything together from chemicals, glassware, equipment to music, a piece of news, a joke. I have to mention Victoria, who is always polite, elegant and very thoughtful, she brought us some interesting characteristics of Germans: discipline and preciseness. A word of thanks goes to Nicolas as well, who is really helpful whenever people need; open to any discussions and easy to get along with. I felt really happy to work in such a united and coherent laboratory like that for more than four years.

I would also like to thank the members in the group of Professor Cramer, Professor Waser, Professor Hu and Professor Gerber for fruitful and excellent discussions, for sharing chemicals; especially Joachim Ahlin, Frank Le Vaillant, Francois Naverraz, Raphael De Matos, Ivan Buslov…

Special thanks to Ngoc Duc Tran and Manh Van Pham – Vietnamese PhD students from Professor Cramer's group. Their help and assistance particularly at the beginning of thesis was really important for me to go through this four-year period. I really enjoyed the discussions with Manh, and learnt many things from them. It is my great luck for me to meet them here, in a broad country.

From the bottom of my heart, I would like to send my gratefulness to my family and my close friends for their unconditional love, inspiration and concern. I could never have started all of this without their supports. Huge and special thanks are kept for Nguyen Thuy Linh, my lovely girlfriend who always standby, support and encourage me all the time. I really appreciate her sacrifice and her understanding during such hard time.

Finally, I would like to thank everybody who was important to the successful realization of thesis, as well as expressing my apology that I could not mention personally one by one.

*Lausanne, November 2016*

# Abstract

The thesis deals with the development of transition metal-catalyzed difunctionalization of alkenes and alkynes, which can be categorized into two major topics: (1) palladium-catalyzed diamination of alkynes for the synthesis of tetracycles; (2) copper-catalyzed cyanoalkylation-initiated double functionalization of alkenes. The first part of this thesis describes the synthesis of free NH tetracyclic indoles by palladium-catalyzed diamination of triple bonds. In the presence of palladium catalyst, 1,2-diarylethynes bearing an *N*-methyl-*N*-[2-(methoxy-carbonyl)ethyl]amino and an aminocarbonyl/aminosulfonyl group at the *ortho* positions of the two aromatic rings underwent double cyclization in a highly ordered fashion to afford *N*-2-(methoxycarbonyl)ethylaed indolo[3,2-c]isoquinolinone or indolobenzothiazine S,S-dioxide with complete chemoselectivity. Subsequently, the *N*-[2-(methoxycarbonyl)ethyl] group is readily removed under basic conditions (DBU, DMF, 120 °C) to afford tetracycles with indolyl nitrogen unprotected. We subsequently developed a transition metal-free diamination process to access the tetracyclic quindolinones. In the presence of acetic acid and a hydride donor (Hantsch's ester) under oxygen atmosphere, double cyclization of 1,3-diarylprop-2-yn-1-ones bearing an *N,N*-dialkylated amino and an *N*-monoalkylated amino group at *ortho* positions of aromatic rings occurred smoothly to provide tetracyclic quindolinones. In the second part of thesis, copper-catalyzed cyanoalkylative difunctionalization of alkenes with alkylnitriles as alkylative reagents was addressed. We developed catalytic conditions (copper salt, ligand, peroxide, base) that allowed us to convert unactivated alkenes to 1,2-difunctionalized alkanes or its cyclic variants. The domino process proceeded through following key elementary steps: a) generation of cyanolakyl radicals; b) addition of cyanoalkyl radical to unactivated double bond; c) interception of this adduct radical by a suitable reagent, or more frequently, oxidation of adduct radical to carbenium; d) trapping of the carbocation by an internal/or external nucleophile. By applying this strategy, a series of value-added molecules such as dihydroisobenzofurans, γ-lactones, aziridines and γ-azidobutyronitriles, were readily synthesized from simple alkenes.

***Keywords:*** *Difunctionalization, palladium, copper, catalyst, alkyne, alkene, domino-reaction, tetracycle, indolo[3,2-c]isoquinolinone, indolobenzothiazine S,S-dioxide, quindolinone, alkylnitrile, dihydroisobenzofuran, γ-lactone, aziridine, γ-azidobutyronitrile.*

# Résumé

La thèse traite du développement de la difonctionalisation d'alcènes et d'alcynes, catalysée par un métal de transition, qui peuvent être catégorisé en deux principaux thèmes: (1) diamination d'alcynes catalysée par le palladium pour la synthèse de tetracycles ; (2) double fonctionalisation d'alcènes initiée par une cyanoalkylation catalysée au cuivre. La première partie de cette thèse décrit la synthèse d'indole tetracyclique non-protégé par une diamination de triples liaisons catalysée par le palladium. En présence du catalyseur au palladium, les 1,2-diarylethynes portant un groupe *N*-methyl-*N*-[2-(methoxy-carbonyl)ethyl]amino et un groupe aminocarbonyl/aminosulfonyl en position *ortho* des deux cycles aromatiques réagissent via une double cyclisation d'une manière très ordonnée pour donner *N*-2-(methoxycarbonyl)ethylaed indolo[3,2-c]isoquinolinone ou indolobenzothiazine S,S-dioxide avec une chemosélectivité totale. Par la suite, le groupe *N*-[2-(methoxycarbonyl)ethyl] peut être réduit dans des conditions basique (DBU, DMF, 120 °C) pour donner les indoles tetracycliques non-protégés. Nous avons ensuite développé un procédé de diamination sans métaux de transition pour accéder à des quindolinones tetracycliques. En présence d'acide acétique et d'un donneur d'hydrure (ester de Hantsch) sous atmosphère d'oxygène, une double cyclisation de 1,3-diarylprop-2-yn-1-ones, portant un groupe *N*,*N*-dialkylated amino et un groupe *N*-monoalkylated amino en position *ortho* des cycles aromatiques, se produit pour donner des quindolinones tetracycliques. Dans la deuxième partie de la thèse, la difonctionalisation d'alcènes initiée par une cyanoalkylation et catalysée par le cuivre avec des alkylnitriles comme réactifs alkylants a été étudié. Nous avons développé des conditions catalytiques (sel de cuivre, ligand, peroxide, base) qui nous permettent de convertir des alcènes non-activées en alcanes 1,2-difonctionalisés ou en leur forme cyclique. Ce procédé domino se produit en suivant les étapes élémentaires suivantes : a) génération du radical cyanoalkyl ; b) addition du radical cyanoalkyl à la double liaison non-activée ; c) interception du nouveau radical formé par un réactif adapté ou plus souvent, oxidation du nouveau radical formé en carbenium ; d) piégeage du carbocation par un nucléophile interne/ou externe. En appliquant cette stratégie, une série de molécule de valeur telle que les dihydroisobenzofurans, les γ-lactones, les aziridines et les γ-azidobutyronitriles ont été synthétisées à partir de simple alcènes.

***Mots clés:*** *Difonctionalisation, palladium, cuivre, catalyseur, alcyne, alcène, réaction domino, tetracycle, indolo[3,2-c]isoquinolinone, indolobenzothiazine S,S-dioxide, quindolinone, alkylnitrile, dihydroisobenzofuran, γ-lactone, aziridine, γ-azidobutyronitrile.*

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# Abbreviations

| | |
|---|---|
| **AcO** | Acetate |
| **Acac** | Acetylacetonate |
| **Atm** | Atmospheric |
| **Aq** | Aqueous |
| **Ar** | Aryl |
| **BDE** | bond-dissociation energy |
| **BINAP** | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl |
| **Bipy** | 2,2′-Bipyridine |
| **Bn** | Benzyl |
| **BQ** | 1,4-Benzoquinone |
| **Calcd** | Calculated |
| **CDC** | cross-dehydrogenative coupling |
| **$CDCl_3$** | Deuterated chloroform |
| **cod** | cyclooctadiene |
| **Cu(hfacac)2** | Copper(II) hexafluoroacetylacetonate |
| **CuTC** | Copper(I)-thiophene-2-carboxylate |
| **Cy** | Cyclohexyl |
| **dba** | Dibenzylideneacetone |
| **DBN** | 1,5-Diazabicyclo[4.3.0]non-5-ene |
| **DBU** | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| **DCE** | 1,2-Dichloroethene |
| **DCP** | dicumylperoxide |
| **DiPPF** | diisopropylphosphinoferrocene |

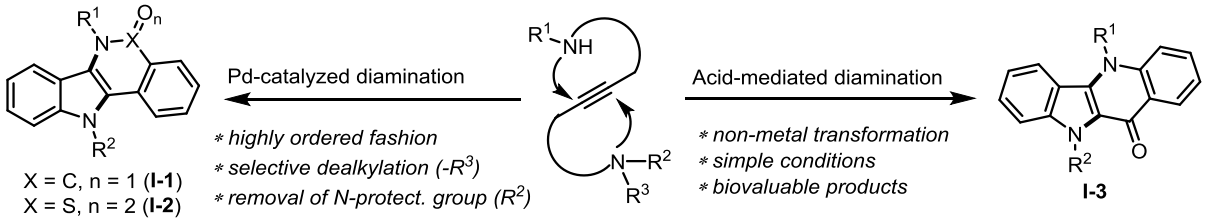
| | |
|---|---|
| **DIPEA** | *N*,*N*-Diisopropylethylamine |
| **DMA** | Dimethylacetamide |
| **DMF** | Dimethylformamide |
| **DMSO** | Dimethyl sulfoxide |
| **DPEPhos** | Bis[(2-diphenylphosphino)phenyl] ether |
| **DPPA** | diphenylphosphoryl azide |
| **Dppe** | 1,2-Bis(diphenylphosphino)ethane |
| **Dppf** | 1,1′-Bis(diphenylphosphino)ferrocene |
| **DPPBz** | 1,2-bis(diphenylphosphino)benzene |
| **DTBP** | Di-*tert*-butyl peroxide |
| **dr** | diastereomeric ratio |
| **ee** | enantiomeric excess |
| **equiv** | Equivalent |
| **ESI** | electrospray ionization |
| **Et** | Ethyl |
| **$Ir(ppy)_3$** | Tris-(2-phenylpyridine) iridium |
| **HPMA** | *N*-(2-Hydroxypropyl)methacrylamide |
| **HRMS** | High resolution mass spectrometry |
| **LAH** | Lithium aluminium hydride |
| **LDA** | lithium diisopropylamide |
| **MAC15A** | Murine Adenocarcinoma of the Colon 15A |
| ***m*-CPBA** | *meta*-chloro-peroxybenzoic acid |
| **Ms** | Mesyl |
| **M.S** | Molecular sieves |
| **NaHMDS** | Sodium bis(trimethylsilyl)amide |

| | |
|---|---|
| ***n*-BuLi** | *n*-butyllithium |
| **NET** | norepinephrine transporter |
| **NMP** | *N*-Methyl-2-pyrrolidone |
| **NBS** | *N*-Bromoosuccinimide |
| **NCS** | *N*-Chlorosuccinimide |
| **$Ni(cod)_2$** | Bis(cyclooctadiene)nickel |
| **OTf** | Triflate |
| **$Pd_2(dpa)_3$** | Tris(dibenzylideneacetone)dipalladium(0) |
| **Pd(TFA)2** | Palladium(II) trifluoroacetate |
| **Ph** | Phenyl |
| **PIDA** | Phenyliodonium Diacetate |
| **PIFA** | Phenyliodine bis(trifluoroacetate) |
| **PTSA** | *p*-Toluenesulfonic acid |
| **$[Ru(bpy)_3]Cl_2$** | Tris(bipyridine)ruthenium(II) chloride |
| **SERT** | serotonin transporter |
| **SEGPHOS** | 4,4'-Bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane) |
| **SPhos** | 2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl |
| ***t*-AmOH** | 2-methylbutan-2-ol |
| ***t*-Bu** | *Tert*-butyl |
| **TFA** | Trifluoroacetic acid |
| **TFE** | Tetrafluoroethylene |
| **TMEDA** | Tetramethylethylenediamine |
| **Tol** | Toluyl |
| **Ts** | Tosyl |
| **XPhos** | 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl |

# General Introduction

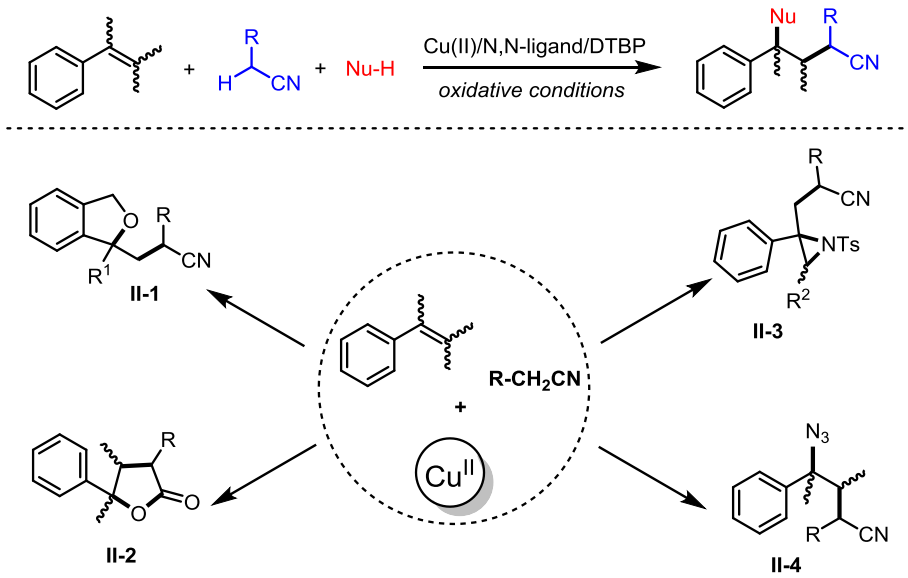
Difunctionalization of C-C multiple bonds has drawn a considerable attention, due to the availability of the starting materials and the possibility to reach high complexity and diversity of products in single step. Our group has recently developed a series of metal-catalyzed difunctionalization of double or triple bonds for the synthesis of heterocycles or complex molecules. The subject of my thesis resides on the development of intramolecular palladium-catalyzed diamination of triple bonds for the synthesis of tetracycles and copper-catalyzed cyanomethylation-initiated double 1,2-difunctionalization of unactivated alkenes for the synthesis of value-added molecules.

Significant progress has been made in palldadium-catalyzed diamination of alkenes during last decade. They have become powerful and reliable methods to access highly complex molecules, including natural products. The analogous diamination of alkynes, however, was restricted to few examples. Interested in this underexplored research area, we turned our attention to the development of palladium-catalyzed diamination of alkynes aimed at developing efficient access to biologically relevant nitrogen-containing heterocycles. In the first part of thesis, we will focus on the synthesis of polycyclic indoles such as indolo[3,2-*c*]isoquinolinones (**I-1**) and indolobenzothiazine *S*,*S*-dioxides (**I-2**) by intramolecular double cyclization of bis-nitrogen nucleophiles to triple bond under palladium catalysis. The development of a removable *N*-protecting group for indoles in these palladium catalyzed process to reach free NH indoles will be presented. Additionally, the development of a simple acid-mediated diamination of alkynes for the synthesis of bioactive tetracyclic quindolinone (**I-3**) will be documented.




Copper-catalyzed difunctionalization of alkenes will be the main topic of the second part of this thesis. Although copper-catalyzed carbooxygenation/carboamination of alkenes involving the formation $C(sp^3)$-$C(sp^2)$ bond was well-established, the corresponding transformations involving the formation of $C(sp^3)$-$C(sp^3)$ bond are limited to trifluoromethylation. To exploit this underexplored research area, we implemented the development of copper-catalyzed 1,2-difunctionalization of unactivated alkenes. The working hypothesis that guided our reaction design are as follows: a)

generation of cyanolakyl radical in the presence of appropriate catalytic conditions (copper salt, ligand, DTBP); b) addition of cyanoalkyl radical to unactivated double bond; c) interception of this adduct radical by a suitable reagent, or more frequently, oxidation of adduct radical to carbenium; d) trapping of the carbocation by an internal/or external nucleophile. We will present in this section copper-catalyzed amino-cyanoalkylation, azido-cyanoalkylation, oxy-cyanoalkylation of unactivated alkenes via formation of a C($sp^3$)-C($sp^3$) and a C($sp^3$)-X (X = N, O) bonds. These reactions provided novel access to different scaffolds including dihydroisobenzofurans (**II-1**), γ-lactones (**II-2**), aziridines (**II-3**) and γ-azidobutyronitriles (**II-4**) of significant importance in medicinal chemistry and in organic synthesis as building blocks. The synthetic potential of these domino processes will be illustrated by developing efficient synthesis of citalopram (a marketed antidepressant) and sacidumligan (natural product).



# PART I

# Palladium-Catalyzed Diamination of Alkynes in Synthesis of Tetracycles

# CHAPTER 1

# Introduction

## 1. 1. Palladium-Catalyzed Difunctionalization of Alkynes in Indole Synthesis

The indole ring is one of the most ubiquitous heterocycles found in nature. Indole moiety can be found in tryptophan - a proteinogenic aminoacid, in serotonin, melatonin – neurotransmitters, and in many natural products such as alkaloid family. Owing to the broad spectrum of biological activities, indole scaffold holds a privileged position in medicinal chemistry.[1] As a result, numerous indoles have been found in pharmaceutically active compounds (Scheme 1). Furthermore, it has also become an important structural motif in other research areas such as agriculture, materials, dyes and perfumes.[2]

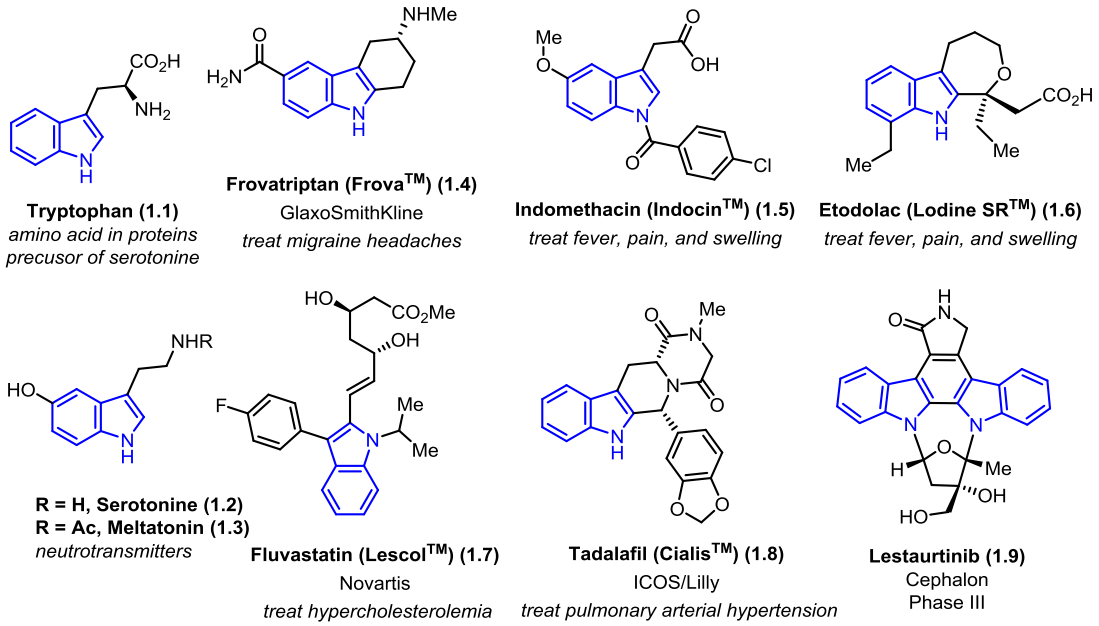


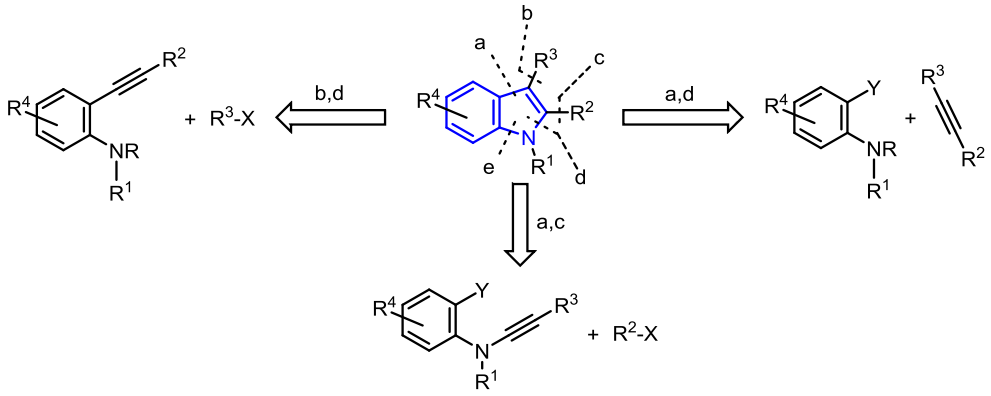

**Figure 1.1: Examples of biologically active indoles**

Due to the prominent role of indole compounds in multidisciplinary fields, the synthesis and functionalization of this heterocycle has been one of major interests in organic chemistry and huge numbers of different synthetic approaches have been developed for over 100 years.[3] Despite of plenty of available synthetic methodologies nowadays, development of novel processes which can lead efficiently and rapidly to indoles, and tolerate wide range of functional groups is still a continuously active field of research. Among many synthetic approaches for the synthesis of indoles, palladium-catalyzed difunctionalization of alkynes is now emerging as very powerful and versatile method to produce a variety of substituted indoles.[4]

[1] Humphrey, G. R.; Keuthe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
[2] Barden, T. In *Heterocyclic Scaffolds II:*; Gribble, G. W., Ed.; Springer Berlin Heidelberg, **2010**; *Vol. 26*; pp 31.
[3] Recent review on indole synthesis: (a) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (b) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (c) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*,421.
[4] Review on paladdium-catalyzed indole synthesis: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Arkivoc* **2010**, *1*, 390. (c) Shi, Z.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 9220.

Difunctionalization of carbon-carbon multiple bonds, the addition of two functional groups across an alkene or alkyne, is one of the most powerful chemical transformations in organic synthesis.[5,6] It allows quick accessing of highly complex organic compounds by introducing two functional groups through a single step. Moreover, due to the availability, price and synthetic accessibility of alkenes and alkynes, this transformation is practically and economically useful for chemical and pharmaceutical industries. Palladium-catalyzed difunctionalization of carbon-carbon multiple bonds normally implies a concept of domino process, which is a combination of two and more bond-forming reactions under identical conditions wherein subsequent reaction result as a consequence of the functionality formed in the previous step.[7] Those transformations such as carboamination, carbooxygenation, aminooxygenation and diamination have been considered as attractive synthetic approaches for construction of heterocyclic compounds. In this part of manuscript, palladium catalysis for difunctionalization of alkynes in indole synthesis will be the main topic for discussion.

From viewpoint of difunctionalization of alkynes, indoles could be approached based on three different bond disconnections as summarized in Scheme 1.1: intramolecular amination reaction of *o*-alkynylaniline (disconnection path b,d); intermolecular cycloaddition of 2-halogenanilines with internal alkynes (disconnection path a,d) and heteroannulation of *N*-alkynyl-2-halogenanilines (disconnection path a,c).




**Scheme 1.1: Indole synthetic strategy by palladium-catalyzed difunctionalization of alkynes**

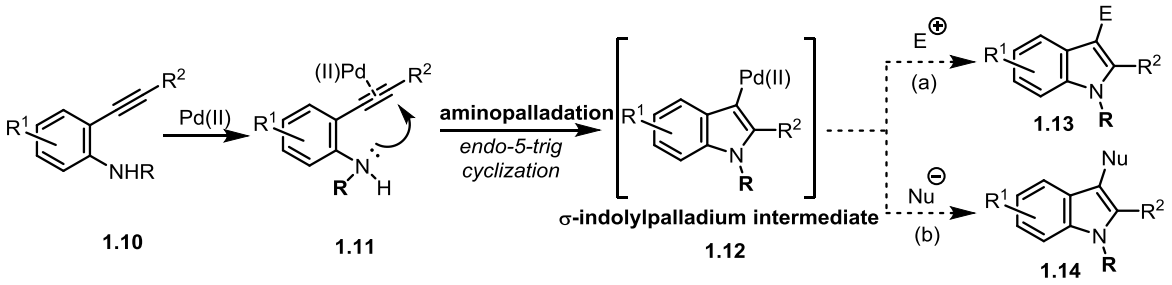
[5] Review on Pd-catalyzed difunctionalization of alkenes: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *3*, 351. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (c) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem*. **2008**, *6*, 4083. (d) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (e) Wu, W.; Jiang, H. *Acc. Chem. Res*. **2012**, *45*, 1736. (f) Kocovsky, P.; Bäckvall, J.-E. *Chem. Eur. J*. **2015**, *21*, 36. Reviews on Cu-catalyzed difunctionalization of alkenes: (g) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed*. **2011**, *50*, 11062. (i) Shimizu,Y.; Kanai, M. *Tetrahedron Lett*. **2014**, *55*, 3727.

[6] Review on hypervalent iodane mediated difunctionalization of alkenes: (a) Romero, R. M.; Woste, T. H; Muniz, K. *Chem. Asian. J*. **2014**, *9*, 972. (b) Arnold, A. M.; Ulmer, A.; Gulder, T. *Chem. Eur. J*. **2016**, *22*, 8728.

[7] Tietze, L. F. *Chem. Rev*. **1996**, *96*, 115.

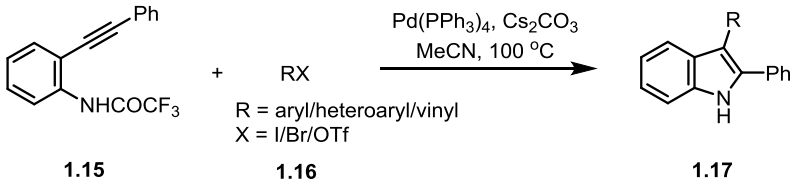
### 1. 1. 1. Palladium-Catalyzed Intramolecular Amination of *o*-alkynylaniline in Synthesis of 2,3-Disubstituted Indoles

It is well-known that *o*-alkynylaniline derivatives, which are easily accessible by Sonogashira coupling reaction of *o*-iodoanilines and the corresponding alkynes, are excellent substrates for palladium-catalyzed domino difunctionalization to indoles. In these transformations, aminometalation of *o*-alkynylaniline/*o*-alkynylphenol **1.10** affords σ-indolylpalladium intermediate **1.12** which could subsequently be trapped by suitable electrophiles (Scheme 1.2, path a) or nucleophiles (Scheme 1.2, path b) to generate various substituted indoles **1.13** or **1.14**. In this part, we only focus on discussion on the pathway (a); the latter will be mentioned in the chapter 1.2.1.




**Scheme 1.2: Palladium-catalyzed indole synthesis of *o*-alkynylaniline derivatives**

The pathway (a) approach is complementary to the classic Cacchi indole synthesis that involved reaction of (hetero)arylhalides or vinyl halides **1.16** with ortho-alkynyl acetinilides **1.15** in the presence of Pd(0) catalyst to afford 2,3-disubstituted indoles **1.17** (Scheme 1.3).[8]

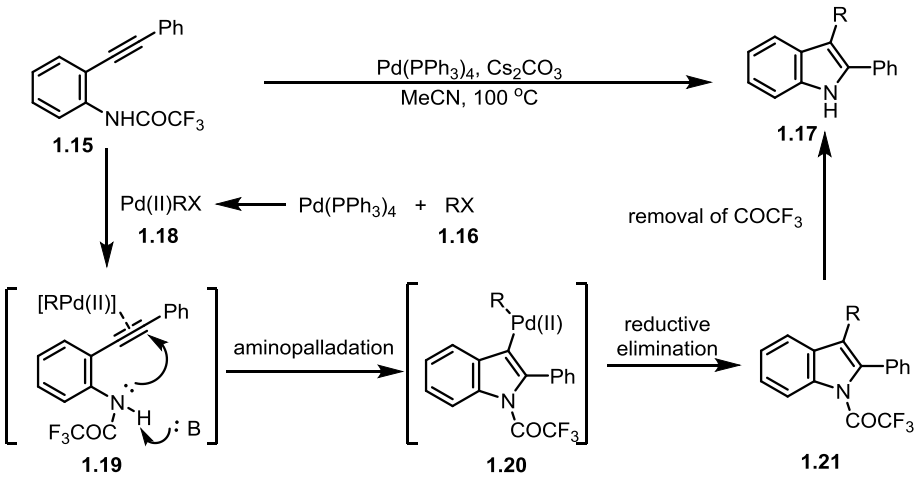



**Scheme 1.3: Synthesis of 2,3-disubstituted indoles by Cacchi**

The reaction mechanism was postulated to proceed through coordination of organopalladium(II) complex **1.18**, generated *in situ* from aryl halides or vinyl triflates **1.16** and $Ph(PPh_3)_4$, to the alkyne **1.15** to form π-alkyne-organopalladium complex **1.19**. Subsequent intramolecular nucleophilic attack by nitrogen atom across the triple bond generates σ-indolylpalladium complex **1.20**, which undergoes reductive elimination to afford 2,3-disubstituted indole **1.21**. The *N*-trifluoroacetyl group, which is

[8] (a) A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915. (b) A. Arcadi, S. Cacchi, A. Cassetta, G. Fabrizi, L. M. Parisi, *Synlett* **2001**, 1605. (c) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synthesis* **2003**, 728. (d) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synthesis* **2004**, 1889.

renders the NH more acidic hence easily deprotonated, can be readily removed during the reaction or by workup to form free (NH) indole **1.17** (Scheme 1.4).

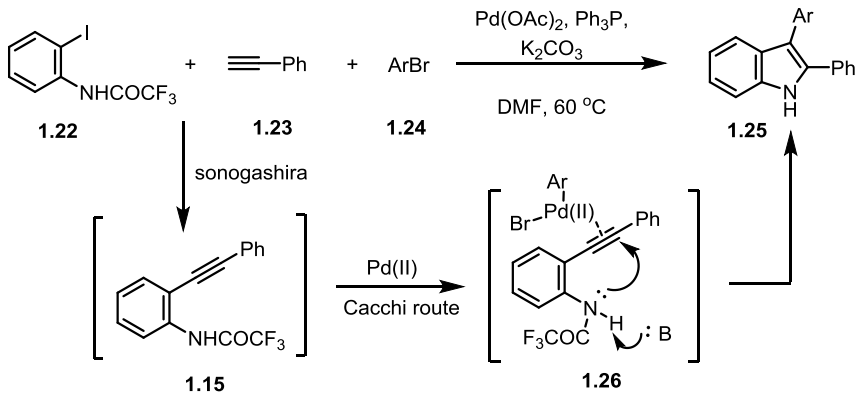



**Scheme 1.4: Mechanism of Cacchi indole synthesis**

This straightforward indole synthesis tolerated well a variety of functional groups, including aldehyde, ketone, ester, nitro and nitrile groups. A wide range of electrophiles has been utilized in this process, such as arenediazonium salts,[9a] ethyl iodoacetates,[9b] benzyl bromides,[9b] bromoalkynes,[9c] aldehydes,[9d] isocyanates,[9e] nitriles[9f]… affording various 2,3-disubstituted indoles. Moreover, aryl chlorides, less reactive in oxidative addition step, are also suitable starting materials by using XPhos as a ligand.[10] Cacchi-type synthesis generally provides 2,3-disubstituted indoles in moderate to good yield as result of C-N, C-C bond formation on alkyne substrates. However, alternative transition metal-catalyzed domino process for diamination or aminoetherification in this fashion is relatively rare (see chapter 1.2.2.a).

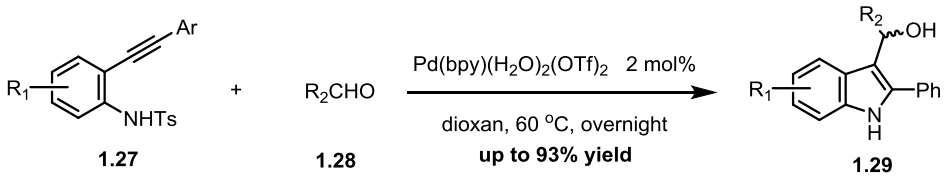
As an improvement of Cacchi methodology, Lu and co-workers later reported a practical one-pot, regiospecific three-component process for the synthesis of 2,3-disubstituted indoles **1.25** by combination of Sonogashira and Cacchi cyclization (Scheme 1.5).[11] In order to find a proper condition for both processes: Sonogashira reaction and aminopalladation, aryl iodide was replaced by aryl bromide which reacts with alkyne more slowly to avoid side Sonogashira reaction. CuI should not be used as co-catalyst to avoid the non-Pd(II)-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides **1.15**. Overall, in the presence of $Pd(OAc)_2$ catalyst, $Ph_3P$ and $K_2CO_3$ in DMF at 60 °C, 2,3-disubstituted indoles **1.25** were isolated in good yields from a mixture of *o*-iodoanilines **1.22**, terminal alkynes **1.23** and aryl bromides **1.24**.

[9] (a) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synlett* **2000**, 394. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213. (d) X. Han, X. Lu, *Org. Lett.*, **2010**, *12*, 3336. (e) Mizukami, A.; Ise, Y.; Kimachi, T.; Inamoto, K. *Org. Lett.* **2016**, *18*, 748. (f) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, *16*, 2058.
[10] S. Cacchi, G. Fabrizi, L. M. Parisi, *Adv. Synth. Catal.* **2006**, *348*, 1301.
[11] B. Z. Lu, W. Zhao, H. –X. Wei, M. Dufour, V. Farina, C. H. Senanayake, *Org. Lett.* **2006**, *8*, 3271.



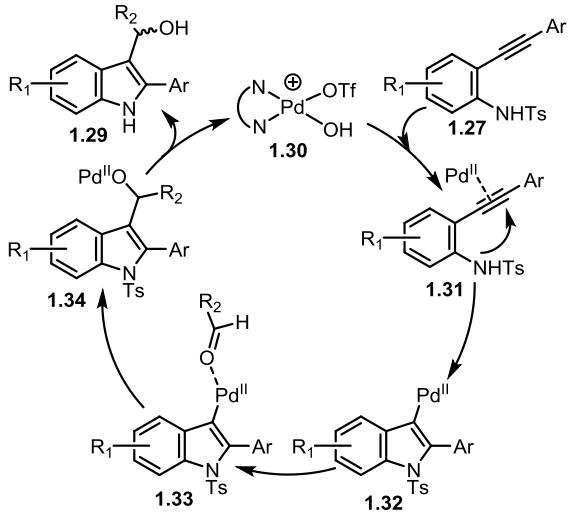

**Scheme 1.5: Multi-component reactions to synthetize 2,3-disubstituted indoles by Lu**

Besides Cacchi aminopalladation – reductive elimination process, Lu and Han described a novel cationic Pd(II)-catalyzed synthesis of substituted 3-hydroxymethyl indoles **1.29** from *o*-alkynylanilines **1.27** and aldehydes **1.28** in moderate to good yields (Scheme 1.6).[12]




**Scheme 1.6: Synthesis of substituted 3-hydroxymethyl indoles by Lu and Han**

The mechanism was postulated to proceed through the formation of σ-indolylpalladium complex **1.32** by intramolecular aminopalladation of the alkyne **1.27**, then addition of this resulting intermediate to the carbonyl group which acts as an electrophile, to quench the carbo-palladium bond and complete the catalytic cycles by regeneration of Pd(II) **1.30** (scheme 1.7).

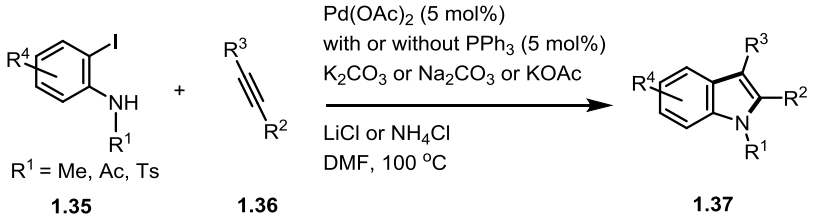



**Scheme 1.7: Cationic Pd(II)-catalyzed synthesis of substituted 3-hydroxymethyl indoles**

[12] X. Han, X. Lu, *Org. Lett.*, **2010**, *12*, 3336.

### 1. 1. 2. Palladium-Catalyzed Heteroannulation of 2-Haloanilines with Alkynes in to 2,3-Disubstitutedindoles

Another pathway to access 2,3-disubstituted indoles by taking advantage of carboamination of alkynes that involves formation of C-C and C-N bonds was successfully developed by Larock and coworkers.[13] A wide variety of 2,3-disubstituted indoles **1.37** can be prepared in good to excellent yields by heteroannulation between *o*-iodoanilines **1.35** and internal alkynes **1.36** in the presence of $Pd(OAc)_2$, $NH_4Cl$ or LiCl and carbonate/acetate bases (Scheme 1.8). Interestingly, *o*-iodoanilines **1.35** bearing *N*-methyl, *N*-acetyl and *N*-tosyl are all tolerated under these reaction conditions, making this methodology more versatile and practical. Lately, other alternatives to *o*-iodoanilines such as *o*-bromo, *o*-chlorooanilines and *o*-iodobenzoic acids were also effectively introduced into this annulation.[14]




**Scheme 1.8: Pd-catalyzed heteroannulation in indole synthesis by Larock**

Different from above synthetic strategy which is initiated by aminopalladation, Larock indole synthesis presumably proceeds through carbopalladation of alkynes **1.36** to form C-C bond first, followed by formation of C-N bond. The complete mechanism can be described as follows (Scheme 1.9): (1) oxidative addition of *o*-iodoanilines **1.35** with Pd(0) to form organopalladium(II) complex **1.38**; (2) coordination of Pd(II) intermediate **1.38** to alkynes **1.36**; (3) carbopalladation to afford vinylpalladium intermidate **1.40**; (4) ligand exchange between nucleophilic nitrogen atom and iodide on vinylpalladium intermediate **1.40** to form 6-membered ring palladacycle **1.41**; (5) reductive elimination to form C-N bond and indole **1.37**, with concurrent regeneration of Pd(0) to complete catalytic cycle.

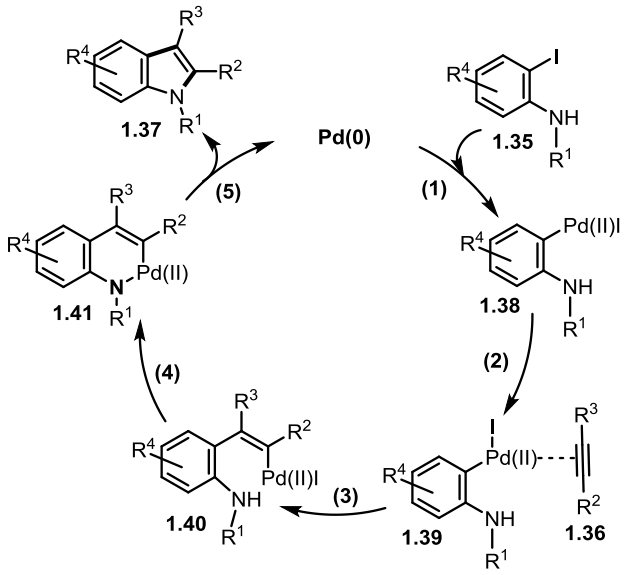
Similar to Fisher indole synthesis, the lack of regioselectivity is a major drawback of this important reaction when a dissymmetric alkyne is employed.[15] The regioselectivity could be mainly determined at carbopalladation step in which carbon-carbon bond and vinylpalladium intermediate is formed. As a result, steric effect could be one of the major factors to influence the outcome of reaction. The insertion of dissymmetric alkynes to arylpalladium intermediate **1.39** favourably takes

[13] (a) Larock, R. C.; Kgun Yum, E. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412

[14] (a) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (b) Leogane, O.; Lebel, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 350.

[15] Kumi, S.; Hiroshi, Y.; Toshio, N.; Minoru, I. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2092.

place on the carbon atom of alkynes which has less steric hindrance, resulting in 2,3-disubstituted indole with bulkier substituent located on C-2 position as a major product. Moreover, coordinating effect could also influence on the regioselectivity of this transformation. The substituent with functional moiety which can stabilize vinylpalladidum **1.40** by coordination usually resides at the C-2 position of indoles.



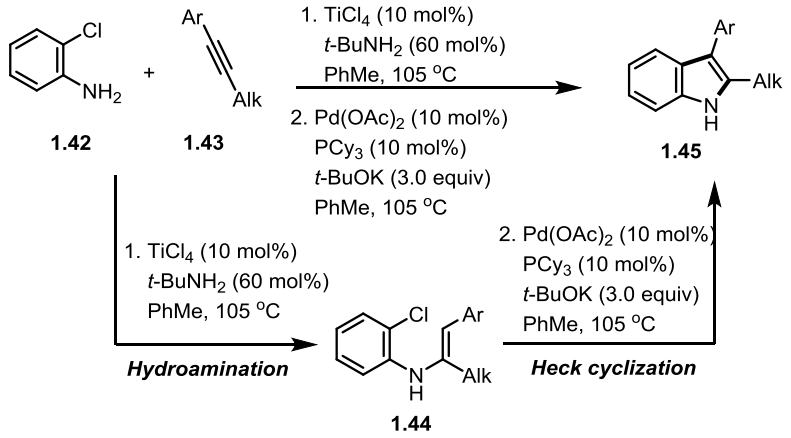

**Scheme 1.9: Mechanism of Pd-catalyzed indole synthesis by Larock**

Taking advantage of steric effect on regioselectivity, many silylalkynes are employed in Larock reactions to afford 2-silylindoles which upon removal of silyl moieties, furnishing 3-monosubstituted indoles. Indeed, this approach was well-recognized and applied in syntheses of many complex natural products.[16]

Another regioselective heteroannulation of free NH *o*-chlorooanilines **1.42** with phenylacetylene derivatives **1.43** was described by Ackermann (Scheme 1.10).[17] This one-pot reaction, however, is different from Larock indole synthesis in that the C-N bond was formed before the C-C bond. Mechanistically, it proceeds through two major steps: (1) $TiCl_4$-catalyzed regioselective anti-Markovnikov hydroamination[18] of phenylacetylene **1.43** to generate *in situ* enamine intermediate **1.44**; (2) palladium–catalyzed intramolecular Heck-type cyclization of intermediate **1.44** to furnish 2-alkyl-3-aryl substituted indoles **1.45**. An alternative transformation, in which both terminal and internal

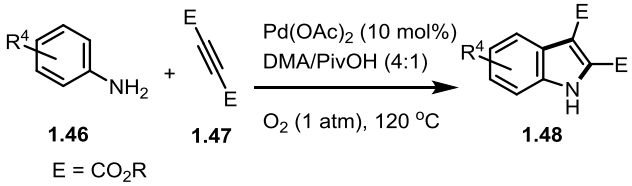
[16] (a) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339. (b) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921. (c) Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Takizawa, S.; Shimamura, H.; Tomishima, M.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, 16036. (d) Shimamura, H.; Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776.
[17] (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Comm.* **2004**, 2824. (b) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2008**, *64*, 769.
[18] (a) Ackermann, L. *Organometallics* **2003**, *22*, 4367e4368. (b) Ackermann, L.; Kaspar, L. T. *J. Org. Chem.* **2007**, *72*, 6149.

alkynes are compatible, was reported by the same group by switching $TiCl_4$ catalyst to ruthenium catalyst in the hydroamination step.[19]




**Scheme 1.10: Pd-catalyzed heteroannulation in indole synthesis by Ackermann**

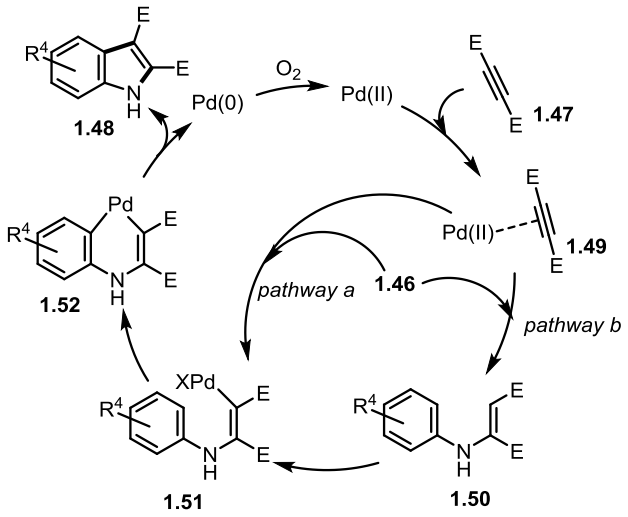
As an improvement of Larock's and Ackermann's methodologies, an oxidative heteroanullation of simple anilines **1.46** with internal alkynes **1.47** taking advantage of C-H activation was reported by Jiao and coworkers (Scheme 1.11).[20] Direct carboamination of butynedioate derivatives in the presence of $Pd(OAc)_2$ under oxygen atmosphere afforded 2,3-disubstituted indoles **1.48** in moderate to excellent yields. Pleasingly, both *N*-nonsubstituted and *N*-alkyl monosubstituted anilines can be transformed successfully into corresponding indoles.




**Scheme 1.11: Pd-catalyzed heteroannulation in indole synthesis by Jiao**

The reaction mechanism can be postulated as following: By activation of alkyne **1.47** with Pd(II) catalyst, aminopalladation could occur to form a vinylpalladium intermediate **1.51** which undergoes C-H activation to produce a 6-membered palladacycle **1.52**. Desired product can be obtained by reductive elimination of the resulting intermediate. Oxidation of Pd(0) by oxygen molecule generated Pd(II) species (*pathway a*, Scheme 1.12). Alternatively, similar to Ackerman's approach, Pd(II)-catalyzed hydroamination leading to enamine intermediate **1.50** could not be ruled out. The subsequent double C-H activation generated the same intermediates as described above **1.51** and **1.52** which undergo reductive elimination to give indole product (*pathway b*, Scheme 1.12).

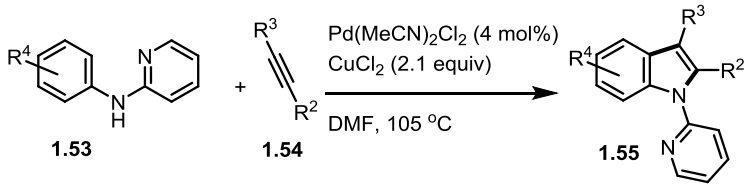
[19] Ackermann, L.; Althammer, A. *Synlett* **2006**, *3*, 3125.
[20] Jiao, N.; Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.




**Scheme 1.12: Mechanism of Pd-catalyzed indole synthesis by Jiao**

A complementary method to Jiao's was reported by Lu and Wang.[21] $PdCl_2$-catalyzed oxidative heteroannulation of anilines with diarylacetylenes in the presence of copper salts and $Na_2CO_3$ afforded 2,3-diarylindoles in moderate to good yields.

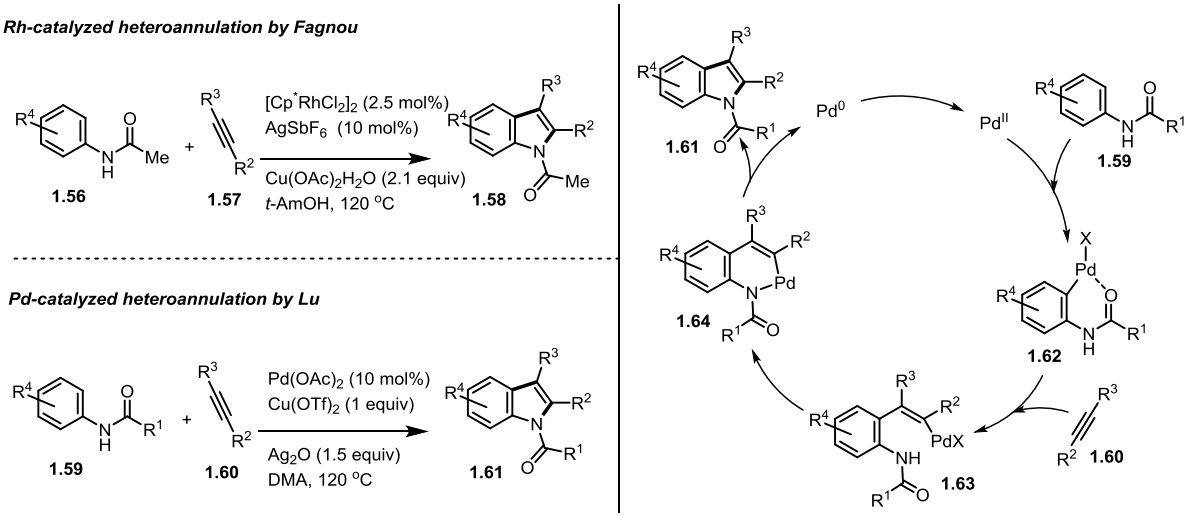
Another palladium-catalyzed oxidative coupling was exploited using *N*-2-pyridyl as a directing group (Scheme 1.13).[22] This reaction displayed a very good substrate scope and regioselectivity with respect of the alkyne part.




**Scheme 1.13: Pd-catalyzed heteroannulation in indole synthesis by Li**

Using anilines as starting materials, an alternative synthetic strategy to indole was also exploited by employing a directing group on nitrogen atom. The first example of this approach is rhodium-catalyzed heteroannulation between alkynes **1.57** and *N*-acetyl anilines **1.56** reported by Fagnou and coworkers (Scheme 1.14).[23] The same reaction can also be catalyzed by palladium catalysis (Scheme 1.14).[24] Oxidative conditions were performed in the presence of stoichiometric amount of oxidants such as $Ag_2O$ and $Cu(OTf)_2$. Mechanistically, the reaction proceeds through (1) *ortho*- C-H activation by assistance of acetyl group to form arylpalladium intermediate **1.62**; (2) insertion to alkynes **1.60** to form vinylpalladium intermediate **1.63**; (3) ligand exchanging to form 6-membered palladacycles **1.64**; (4) reductive elimination to product **1.61** and Pd(0); (5) regeneration of Pd(II) by external oxidants.

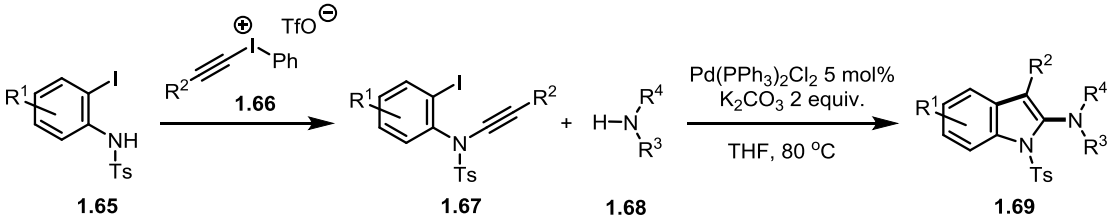
[21] (a) Chen, X.; Li, X.; Wang, N.; Jin, J.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2012**, *23*, 4380.
[22] Chen, J.; Pang, Q.; Sun, Y.; Li, X. *J. Org. Chem.* **2011**, *76*, 3523.
[23] Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.
[24] Zhou, F.; Han, X.; Lu, X. *Tetrahedron Lett.* **2011**, *52*, 4681.




**Scheme 1.14: Heteroannulation in indole synthesis by C-H activation**

## 1. 1. 3. Palladium-Catalyzed Heteroannulation of *N*-alkynyl-2-Haloanilines in Synthesis of 2-Substituted Indoles

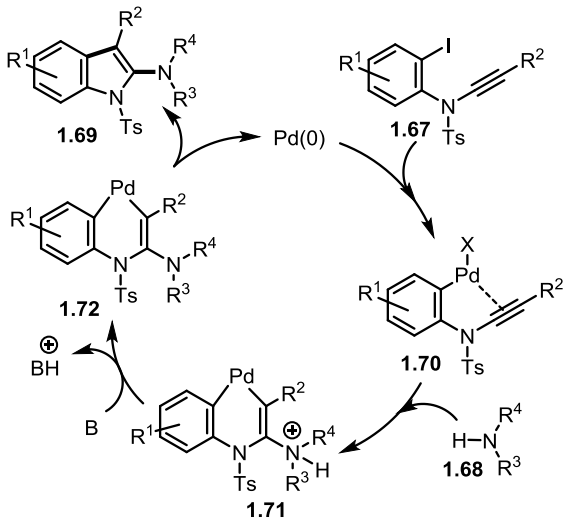
The last disconnection for indole synthesis by difunctionalization of alkynes involves intramolecular cyclization of *N*-alkynyl-2-iodonilines in the presence of palladium catalyst and amine to afford 2,3-disubstituted indoles (Scheme 1.15).[25] The amination-cyclization is tolerated with primary, secondary amines and anilines to afford a wide range of 2-aminoindoles. However, only *N*-tosyl as a protecting group of nitrogen is reported. The limitation in employing protecting group could be accounted for by the requirement of tosyl for the stability and the synthesis of *N*-alkynyl-2-iodonilines **1.67** from alkynyliodonium salts **1.66**.




**Scheme 1.15: Pd-catalyzed amino-cyclization in indole synthesis by Witulsky**

The reaction mechanism was described in Scheme 1.16. Firstly, the oxidative addition of **1.67** to Pd(0) afforded palladium(II) complex **1.70**. Subsequent aminopalladation of **1.70** afforded **1.71**, which upon deprotonation provided the palladacycle intermediate **1.72**. Reductive elimination from **1.72** gave indole **1.69** with concurrent regeneration of Pd(0) species.

[25] Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257.




**Scheme 1.16: Mechanism of Pd-catalyzed amino-cyclization by Witulsky**

To the best our knowledge, above transformation is the sole example of this synthetic strategy using palladium catalysis. However, similar reactions using copper[26] and gold[27] as catalyst/promotor are known.

[26] Frischmuth, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10084.
[27] Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567.

## 1. 2. Metal-Catalyzed Diamination of Alkynes

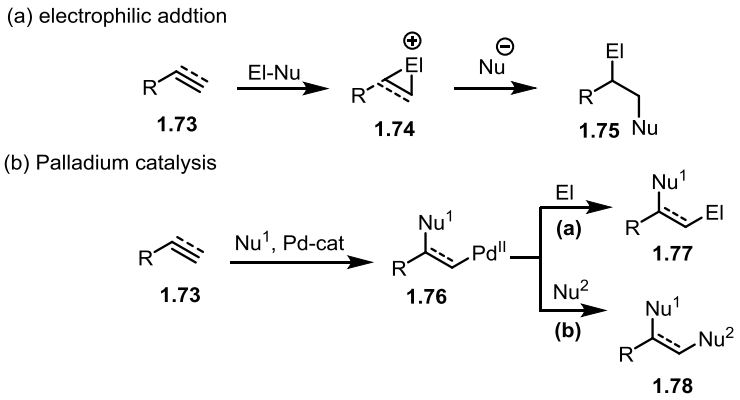
Vicinal diamines are important structural moieties which are present in a variety of natural products, biologically active molecules. Chiral vicinal diamines are also widely used as chiral ligands or chiral moieties in catalyst for asymmetric reactions.[28] As a result, they have become an attractive target for synthetic chemists and plenty of methodologies have been established to construct this class of compound.[29] Among them, a direct diamination of C-C multiple bonds, double introduction of C-N bond across alkenes or alkynes, is the most appealing synthetic approach. Indeed, transition metal-catalyzed diamination of alkenes have drawn much attention and significant progress has been made for this challenging transformation for last decade.[30] They have been further established as reliable methods that are applicable to complex natural product synthesis[31] or bioactive compounds.[32] However, the corresponding diamination of alkynes which can be anticipated to contribute efficient synthetic access to nitrogen-containing heterocycles, was surprisingly far less studied.

As a related topic to our research field, herein we will summarize precedent works on metal-catalyzed diamination of alkynes in the literature. They will be categorized based on the different metal catalysts which are the most useful for this kind of transformation, including: palladium, copper and gold.

[28] (a) Michalson, E. T.; Szmuszkovicz, J. *Prog. Drug Res.* **1989**, *33*, 135. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (c) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.
[29] De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067.
[30] Reviews on vicinal diamines: (a) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (b) De Figueiredo, R. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1190. (c) Muniz, K.; Martinez, C. *J. Org. Chem.* **2013**, *78*, 2168. (d) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665.
[31] Ding, H.; Chen, D. Y.-K. *Angew. Chem. Int. Ed*. **2011**, *50*, 676.
[32] (a) Fu, R.; Zhao, B.; Shi, Y. *J. Org. Chem.* **2009**, *74*, 7577. (b) Wen, Y.; Zhao, B.; Shi, Y. *Org. Lett.* **2009**, *11*, 2365.

### 1. 2. 1. Palladium-Catalyzed Diamination of Alkynes

Different from electrophilic addition on alkenes or alkynes which can be easily initiated by electrophilic attack, nucleophilic additions on unactivated C-C multiple bonds are rare. This could be reasoned by the fact that they both represent electron rich property. However, by coordination to metal such as palladium(II), the addition of nucleophiles such as amine or amides to C-C multiple bonds becomes feasible (Scheme 1.17). The resulting palladium intermediate **1.76** could be further functionalized with suitable electrophile (path a) or another nucleophile (path b) to complete difunctionalization process. As a result, in principal, palladium-catalyzed or generally metal-catalyzed diamination of C-C multiple bonds could be achieved by employing either 1 nitrogen nucleophile, 1 nitrogen electrophile or bisnitrogen nucleophiles.

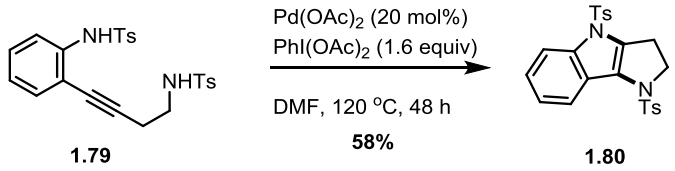



**Scheme 1.17: Different approaches in difunctionalization of C-C multiple bond**

In contrast to diamination of alkenes, the corresponding palladium-catalyzed reaction of alkynes proceeds through σ-vinylpalladium intermediate **1.76** which is relatively more stable than σ-alkyl palladium intermediate, the latter being susceptible for β-hydride elimination. The end-stage trapping with second functional groups, therefore, is more promising. However, diamination of alkynes preserves a C-C unsaturated bond after the reaction; so that this transformation is only effective for the synthesis of cyclic and aromatized products. Subsequently, tailoring the reaction fashion for this transformation is crucial factor to its success.

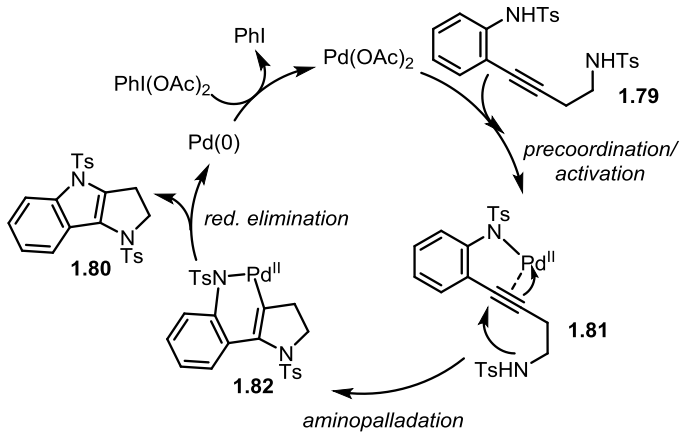
As mentioned previously, *o*-alkynylanilines, relevant substrates for palladium-catalyzed domino process, could be appropriate to diamination as well. Apart from trapping σ-indolylpalladium intermediate with electrophiles (see Scheme 1.2), other methodologies employing nucleophilic spices to functionalize indoles have been studied recently. In this case (pathway b), it can be envisioned that σ-indolylpalladium **1.12** can undergoes nucleophilic attack or ligand exchanging, then the resulting intermediate follows reductive elimination to generate Pd(0). To complete the catalytic cycles, the suitable oxidant is required to regenerate Pd(II) for activation of the triple bond.

The first example of diamination of triple bond was described by Muniz in the subscope investigation of Pd(II)-catalyzed bisindoline synthesis (Scheme 1.18).[33] However, this reaction requires 20% mol of $Pd(OAc)_2$, high temperature and long time to afford desired product in moderate yield.



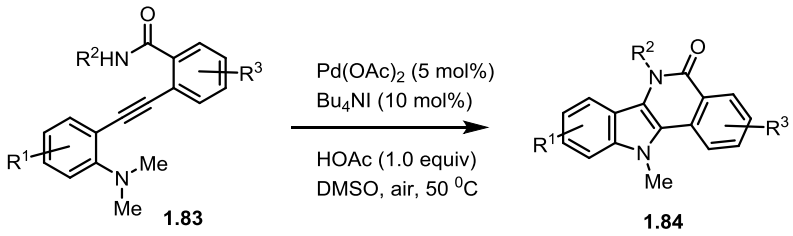

**Scheme 1.18: Pd(II)-catalyzed diamination by Muniz**

The formation of this 3-aminoaindole **1.80** can be explained by a domino process involving precoordination/activation, aminopalladation, reductive elimination and regeneration of Pd(II) catalyst as shown in Scheme 1.19.




**Scheme 1.19: Mechanism of Pd(II)-catalyzed diamination by Muniz**

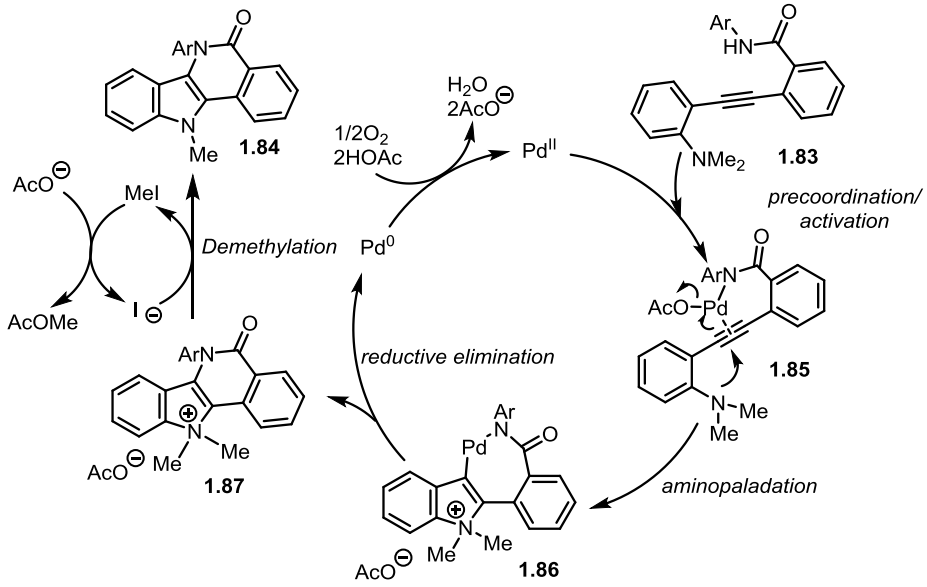
Our group recently discovered a novel Pd(II)-catalyzed domino transformation of *o*-(1-alkynyl)benzamide **1.83** to smoothly afford indolo[3,2-*c*]isoquinolinones **1.84**, in which an internal amide can act as a nucleophile to functionalize at position C-3 of indole when the Cacchi cyclization was carried out under oxidative condition (Scheme 1.20).[34]




**Scheme 1.20: Pd(II)-catalyzed diamination by Zhu**

[33] Muniz, K. *J. Am. Chem. Soc.*, **2007**, *129*, 14542.
[34] Yao,B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5170.

The double cyclization proceeded through a domino process involving three major steps: aminopalladation, reductive elimination and demethylation.[35] The domino process is initiated by double coordination to Pd(II) catalyst by both amide and alkyne functionalities. Following deprotonation leads to formation of π,σ-chelated Pd(II) complex **1.85**. The subsequent intramolecular nucleophilic attack of nitrogen atom across the activated triple bond affords σ-indolium-Pd(II) complex **1.86**. The resulting intermediate undergoes reductive elimination to form the second C-N bond and tetracyclic indolium salt **1.87**, concomitantly release Pd(0), which is oxidized by atmospheric oxygen to regenerate Pd(II) and complete catalytic cycles. Demethylation by $S_N2$ reaction of **1.87** with iodide ion furnishes final tetracyclic product and MeI. Iodide anion possibly can be regenerated by reaction between acetate ion and MeI, then back to catalytic cycles, allowing the reaction to be performed in the presence of a catalytic amount of $n$Bu$_4$NI (scheme 1.21).

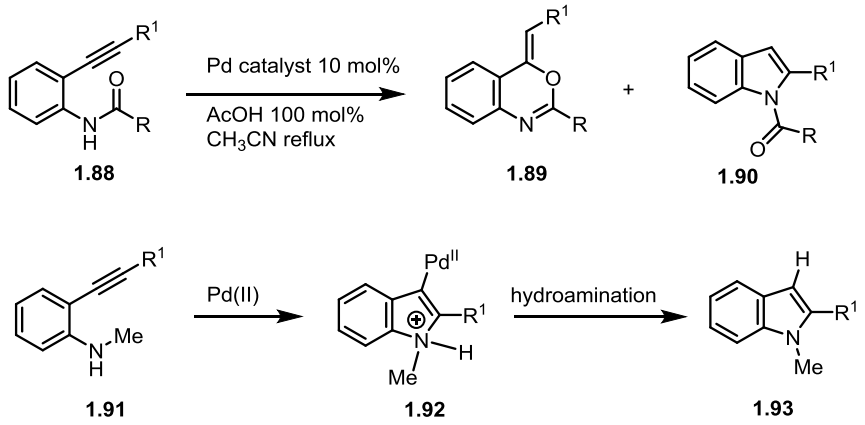



**Scheme 1.21: Mechanism of Pd(II)-catalyzed diamination by Zhu**

This designed model employing *N*,*N*-dimethyl *o*-alkynylaniline derivative **1.83**, acidic and atmospheric medium makes our synthetic method unique among other "conventional" Cacchi indole synthesis in which *o*-alkynyltrifluroacetanildes **1.15**, Pd(0) and tricky deoxygenated and basic conditions are mandatory (see Scheme 1.3). After detailed investigation on the substrate scope, *N*,*N*-dimethy *o*-alkynylanilines **1.83** was found to be the most suitable for our method. It is noteworthy that *o*-alkynylacetanilides **1.88** in the presence of $Pd(OAc)_2$ under acidic condition can lead to either 6-*exo*-dig oxopalladation or 5-*endo*-dig aminopalladation to form the corresponding products **1.89** and **1.90**.[36] In addition, monosubstituted *N*-methyl *o*-alkynylaniline **1.91** failed to produce the biscyclization product due most probably to the strong coordination of the secondary amine to

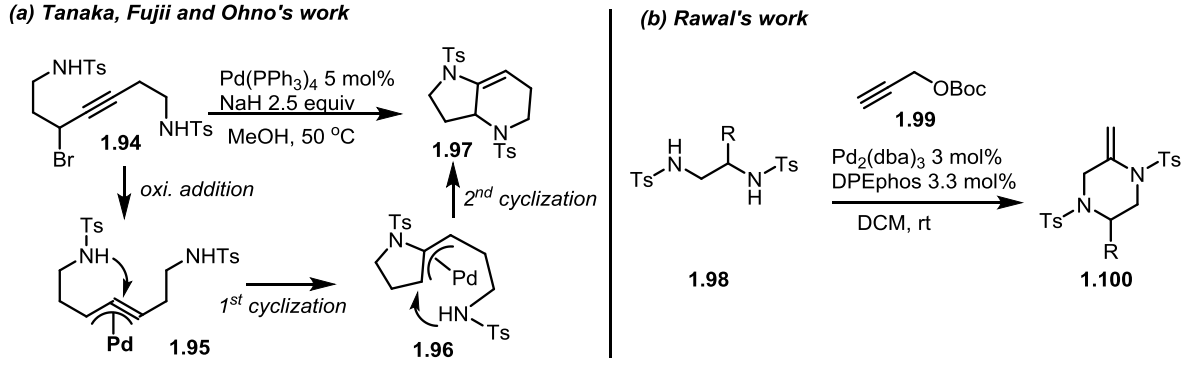
[35] Yao, B.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2014**, *20*, 12255.
[36] T. Saito, S. Ogawa, N. Takei, N. Kutsumura, and T. Otani, *Org. Lett*. **2011**, *13*, 1098.

palldadium species. A palladidum catalyzed hydroamination of **1.91** could also occur to form a side product **1.93** (Scheme 1.22).[37]




**Scheme 1.22: Influence of substitutents on nitrogen to Pd-catalyzed cyclization**

Interestingly, palladium-catalyzed difunctionalization by two nucleophiles could be performed under neutral-redox conditions when propargyl bromide or propargyl carbonates was employed as alkyne substrates. Tanaka, Fujii and Ohno reported a palladium-catalyzed double cyclization of propargyl bromide **1.94** by two tethered nucleophilic nitrogens to construct bicyclic heterocycles **1.97** (Scheme 1.23-a).[38] This transformation proceeds through formation of $\eta^3$-propargylpalladium **1.95** by oxidative addition, followed by double intramolecular nucleophilic attack by NHTs. Alternatively, intermolecular diamination of propargyl carbonates with bisnitrogen nucleophiles to afford highly substituted piperazines was published by Rawal *et al.* (Scheme 1.23-b).[39] Although in those examples, both nucleophiles are not added across the triple bonds, they imply the efficient utilization of palladium catalysis in diamination of alkynes.




**Scheme 1.23: Pd-catalyzed double cyclization of propagyl bromide/carbonates**

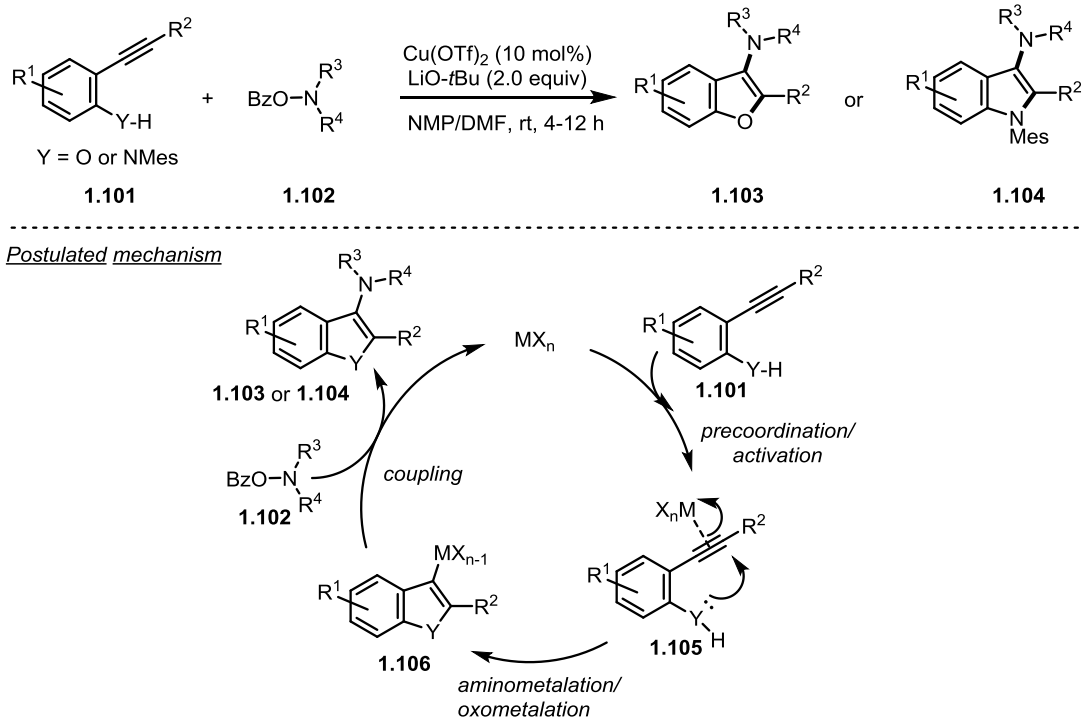
[37] Majumdar, K. C.; Nirupam De, B. Roy, *Synthesis*, **2010**, *24*, 4207.
[38] Okano, A.; Tsukamoto, K.; Kosaka, S.; Maeda, H.; Oishi, S.; Tanaka, T.; Fujii, N.; Ohno, H. *Chem. Eur. J.* **2010**, *16*, 8410.
[39] Montgomery, T. D.; Rawal, V. H. *Org. Lett.* **2016**, *18*, 740.

### 1. 2. 2. Copper-Catalyzed Diamination of Alkynes

Copper catalysts represent multiple properties in chemical transformations, such as Lewis acid, π-acid, a single-electron mediator and a two-electron mediator. As a result, copper-catalyzed transformation becomes a powerful tool to difunctionalize C-C multiple bonds. Herein we would like to list out precedent works in literature on diamination of alkynes using copper catalysis.

*a) Copper-catalyzed diamination of alkynes by a nucleophilic and an electrophilic nitrogen*

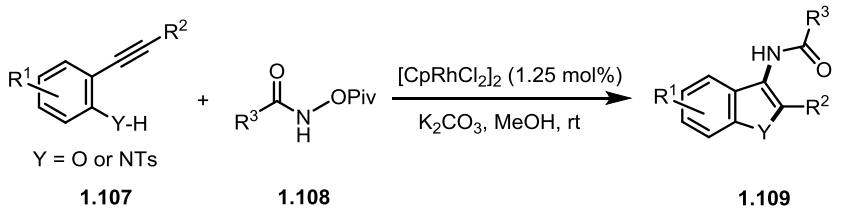
Hirano and Miura reported a copper-catalyzed annulative amination of *o*-iodoanilines/*o*-iodophenols for synthesis of 3-aminobenozfurans and -indoles in mild conditions.[40] Successful aminoetherification and diamination were achieved by trapping σ-benzoheteroylcuprate (as shown in scheme 1.2 or 1.17) with electrophilic amination reagents, *O*-acylated hydroxylamines. The mechanism was postulated to proceed through the formation of σ-benzoheteroyl metal species **1.106** *via* intramolecular *anti*-oxometalation or -aminometalation by nucleophilic attack of pendant nucleophile to triple bond, then subsequent coupling of this resulting intermediate to *O*-acylated hydroxylamines to afford desired 3-aminobenzoheteroles **1.103** or **1.104** along with regeneration of copper catalyst (Scheme 1.24).




**Scheme 1.24: Hirano and Miura's copper catalysed annulative amination**

[40] (a) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617.

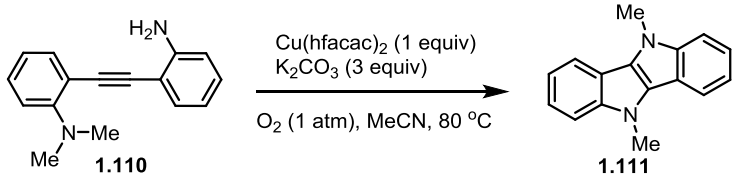
Related to Hirano and Miura's work, a rhodium(III)-catalyzed cascade cyclization/electrophilic amidation of *o*-iodoanilines/*o*-iodophenols with *N*-pivaloyloxylamines as electrophilic reagents was reported by Tong and Liu.[41] Addition of both pendant nucleophilic oxygen/nitrogen and electrophilic nitrogen amide across triple bond was also proceeded smoothly in the presence of rhodium catalyst under mild conditions to afford 3-amidobenzofurans or 3-amidoindoles (Scheme 1.25).




**Scheme 1.25: Tong and Liu's rhodium(III)-catalysed cascade cyclization/amidation**

*b) Copper-catalyzed/mediated diamination of alkynes by bisnucleophilic nitrogens*

Complementary to Muniz's and our works, a copper-mediated intramolecular double-cyclization of bis(2-aminophenyl)acetylene was reported recently by Yamamoto and Jin.[42] bis(2-aminophenyl)acetylene **1.110** bearing both *N*,*N*-dimethyl and primary amine groups was converted into tetracyclic 5,10-dihydroindolo[3,2-b]indoles **1.111** in good yield under oxidative $Cu(hfacac)_2/O_2$ system (Scheme 1.26). The designing of substituents on nitrogen atoms is crucial to the success of the reaction, in which intermolecular methyl transferring from *N*,*N*-dimethyl amine to primary amine was observed by deuterium labelling experiments.

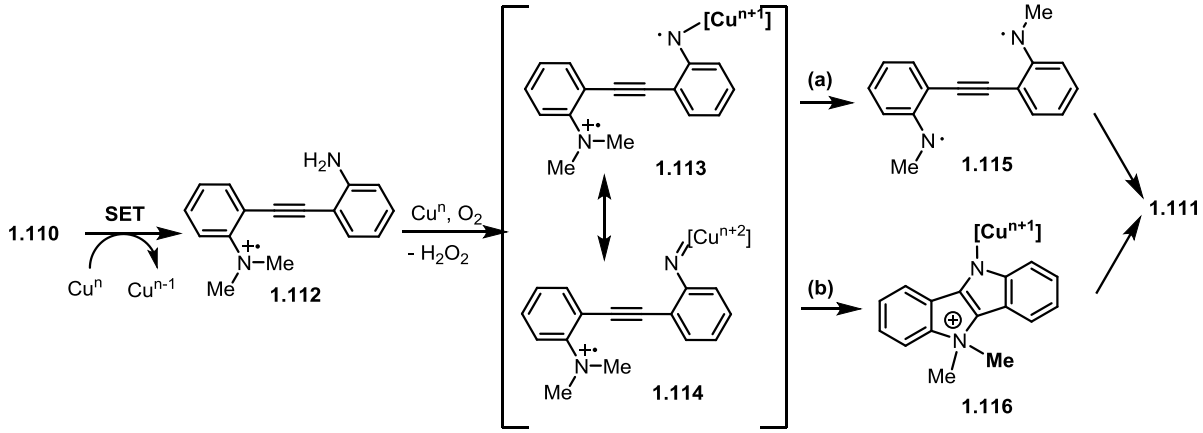



**Scheme 1.26: Copper-mediated diamination of alkynes by Yamamoto and Jin**

The reaction mechanism of double cyclization is not fully understood. However, based on the experimental observations, the following route could be suggested (Scheme 1.27): bis(2-aminophenyl)acetylene can be oxidized on electron-rich *N*,*N*-dimethylamine by single electron transfer with copper salts to form cation radical **1.112** which is further oxidized by copper and oxygen molecule to give aniline-copper radical species **1.113**. This intermediate should be stabilized by its resonance form of Cu-nitrenoid intermediate **1.114**. Subsequently, intermolecular *N*-methyl transfer of **1.113** from *N*,*N*-dimethyl amine to primary amine could take place to provide symmetrical *N*-methylamine radical **1.115** which undergoes radical cyclization across triple bond to afford desired

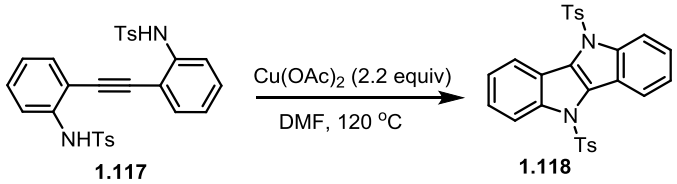
[41] Hu, Z.; Tong, X.; Liu, G. *Org. Lett.* **2016**, *18*, 2058.
[42] Ho, H. E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2016**, *18*, 2487.

tetracyclic product (pathway a). Alternatively, radical addition of **1.113** or **1.114** across the triple bond, and followed by intermolecular *N*-methyl transfer could be considered to form the same desired product (pathway b).




**Scheme 1.27: Suggested mechanism of copper-mediate diamination by Yamamoto and Jin**

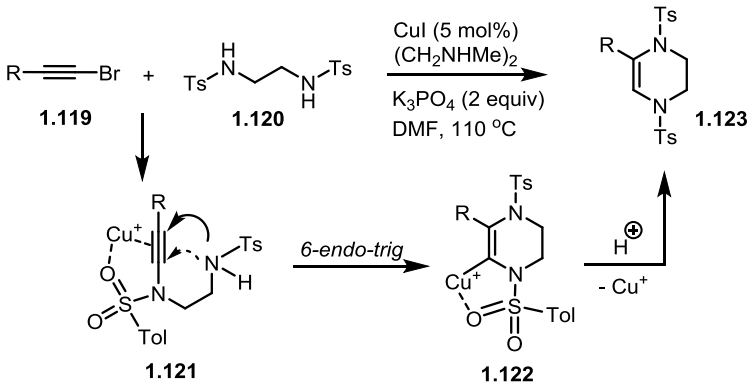
Lately, a similar intramolecular double cyclization of bis(2-aminophenyl)acetylene **1.117** to afford the same tetracycles 5,10-dihydroindolo[3,2-b]indoles **1.118** via $Cu(OAc)_2$-mediated reactions was published by Du and coworkers (Scheme 1.28).[43] Different from previous work, double sulfonylated amines are required to the success of diamination.




**Scheme 1.28: Copper-mediated diamination of alkynes by Du**

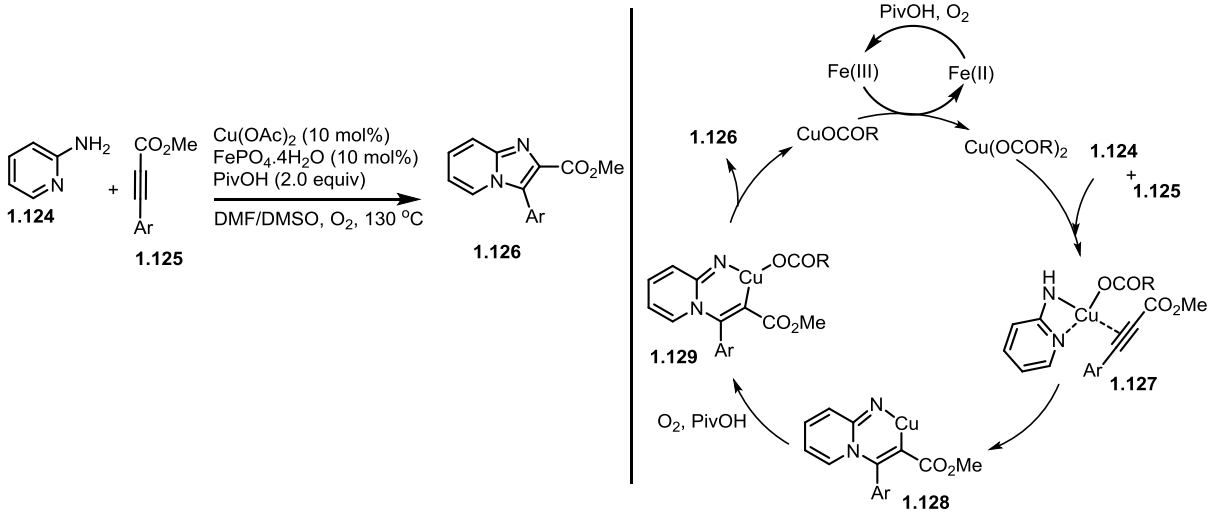
Urabe et al. first revealed an intermolecular diamination of alkynes between 1-halo-1alkynes **1.119** and bisnitrogen nucleophiles **1.120** to afford tetrahydropyrazines **1.123** by copper-catalyzed reactions in neutral redox conditions (Scheme 1.29).[44] The reaction mechanism proceeds through copper(I)-catalyzed *N*-alkynylation[45] to form the first C-N bond and ynamine intermediate **1.121**. Interestingly, **1.121** can exclusively undergo 6-endo-trig cyclization instead of 5-exo-trig (which is normally more favourable) by copper-coordination and nucleophilic attack of the second NHTs to produce 6-membered ring intermediate **1.122**. The regioselectivity of cyclization could be reasoned by coordination effect of sulfonamide functional group as depicted in scheme 1.29. The subsequent protonation of **1.122** provided desired tetrahydropyrazines **1.123** and release Cu(I) to continue catalytic cycles.

[43] Yu, J.; Zhang-Negrerie, D.; Du, Y. *Org. Lett.* **2016**, *18*, 3322.
[44] Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.
[45] Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727.




**Scheme 1.29: Copper-catalyzed diamination of alkynylbromides by Urabe**

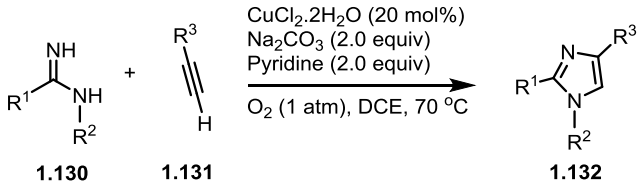
Copper-catalyzed intermolecular diamination of alkynes was later reported by Liu and coworkers.[46] The heteroannulation of 2-aminopyridines **1.124** with propiolate derivatives **1.125** was catalyzed by copper/iron catalyst system in oxidative conditions to afford imidazo[1,2-α]pyridines **1.126** with high chemoselectivity and regioselectivity (Scheme 1.29). This transformation is well-tolerated with different aromatic substituted on alkynes; however, an activating functional group (electro-withdrawing groups) on alkynes such as carboxylate is mandatory. The reaction proceeded through the following steps: (1) coordination of 2-aminopyridine **1.124** and alkyne **1.125** to copper to form complex **1.127**; (2) *syn*-nucleocupration with pyridine nitrogen, which is more nucleophilic, led to copper(II) intermediate **1.128**, along with dearomatization of pyridine ring; (3) Oxidation of **1.128** to form cyclic copper(III) intermediate **1.129**; (4) reductive elimination to form the second C-N bond and desired product **1.126**, with concomitant release of copper(I); (5) regeneration of copper(II) by a sequence of redox cycles.




**Scheme 1.30: Copper-catalyzed diamination of alkynes by Liu**

[46] Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X. W. *Org. Lett.* **2012**, *14*, 4386.

Analogously, Neuville reported an efficient copper-catalyzed 1,2,4-trisubstituted imidazole synthesis by diamination of terminal alkynes with amidines under oxidative conditions (Scheme 1.31).[47] This transformation tolerated a wide range of functional groups leading to a broad scope of imidazoles. Both aliphatic and aromatic terminal alkynes without activating groups are suitable substrates.



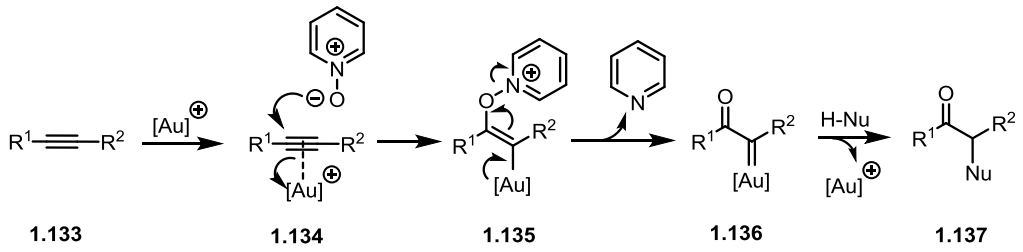

**1.130** **1.131** **1.132**

**Scheme 1.31: Copper-catalyzed diamination of terminal alkynes by Neuville**

[47] Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752.

### 1. 2. 3. Gold-Catalyzed Diamination of Alkynes

Gold complexes, powerful soft Lewis acids which can activate alkynes toward nucleophilic attack have attracted great attention recently.[48] Gold-catalyzed transformations provide efficient methods with mild conditions, good chemo- and regioselectivity for straightforward synthesis of heterocycles, polycyclic scaffolds and natural products.[49] In recent years, α-carbonyl gold carbenes[50] have emerged as promising and valuable intermediates for complex organic transformations, especially, 1,2-difunctionalization of alkynes. The mechanism of generation of α-carbonyl gold carbene from oxidation (such as pyridine *N*-oxide) of alkynes can be postulated through addition of *N*-oxide to gold-activated alkyne **1.134** to form vinyl gold intermediate **1.135** which undergoes rearrangement to form α-carbonyl gold carbene **1.136** and release pyridine as byproduct (Scheme 1.32). The most viable transformation of this highly active intermediate is nucleophilic addition to obtain α-functionalized carbonyl product **1.137**.

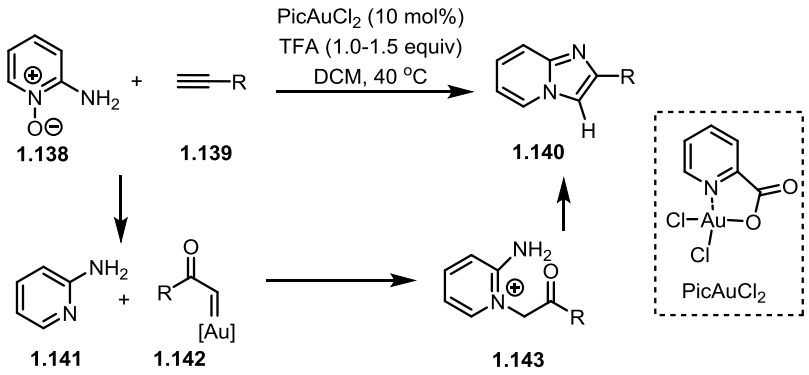



**Scheme 1.32: Gold-catalyzed oxidation/nucleophilic addition of alkynes**

This mechanic course of transformation has been further exploited in difunctionalization of alkynes. Herein, we will sort out several examples of gold-catalyzed diamination of alkynes related to the formation of carbenoid intermediate.

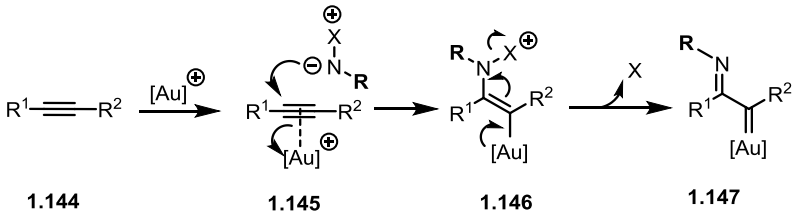
Toste and coworkers developed a mild, atom economical gold-catalyzed synthesis of imidazo[1,2-α]pyridines **1.140** from 2-aminopyridine *N*-oxide **1.138** and terminal alkynes **1.139** (Scheme 1.33).[51] The synthetic strategy takes advantage of formation of 2-aminopiridine byproduct **1.141** as bisnitrogen nucleophiles to trap α-carbonyl gold carbene **1.142**. This synthetic approach could be considered as a complementary method to copper-catalyzed heteroannulation as mentioned previously (see Scheme 1.31).

[48] For review on gold catalysis: (a) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462. (b) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (c) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953.
[49] For review on gold catalysis in heterocycles synthesis and total synthesis: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Debrouwer, W.; Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Adv. Synth. Catal.* **2015**, *357*, 2975. (c) Pflasterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331.
[50] Review on α-carbonyl gold carbenes: Xiao, J.; Li, X. *Angew. Chem. Int. Ed*., **2011**, *50*, 7226.
[51] Talbot, E. P. A.; Richardson, M.; McKenna, J. M.; Toste, F. D. *Adv. Synth. Catal.* **2014**, *356*, 687.




**Scheme 1.33: Gold-catalyzed diamination of alkynes by Toste**

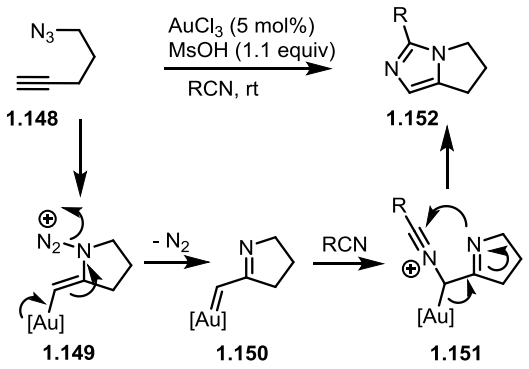
Alternative to α-carbonyl gold carbene, imino carbene intermediate has attracted great attention recently.[52] The formation of imino gold carbene intermediates could occur from nucleophilic addition of appropriate nitrogen-based reagents across a gold-activated triple bond **1.145** to get vinyl gold intermediate **1.146** which follows rearrangement to form imino carbene **1.147** (Scheme 1.34). The reactions involving with this intermediate should offer the great potential to construct nitrogen-containing molecules. Rationally, using another nitrogen nucleophile for trapping **1.147**, a diamination of alkynes could be achieved.




**Scheme 1.34: General formation of imino gold carbenes**

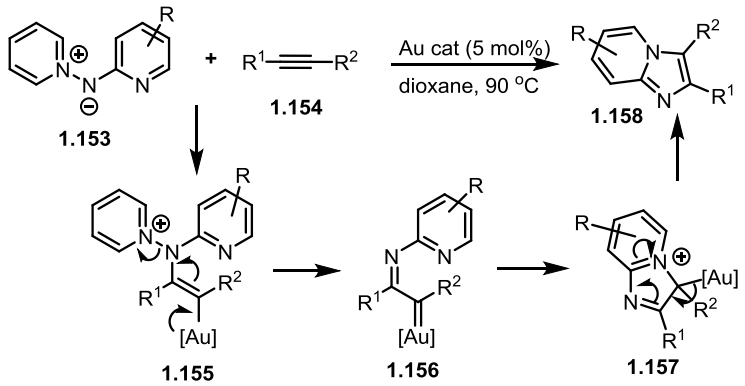
Indeed, the trapping of this intermediate with nitriles to afford bicyclic imidazoles was reported by Xiao and Zang (Scheme 1.35).[53] In this transformation, a cyclic α-imino gold carbine intermediate **1.150** is generated *in situ* via intramolecular nucleophilic addition of azido group, followed by extrusion of $N_2$ molecule. The highly electrophilic intermediate **1.150** is then trapped by a nitrile to form intermediate **1.151** which cyclizes to furnish bicyclic imidazole **1.152**. A variety of nitriles could be employed successfully to the system, including aliphatic, aromatic, and functional-group-containing nitriles. However, the utilization of nitriles as solvents is mandatory to its success.

[52] (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (b) Wetzel, A.; Gagosz, F. *Angew. Chem, Int. Ed.* **2011**, *50*, 7354. (c) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8358.
[53] Xiao, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 4662.




**Scheme 1.35: Gold catalyzed diamination of alkynes via imino carbene by Zang**

Davies et al. has developed a novel nitrogen-based reagent for imino carbene generation. Pyridium *N*-(heteroaryl)amines **1.153** were used to react with internal alkynes **1.154** for the synthesis of fused imidazole compounds **1.158** (Scheme 1.36).[54] Diamination of alkynes was achieved under the catalysis of either gold(I) or gold(III) in simple conditions. A broad scope of alkynes bearing alkyl chain, aryl, heterocycles, functional groups are applicable to this reaction.




**Scheme 1.36: Gold catalyzed diamination of alkynes via imino carbene by Davies**

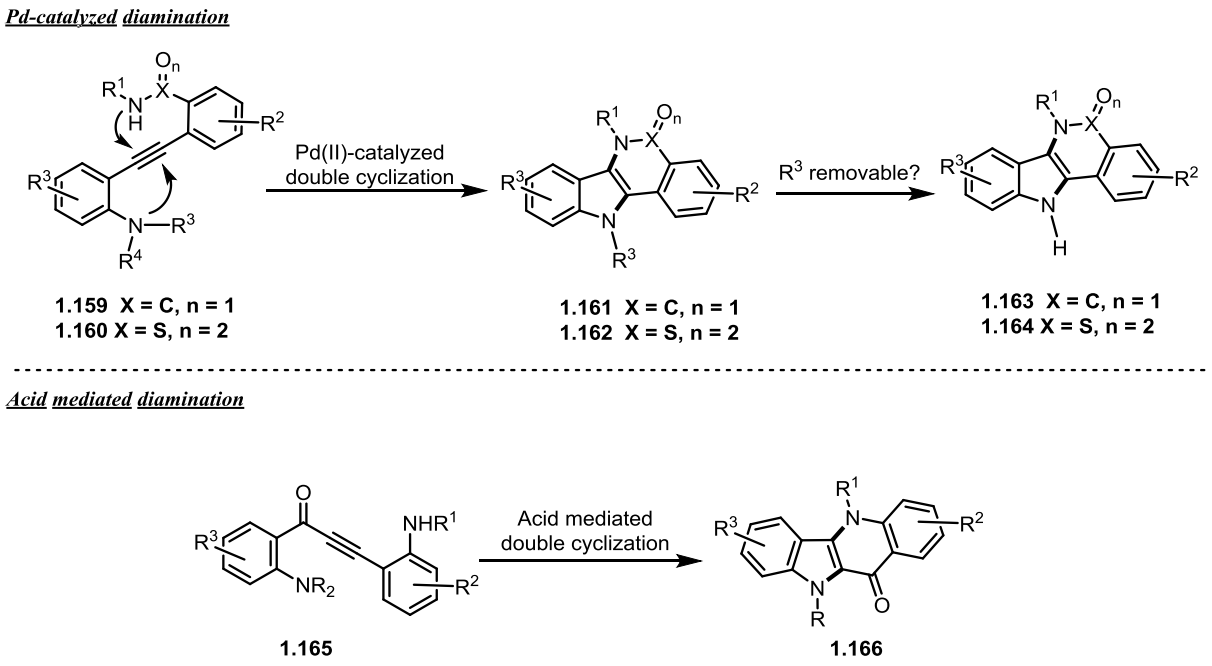
[54] Garzón, M; Davies, P. W. *Org. Lett*. **2014**, *16*, 4850.

## 1. 3. Goals of The First Part of Thesis

Given the advanced synthetic applicability of difunctionalization, development of new diamination or aminoacetoxylation/aminoetherification methodologies to rapidly construct heterocycles from readily available alkynes has become an active area of study. Our group has deep interests in developing efficient syntheses of nitrogen-heterocyclic compounds, especially, indoles and indole-containing natural products.[55] As continuation of this topic, we have decided to develop novel diamination transformations of alkynes that could be applied to the synthesis of polycyclic indoles.

The first part of this manuscript, therefore, will deal with Pd(II)-catalyzed intramolecular double cyclization of 1,2-diarylethynes bearing bisnitrogen nucleophiles to afford tetracyclic indoles (Scheme 1.37). Studies on removable *N*-protecting group for indoles in those palladium catalysis systems to access free NH indoles will also be discussed.

The investigation on palladium-catalyzed and acid-mediated intramolecular double clization of 1,3-diarylprop-2-yn-1-ones bearing bisnitrogen nucleophiles to afford indolo[3,2-b]quinolinones scaffolds will also be detailed in this part (Scheme 1.37).




**Scheme 1.37: Synthesis of tetracyclic indoles by pd(II)-cat. or acid mediated diamination of alkynes**

[55] (a) Wang, Z. H.; Bois-Choussy, M.; Jia, Y. X.; Zhu, J. *Angew. Chem. Int. Ed*., **2010**, *49*, 2018; (b) Gerfaud, T.; Xie, C.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed*., **2011**, *50*, 3954; (c) Buyck, T.; Wang, Q.; Zhu, J. *Org. Lett.*, **2012**, *14*, 1338; (d) Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.*, **2013**, *52*, 3272.

# CHAPTER 2

# Synthesis of Indoloisoquinolinones by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes. 2-(Methoxycarbonyl)ethyl as a Removable *N*-Protecting Group

*Note: This project was realized in collaboration with Dr. Yao Bo*

## 2.1. Introduction

Indole scaffold holds a privileged position in medicinal chemistry with broad spectrum of biological activities.[1] In particular, polyheterocycles embedded with 3-aminoindole moiety and their derivatives have been found in a number of natural products (**1.167-1.170**, Figure 1.2)[56] and bioactive synthetic compounds (**1.171**, Figure 1.2).[57] They showed various biological activities such as anti-malarial, anti-muscarinic, anti-bacterial, anti-viral and anti-plasmodial.[56, 58] The synthesis of these compounds, therefore, has attracted significant attention from synthetic chemists.[56,59] Interested in this scaffold, we have developed a synthesis of tetracyclic free NH indolo[3,2-*c*]isoquinolinones **1.171** by palladium catalysis, which will be described in this chapter.

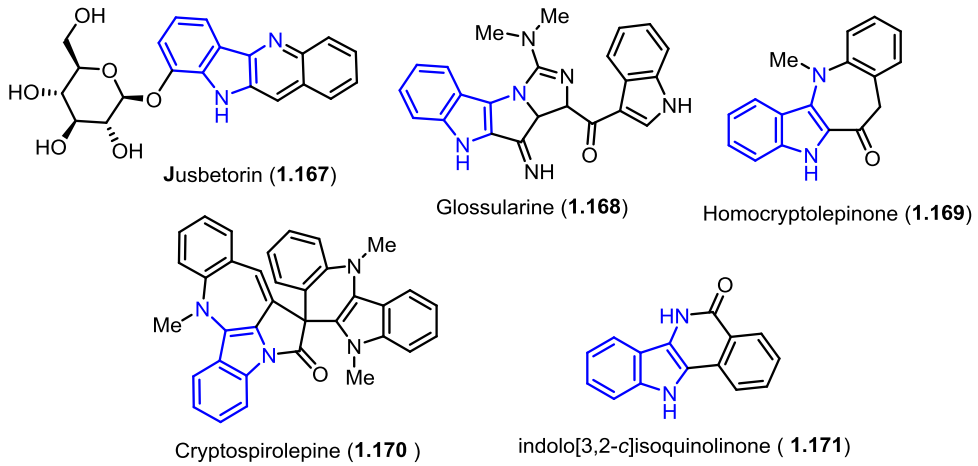



**Figure 1.2: Natural and synthetic compounds embedded with 3-aminoindole moiety**

As introduced in the first part of this thesis, many transformations require an appropriate *N*-protective group leading to *N*-substituted heterocycles and in many cases, the nature of the *N*-substituent is crucial to the success of the reaction. While electron-withdrawing *N*-acyl, *N*-carbamoyl or *N*-sulfonyl protecting groups are frequently introduced to the cyclization precursors as they are easily removable, the *N*-alkylation is sometimes mandatory to ensure the occurrence of the desired transformation. For example, in Solé's synthesis of 1-methyl-2,3-dihydroquinolin-4(1*H*)-ones **1.173**,

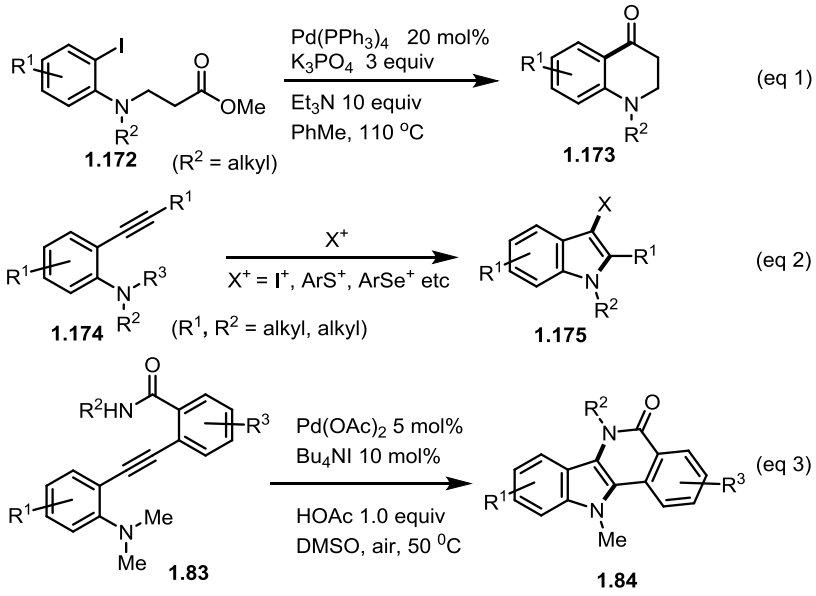
[56] (a) Crouch, R. C.; Davis, A. O.; Spitzer, T. D.; Martin,G. E.; Sharaf, M. M. H.; Schiff, Jr.,P. L.; Phoebe, Jr., C. H.; Tackie, A. N. *J. Heterocycl. Chem.* **1995**, *32*, 1077. (b) Tackie, A. N.; Boye, G. L.; Sharaf, M. H. M.; Schiff, Jr., P. L.; Crouch, R. C.; Spitzer, T. D.; Johnson, R. L.; Dunn, J.; Minick, D.; Martin, G. E. *J. Nat. Prod.* **1993**, *56*, 653. (c) Sharaf, Jr., M. H. M.; Schiff, Jr., P. L.; Tackie, A. N.; Phoebe, Jr., C. H.; Davis, A. O.; Andrews, C. W.; Crouch, R. C. *J. Heterocycl. Chem.* **1995**, *32*, 1631.

[57] Li, L.; Chua, W. S. *Tetrahedron Letters* **2011**, *52*, 1574.

[58] (a) Gorlitzer, K.; Kramer, C.; Meyer, H.; Walter, R. D.; Jomaa, H.; Wiesner, J. *Pharmazie*, **2004**, *59*, 243. (b) Arzel, E.; Rocca, P.; Grellier, P.; Labaed, M.; Frappier, F.; Guritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quguiner, G. *J. Med. Chem.* **2001**, *44*, 949.

[59] (a) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Letters* **2010**, *51*, 6022. (b) Cirrincione, G.; Almerico, A. M.; Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Pani, C. A.; Murtas, P.; Minnei, C.; Marongiu, M. E.; Colla, P. *J. Med. Chem.* **2009**, *42*, 2561.

the aniline nitrogen in the cyclization substrate **1.172** has to be *N*-alkylated (eq 1, Scheme 1.38).[60] The same trend was encountered in the electrophilic cyclization of anilines developed by Larock and co-workers.[61] Indeed, only *N*,*N*-dialkylated *o*-alkynyl anilines **1.174** underwent cyclization under their optimized conditions leading to 3-iodo, 3-sulfenyl and 3-selenylindoles **1.175**. No cyclization occurred if the aniline nitrogen was left unproctected, mono *N*-alkylated, *N*-acylated or *N*-carbamoylated (eq 2, Scheme 1.38). The *N*-carbamoyl and *N*-tosyl derivatives failed to undergo cyclization due probably to unfavourable conformational properties of these compounds. Another example discussed in chapter 1.2.1 is our methodology on double cyclization of *o*-(1-alkynyl)benzamide **1.83**. *N*,*N*-dimethylamine is mandatory for the success of transformation, resulting in the formation of *N*-methylated indolo[3,2-*c*]isoquinolinones **1.84** (eq 3, Scheme 1.38).[34] No desired product was observed if *N*-acylated, *N*-monosubstituted and *N*-unsubstituted amines were employed. Due to this limitation and the challenging in removal of methyl group on indole nitrogen atom, compound **1.84** cannot be further functionalized to modulate physical, chemical and biological properties.



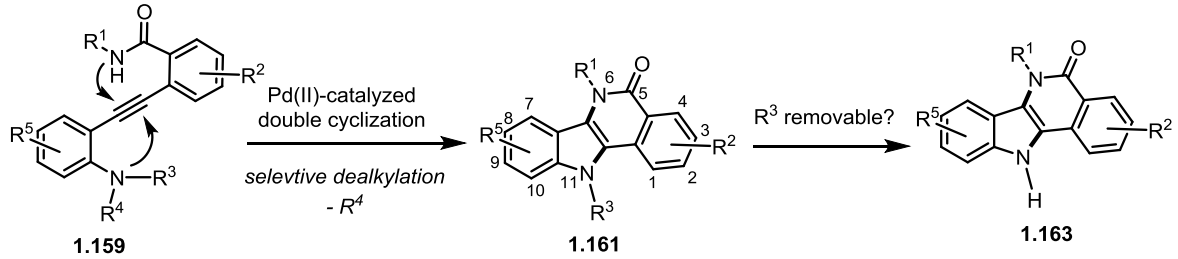

**Scheme 1.38: Impact of N-alkyl substituent in cyclization**

In light of the recurrence of *N*-alkyl substituent in heterocycle synthesis, the difficulties associated with its removal and the importance of N-H function in the bioactivity of heterocycles, the development of an easily removable *N*-alkyl group is of high importance. This *N*-alkyl group should be easily introduced to the starting materials, compatible with the desired transformations but readily

[60] (a) Solé, D.; Serrano, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 7270. (b) Solé, D.; Vallverdu, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

[61] (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem*. **2006**, *71*, 62. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243. (d) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (e) Du, H.-A.; Tang, R.-Y.; Deng, C.-L.; Liu, Y.; Li, J.-H.; Zhang, X.-G. *Adv. Synth. Catal*. **2011**, *353*, 2739. (f) Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274. Friedel-Crafts type cyclization: (g) Moody, C. J.; Swann, E. *Synlett* **1998**, 135.

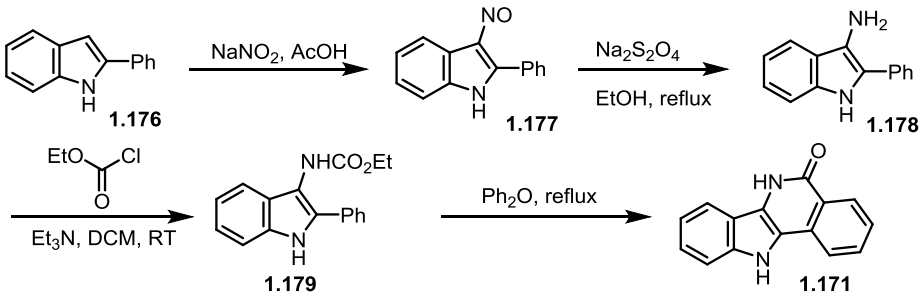
removed after cyclization. In order to extend the scope and practical aspect of our method,[34] we set out to investigate a newly designed model for Pd(II)-catalyzed intramolecular diamination with the aim of synthesizing tetracyclic free NH indoles. In this designed transformation, *o*-(1-alkynyl)benzamide **1.159** bearing appropriate dialkyl substituents ($R^3$, $R^4$) on nitrogen atom could undergo double cyclization to afford $N_{11}$-alkylated (*N*-$R^3$) indolo[3,2-*c*]isoquinolinones **1.161**. Subsequently, **1.161** should be converted into free NH indoles **1.163** by removal of alkyl group ($R^3$) (Scheme 1.139). It is worthy to note that the double cyclization should be controlled to proceed through a selective *N*-dealkylation in order to afford the sole desired product if two different alkyl substituents are employed.




**Scheme 1.39: Synthesis of tetracyclic free NH indoles by Pd(II)-catalyzed diamination of alkynes and removal of N-alkyl group**

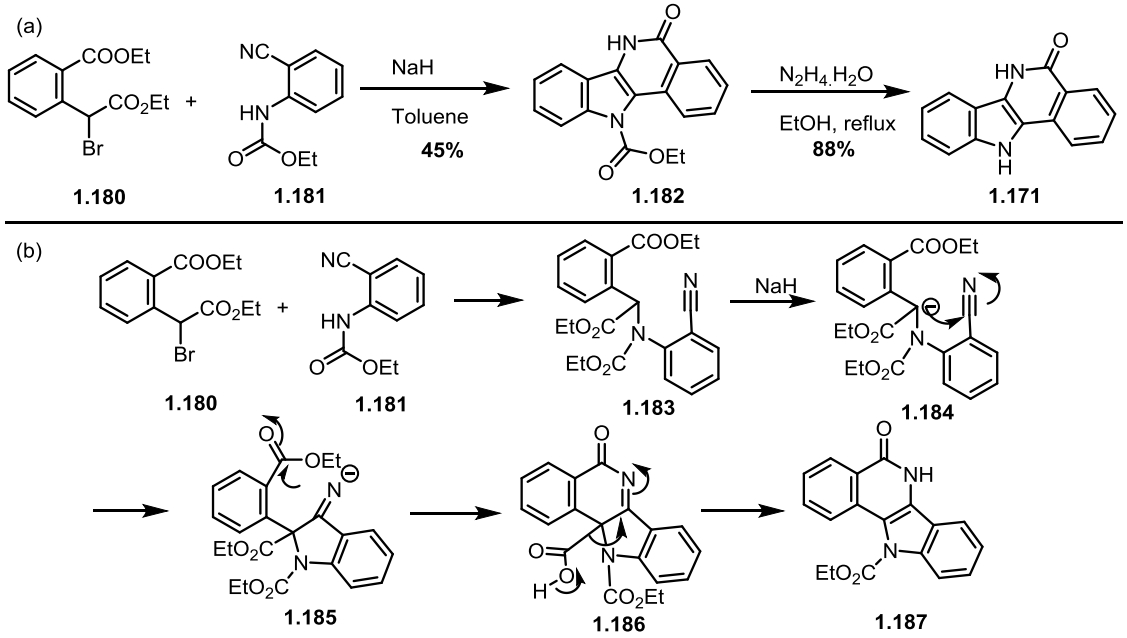
## 2.2. Precedent Synthetic Approaches to Indolo[3,2-*c*]isoquinolinones

Indolo[3,2-c]isoquinolinones are generally synthesized by multiple steps from unstable 3-aminoindole derivatives which normally in turn are prepared by nitrosation or nitration of indoles (Scheme 1.40).[62] In addition, this approach cannot provide structural diversity, due to the limitation in accessing starting materials.




**Scheme 1.40: Synthesis of indolo[3,2-*c*]isoquinolinone from 3-aminoindole**

Another facile and convenient synthesis of indolo[3,2-*c*]isoquinolinones was developed by Jagtap's group.[63] Tetracyclic compound embedded 3-aminoindole can be easily accessed by base-promoted condensation between ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (**1.180**) and ethyl (2-cyanophenyl)carbamate (**1.181**) followed by removal of carbamate group by hydrazine (Scheme 1.41a). The formation of **1.171** was proposed through a sequence of reactions involving nucleophilic substitution, base-promoted condensation, and decarboxylation (Scheme 1.41b).

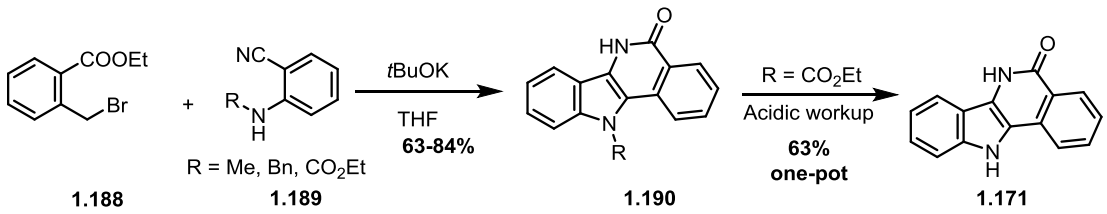



**Scheme 1.41: Synthesis of indolo[3,2-*c*]isoquinolinone by base-promoted condensation**

[62] a) Jagtap, P. G. et. al., US 2004/0039009 b) Jagtap, P. G. et. al., WO 2005/082368.

[63] Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Salman, A.; Szabó, C. *Org. Lett.*, **2005**, *7*, 1753.

Based on Jagtap's method, Chua and coworkers recently reported one-pot multiple synthesis of indolo[3,2-c]isoquinolin-5-one (**1.171**) from methyl 2-(bromomethyl)benzoate (**1.188**) and *N*-protected 2-aminobenzonitriles **1.189** in the presence of KO*t*-Bu.[57] By switching ethyl 2-(1-bromo-2-ethoxy-2-oxoethyl)benzoate (**1.180**) into **1.188**, the cascade reaction proceeded smoothly with various substituted substrates; *N*-methyl, *N*-benzyl, *N*-ethyl carbamate indolo[3,2-*c*]isoquinolinones were obtained in moderate to good yields (Scheme 1.42).



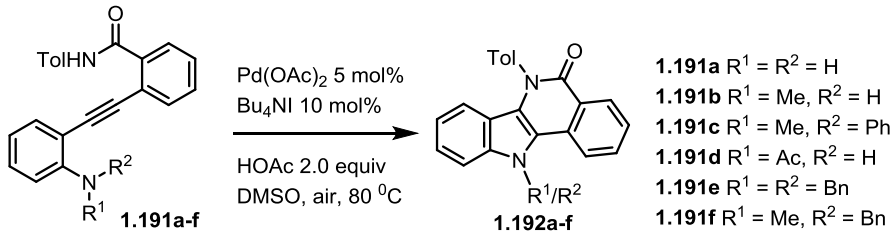

**Scheme 1.42: Synthesis of indolo[3,2-c]isoquinolinone by Chua**

Mechanism of this reaction is similar to Jagtap's one (Scheme 1.41), excluding decarboxylation step which is replaced by deprotonation by strong base *t*BuOK. This synthesis enables quite broad scope of tetracyclic indoles. However, the introduction of substituents in aromatic ring of 2-(bromomethyl)benzoate (**1.188**) is quite limited. Moreover, this reaction is base-promoted condensation, so that it might not tolerate many functional groups such as ester, nitrile or hydroxyl that may interfere to the formation of desired product.

## 2.3. Results and Discussion

### 2.3.1. Primary results

Our initial study focused on the choice of appropriate substituents on nitrogen atom. Several *o*-(1-alkynyl)benzamide substrates **1.191a-f** were prepared to examine the double cyclization under standard conditions reported previously by our group (Scheme 1.43).[34] Unfortunately, unsubstituted, monosubstituted anilines **1.191a,b,d** and *N*-methyl-*N*-phenylaniline **1.191c** did not cyclize, and were recovered after the reactions. Strong coordination of primary and secondary amines to palladium catalyst could poison the catalyst system in cases of **1.191a,b,d**. Furthermore, significant decrease of the nucleophilicity of nitrogen atom by conjugation could result in non-cyclization in case of **1.191c**. *N,N*-dibenzyl substrate **1.191e** did cyclize but afforded only a trace amount of the desired product after elongated time. On the other hand, *N*-benzyl-*N*-methylaniline **1.191f** underwent the double cyclization, however, to provide *N*-methylated tetracycle **1.192f** indicating that the *N*-debenzylation is faster than the *N*-demethylation under these oxidative conditions.



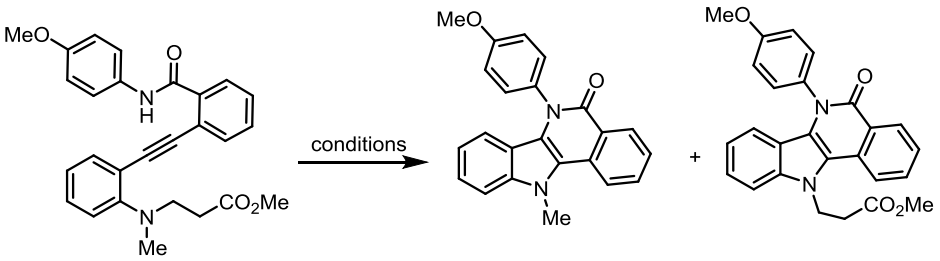

**Scheme 1.43: Primary study on impact of substituents on nitrogen atom to cyclization**

Early failure in double cyclization prompted us to redesign our model substrates. As mentioned previously, *N,N*-dialkyl substituents, crucial factor to the success of cyclization, can facilitate aminopalladation because they can increase the nucleophilicity of aniline functional group by inductive effect and sterically deconjugating effect between nitrogen and aromatic ring. Moreover, substrates with bulky *N,N*-dialkyl anilines such as **1.191e** should be avoided due to steric hindrance which could slow down the aminopalladation step. As a result, an *N*-methyl-*N*-alkyl substrate could be a relevant option. Additionally, an *N*-demethylation pathway under diamination conditions could be controlled to provide *N*-alkylated tetracycle which, upon removal of the *N*-alkyl group, would provide the tetracycle with an *N*-unprotected indole unit. To reach this goal, we turned our attention on *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]-*o*-alkylnylanilines **1.193** (see below) as a test substrate to investigate this intramolecular diamination.

### 2.3.2. Screening conditions

Using *N*-methyl-*N*-[2-(methoxycarbonyl)ethyl]-*o*-alkylnylanilines **1.193a** as test substrate, condition screening for oxidative diamination was carried out by varying palladium sources, additives, solvents, temperatures etc. The results are summarized in Table 1.1.

**Table 1.1: Optimization of conditions for oxidative diamination of 1.193a**



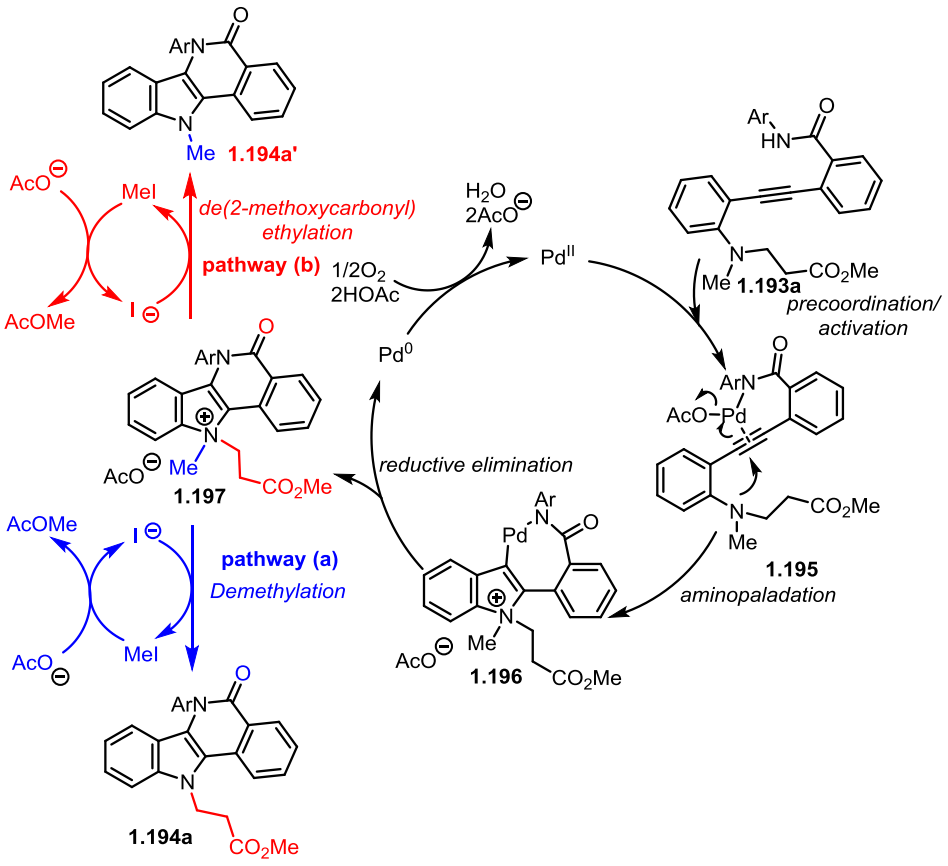

**1.193a** **1.194a'** **1.194a**

| Entry | Pd(II) (mol%) | Additives (equiv) | T (°C) | Time (h) | Conversion (1.194a/1.194a') | Yield [%] |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (05) | $nBu_4NI$ (0.1), HOAc (2.0) | 80 | 13 | 25% (1:1) | 10%[(b)] |
| 2 | $Pd(OAc)_2$ (10) | $nBu_4NI$ (1.0), HOAc (2.0) | 50 | 13 | 50% (1:12.5) | 38%[(b)] (**1.194a'**) |
| 3 | $Pd(OAc)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0) | 80 | 13 | 100% (1:12.5) | 56% |
| 4 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0) | 50 | 1.5 | 30% (4:1) | - |
| 5 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0) | 50 | 17 | 70% (6:1) | - |
| 6 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0) | 80 | 17 | 85% (10:1) | - |
| 7 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0), **TsOH (0.1)** | 50 | 21 | 77% (>30:1) | 60% (**1.194a**) |
| 8 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0), **1,10-phen (0.1)** | 80 | 14 | 38% (1.5:1) | - |
| 9 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (4.0), **$Cu(OTf)_2$ (0.2)** | 50 | 26 | 53% (17:1) | - |
| 10 | $Pd(TFA)_2$ (10) | $nBu_4NI$ (1.0), HOAc (1.0), **$Cu(OTf)_2$ (0.25)** | 80 | 14 | 100% (>30:1) | 71% (**1.194a**) |

(a) Reaction conditions: A solution of **1.193a** (0.05 mmol), Pd(II), additives in 2.0 mL DMSO was heated under air atmosphere. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard

Using the previously optimized conditions [$Pd(OAc)_2$ (5 mol%), *n*-$Bu_4NI$ (10 mol%), HOAc (2.0 equiv), air (1 atm), DMSO (0.025 M), 80 °C],[34,35] only 25% of starting material was consumed after 13 hours (duration needed for full conversion with *N*,*N*-dimethyl 2-alkynylanilines **1.83**). Both desired product **1.194a** and side product **1.194a'** resulting from *N*-demethylation and *N*-de(2-methoxycarbonyl)ethylation respectively (see mechanism in Scheme 1.21, chapter 1.2.1), were formed (1:1 ratio) in approximately ~10% yield each by NMR (entry 1, Table 1.1). The low conversion demonstrated the low activity of compound **1.193a**. The steric hindrance and electron-withdrawing effect of the ester group could reduce nucleophilicity of the nitrogen atom, inhibiting therefore the cyclization.

We presumed that catalytic amount of iodide was not guaranteed to promote the reaction with such low activity. A stoichiometric amount of *n*$Bu_4NI$ was applied (entry 2,3). Interestingly, the conversion increased dramatically; full conversion was observed at 80 °C after 13 hours. However, regioselectivity of dealkylation step remained moderate (**1.194a/1.194a'** = 1:12.5) and favoured to formation of side product through *N*-de(2-methoxycarbonyl)ethylation pathway. These unexpected results prompted us to revise the mechanic hypothesis to figure out the factors controlling the regioselectivity (Scheme 1.44).




**Scheme 1.44: Possible mechanism of Pd(II)-catalyzed diamination of 1.193a**

Domino process involves several consecutive steps: aminopalladation, reductive elimination, demethylation, and regeneration of Pd(II). As discussed in 1.2.1of this thesis, demethylation is the key step to drive the formation of desired product. In this case, an expected demethylation can occur by a $S_N2$ attack of iodide ion to methyl group, leading the formation of 2-(methoxycarbonyl)ethylated indole **1.194a** (pathway a), whereas, a $S_N2$ attack on *N*-(2-methoxycarbonyl)ethyl group could drive the reaction to form a tetracyclic *N*-methylated indole **1.194a'** (pathway b). Rationally, methyl group is much more favourable to nucleophilic attack than a secondary 2-(methoxycarbonyl)ethyl. That means formation of **1.194a** should dominate as a major product. However, the experimental results showed contradictory evidences. To explain this observation, we proposed that, the removal of 2-(methoxycarbonyl)ethyl group which leads to formation of side product, can be conducted in another fashion. Particularly, an anion such as acetate can act as a base to promote retro-Michael reaction to remove ester side-chain through $E_{1cb}$ mechanism. This explanation could be reasonable, because in DMSO, acetic acid is not really a strong acid ($pK_a$=12.3);[64] consequentially, conjugated acetate ion is strong base. At high temperature, it can promote a retro-Michael reaction.

To confirm our hypothesis, we replaced $Pd(OAc)_2$ catalyst by $Pd(TFA)_2$ because trifluoroacetate anion is much weaker base compared to acetate ($pK_a$ TFA in DMSO = 3.45).[63] As expected, regioselectivity was switched to formation of **1.193a** as a major product (entry 4,5,6), although the conversion was slightly lower than $Pd(OAc)_2$-mediated condition (see entry 6 and 3). To assist the catalyst system, several additives were also added (entry 7-10). Catalytic amount of TsOH further improved the selectivity in favour of the desired product **1.194a** (entry 7); whereas, 1,10-phenanthroline performed poor activity and poor selectivity (entry 8). Probably, 1,10-phenanthroline in this circumstance can react with acetic acid to produce a significant amount of acetate anion which is harmful to catalytic system. Finally, when $Cu(OTf)_2$ was introduced (entry 9, 10), a full conversion with 71% isolated yield of **1.194a** was obtained, implying that $Cu(OTf)_2$ plays an important role in this catalytic system. It may participate directly as a co-catalyst or may support for regeneration of Pd(II) as a co-oxidant. Overall, the optimum conditions consisted of performing the intramolecular diamination of **1.193a** in DMSO (*c* 0.025 M) at 80 °C in the presence of $Pd(TFA)_2$ (0.1 equiv), $Cu(OTf)_2$ (0.25 equiv), HOAc (1.0 equiv), and $n$Bu$_4$NI (1.0 equiv). Under these conditions, double cyclization of **1.193a** took place smoothly to afford desired product **1.194a** in 71% isolated yield with almost complete chemoselectivity.

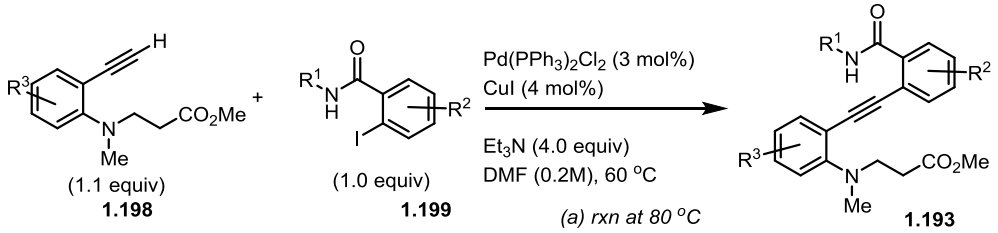
[64] Bordwell, F.G. *Acc. Chem.Res.* **1988**, *21*, 456.

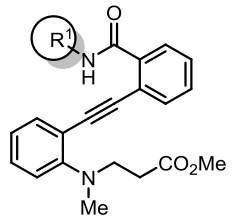
## 2.2.3. Substrate scope for Pd(II)-catalyzed oxidative diamination

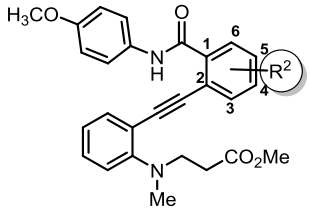
### 2.2.3.1. Synthesis of *o*-(1-alkynyl)benzamide derivatives

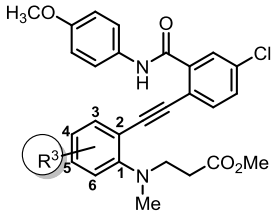
*o*-(1-alkynyl)benzamide **1.193** were synthesized by Sonogashira reaction (Table 1.2). In the presence of 1.10 equiv of **1.198**, 3 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% CuI, 4.0 equiv of $Et_3N$ in DMF at 60 °C or 80 °C, 2-iodobenzamide derivatives **1.199** were converted smoothly into **1.193** in average 75% yield. At 80 °C, **1.199** were consumed totally after 30 minutes, whereas, the condition at lower temperature (60 °C) took 2-3 hours to complete but furnished cleaner reaction and better yield. The reaction tolerated a variety of substituents on both aromatic rings.

**Table 1.2: Synthesis of *o*-(1-alkynyl)benzamide derivatives 1.193**





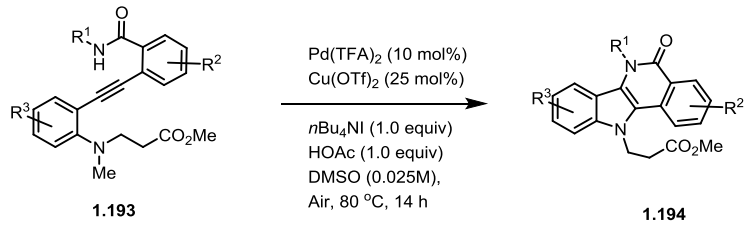


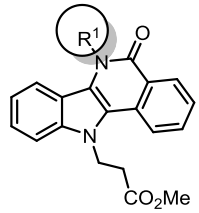
| | $R^1$ = | | | $R^2$ = | | | $R^3$ = | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.193a** | 4-$MeOC_6H_4$ | 72%[a] | **1.193h** | 4-MeO | 75% | **1.193o** | 4-MeO | 78% |
| **1.193b** | Me | 26%[a] | **1.193i** | 6-Me | 84% | **1.193p** | 4-Me | 91% |
| **1.193c** | 4-$MeC_6H_4$ | 70%[a] | **1.193j** | 5-Me | 84% | **1.193q** | 4-Cl | 73% |
| **1.193d** | $C_6H_5$ | 80%[a] | **1.193k** | 6-Cl | 78% | **1.193r** | 4-F | 64% |
| **1.193e** | 4-$ClC_6H_4$ | 73%[a] | **1.193l** | 5-Cl | 89% | **1.193s** | 5-MeO | 85% |
| **1.193f** | 3-$FC_6H_4$ | 79% | **1.193m** | 4-Cl | 95% | **1.193t** | 5-Me | 94% |
| **1.193g** | 3-$CF_3C_6H_4$ | 66% | **1.193n** | 5-F | 86% | **1.193u** | 5-Cl | 86% |

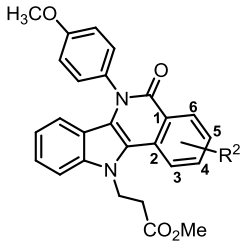
### 2.2.3.2. Substrate scope for Pd(II)-catalyzed oxidative diamination

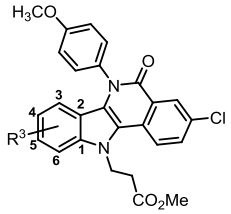
With the aforementioned conditions, we explored the generality of this deamination process with different alkynes. The results are summarized in the following table (Table 1.3).

**Table 1.3: Scope of Pd(II)-catalyzed diamination of *o*-alkynylanilines 1.193**







| | $R^1$ = | | | $R^2$ = | | | $R^3$ = | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.194a** | 4-$MeOC_6H_4$ | 71% | **1.194h** | 4-MeO | 79% | **1.194o** | 4-MeO | 82% |
| **1.194b** | Me | 78% | **1.194i** | 6-Me | 82% | **1.194p** | 4-Me | 80% |
| **1.194c** | 4-$MeC_6H_4$ | 76% | **1.194j** | 5-Me | 61% | **1.194q** | 4-Cl | 62% |
| **1.194d** | $C_6H_5$ | 71% | **1.194k** | 6-Cl | 48% | **1.194r** | 4-F | 70% |
| **1.194e** | 4-$ClC_6H_4$ | 72% | **1.194l** | 5-Cl | 85% | **1.194s** | 5-MeO | 87% |
| **1.194f** | 3-$FC_6H_4$ | 64% | **1.194m** | 4-Cl | 68% | **1.194t** | 5-Me | 75% |
| **1.194g** | 3-$CF_3C_6H_4$ | 66% | **1.194n** | 5-F | 75% | **1.194u** | 5-Cl | 81% |

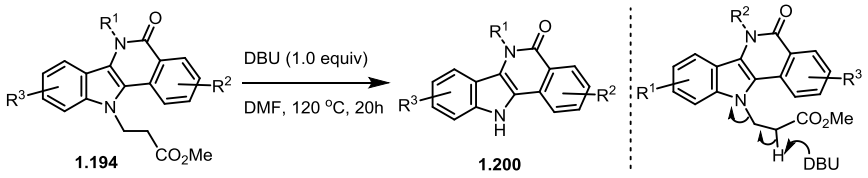
The optimized condition tolerated different substituents at different positions on aromatic rings including chlorine atom, which provides a handle for further functionalization. For substituents $R^1$ and $R^3$, the electron-donating groups provided better results than the electron-withdrawing groups. Basically, these electron-donating groups can increase nucleophilicity of nitrogen atom, therefore facilitating the aminopalladation step. Both aliphatic (**1.193b**) and aromatic benzamides **1.193** were applicable to afford tetracyclic indoles. For $R^2$ substituents, it is ambiguous to clarify their electron effects. However, at certain position, we are still able to explain the results. For example, at position 5,

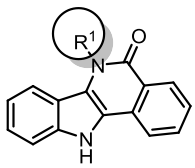
electron-withdrawing groups such Cl and F are favourable to reaction. That can be interpreted by the increased electrophilicity of the triple bond.

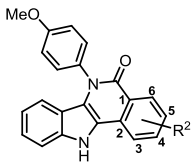
### 2.2.4. Synthesis of tetracyclic free NH indoles by retro-Michael reaction

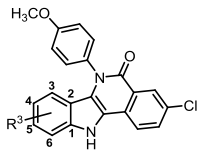
The second major goal in this thesis is to prepare tetracyclic free (NH) indoles. The removal of side chain alkyl group could be expected by retro-Michael reaction. Although the retro-Michael reaction have been known to occur in some biological process,[65] but only few examples able to apply in organic synthesis, have been described in the literature.[66] Gratefully, simply heating a DMF solution of **1.194a** in the presence of DBU (1.0 equiv) at 120 ºC afforded the desired free NH product **1.200a** in 97% yield.[66a] These conditions were found to be generally applicable to a wide range of substrates **1.193** as summarized in Table 1.4.

**Table 1.4: Synthesis of tetracyclic free NH indoles by retro-Michael reaction of 1.194**







| | $R^1$ = | | | $R^2$ = | | | $R^3$ = | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.200a** | 4-$MeOC_6H_4$ | 97% | **1.200h** | 4-MeO | 85% | **1.200o** | 4-MeO | 95% |
| **1.200b** | Me | 87% | **1.200i** | 6-Me | 92% | **1.200p** | 4-Me | 95% |
| **1.200c** | 4-$MeC_6H_4$ | 95% | **1.200j** | 5-Me | 96% | **1.200q** | 4-Cl | 92% |
| **1.200d** | $C_6H_5$ | 95% | **1.200k** | 6-Cl | 89% | **1.200r** | 4-F | 96% |
| **1.200e** | 4-$ClC_6H_4$ | 96% | **1.200l** | 5-Cl | 90% | **1.200s** | 5-MeO | 95% |
| **1.200f** | 3-$FC_6H_4$ | 97% | **1.200m** | 4-Cl | 95% | **1.200t** | 5-Me | 93% |
| **1.200g** | 3-$CF_3C_6H_4$ | 97% | **1.200n** | 5-F | 97% | **1.200u** | 5-Cl | 96% |

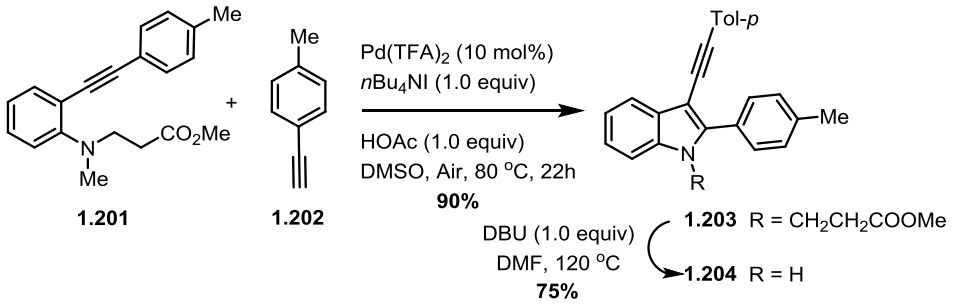
[65] (a) Shabat, D.; Rader, C.; List, B.; Lerner, R. A.; Barras III, C. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 6925. (b) Chen, J.; Armstrong, R. N. *Chem. Res. Toxicol.* **1995**, *8*, 580.

[66] (a) Boncel, S.; Maczka, M.; Walczak, K. Z. *Tetrahedon* **2000**, *66*, 8450. (b) Chen, W.; Yu, W. –G.; Shi, H. –B.; Lu, X. –Z. *Chemical Papers* **2012**, *66*, 308. (c) Sánta-Csutor, A.; Mucsi, Z.; Finta, Z.; Gönczi, C.; Halász, J.; Csikós, É.; Hermecz, I. *Eur. J. Org. Chem.* **2006,** 1769.

These results were quite surprising. Retro-Michael reactions normally proceed reversibly; therefore, the yields of these reactions are never high. However, analysis of desired product **1.200** by $^1$H-NMR showed that indolylic N-H is quite acidic, its signal appears at very low field δ ~ 12 ppm (in DMSO). This experimental result could account for its excellent ability as a leaving group.

### 2.2.5. Application of *N*-2-(methoxycarbonyl)ethyl as a protecting group in other transformations

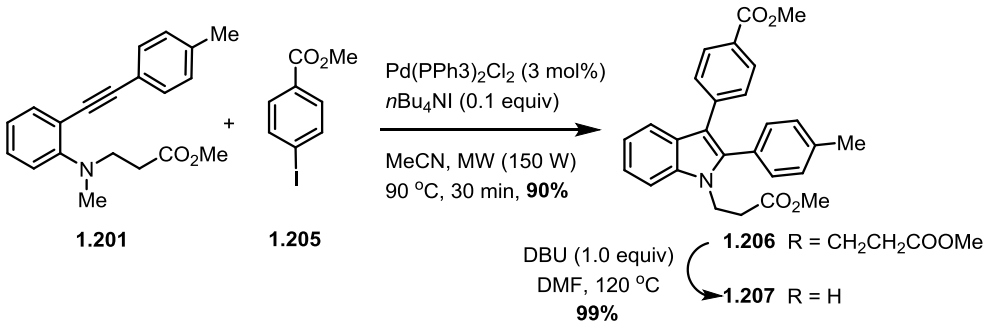
To demonstrate the utility of this *N*-2-(methoxycarbonyl)ethyl group in heterocycle syntheses, other cyclizations reported in literature were examined. Firstly, *N*-2-(methoxycarbonyl)ethyl was employed as a masked protecting group in Pd(II)-catalyzed coupling of *o*-alkynylanilines with terminal alkynes under aerobic conditions developed by our group.[67] The coupling of *N*-methyl-*N*-2-(methoxycarbonyl)ethyl *o*-alkylnylaniline **1.201** with *p*-tolylacetylene **1.202** took place smoothly to afford *N*-2-(methoxycarbonyl)ethylated 2,3-disubstituted indole **1.203** in 90% yield. Analogously, switching $Pd(OAc)_2$[66] into $Pd(TFA)_2$ is a key factor to guide reaction through *N*-demethylation pathway. Deprotection of **1.203** by a retro-Michael reaction provided 2,3-disubstituted free NH indole **1.204** in 75% yield (eq 1, Scheme 1.45).




**Scheme 1.45: *N*-2-(methoxycarbonyl)ethyl as protecting group in Pd(II)-catalyzed coupling of *o*-alkynylanilines with terminal alkynes**

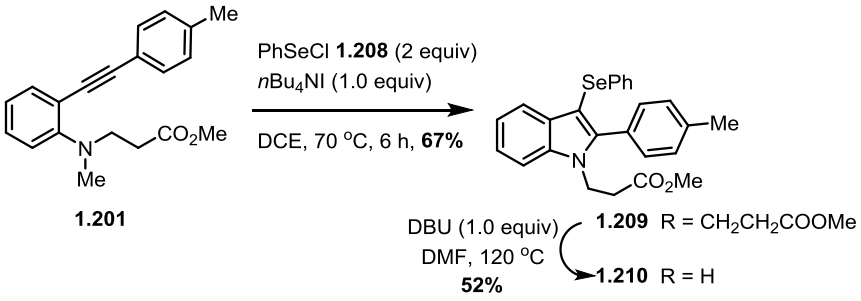
*N*-methyl-*N*-2-(methoxycarbonyl)ethyl *o*-alkylnylaniline **1.201** was also successfully coupled with 4-iodobenzoate **1.205** under slightly modified Larock's condition[68] to afford 2,3-diarylindoles **1.206** which can undergo *N*-deprotection to obtain free NH **1.207** in almost quantitative yield (Scheme 1.46).

[67] Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 12311.
[68] Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908.




**Scheme 1.46: *N*-2-(methoxycarbonyl)ethyl as protecting group in Larock's Pd(II)-catalyzed indole synthesis**

Finally, compound **1.201** was found to be applicable in electrophilic cyclization with arylselenyl **1.208** under Larock's standard conditions to provide 2-selenyl-substituted indole **1.209**.[69] Removal of 2-(methoxycarbonyl)ethyl by DBU (1.0 equiv) afforded free NH indole **1.210** in 52% yield, together with its deselenylated product in 20% (Scheme 1.47).

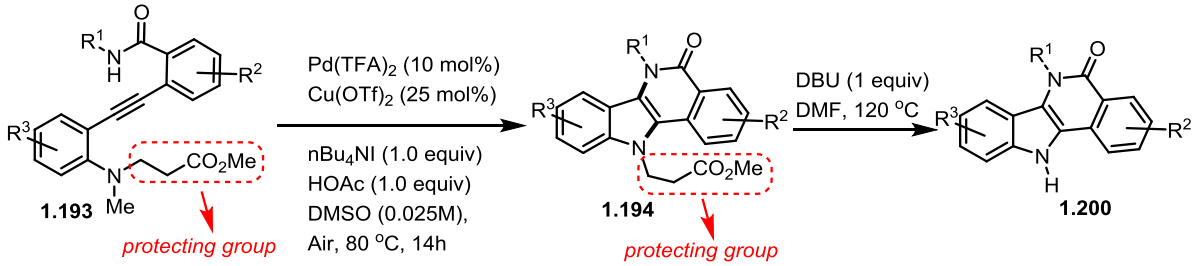



**Scheme 1.47: *N*-2-(methoxycarbonyl)ethyl as protecting group in Larock's electrophilic cyclization with arylselentyl**

[69] Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173.

### 2.2.6. Conclusion

In summary, we developed a novel Pd(II)-catalyzed double cyclization of 1,2-diarylethynes **1.193** bearing an *N*-methyl-*N*-[2-(methoxy-carbonyl)ethyl]amino and an aminocarbonyl group at the *ortho* positions of the two aromatic rings to afford the tetracyclic *N*-[2-(methoxycarbonyl)-ethyl]indoloisoquinolinones **1.194** in good to excellent yields. The *N*-[2-(methoxycarbonyl)ethyl] group is readily removed under basic conditions (DBU, DMF, 120 °C) to afford the corresponding tetracycles **1.200** with a free indolyl nitrogen in excellent yields (Scheme 1.48).[70]




**Scheme 1.48: Pd-catalyzed diamination of alkynes 1.193 and removal of protecting group**

The 2-(methoxycarbonyl)ethyl as a removable *N*-protecting group is illustrated in other Pd(II)- and Pd(0)-catalyzed and selenium-mediated transformations.

[70] Ha, T. M.; Yao, B.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1750.

# CHAPTER 3

## Synthesis of Tetracyclic Indolobenzothiazine S,S‑Dioxides by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes.

## 3.1. Benzothiazine *S,S*-dioxide: Application and Synthesis

The sulfonamides and their analogs are important structural motifs in medicincal chemistry due to their various biological activities, such as anti-bacterial, hypoglycemic, anti-convulsant, anti-thyoid, anti-inflammatory and anti-cancer activities.[71] Particularly, sultams (cyclic sulfonamides) which usually exhibit versatile inhibitory properties, are privileged structures ubiquitously utilized in many bioactive compounds and drugs (Firgue 1.3). Among them, 1,2-benzothiazine *S,S*-dioxide (Figure 1.3) is a pharmacophore found in a number of marketed drugs, such as nonsteroidal anti-inflammatory meloxicam (**1.215**) and piroxicam[72] (**1.216**); and carbonic anhydrase inhibitor brinzolamide (**1.217**)[73] for treatment of glaucoma. Moreover, numerous compounds containing this moiety have been unveiled to exhibit other valuable activities such as: 11β-HSD2 inhibitor (**1.218**), calpain inhibitor (**1.219**) and anti-HIV (**1.220**) etc.[74]

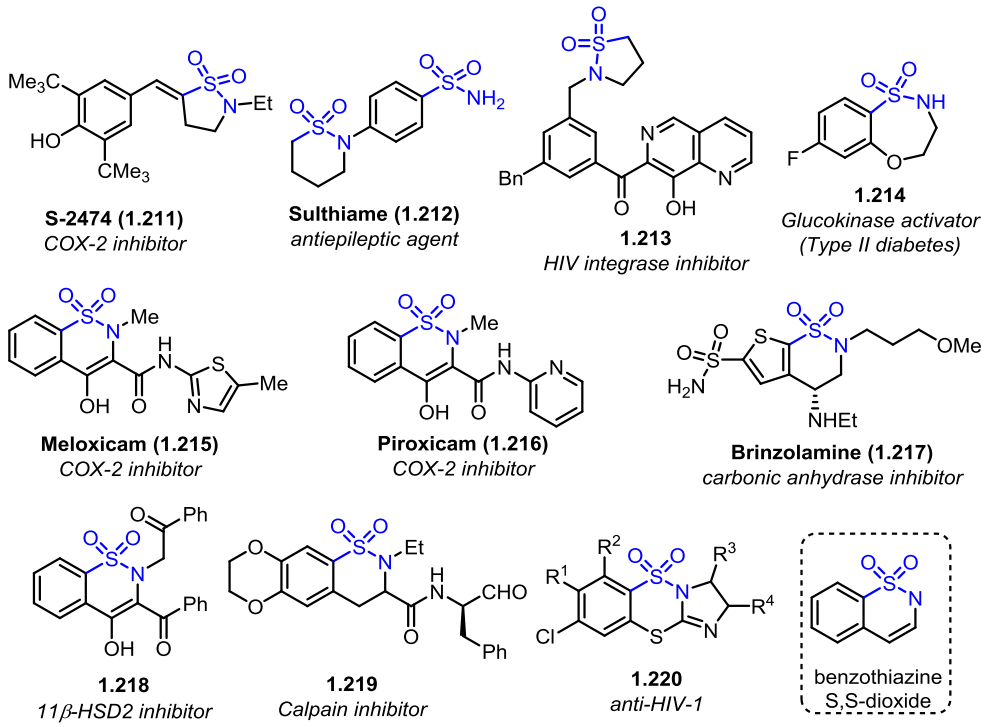
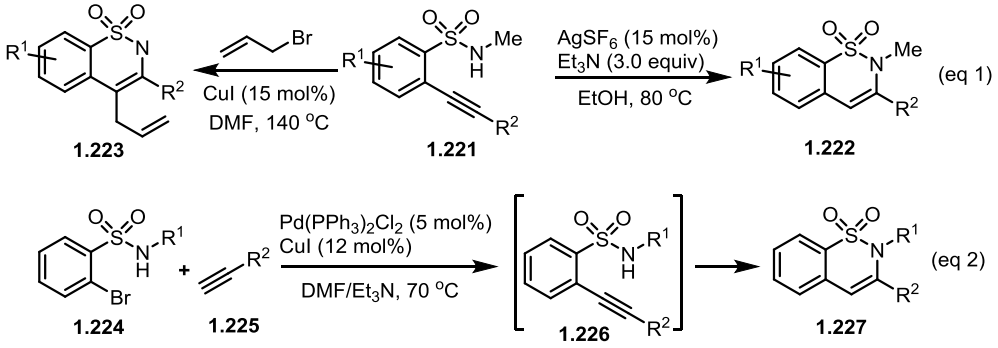



**Figure 1.3: Biologically active sultams**

Owing to the pharmaceutical importance of 1,2-benzothiazine *S,S*-dioxide, the development of synthetic methodologies to this heterocycle has attracted particular attention. Indeed, several synthetic

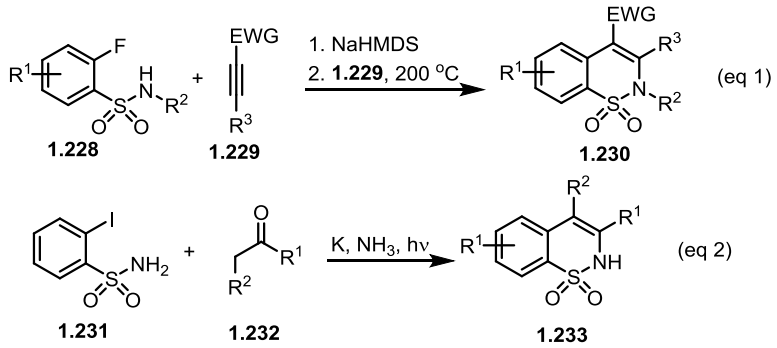
[71] (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925. (b) Shah, S. S. A.; Rivera, G.; Ashfaq, M. *Mini-Reviews in Medicinal Chemistry* **2013**, *13*, 70. (c) Drews, J. *Science* **2000**, *287*, 1960.
[72] Rabasseda, X.; Hopkins, S. J. *Drugs Today* **1994**, *30*, 557.
[73] Wroblewski, T.; Graul, A.; Castaner, J. *Drugs Future* **1998**, *23*, 365.
[74] (a) Brzozowski, F.; Saczewski, F.; Neamati, N. Bioorg. *Med. Chem. Lett.* **2006**, *16*, 5298. (b) Wells, G. J.; Tao, M.; Josef, K. A.; Rihovsky, R. *Med. Chem. Lett.* **2001**, *44*, 3488. (c) Bihovsky, R; Tao, M.; Mallamo, J. P.; Wells, G. J. *Med. Chem. Lett.* **2004**, *14*, 1035. (d) Kim, S. H.; Ramu, R.; Kwon, S. W.; Lee, S. H.; Kim, C. H.; Kang, S. K.; Rhee, S. D.; Bae, M. A.; Ahn, S. H.; Ha, D. C.; Cheon, H. G.; Kim, K. Y.; Ahn, J. H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1065.

approaches toward 1,2-benzothiazine S,S-dioxide were reported in the literature. For instance, Pal et al. reported transition metal-catalyzed intramolecular cyclization of *o*-(1-alkynyl)benzenesulfonamides **1.221** to afford 3-substituted **1.222** or 3,4-disubstituted benzothiazine S,S-dioxides **1.223** (eq 1, Scheme 1.49).[75] Alternatively, a one-pot methodology combining Sonogashira coupling and intramolecular cyclization of 2-bromobenzenesulfonamides **1.224** and terminal alkynes **1.225** was later developed by Mondal using palladium catalysis (eq 2, Scheme 1.49).[76]




**Scheme 1.49: Synthesis of benzothiazine by transition metal-catalyzed intramolecular cyclization**

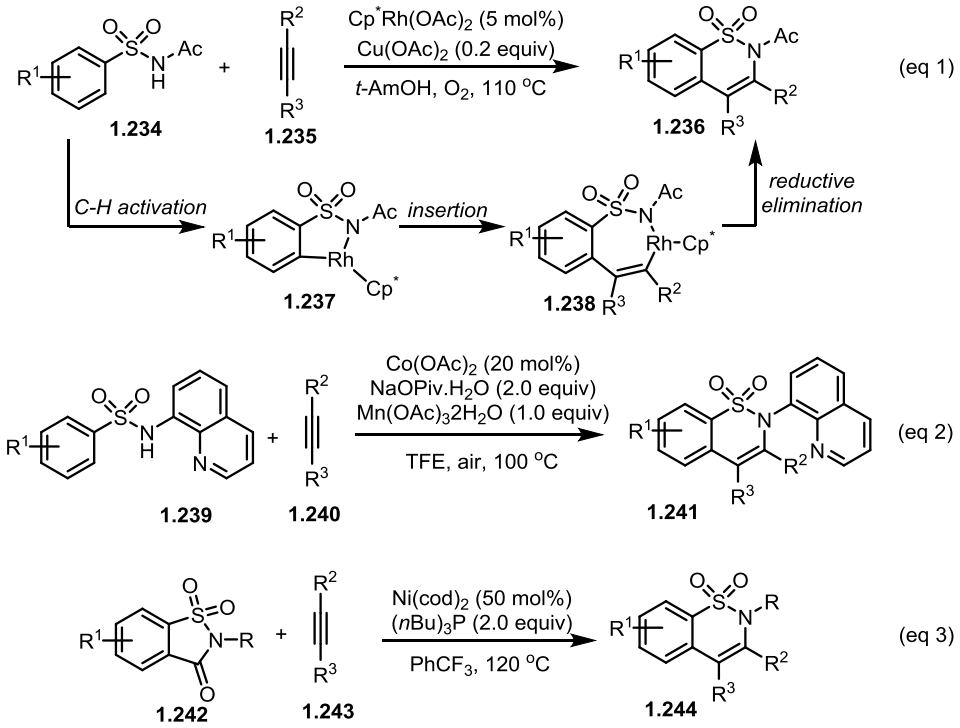
An intermolecular heteroannulation of *o*-fluoro arene sulfonamides **1.228** with activated internal alkynes **1.229** to afford benzothiazine rings was reported by Juhl (eq 1, Scheme 1.50).[77] The transformation proceeds through a domino process including a nucleophilic addition, followed by an aromatic nucleophilic substitution. Wolfe and coworkers developed another intermolecular heteroannulation of *o*-iodobenzenesulfonamide **1.231** with ketone enolate via photosimulated radical nucleophilic aromatic substitution to yield disubstituted 1,2-benzothiazine *S,S*-dioxide **1.233** (eq 2, Scheme 1.50).[78] However, due to tricky reaction conditions and limited substrate scopes, those transformations are not practically useful.




**Scheme 1.50: Synthesis of benzothiazine by intermolecular heteroannalation**

[75] Barange, D. K.; Nishad, T. C.; Swamy, N. K.; Bandameedi, V.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Pal, M. *J. Org. Chem.* **2007**, 8547.
[76] Debnath, S.; Mondal, S. *J. Org. Chem.* **2015**, *80*, 3940.
[77] Nørager, N. G.; Juhl, K. *Synthesis* **2010**, *24*, 4273.
[78] Layman, W. J.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem.* **2005**, *70*, 9147.

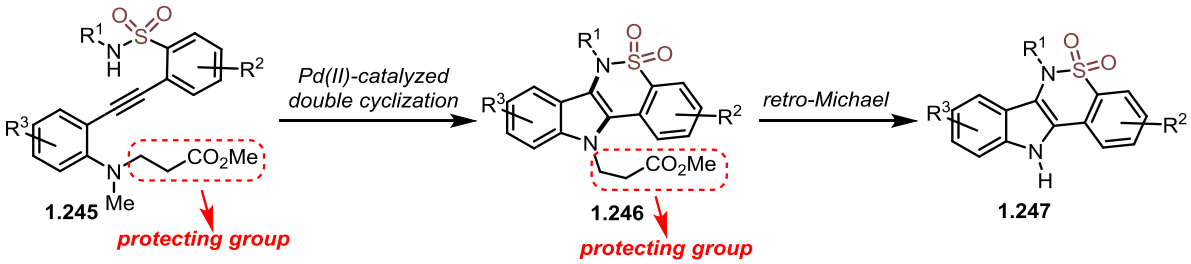
In light of synthetic versatility of C-H activation in heterocycle synthesis, transition metal-catalyzed cyclization towards benzothiazine scaffolds from simple benzene sulfonamides and alkynes has been reported recently. Cramer reported a rhodium-catalyzed heteroannulation of benzosultams **1.236** via C-H activation of sulfonamides (eq 1, Scheme 1.51).[79] A similar approach was introduced by Whiteoak and Ribas using cobalt catalyst system under oxidative conditions (eq 2, Scheme 1.51).[80] Complementary to those, Bi and coworkers recently developed decarbonylative cycloaddition of saccharins **1.242** with internal alkynes **1.243** by nickel catalysis (eq 3, Scheme 1.51).[81]




**Scheme 1.51: Synthesis of benzothiazine by transition metal-catalyzed cycloaddition**

[79] Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610.
[80] Planas, O.; Whiteoak, C. J.; Company, A.; Ribas, X. *Adv. Synth. Catal.* **2015**, *357*, 4003.
[81] Mi, P.; Liao, P.; Tu, T.; Bi, X. *Chem. Eur. J.* **2015**, *21*, 5332.

In this chapter, the synthesis of 1,2-indolobenzothiazine S,S-dioxides by Pd(II)-catalyzed intramolecular double nucleophilic addition to alkynes, involving sulfonamide and aniline as internal nucleophiles, will be described (Scheme 1.52). As a continuation of our previous work, the synthetic strategy will employ *N*-methyl-*N*-[2-(methoxycarbonyl)-ethyl]anilines as substrates in order to reach tetracyclic free NH indoles containing sulfonamide moiety.




**Scheme 1.52: Synthesis of indolobenzothiazine S,S-dioxide by Pd(II)-catalyzed diamination of alkynes**

## 3.2. Results and Discussion

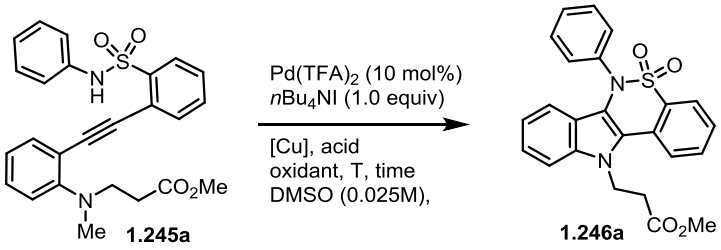
### 3.2.1. Screening conditions

We began our investigation using an easily accessible *N*-phenyl sulfonamide 2-alkynylaniline **1.245a** as a test substrate. Desired product indolobenzothiazine S,S-dioxides **1.246a** was indeed obtained, albeit in moderate yield 42% (entry 1, table 1.5), when **1.245a** was submitted to the optimized conditions for the benzamide counterpart [see chapter 2, conditions: $Pd(TFA)_2$ (0.1 equiv), $Cu(OTf)_2$ (0.25 equiv), HOAc (1.0 equiv), and $n$Bu$_4$NI (1.0 equiv) in DMSO (*c* 0.025 M) at 80 ºC]. This result can be predictable based on the previous observation: **1.193f** or **1.193g** bearing an electron withdrawing group, with $pK_a$ or acidity of N-H approximate to sulfonamide's, only provide moderate yield (see table 1.3) in this transformation. Moreover, the more acidic N-H functionality of sulfonamide is, the less activity of **1.245a** is, in terms of the nucleophilicity. Another reason could not be ruled out for this moderate result is the fact that **1.245a** can undergo monoamination via 5-exo-dig or 6-endo-dig cyclization involving sulphonamide as an internal nucleophile.

Since using $Pd(OAc)_2$ as a catalyst led to a nonselective *N*-dealkylation process, $Pd(TFA)_2$ was kept as a palladium source in our survey for reaction conditions. With intention to remove acetate anion, AcOH was replaced by TFA (entry 2, 4) but almost no desired product was formed. One possible explanation is that TFA is too acidic, it can protonate aniline so that totally inhibits the cyclization of substrates. To examine the role of copper sources in this transformation, we removed $Cu(OTf)_2$ in entry 3 and 4; only trace amount of desired product was observed in crude NMR. This evidences copper source may have significant roles; it is not only a co-oxidant, but also a co-catalyst mediating the reaction process. Screening copper sources later showed the best ones are $Cu(OTf)_2$ or $CuCl_2$, whereas, $Cu(OAc)_2$ has no activity at all (entry 5-8, 1.0 equiv of copper salt). However, the low yields from these experiments indicated significant degradation of the reaction mixture which may also be triggered by metal catalysts. To overcome the low activity of this substrate, changing temperature was implemented when 35 mol% of $Cu(OTf)_2$ was used as co-catalyst under oxygen balloon (entry 9-13). As expected, the yield of **1.246a** was slightly increased along with temperature and desired product was obtained in 75% yield at 100 ºC. Further increase in temperature decreased the yield of the product due most probably to the degradation. Further survey of the reaction conditions indicated that the reaction outcome was very sensitive to the stoichiometry of $Pd(TFA)_2$ and $Cu(OTf)_2$. A higher or lower loading of $Cu(OTf)_2$ (30 mol%) led to a diminished yield of **1.246a** (entry 12, 14, 15). Decrease of palladium loading to 5% showed significant drop in yield (entry 12, 16). Last but not least, oxygen source was proven to be an influential factor to promote the reaction (entry 12, 17); oxygen balloon which although is not really practical, is much more effective than atmospheric air. Overall, the optimum conditions consisted of heating a DMSO solution (*c* 0.025 M)

of **1.245a** to 100 ºC in the presence of $Pd(TFA)_2$ (10 mol%), $Cu(OTf)_2$ (35 mol%), $n$Bu$_4$NHI (1.0 equiv), and HOAc (1.0 equiv) under oxygen atmosphere (entry 12).

**Table 1.5: Optimization for oxidative diamination of 1.245a[(a)]**



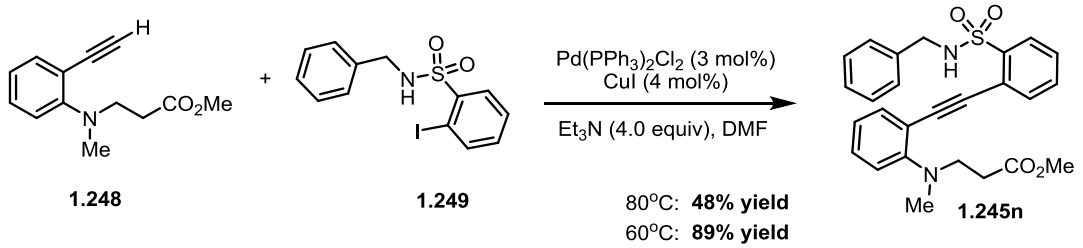

| Entry | [Cu] (mol%) | HX | T (ºC) | Time (h) | Oxidant | Yield[(b)] [%] |
|---|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ (25) | **HOAc** | 80 | 13 | air | 42 |
| 2 | $Cu(OTf)_2$ (25) | **TFA** | 80 | 21 | air | <10 |
| 3 | --- | **HOAc** | 80 | 21 | air | <5 |
| 4 | --- | **TFA** | 80 | 21 | air | <5 |
| 5 | **$Cu(OTf)_2$ (100)** | HOAc | 90 | 12 | $O_2$ | 27 |
| 6 | **$Cu(OAc)_2$ (100)** | HOAc | 90 | 12 | $O_2$ | 0 |
| 7 | **$CuCl_2$ (100)** | HOAc | 90 | 12 | $O_2$ | 25 |
| 8 | **CuI (100)** | HOAc | 90 | 12 | $O_2$ | 13 |
| 9 | $Cu(OTf)_2$ (35) | HOAc | **65** | 12 | $O_2$ | 31 |
| 10 | $Cu(OTf)_2$ (35) | HOAc | **80** | 12 | $O_2$ | 62 |
| 11 | $Cu(OTf)_2$ (35) | HOAc | **90** | 12 | $O_2$ | 65 |
| 12 | $Cu(OTf)_2$ (35) | HOAc | **100** | 12 | $O_2$ | 76 (75) |
| 13 | $Cu(OTf)_2$ (35) | HOAc | **110** | 12 | $O_2$ | 59 |
| 14 | $Cu(OTf)_2$ (**25**) | HOAc | 100 | 12 | $O_2$ | 34 |
| 15 | $Cu(OTf)_2$ (**45**) | HOAc | 100 | 12 | $O_2$ | 49 |
| 16[(c)] | $Cu(OTf)_2$ (35) | HOAc | 100 | 12 | $O_2$ | 42 |
| 17 | $Cu(OTf)_2$ (35) | HOAc | 100 | 12 | **Air** | 56 |

(a) Reaction conditions: A solution of **1.245a** (0.05 mmol), 10 mol% $Pd(TFA)_2$, 1.0 equiv $nBu_4NI$, 1.0 equiv HX, and additives in 2.0 mL DMSO was heated for a given time. (b) Yields determined by $^1H$-NMR spectroscopy with $CH_2Br_2$ as an internal standard, yield of isolated products in parenthesis. (c) 5 mol% $Pd(TFA)_2$ was used.

## 3.2.2. Substrate scope for Pd(II)-catalyzed oxidative diamination

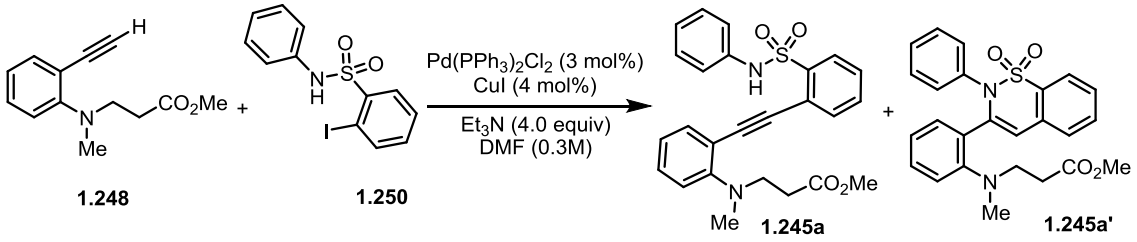
### 3.2.2.1. Synthesis of *o*-(1-alkynyl)sulfonamide derivatives

The initial attempts to synthesize sulfonamide *o*-alkynylaniline **1.245** were performed in the same conditions described previously. However, only *N*-benzyl-2-iodobenzenesulfonamide **1.249** was converted to desired product **1.245n** in 48% yield at 80 °C and 80% yield at 60 °C (Scheme 1.53).




**Scheme 1.53: Synthesis of *N*-benzyl sulfonamide *o*-alkynylaniline 1.245n**

In case of *N*-phenyl-2-iodobenzenesulfonamide **1.250**, a mixture which cannot be separated by chromatography column was obtained in 60% total yield, including desired product **1.245a** and a side product **1.245a'** resulting from a monocyclization of **1.245a** (Scheme 1.54).

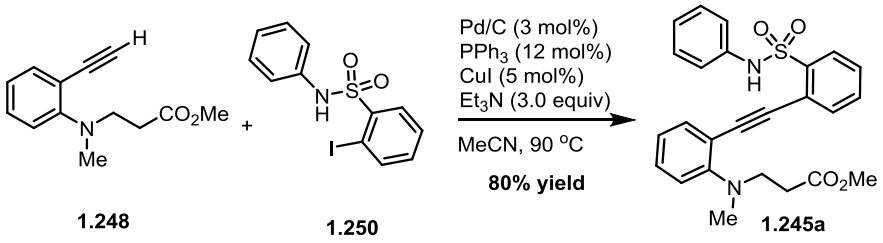



**Scheme 1.54: Initial attempt in synthesis of *N*-phenyl sulfonamide 2-alkynylaniline 1.245a**

This result could be explained by an intramolecular 6-endo-dig cyclization by base-promoted nucleophilic attack across the triple bond which is activated by either CuI or Pd(II). These transformations were well described in the literature.[75, 82] The inconsistent results between carboxamides **1.193** and sulfonamides **1.245** synthesis might be reasoned by different acidity of the NH moiety. The N-H of sulfonamide being more acidic is readily deprotonated under basic condition of Sonogashira coupling reaction, therefore facilitating the cyclization. Indeed, these conditions were used for one-step combination of Sonogashira coupling and cyclization to 1,2-benzosultams reported by Mondal recently (see Scheme 1.49).[76]

[82] M. Harmata, K. Rayanil, M. G. Gomes, P. Zheng, N. L. Calkins, S. Kim, Y. Fan, V. Bumbu, D. R. Lee, S. Wacharasindhu, X. Hong, *Org. Lett.* **2005**, *7*, 143.

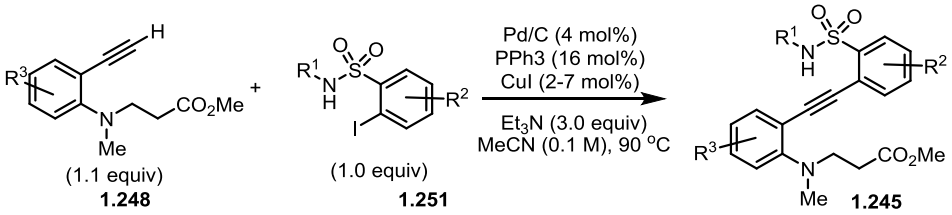
Another condition for synthesis of these compounds was carried out according Pal and co-workers.[75] *N*-phenyl-2-iodobenzenesulfonamide **1.250** was converted smoothly to desired product **1.245a** without the formation of monocyclized adduct in the presence of catalytic amount of Pd/C, CuI in acetonitrile at 90 ºC (Scheme 1.55).

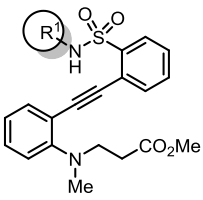


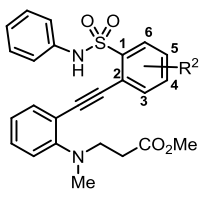

**Scheme 1.55: Synthesis of *N*-phenyl sulfonamide 2-alkynylaniline 1.245a**

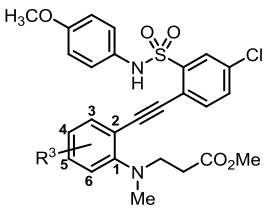
This condition was later applied to prepare other substrates; however, it generally was not well-tolerated with substrates containing electron withdrawing groups in the aromatic of benzasulfonamide. The same trend was observed with substituents on sulfonyl aromatic ring. The synthesis of starting material for Pd(II)-diamination was summarized in Table 1.6.

**Table 1.6: Synthesis of sulfonamide *o*-alkynylaniline 1.245**

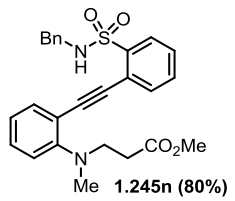
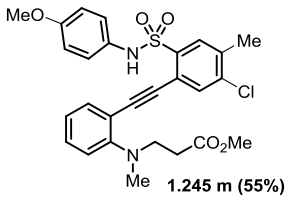






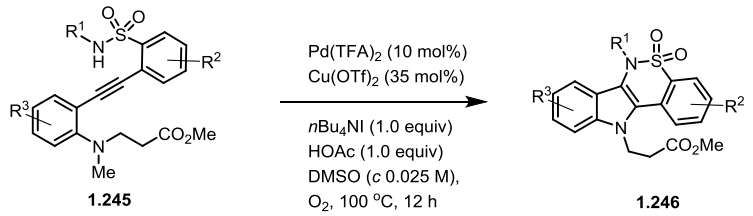
| | $R^1$ = | | | $R^2$ = | | | $R^3$ = | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.245a** | $C_6H_5$ | 80% | **1.245d** | 5-MeO | 41% | **1.245f** | 4-MeO | 50% |
| **1.245b** | 4-MeO $C_6H_4$ | 75% | **1.24e** | 4-Cl-5-Me | 53% | **1.245g** | 4-Me | 53% |
| **1.245c** | 4-Me$C_6H_4$ | 85% | | | | **1.245h** | 4-Cl | 69% |

| | | | | |
|---|---|---|---|---|
|  1.245n (80%) |  1.245 m (55%) | **1.245i** | 4-F | 66% |
| | | **1.245j** | 5-MeO | 79% |
| | | **1.245k** | 5-Me | 75% |
| | | **1.245l** | 5-Cl | 74% |

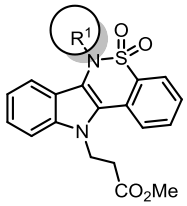
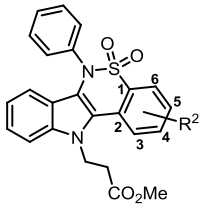
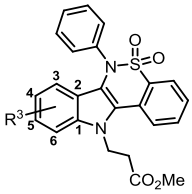
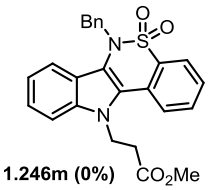
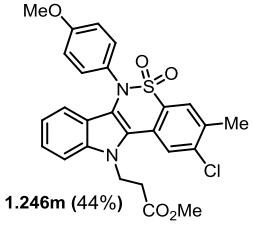
### 3.2.2.2. Substrate scope for Pd(II)-diamination of sulfonamide 2-alkynylanilines and Retro-Michael for synthesis of free NH indoles

With optimized condition in hand, the generality of this Pd(II)-catalyzed diamination was next examined by varying substituents on aromatic rings of alkyne substrates **1.245**. The results were summarized in Table 1.7.

**Table 1.7: Scope of Pd(II)-catalyzed diamination of sulfonamide *o*-alkynylanilines 1.245**



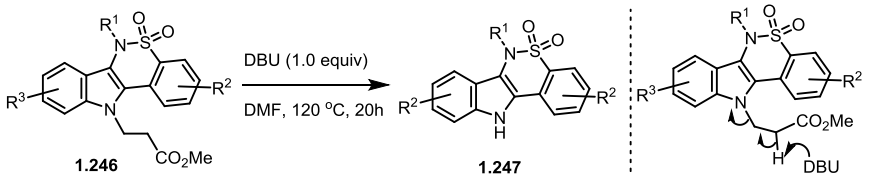

1.245 → 1.246

| | | | | | |
|---|---|---|---|---|---|
|  | $R^1$ = | |  $R^2$ = | |  $R^3$ = |
| | **1.246a** | $C_6H_5$ 75% | **1.246d** | 5-MeO 74% | **1.246f** 4-MeO 76% |
| | **1.246b** | 4-MeO $C_6H_4$ 41% | **1.246e** | 4-Cl-5-Me 72% | **1.246g** 4-Me 73% |
| | **1.246c** | 4-Me$C_6H_4$ 70% | | | **1.246h** 4-Cl 53% |
|  1.246m (0%) | | |  1.246m (44%) | | **1.246i** 4-F 62% |
| | | | | | **1.246j** 5-MeO 78% |
| | | | | | **1.246k** 5-Me 80% |
| | | | | | **1.246l** 5-Cl 49% |

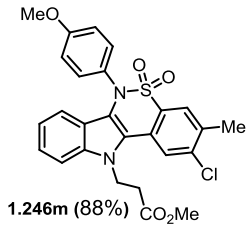
Alkynes with both electron-donating and electron-withdrawing groups on aromatic rings were applicable in this double cyclization. Surprisingly; when the $R^1$ substituents were changed, the yields decrease along with the increase in strength of electron donating groups. In principal, electron-donating groups will increase nucleophilicity of nitrogen atom, as a result, accelerate the diamination. However, the results showed an opposite trend. When $R^1$ is strong electron-donating group such as *p*-MeO (**1.245b**), desired product **1.246b** was obtained in moderate yield. *N*-benzyl substrate (**1.245n**) was not converted to desired product at all; even after long reaction time, we were able to recover more than 90% of starting material. Perhaps, an extraordinarily strong coordination between highly nucleophilic N-H of sulfonamide with metal catalysts halts them to function normally in the catalytic cycle. For the rest examples, no significant electron effect was observed and the presence of different electron-donating groups, electron-withdrawing groups is well tolerated. As expected, aryl chloride was inert under these conditions providing compounds with a handle for further functionalization.

The removal of *N*-methyl-*N*-[2-(methoxycarbonyl)-ethyl] group via retro-aza-Michael reaction was next investigated in order to access free NH indoles containing sulfonamide moiety. Gratefully, simply heating a DMF solution of **1.246** in the presence of DBU (1.0 equiv) at 120 ºC afforded the desired N-deprotected products in good to excellent yields. The conditions were found to be generally applicable to wide range of substrates which are summarized in Table 1.8.

**Table 1.8: Synthesis of tetracyclic free NH indoles containing sulfonamide moiety**

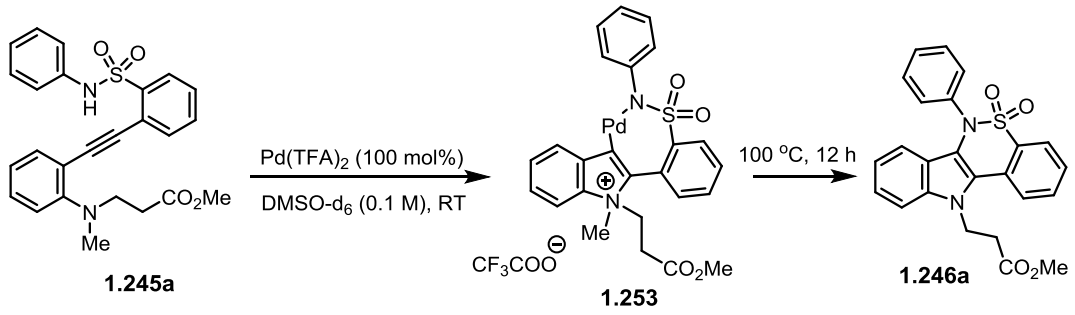



| | $R^1$ = | | | $R^2$ = | | | $R^3$ = | | |
|---|---|---|---|---|---|---|---|---|---|
| **1.247a** | $C_6H_5$ | 93% | **1.247d** | 5-MeO | 93% | **1.247f** | 4-MeO | 94% |
| **1.247b** | 4-MeO $C_6H_4$ | 84% | **1.247e** | 4-Cl-5-Me | 83% | **1.247g** | 4-Me | 87% |

| | | | | | | |
|---|---|---|---|---|---|---|
| **1.247c** | 4-Me$C_6H_4$ | 90% |   **1.246m** (88%) | **1.247h** | 4-Cl | 90% |
| | | | | **1.247i** | 4-F | 93% |
| | | | | **1.247j** | 5-MeO | 87% |
| | | | | **1.247k** | 5-Me | 92% |
| | | | | **1.247l** | 5-Cl | 88% |

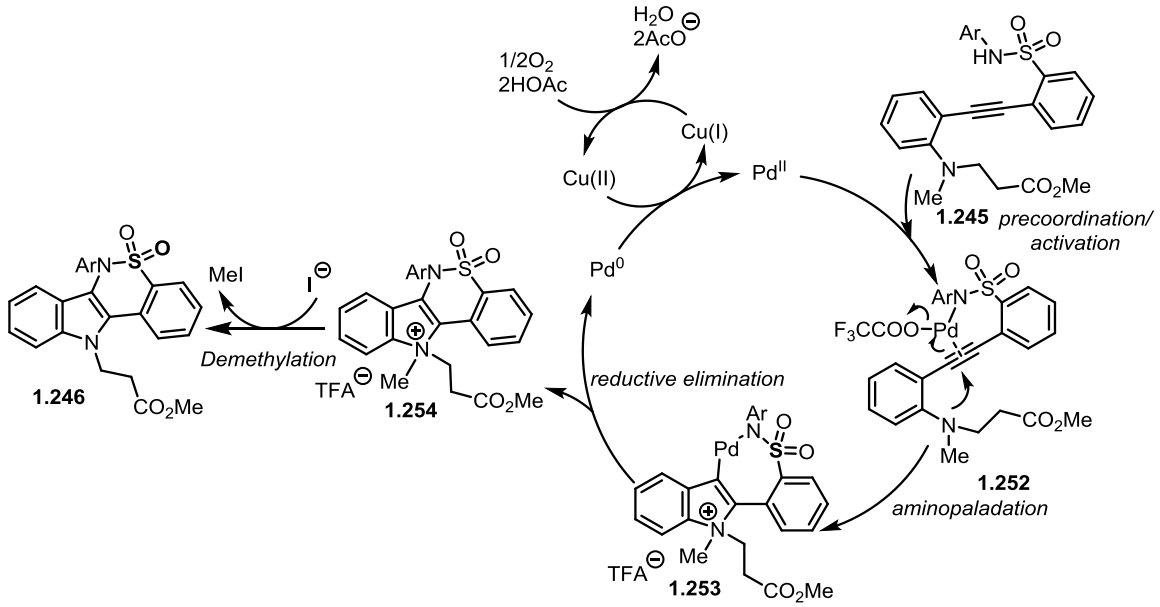
## 3.3. Mechanistic insight

Although the mechanistic study of Pd(II)-catalyzed oxidative diamination of *o*-(1-alkynyl)benzamide **1.83** was well-studied by our group.[34,35] it could not be ruled out that the slightly change of substrate structure may entail the adjustment in mechanistic pathway. To gain insight into mechanism of this transformation, characterization of the intermediates were attempted. Gratefully, the reaction of **1.245a** with $Pd(TFA)_2$ (1.0 equiv) in DMSO-$d_6$ for 45 min at room temperature afforded a compound whose spectroscopic data are in agreement with σ-indolylpalladium complex **1.253**. Subsequent heating the solution of this complex at 100 ºC provided tetracyclic indole **1.246a**, indicating that **1.253** could indeed be an intermediate for our oxidative diamination (Scheme 1.56).




**Scheme 1.56: Observation of σ-indolylpalladidum intermediate**

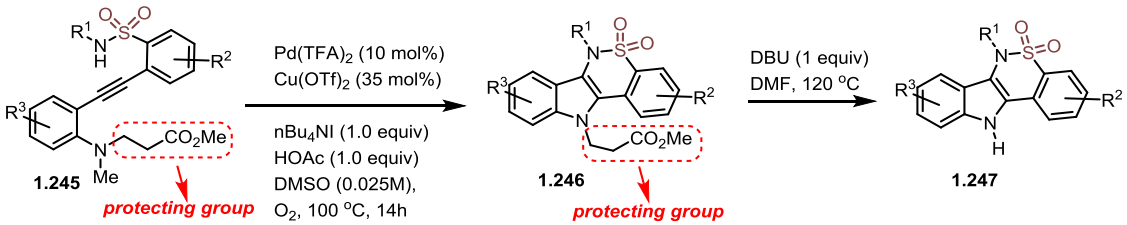
Based on above observation and previous studies, a postulated mechanism for double cyclization of **1.245** could be described as following (Scheme 1.57): Coordination of both alkyne and sulfonamide to Pd(II) species followed by deprotonation of sulfonamide N-H would afford σ,π-chelated palladium complex **1.252**. Subsequent *anti*-aminopalldation via nucleophilic attack of *N*-methyl-*N*-[2-(methoxycarbonyl)-ethyl]aniline to triple bond would provide an σ-indolyl palladium intermediate **1.253** which was experimentally observed. The subsequent reductive elimination of **1.253** would give an ammonium salt **1.254** and Pd(0). Chemoselective dealkylation of ammonium salt via a nucleophilic attack of iodide ion to *N*-methyl group would furnish desired product **1.246**. Finally, regeneration of Pd(II) from Pd(0) would be achieved by Cu(II)/$O_2$ oxidative system to complete catalytic cycles (Scheme 1.57).




**Scheme 1.57: Proposed mechanism of Pd(II)-catalyzed double cyclization of 1.245**

## 3.4. Conclusion

In summary, a Pd(II)-catalyzed oxidative double cyclization of the 1,2-diarylethynes **1.245** bearing an *N*-methyl-*N*-(2-methoxycarbonyl)ethylamino and an aminosulfonyl group was developed to afford indolobenzothiazine *S*,*S*-dioxides **1.246** in good to excellent yields. The 2-(methoxycarbonyl)ethyl group attached to the indolyl nitrogen is readily removed under basic conditions (DBU, DMF, 120 °C) to provide the corresponding tetracycles **1.247** with a free indolyl nitrogen in excellent yields (Scheme 1.58).[83]




**Scheme 1.58: Synthesis of free NH indolobenzothiazine S,S-dioxide by Pd(II)-catalyzed diamination of alkynes**

[83] Ha, T. M.; Yao, B.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 5256.

# CHAPTER 4

## Synthetic Approaches to Quindolinones by Palladium-Catalyzed and Acid-Meidated Reactions

## 4.1. Indolo[3,2-b]quinolinone: Application and Synthesis

Tetracyclic indolo[3,2-b]quinoline (quindoline) and indolo[3,2-b]quinolinone (quindolinone) rings constitute an important structural scaffolds in many natural products which exhibit numerous biologically activities, such as: antibacterial, antifungal, antiprotozoal, antitumoral, anti-inflamatory, hypotensive, anthithrombotic. [84] The simplest natural products containing these moieties are cryptolepine (**1.257**) and cryptolepinone (**1.259**) with a methyl substituent at *N*-5 position (Figure 1.4). Along with other indoloquinonline alkaloids (Figure 1.4), they are isolated from the root and stem of the West African plant *Cryptolepsis sanguinolenta,* [85] which have been used as dye and traditional medicine to treat a variety of health disorders, including: rheumatism, urinary and respiratory tract infections, and malaria.[86]

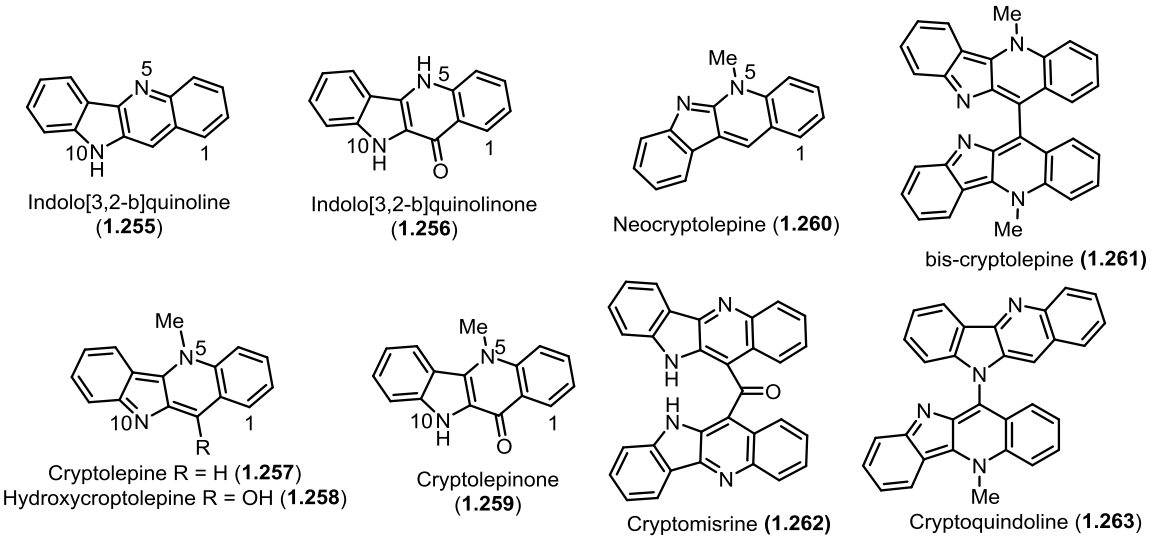



**Figure 1.4: Indolo[3,2-b]quinoline and Indolo[3,2-b]quinolinone**

Owing to broad spectra of bioactivities, indolo[3,2-b]quinoline have become an attractive pharmacophore to exploit in medicinal chemistry. As a result, many analogues of quindoline incorporating various functional groups have been studied in order to evaluate biological activities. For instance, simple $N_5$-alkylated cryptolepine **1.264** was reported to possess more expanded

[84] Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010,** 17, 2348

[85] (a) Gellbert, E.; Hamet, R.; Schlitter, E. *Helv. Chim. Acta.* **1951**, *34*, 642. (b) Dwuma-Badu, D.; Ayin, J. S. K.; Figabe, N. I. Y.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 433. (c) Tackie, A. N.; Sharaf, M. H. M.; Schiff, P. L.; Boye, G. L.; Crouch, R. C.; Martin, G. E. *J. Heterocyclic Chem.* **1991**, *28*, 1429. (d) Crouch, R. C.; Davis, A. O.; Spitzer, T. D.; Martin, G. E.; Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N. *J. Heterocyclic Chem.* **1995**, *32*, 1077. (e) Paulo, A.; Gomes, E. T.; Houghton, P. J. *J. Nat. Prod.* **1995**, *58*, 1485.

[86] (a) Gorlitzer, K.; Ventzke-Nue, K. *Pharmazie* **1998**, *53*,1. (b) Oliver-Bever, B. E. P. *Medicinal Plants in Tropical West Africa*; Cambridge University Press: Cambridge, **1986**; pp 18, 41, 131. (c) Boakye-Yiadom, K. *Quart. J. Crude Drug Res.* **1979**, *17*,7. (c) Boye, G. L. *Proceedings of the International Symposium on East-West Medicine*, Oct. 10-11, 1989, Seoul, Korea; **1990**, pp 243. (d) Luo, J.; Fort, D. M.; Carlson, T. J.; Noamesi, B.; nii-Amon-Kotei, D.; King, S. R.; Tsai, J.; Quan, J.; Hobensack, C.; Lapresca, P.; Waldeck, N.; Mendez, C. D.; Jolad, S. D.; Bierer, D. E.; Reaven, G. M. *Diabetic Med.* **1998**, *15*, 367.

antibacterial spectrum compared to the monomeric counterparts by Ablordeppey (Figure 1.5).[87] Wright reported 8,11-dichloro-5-methylquindoline **1.265** with 4-5 fold more cytotoxicity to MAC15A cancer cell line than cryptolepine.[88] Modified quindoline **1.266** and **1.267** with strong electron donor substituents at C-11 position was proven to exhibit stronger binding-activity with telomeric G-quadruplex (potential target for cancer therapy) with $IC_{50}$ 0.55 µM and 0.44 µM, respectively, as compared to **1.255** with $IC_{50}$ >138 µM.[89]

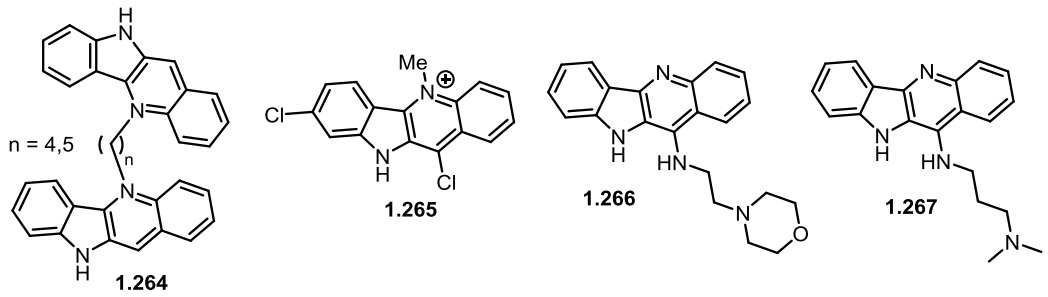
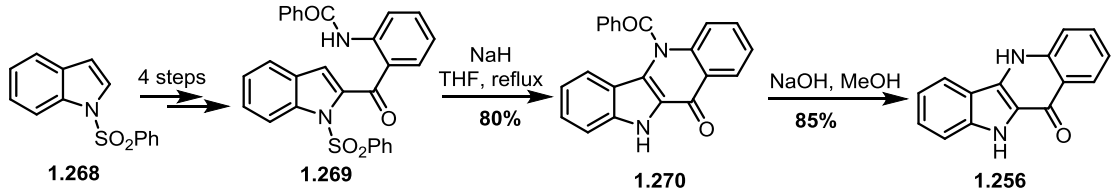



**Figure 1.5: Examples of bioactive analogues of quindoline**

Development of synthetic method to quindolines has drawn great attention due to its potential application in pharmaceutical research. As related to our research, we summarize herein the literature precedents toward indolo[3,2-b]quinolinones (quindolinones) which are readily converted into quindolines in 1 or 2 steps.[90]

Joule reported the synthesis of quindolinone **1.256** using intramolecular nucleophilic β-substitution of 1-phenylsulfonyl-2-acylindole **1.269** as key step (Scheme 1.59).[91] However, this approach requires multiple steps and provides desired tetracycle in very modest yield.

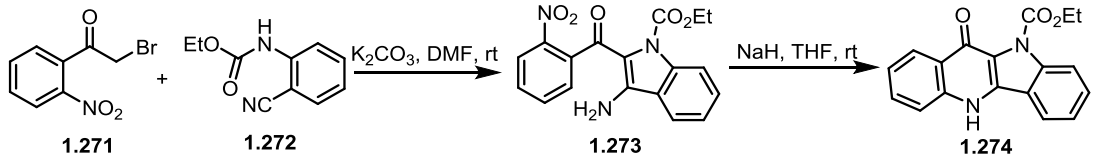



**Scheme 1.59: Synthesis of quindolinone by Joule**

Radle reported an efficient two-step synthesis of quindolinone **1.274** involving condensation of (2-nitrophenyl)acyl bromide **1.271** and ethyl (2-cyanophenyl)carbamate **1.272**, followed by intramolecular nucleophilic aromatic substitution (Scheme 1.60).[92] This method provided

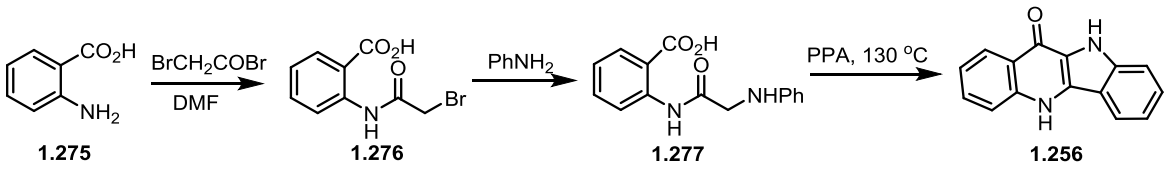
[87] Mardenborough, L. G.; Zhu, X. Y.; Fan, P.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. *Bioorganic Med. Chem.* **2005**, *13*, 3955.
[88] Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Y.; Kendrick, H.; Philips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187.
[89] Lavrado, J.; Borralho, P. M.; Ohnmacht, S. A.; Castro, R. E.; Rodrigues, C. M. P.; Moreira, R.; Dos Santos, D. J. V. A.; Neidle, S.; Paulo, A. *ChemMedChem* **2013**, *8*, 1648.
[90] Kumar, E. V. K. S.; Etukala, J. R.; Ablordeppey, S. Y. *Mini Rev. Med. Chem.* **2008**, *8*, 538.
[91] Cooper, M. M.; Lovell, J. M.; Joule, J. A. *Tetrahedron Lett.* **1996**, *37*, 4283.
[92] Rádl, S.; Konvička, P.; Váchal, P. A. *J. Heterocyclic Chem.* **2000**, *37*, 855.

quindolinones with various substituents on aromatic rings. Analogous benzofuro[3,2-b]quinolinones and benzothieno[3,2-b]quinolinones are also accessible by this approach.



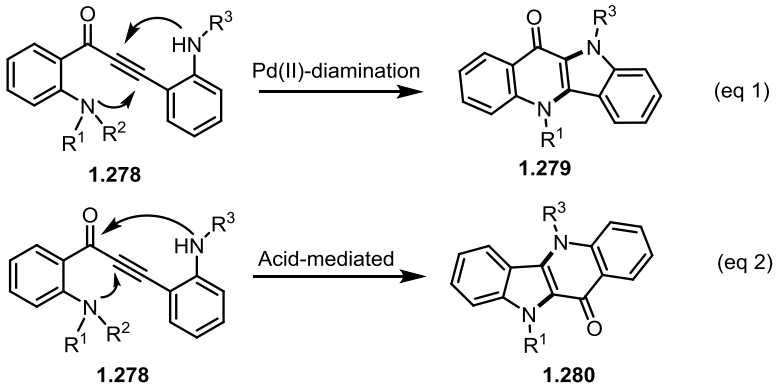

**Scheme 1.60: Synthesis of quindolinone by Radle**

Lately, an improvement in synthesis of quindolinone was achieved by Bierer (Scheme 1.61).[93] Treatment of anthranilic (**1.275**) with bromoacetyl bromide provided compound **1.276** which was converted to anthranilic acid **1.277**. Acid-promoted cyclization of **1.277** with polyphosphoric acid led to *N*-unprotected quindolinone **1.256**. This method employed simple starting materials and provided wide range of quindolinones in good overall yields. As a result, it was widely used in medicinal chemistry.




**Scheme 1.61: Synthesis of quindolinone by Biere**

As continuation of our interests in constructing tetracycles, we focused our attention on the development of novel synthesis of quindolinones. In this chapter, we will describe two synthetic approaches to tetracyclic quindolinones. 1,3-diarylprop-2-yn-1-ones **1.278** bearing two internal amino groups at *ortho* positions of aromatic rings could be successfully converted into quindolinones by either Pd(II)-catalyzed diamination (eq 1, Scheme 1.62) or acid-mediated double cyclization (eq 2, Scheme 1.62).



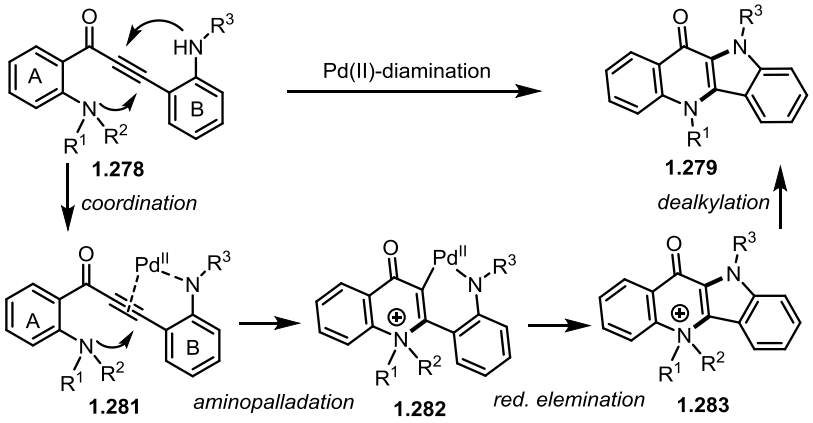

**Scheme 1.62: Our synthetic approaches to quinolinones**

[93] Bierer, D. E.; Dubenko, L. G.; Zhang, P.; Lu, Q.; Imbach, P. A.; Garofalo, A. W.; Phuan, P. W.; Fort, D. M.; Litvak, J.; Gerber, R. E.; Sloan, B.; Luo, J.; Cooper, R.; Reaven, G. M. *J. Med. Chem.* **1998**, *41*, 2754.

## 4.2. Synthesis of Quindolinones by Palladium Catalysis

### 4.2.1. Primary results

Inspired by previous work on Pd(II)-catalyzed diamination of alkyne,[34,35] we assume indolo[3,2-b]quinolinone **1.279** could also be obtained by a similar pathway from 1,3-diarylprop-2-yn-1-ones **1.278** bearing two amino groups at *ortho* positions of aromatic rings (Scheme 1.63). This transformation could proceed through coordination of palladium species to triple bond and nitrogen atom to form σ,π-palladium complex **1.281**, followed by aminopalladation via intramolecular nucleophilic attack to afford vinylpalladium intermediate **1.282**. Subsequent reductive elimination and dealkylation could provide tetracycle **1.279** as final product.




**Scheme 1.63: Synthetic approaches to quinolinones by Pd(II)-diamination**

Initially, we focused on examining the suitable substrates to our designed transformation by changing different substituents $R^1$, $R^2$, and $R^3$. The primary results showed that substrates **1.278** with unsubstituted ($R^1$ = $R^2$ = H) or monosubstituted ($R^1$ = H, $R^2$ = Me) aniline on aromatic ring A (see Scheme 1.63) are generally unstable and were not converted into desired product under previously reported conditions.[34] The substrate with unsubstituted aniline ($R^3$ = H) on aromatic ring B was synthetized in very moderate yield and was relatively unstable. Moreover, synthesis of **1.278** with $R^3$ as an electron-withdrawing group such as acyl or tosyl was not successful. The instability of those substrates might be reasoned by either cyclization via Aza-Michael addition of aniline to triple bond or condensation between unsubstituted aniline with carbonyl functional group. Subsequently, we turned our attention on *N*,*N*,*N*-trialkylated **1.278**. Fortunately, these substrates can be accessed in reasonable yields and were sufficiently stable.

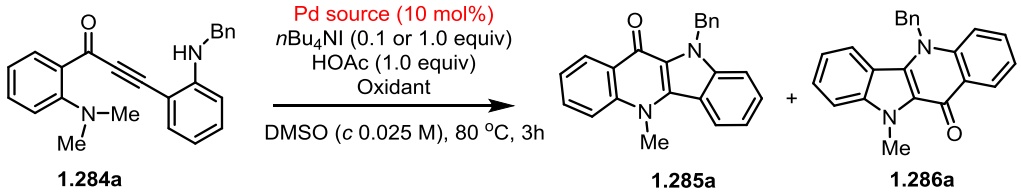
### 4.2.2. Conditions survey

We began our investigation using 3-[2-(benzylamino)phenyl]-1-[2-(dimethylamino)-phenyl]prop-2-yn-1-one (**1.284a**) as test substrate. Condition survey was carried out by varying palladium sources, additives, acids, oxidants, temperature and reaction time.

#### 4.2.2.1. Screening conditions: Palladium sources

When **1.284a** was submitted into the previously optimized conditions [$Pd(OAc)_2$ (10 mol%), $n$$Bu_4NI$ (1.0 equiv), HOAc (1.0 equiv), $O_2$ (1 atm), DMSO (0.025 M), 80 °C],[34,35] only a trace amount of desired quindolinone **1.285a** was observed by NMR spectra, along with side product **1.286a** which have the same tetracyclic motif as **1.285a** (entry 1, Table 1.9). Formation of **1.285a** and **1.286a** might result from 6-endo-dig cyclization and 5-exo-dig cyclization, respectively.

**Table 1.9: Palladium source screening** [(a)]




| Entry | Pd source (mol%) | $n$$Bu_4NI$ (equiv) | Oxidant (equiv) | Yield[(b)] of 1.285a | Ratio 1.285/1.286 |
|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | 1.0 | $O_2$ | <10 | 2.6 : 1.0 |
| 2 | $Pd(TFA)_2$ (10) | 1.0 | $O_2$ | <10 | 2.2 : 1.0 |
| 3 | $Pd(MeCN)_2Cl_2$ (10) | 1.0 | $O_2$ | <10 | 1.6 : 1.0 |
| 4 | $Pd(PPh_3)_2Cl_2$ (10) | 1.0 | $O_2$ | 40 | 8.7 : 1.0 |
| 5 | $Pd(PPh_3)_2Cl_2$ (10) | 0.1 | $O_2$ | 21 | 6.0 : 1.0 |
| 6 | $Pd(PPh_3)_2Cl_2$ (10) | 1.0 | BQ (5) | 30 | >30 : 1.0 |
| 7 | $Pd(PPh_3)_2Cl_2$ (10) | 0.1 | BQ (5) | 41 | >30 : 1.0 |
| 8 | $PdX_2$ (10) + $PPh_3$ (20) | 0.1 | BQ (5) | 15-24 | 18-30 : 1.0 |
| 9 | $Pd(PPh_3)_2Cl_2$ (10) Phosphine (20) | 0.1 | BQ (5) | 38-40 | >30 : 1.0 |
| 10 | None | none | $O_2$ | 8% | -- : 1.0 |

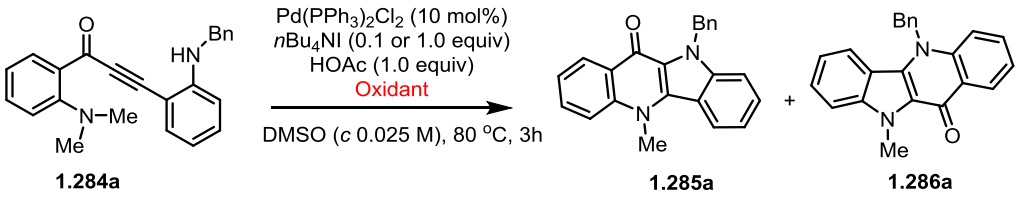
(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 10 mol% Pd source, 0.1-1 equiv $n$$Bu_4NI$, 1.0 equiv HOAc, and oxidant in 2.0 mL DMSO was heated at 80 °C for 3 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

Different palladium sources were later investigated under the same condition. Unfortunately, $Pd(TFA)_2$ and $Pd(MeCN)_2Cl_2$ showed the same activity, affording trace amount of **1.285a** (entry 2,3). Significant improvement was achieved when $Pd(PPh_3)_2Cl_2$ was employed; desired quindolinone was observed in 40% NMR yield (entry 4). Interestingly, quick screening the other parameters indicated that the outcome of reaction was dependent on iodide loading and oxidant sources (entry 4-7). When $O_2$ molecule was used as oxidant, stoichiometric amount of $n$Bu$_4$NI was necessary to provide reasonable yield. On the other hand, when benzoquinone (BQ) was employed, the best result was observed with 0.1 equiv of $n$Bu$_4$NI, furnishing **1.285a** in 41% NMR yield and cleaner reaction (**1.285**/**1.286** > 30:1). Using combined system of $PdX_2$ (X = Cl, OAc, TFA) and $PPh_3$ (entry 8) or $Pd(PPh_3)_2Cl_2$ and phosphine ligand (XPhos, $PCy_3$) (entry 9), the transformation proceeded with either lower conversion or lower yield. In the absence of palladium catalyst, no desired product was observed (entry 10). However, under these conditions, tetracyclic **1.286a** was obtained in 8% NMR yield with low conversion, indicating the side reaction could be mediated by only HOAc.

#### 4.2.2.2. Screening conditions: Oxidants

Beside oxygen molecule and benzoquinone, different oxidants were screened in the presence of $Pd(MeCN)_2Cl_2$ (10 mol%), $n$Bu$_4$NI (0.1 equiv), HOAc (1.0 equiv) at 80 °C. Quindolinone **1.285a** was obtained in low to moderate yield with manganese salts and copper salts as oxidants (entry 1, 2, 4; Table 1.10). The transformation to desired product was totally inhibited when silver salt and strong organic oxidants such as hypervalent iodanes were employed (entry 3, 5, 6). Therefore, benzoquinone was chosen as an oxidant for further optimization.

**Table 1.10: Oxidant screening** [a]




**1.284a** **1.285a** **1.286a**

| Entry | Oxidant (equiv) | $n$Bu$_4$NI (equiv) | Yield[b] [%] | Ratio 1.285/1.286 |
|---|---|---|---|---|
| 1 | $MnO_2$ (4) | 0.1 | 20% | 18 : 1.0 |
| 2 | $Mn(OAc)_3 2H_2O$ (4) | 0.1 | 38% | >30 : 1.0 |
| 3 | $Ag_2CO_3$ (1) | 0.1 | 0% | --- |
| 4 | $CuX_2$ (X = OAc, OTf) | 0.1 | <15% | 5-15 : 1.0 |

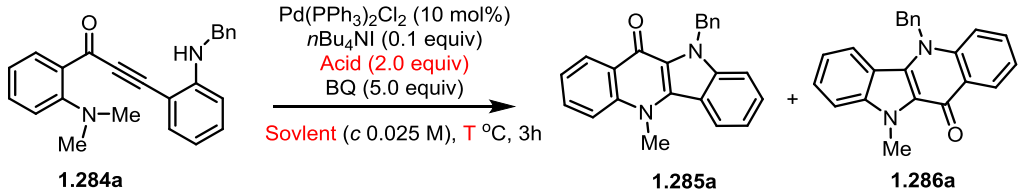
| | | | | |
|---|---|---|---|---|
| 5 | PIDA (1) | 0.1 | 0% | --- |
| 6 | PIFA (1) | 0.1 | 0% | --- |

(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 10 mol% $Pd(MeCN)_2Cl_2$, 0.1 equiv $nBu_4NI$, 1.0 equiv HOAc, and oxidant in 2.0 mL DMSO was heated at 80 ºC for 3 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.2.2.3. Screening conditions: Acid, solvent and temperature

Next, we studied the effect of acids, solvents and temperature on the reaction outcome. The same result was obtained when acetic acid was replaced by pivalic acid (entry 1,2). However, using stronger acids such as benzoic acid and TsOH, the reaction gave inferior yield or no desired product (entry 3,4). Complete protonation of *N*,*N*-dimethylaniline, leading to the decrease in nucleophilicity, might be an account for this observation. It is worthy to note that in the absence of HOAc, an important reagent for regeneration of Pd(II) to catalytic cycles, very low conversion was observed. Additionally, polar solvents were found to be compatible with this transformation (entry 1, 5-10). Best solvents are DMF and DMA; whereas apolar solvents such as DME or toluene did not furnish any desired product. Further optimization indicated that increasing the temperature, and using 1.5 equiv of HOAc provided better outcome (entry 11-14) in which quindolinone **1.285a** was obtained in 53% NMR yield (entry 14).

**Table 1.11: Acid, Solvent, Temperature screening [(a)]**




| Entry | Acid (equiv) | Solvent | Temp. [°C] | Yield[(b)] [%] | Ratio 1.285/1.286 |
|---|---|---|---|---|---|
| 1 | HOAc (2.0) | DMSO | 80 | 42% | >30 : 1.0 |
| 2 | HOPiv (2.0) | DMSO | 80 | 40% | >30 : 1.0 |
| 3 | Benzoic acid (2.0) | DMSO | 80 | 16% | 15 : 1.0 |
| 4 | TsOH (2.0) | DMSO | 80 | 0% | --- |
| 5 | HOAc (2.0) | DMF | 80 | 47% | >30 : 1.0 |
| 6 | HOAc (2.0) | DMA | 80 | 47% | >30 : 1.0 |
| 7 | HOAc (2.0) | MeCN | 80 | 10% | 0.7 : 1.0 |

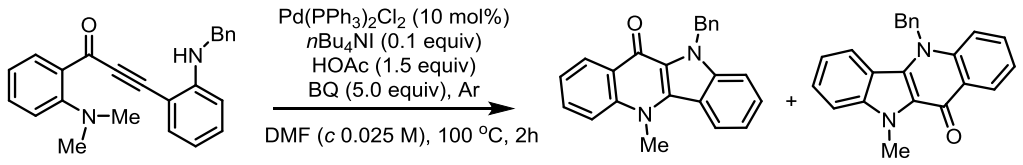
| | | | | | |
|---|---|---|---|---|---|
| 8 | HOAc (2.0) | Dioxane | 80 | <10% | --- |
| 9 | HOAc (2.0) | DME | 80 | trace | --- |
| 10 | HOAc (2.0) | Toluene | 80 | trace | --- |
| 11 | HOAc (2.0) | DMF | 70 | 47% | >30 : 1.0 |
| 12 | HOAc (2.0) | DMF | 100 | 51% | >30 : 1.0 |
| 13 | HOAc (1.0) | DMF | 100 | 50% | >30 : 1.0 |
| 14 | HOAc (1.5) | DMF | 100 | 53% | >30 : 1.0 |

(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 10 mol% $Pd(MeCN)_2Cl_2$, 0.1 equiv $nBu_4NI$, 2.0 equiv HX, and 5.0 equiv BQ in 2.0 mL solvent was heated at T °C for 3 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.2.2.4. Screening conditions: Additional screening

Additional screening was carried out in order to enhance the yield of double cyclization (Table 1.12). Gratefully, replacing $Pd(PPh_3)_2Cl_2$ by $Pd(PPh_3)_2(OAc)_2$, yield of desired product was slightly improved to 60% (entry 2, Table 1.12). Further optimization was achieved by reducing benzoquinone loading to 2.0 equiv affording quindolinone **1.285a** in 63% NMR yield and 55% isolated yield (entry 3). The oxidative system combining benzoquinone and air atmosphere was tested, and was found to be less efficient (entry 4). Finally, using different benzoquinone derivatives as alternative oxidants resulted in diminished yields (entry 5, 6). Particularly, prop-2-yn-1-one **1.284a** was readily decomposed in the presence of strong oxidants such as **O6-O9**.

**Table 1.12: Additional screening [(a)]**




**1.284a** **1.285a** **1.286a**

| Entry | Variation of reaction conditions | Yield[(b)] [%] |
|---|---|---|
| 1 | None | 53% |
| 2 | $Pd(PPh_3)_2(OAc)_2$ (10 mol%) | 60% |
| 3 | $Pd(PPh_3)_2(OAc)_2$ (10 mol%), BQ (2.0 equiv) | 63% (**55% iso.**) |
| 4 | $Pd(PPh_3)_2(OAc)_2$ (10 mol%), BQ (2.0 equiv), air | 60% |

| | | |
|---|---|---|
| 5 | $Pd(PPh_3)_2(OAc)_2$ (10 mol%), **O1-O5** (2.0 equiv) | 21-50% |
| 6 | $Pd(PPh_3)_2(OAc)_2$ (10 mol%), **O6-O11** (2.0 equiv) | <10% |

(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 10 mol% $Pd(MeCN)_2Cl_2$, 0.1 equiv $nBu_4NI$, 1.5 equiv HOAc, and 5.0 equiv BQ in 2.0 mL DMF was heated at 100 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

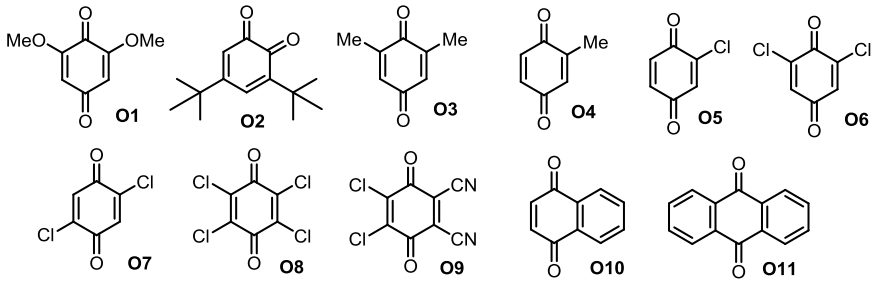
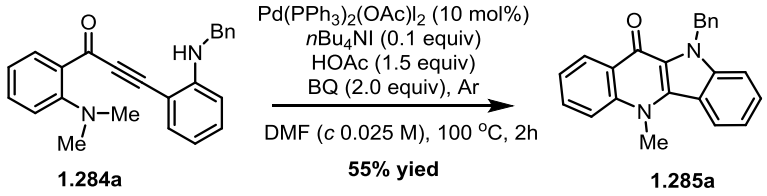



**Figure 1.6: Oxidants for screeing conditions**

Overall, the optimum conditions consisted of performing the double cyclization of **1.284a** in DMF (*c* 0.025 M) at 100 ºC in the presence of $Pd(PPh_3)_2(OAc)_2$ (10 mol%), $nBu_4NI$ (0.1 equiv), HOAc (1.5 equiv) and benzoquinone (2.0 equiv). Under these conditions, intramolecular diamination of 1.**284a** afforded tetracyclic quindolinone **1.285a** in 55% isolated yield. (Scheme 1.64)



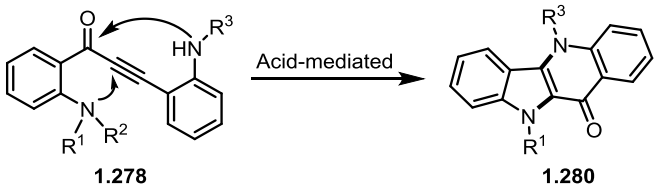

**Scheme 1.64: Optimized condition for Pd-catalyzed deamination of 1.284a**

Unfortunately, the primary scope investigation indicated that this synthetic approach is not widely applicable. Low to moderate yields are obtained when different prop-2-yn-1-one substrates were introduced into optimized conditions. Consequently, we turned our attention on an alternative transformation for constructing quindolinone scaffold.

## 4.3. Synthesis of Quindolinones by Acid-mediated Double Cyclization

### 4.3.1. Introduction

Given the fact that double cyclization of 1,3-diarylpropynone **1.284a** occurred to afford quindolinone **1.286a** in the absence of palladium catalyst (entry 10, Table 1.9), we decided to further exploit this interesting experimental observation. Although the initial result gave only modest conversion and yield of tetracyclic product (8% yield, ~ 50% conversion), development of alternative metal free transformation to access quindolinones is of great interest. In this part, the synthesis of tetracycles **1.280** via acid-mediated double cyclization under oxidative condition will be described (Scheme 1.65).




1.278 1.280

**Scheme 1.65: Synthetic approaches to quinolinones by Acid-mediated double cyclization**

### 4.3.2. Conditions survey

3-[2-(benzylamino)phenyl]-1-[2-(dimethylamino)-phenyl]prop-2-yn-1-one **1.284a** was chosen as test substrate to explore the double cyclization. Condition survey was carried out by varying acid sources, additives, oxidants, temperature and reaction time.

#### 4.3.2.1. Screening conditions: Acids

Desired tetracyclic quindolinone **1.285a** was obtained in 8% NMR yield with 50% conversion of starting material when prop-2-yn-1-one **1.284a** was introduced to the following conditions: HOAc (4.0 equiv) as promoter, in DMSO (*c* 0.025 M), at 80 ºC for 8 h (entry 1, Table 1.13). Different acids were later investigated under the same conditions. Interestingly, double cyclization could also be promoted by pivalic acid, however, giving slightly inferior result (entry 2). Unfortunately, stronger acid TFA and TsOH induced the degradation of starting material (entry 3, 4), milder ones ($SiO_2$ and $NaH_2PO_4$) were not able to promote the cyclization (entry 5, 6). Acetic acid therefore was kept as standard promoter for further optimization.

**Table 1.13: Acid screening [a]**


1.284a 1.286a

| Entry | Acid (equiv) | Conversion[b] [%] | Yield[b] [%] |
|---|---|---|---|
| 1 | HOAc (4) | 50 | 8% |
| 2 | HOPiv (4) | 60 | 5% |
| 3 | TFA (10) | 100 | --- |
| 4 | $TsOH.H_2O$ (4) | 100 | --- |
| 5 | $SiO_2$ (10) | no rxn | --- |
| 6 | $NaH_2PO_4$ (4) | no rxn | --- |

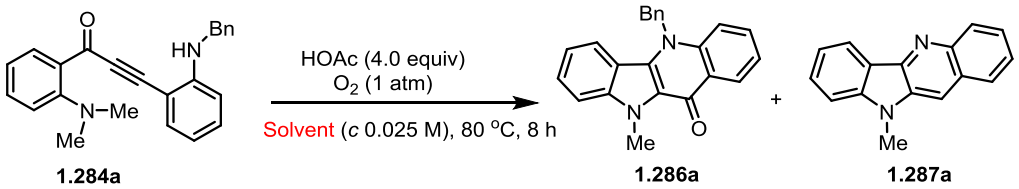
(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 4.0 equiv HX in 2.0 mL DMSO under oxygen (1 atm) was heated at 80 °C for 8 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.3.2.2. Screening conditions: Solvents

Next we investigated the effect of solvents on the cyclization of **1.284a** in the presence of HOAc (4.0 equiv) at 80 °C for 8 h (Table 1.14). The reactions in aprotic polar solvents such as DMSO, DMF and MeCN afforded **1.286a** in modest yields with moderate conversions (entry 1-3). While protic solvents facilitated the reaction with almost full conversion, however, only ethanol gave a promising result with 30% NMR yield (entry 5-8). On other hand, the cyclization in apolar solvents provided quindolinone **1.286a** in 22-28% NMR yield with moderate conversion (entry 9-12). The best result was obtained with 28% NMR yield when *p*-xylene was used as solvent. Interestingly, a side product quindoline **1.287a** was observed in these cases. Attempt of using solvent system of EtOH and *p*-xylene (v/v 1/3) to enhance both conversion and yield was carried out, but only a trace amount of **1.286a** was detected by NMR (entry 13).

Given the fact that *p*-xylene afforded desired product in better yield based on conversion compared to ethanol as solvent, we decided to use *p*-xylene for screening of other parameters.

**Table 1.14: Solvent screening [a]**




| Entry | Solvent | Conversion[b] [%] | Yield[b] of 1.286a | Ratio 1.286/1.287 |
|---|---|---|---|---|
| 1 | DMSO | 50% | 8% | --- |
| 2 | DMF | 52% | 13% | --- |
| 3 | MeCN | 66% | 15% | --- |
| 4 | Dioxane | >90% | <5% | --- |
| 5 | EtOH | 100% | 31% | --- |
| 6 | *i*-PrOH | 100% | <10% | --- |
| 7 | *t*-BuOH | 90% | <10% | --- |
| 8 | TFE | 100% | 0% | --- |
| 9 | Toluene | 75% | 28% | 2 : 1 |
| 10 | *p*-Xylene | 65% | 28% | 2 : 1 |
| 11 | PhCl | >95% | 26% | 2 : 1 |
| 12 | $PhCF_3$ | >95% | 22% | 2 : 1 |
| 13 | Xylene/EtOH (3/1) | 100% | <10% | --- |

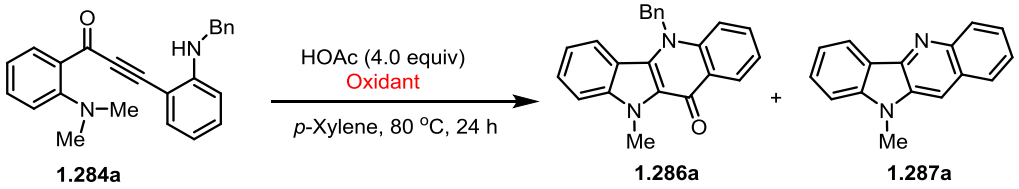
(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 4.0 equiv HOAc in 2.0 mL solvent under oxygen (1 atm) was heated at 80 °C for 8 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

### 4.3.2.3. Screening conditions: Oxidants, concentration, acid loading

The oxidants were screened using the previous best conditions: HOAc (4.0 equiv) as promoter, *p*-xylene as solvent, at 80 °C but for longer time (24 h) in order to force reaction to complete (Table 1.15). Indeed, desired product was obtained in higher yield, but conversion was still halted at 72% (entry 1). Other oxidants including organic oxidant and metal salts were not compatible with reaction system, leading to full conversion but inferior yield (entry 2-6). Gratefully, dilution of reaction concentration, which is rationally favourable to intramolecular transformation, slightly improved the reaction outcome (entry 7). Finally, reaction reached to the completion when acid loading was

increased (entry 8, 9). In the presence of 8 equiv of HOAc, the cyclization of **1.284a** afforded the best result with 55% NMR yield or 52% isolated yield of desired product (entry 8).

**Table 1.15: Oxidant, concentraion and acid loading screening [(a)]**




**1.284a** **1.286a** **1.287a**

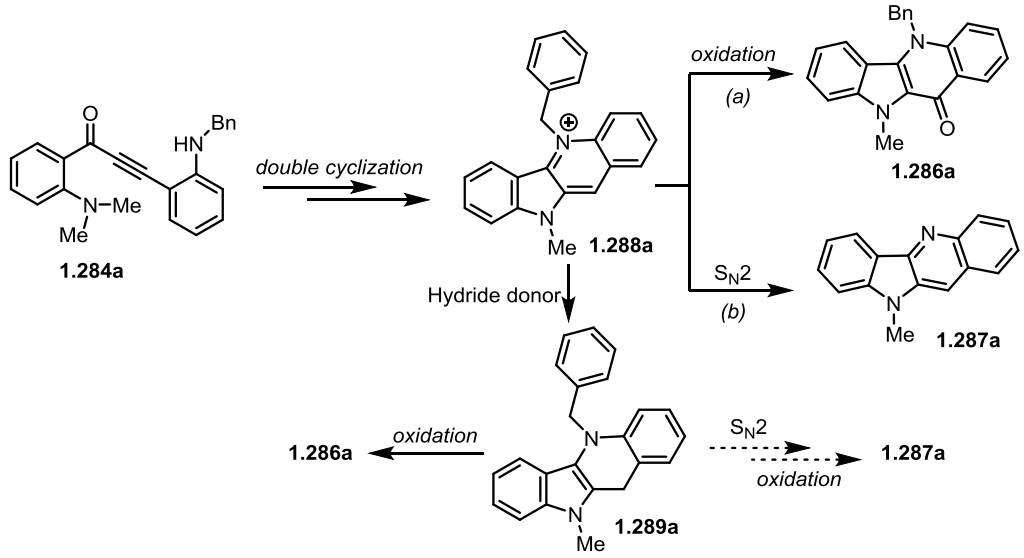
| Entry | Oxidant (equiv) | Conc. [M] | Conv.[(b)] [%] | Yield[(b)] of 1.286a | Ratio 1.286/1.287 |
|---|---|---|---|---|---|
| 1 | $O_2$ (1 atm) | 0.025 | 72% | 36% | 1.5 : 1 |
| 2 | ($t$BuO)$_2$ (1.0) | 0.025 | 88% | 12% | --- |
| 3 | $m$CPBA (2.0) | 0.025 | 100% | 11% | --- |
| 4 | PIDA (2.0) | 0.025 | 100% | 11% | --- |
| 5 | $MnO_2$ (2.0) | 0.025 | 90% | 20% | 0.9 : 1 |
| 6 | $Mn(OAc)_3$ (2.0) | 0.025 | 100% | 15% | --- |
| 7 | $O_2$ (1 atm) | 0.010 | 88% | 46% | 2.0 : 1 |
| 8[(c)] | $O_2$ (1 atm) | 0.010 | 95% | 55% | 2.5 : 1 |
| 9[(d)] | $O_2$ (1 atm) | 0.010 | 100% | 31% | 4.3 : 1 |

(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 4.0 equiv HOAc and 1-2 equiv oxidant in 2.0 mL *p*-xylene was heated at 80 ºC for 24 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) 8.0 equiv of HOAc was used. (d) 12.0 equiv of HOAc was used.

#### 4.3.2.4. Screening conditions: Additives and temperature

Despite of moderate yield of desired product, the transformation of **1.284a** under previous conditions (entry 8, Table 1.15) furnished **1.286a** and **1.287a** in good overall yield (~77% NMR). This result implied that double cyclization indeed occurred with satisfactory outcome. The major issue of our reaction system leading low yield of desired product could be reasoned by modest selectivity in formation of **1.286a** and **1.287a**. This prompted us to take consideration into the mechanism of reaction. We assumed that double cyclization of **1.284a** could form an indoloquinolinium intermediate **1.288a**. The resulting intermediate **1.288a** could undergo either oxidation to afford desired product **1.286a** or nucleophilic substitution with acetate anion to afford side product **1.287a** (Scheme 1.66). Pleasingly, the effect of solvents on the outcome of this transformation (see 4.3.2.2) is in agreement with this hypothesis. In apolar solvent (eg. toluene, *p*-xylene), nucleophilic substitution of **1.288a** with

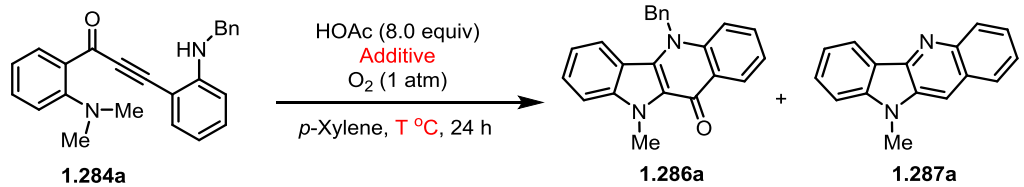
acetate is favourable. As a result, formation of side product (pathway b, Scheme 1.66) was observed when polar solvents (eg. ethanol) were replaced by apolar solvents.




**Scheme 1.66: Hypothesis for the formation of 1.286a and 1.287a**

Based on above hypothesis, we proposed that the formation of side product **1.287a** could be avoided by a quick reduction of indoloquinolinium intermediate **1.288a** to generate dihydroindoloquinoline intermediate **1.289a**. This intermediate is not a suitable subject for $S_N2$ reaction but subsequently could be reoxidized to form tetracyclic **1.286a**. Therefore hydride donors such as dihydropyridines might be potentially suitable additives to ameliorate our transformation.[94] Adding Hantzsch ester (2.0 equiv) to the reaction mixture furnished complete reaction and the sole product **1.286a**, however, no improvement in yield was observed (entry 1). Gratefully, elevating the reaction temperature to 90 ºC provided desired product in 74% NMR yield or 72% isolated yield (entry 2). Further increasing in temperature to 100 ºC led to incomplete reaction (entry 3). This result could be explained by fast consumption of Hantzsch ester at higher temperature under aerobic conditions. To overcome this issue, additional amount of Hantzsch ester (2.5 equiv) was employed, yielding **1.286a** in 81% NMR yield or 77% isolated yield (entry 4).

**Table 1.16: Additive and temperature screening [(a)]**




[94] (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683. (b) You, S. L. *Chem. - An Asian J.* **2007**, *2*, 820. (c) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407. (d) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (e) Richter, D.; Mayr, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1958.

| Entry | Additive (equiv) | Temp. [°C] | Conv.[(b)] [%] | Yield[(b)] of 1.286a | Ratio 1.286/1.287 |
|---|---|---|---|---|---|
| 1 | Hantzsch ester (2.0) | 80 | 100% | 55% | 1 : 0 |
| 2 | Hantzsch ester (2.0) | 90 | 100% | 74% (72%)[(c)] | 1 : 0 |
| 3 | Hantzsch ester (2.0) | 100 | 86% | 60% | 1 : 0 |
| 4 | Hantzsch ester (2.5) | 100 | 100% | 81% (77%)[(c)] | 1 : 0 |

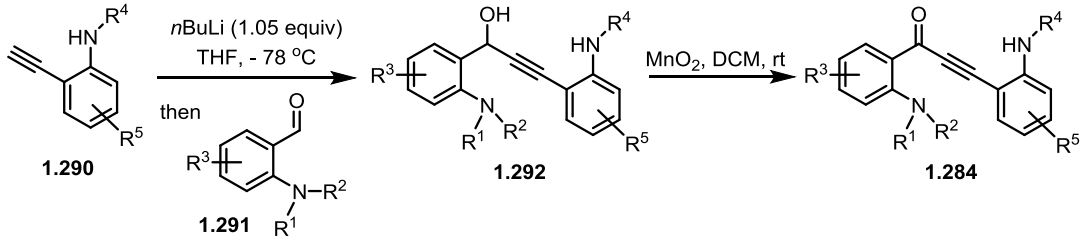
(a) Reaction conditions: A solution of **1.284a** (0.05 mmol), 8.0 equiv HOAc and additive in 2.0 mL *p*-xylene (*c* 0.01 M) was heated at T °C for 15-24 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield.

Overall, the optimum conditions consisted of performing the double cyclization of **1.284a** in *p*-xylene (*c* 0.01 M) at 100 °C in the presence of HOAc (8.0 equiv) and Hantzsch ester (2.5 equiv). Under these conditions, intramolecular diamination of 1**.284a** afforded tetracyclic quindolinone **1.286a** in 77% isolated yield with complete chemoselectivity.

### 4.3.3. Substrate scope for acid-mediated double cyclization

#### 4.3.3.1. Synthesis of starting materials 1.284

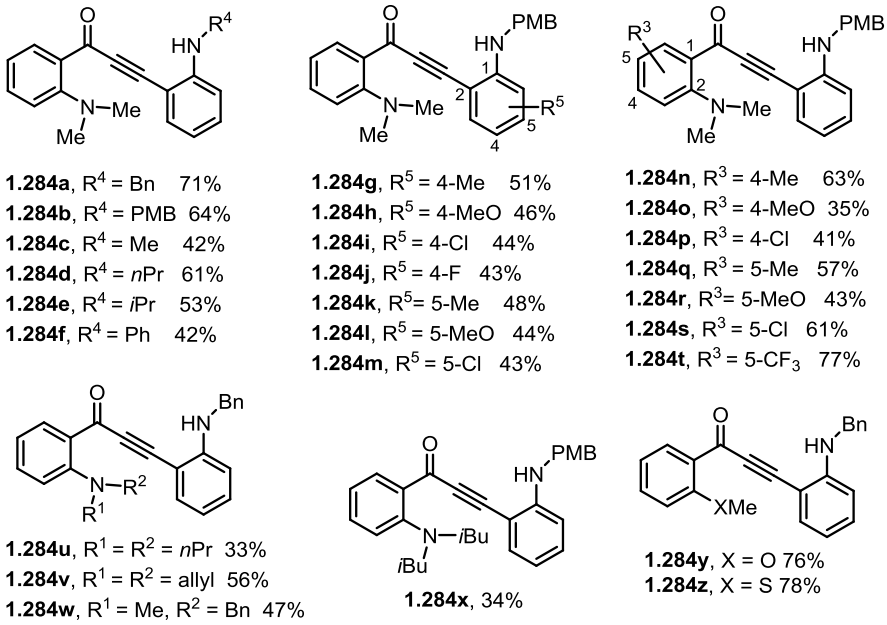
In general, prop-2-yn-1-ones **1.284** were prepared in two steps including: nucleophilic addition of *o*-ethylnylaniline **1.290** with *N*,*N*-dialkylated 2-aminobenzaldehyde **1.291** to form propargylic alcohol **1.292**, followed by oxidation with $MnO_2$ to furnish **1.284** in moderate to good yields over two steps (Scheme 1.67). Due to instability of propargyl alcohol intermediates **1.292** on silic a gel,[95] their crude products were submitted directly to oxidation step without any purification. Therefore, prop-2-yn-1-ones **1.284** were accessed in two steps with single FCC purification.




**Scheme 1.67: Synthesis of prop-2-yn-1-ones 1.284**

Changing the substituent on nitrogen atoms, aromatic rings, a series of prop-2-yn-1-ones **1.284** was collected. The result was summarized in Figure. 1.7.

[95] Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1881.




**1.284a**, $R^4$ = Bn 71%
**1.284b**, $R^4$ = PMB 64%
**1.284c**, $R^4$ = Me 42%
**1.284d**, $R^4$ = *n*Pr 61%
**1.284e**, $R^4$ = *i*Pr 53%
**1.284f**, $R^4$ = Ph 42%

**1.284g**, $R^5$ = 4-Me 51%
**1.284h**, $R^5$ = 4-MeO 46%
**1.284i**, $R^5$ = 4-Cl 44%
**1.284j**, $R^5$ = 4-F 43%
**1.284k**, $R^5$= 5-Me 48%
**1.284l**, $R^5$ = 5-MeO 44%
**1.284m**, $R^5$ = 5-Cl 43%

**1.284n**, $R^3$ = 4-Me 63%
**1.284o**, $R^3$ = 4-MeO 35%
**1.284p**, $R^3$ = 4-Cl 41%
**1.284q**, $R^3$ = 5-Me 57%
**1.284r**, $R^3$= 5-MeO 43%
**1.284s**, $R^3$ = 5-Cl 61%
**1.284t**, $R^3$ = 5-$CF_3$ 77%

**1.284u**, $R^1$ = $R^2$ = *n*Pr 33%
**1.284v**, $R^1$ = $R^2$ = allyl 56%
**1.284w**, $R^1$ = Me, $R^2$ = Bn 47%

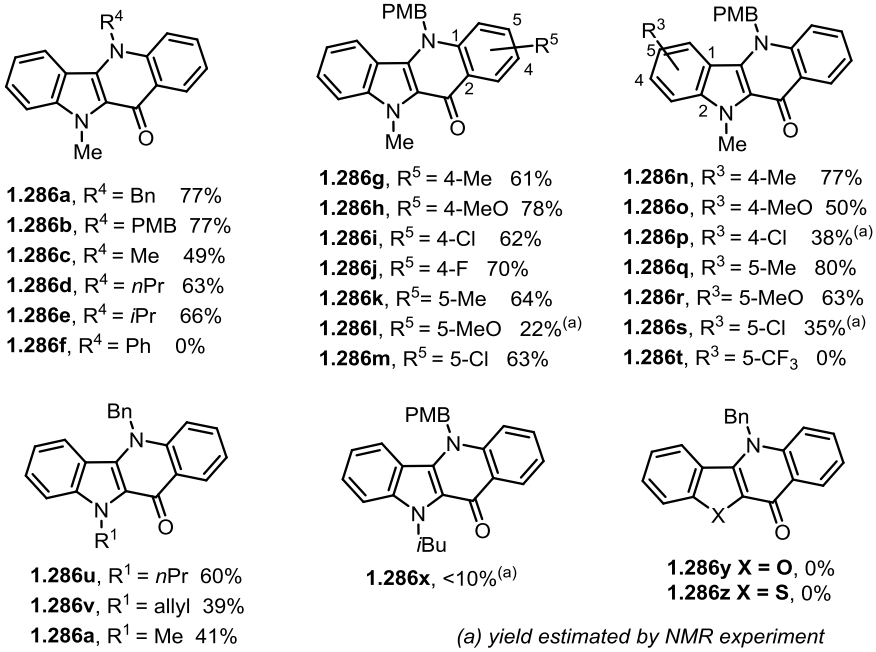
**1.284x**, 34%

**1.284y**, X = O 76%
**1.284z**, X = S 78%

**Figure 1.7: Starting materials for acid-mediated double cyclization**

### 4.3.3.2. Substrate scope of acid-mediated double cyclization

With the optimized conditions in hand, we examined the generality of acid-mediated diamination. The result was summarized in Figure 1.8.




**1.286a**, $R^4$ = Bn 77%
**1.286b**, $R^4$ = PMB 77%
**1.286c**, $R^4$ = Me 49%
**1.286d**, $R^4$ = *n*Pr 63%
**1.286e**, $R^4$ = *i*Pr 66%
**1.286f**, $R^4$ = Ph 0%

**1.286g**, $R^5$ = 4-Me 61%
**1.286h**, $R^5$ = 4-MeO 78%
**1.286i**, $R^5$ = 4-Cl 62%
**1.286j**, $R^5$ = 4-F 70%
**1.286k**, $R^5$= 5-Me 64%
**1.286l**, $R^5$ = 5-MeO 22%[(a)]
**1.286m**, $R^5$ = 5-Cl 63%

**1.286n**, $R^3$ = 4-Me 77%
**1.286o**, $R^3$ = 4-MeO 50%
**1.286p**, $R^3$ = 4-Cl 38%[(a)]
**1.286q**, $R^3$ = 5-Me 80%
**1.286r**, $R^3$= 5-MeO 63%
**1.286s**, $R^3$ = 5-Cl 35%[(a)]
**1.286t**, $R^3$ = 5-$CF_3$ 0%

**1.286u**, $R^1$ = *n*Pr 60%
**1.286v**, $R^1$ = allyl 39%
**1.286a**, $R^1$ = Me 41%

**1.286x**, <10%[(a)]

**1.286y X = O**, 0%
**1.286z X = S**, 0%

*(a) yield estimated by NMR experiment*

**Figure 1.8: S**

**cope of acid-mediated double cyclization**

Firstly, the effect of the substituent ($R^4$) on monoalkylated nitrogen atom was examined. All alkyl substituents are tolerated in oxidative cyclization conditions to afford $N_5$-alkylated quindolinones

**1.286a-e** in moderate to good yields. The outcome is slightly better when bulky substituents were employed. Unfortunately, aryl substituted **1.284f** ($R^4$ = Ph) is not applicable to the double cyclization.

A series of quindolinones **1.286g-m** was synthetized with different substituents ($R^5$) on aromatic ring. In general, substrates with electron donating groups (Me, MeO) resulted in low conversions; therefore, longer reaction time (20-36 hours) was required to obtain significant yield. In other hand, substrates with electron-withdrawing groups (Cl, F) smoothly furnished desired products **1.286i,j,m** after 13 hours in good yields. This observation could be reasoned by the influence of substituents on electron density of triple bond. Particularly, when MeO was introduced at position 5, **1.284l** could dramatically increase the electron density of triple bond *via* conjugating effect, resulting in inactivity of starting material to nucleophilic cyclization; so that very low conversion was observed (after 36 h). In spite of slow reaction, the substrate with MeO at position 4, **1.284h**, could reach to completion after 36 h, and provide **1.286h** in good yield. In this case, MeO would not have significant effect on affinity of alkyne to nucleophilic attack.

Interestingly, the influence of substituents ($R^3$) on another aromatic ring showed totally different observation. Substrates with electron-withdrawing group (Cl, F) generally underwent the double cyclization with low conversions, therefore, resulted in low yield. The dramatical decrease in nucleophilicity of *N,N*-dimethylaniline when electron-withdrawing groups are present could explain to this outcome. Particularly, only 10% of conversion was observed (24 h at 100 ºC) when substrate **1.284t** having a $CF_3$ substituent at position 5 was submitted to standard conditions.

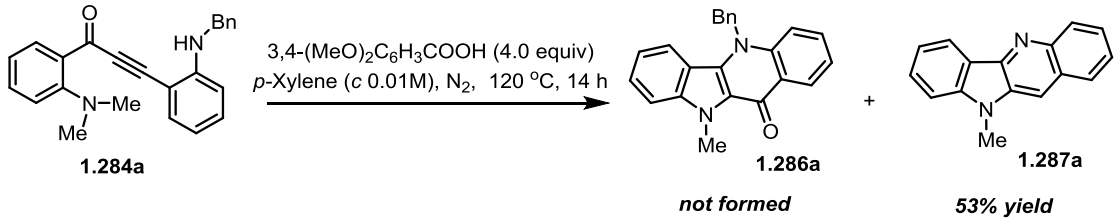
Further exploration the impact of substituents ($R^1$, $R^2$) on dialkylated nitrogen atom was achieved using substrates **1.284u-x**. The success of double cyclization was found to be dependent on the size of alkyl substituents. **1.284u** and **1.284v** were successfully converted into tetracyclic products **1.286u,v** in moderate yields; whereas **1.284x** with sterically hindered alkyl chain demonstrated low activity under the same conditions. Pleasingly, the substrate **1.284w** bearing *N*-methyl-*N*-benzyl moiety exclusively furnished quindolinone **1.286a** in 41% yield, indicating in situ *N*-debenzylation was dominant under these optimized conditions.

Additional attempts to synthesis of benzofuro[3,2-b]quinolinone **1.286y** and benzothieno[3,2-b]quinolinone **1.286z** starting from **1.284y** and **1.284z,** respectively were not successful. Weaker nucleophilicity of OMe, SMe compared to $NMe_2$ could be a reason for their inactivity under our conditions.

### 4.3.4. Mechanistic study

We turned our attention on the reaction mechanism. As mentioned previously, we assumed that the double cyclization of **1.284a** would afford quindolinone **1.286a** and quindoline **1.287a** via oxidation process or nucleophilic substitution respectively of an indoloquinolinium intermediate **1.288a** (see Scheme 1.66). Indeed this proposal was strengthened by successfully guiding the reaction to proceed exclusively via oxidation process when a hydride donor such as Hantzsch ester was employed. To further prove this hypothesis, we decided to control the formation of **1.287a** based on assumption that **1.288a** was a genuine intermediate.

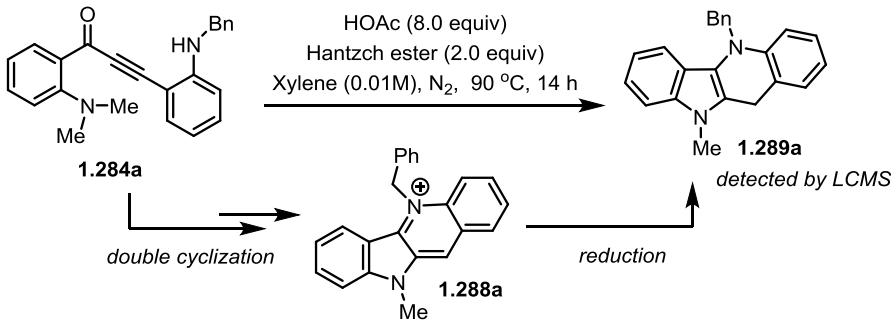
In this context, an oxidation process of **1.288a** should be omitted; so that non-oxidative conditions are highly recommended. Gratefully, simply heating a degassed *p*-xylene solution of **1.284a** (*c* 0.01 M) in the presence of HOAc (4.0 equiv) at 120 °C for 14 h under nitrogen atmosphere, afforded **1.287a** as the sole product in 47% yield. Replacing HOAc by 3,4-dimethoxybenzoic acid, under the same condition, the double cyclization of **1.284a** afforded **1.287a** in 53% isolated yield as the best result (Scheme 1.68).




**Scheme 1.68: Formation of quindoline 1.287a in non-oxidative conditions**

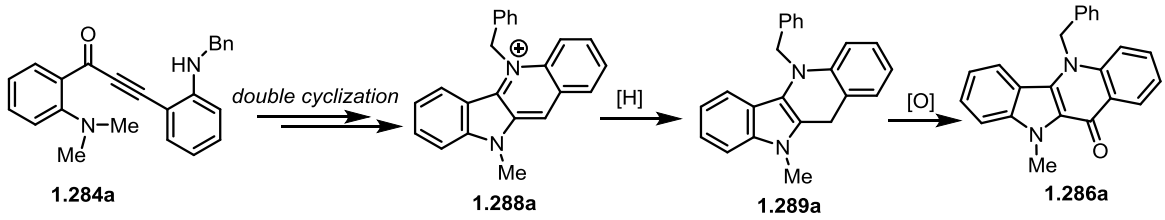
The completely selective formation of quindoline **1.287a** under non-oxidative conditions further bolstered our hypothesis on indoloquinolinium **1.288a** as an intermediate. Additionally, the efficiency of 3,4-dimethoxybenzoic acid over acetic acid and other benzoic derivatives (based on our experimental observation) is in agreement with the postulated nucleophilic substitution of **1.288a** to form **1.287a**.

Moreover, attempt to identify the possible intermediate was implemented by carrying out a double cyclization of **1.284a** in the presence of HOAc (8.0 equiv), Hantzsch ester (2.0 equiv) at 90 °C for 15 h under inert atmosphere. Using LCMS analysis of crude reaction, the mass corresponding to the dihydroindoloquinoline intermediate **1.289a**, a reduced form of **1.288a** was detected, implying again **1.288a** could be an intermediate of the desired product (Scheme 1.69).




**Scheme 1.69: Possible formation of dihydroindoloquinoline 1.289a**

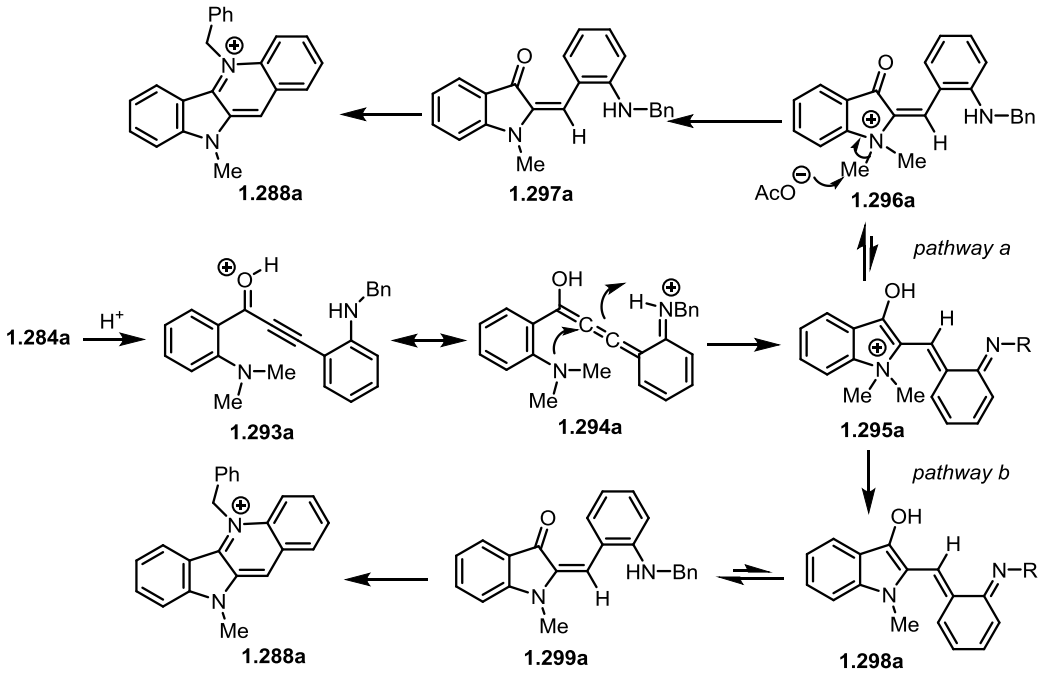
Based on our experimental observation, we proposed that the mechanism of acid-mediated Hantzsch ester-assisted double cyclization of prop-2-yn-1-ones **1.284a** proceeded through two major stages: (1) formation of an indoloquinolinium intermediate **1.288a** by double nucleophilic attack of anilines to triple bond and carbonyl group; (2) sequence of reduction by Hantzsch ester and oxidation by oxygen molecule and HOAc (Scheme 1.70).




**Scheme 1.70: Possible mechanism of acid-mediated Hantzsch ester-assisted double cyclization of 1.284a**

(1) Formation of an indoloquinolinium intermediate **1.288a**

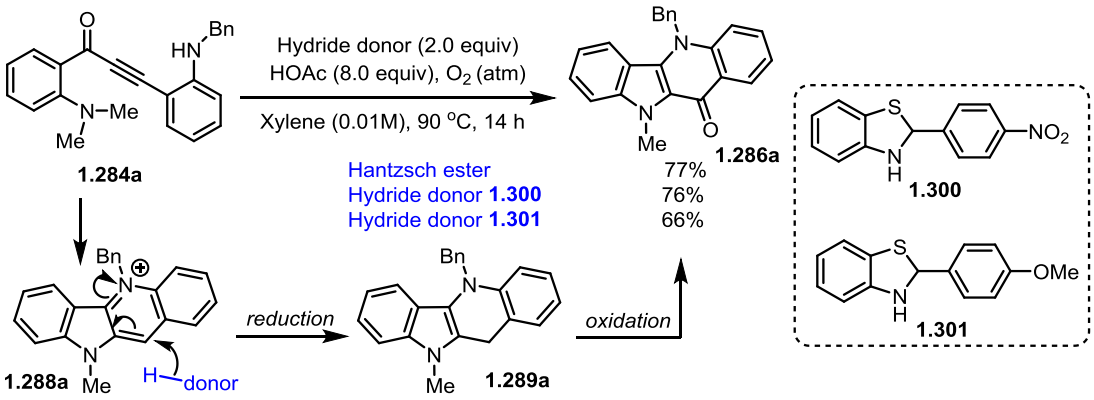
Due to the lack of experimental evidences, we propose herein a possible pathway for formation of intermediate **1.288a** (Scheme 1.71). In the presence of HOAc, prop-2-yn-1-ones **1.284a** could be protonated to form an oxonium intermediate **1.293a**, which would be stabilized by *N*-benzylaniline to provide highly conjugated intermediate **1.294a**. This resulting intermediate would undergo 5-exo-dig cyclization by nucleophilic attack of *N*,*N*-dimethylaniline to allene carbon center, followed by protonation, and tautomerization to give *N*,*N*-dimethyl 3-oxindolium **1.296a**. Subsequent demethylation by nucleophilic attack of acetate anion to methyl group, and a condensation between carbonyl group and aniline would furnish indoloquinolinium intermediate **1.288a** (pathway a). Alternatively, 3-hydroxyindolium **1.295a** would first undergo demethylation to restore the aromatic indole system, followed by tautomerization to give *N*-methyl 3-oxindole intermediate **1.299a**. Finally, **1.288a** could be formed via an intramolecular condensation of **1.299a** (pathway b).




**Scheme 1.71: Possible mechanism for formation of intermediate 1.288a**

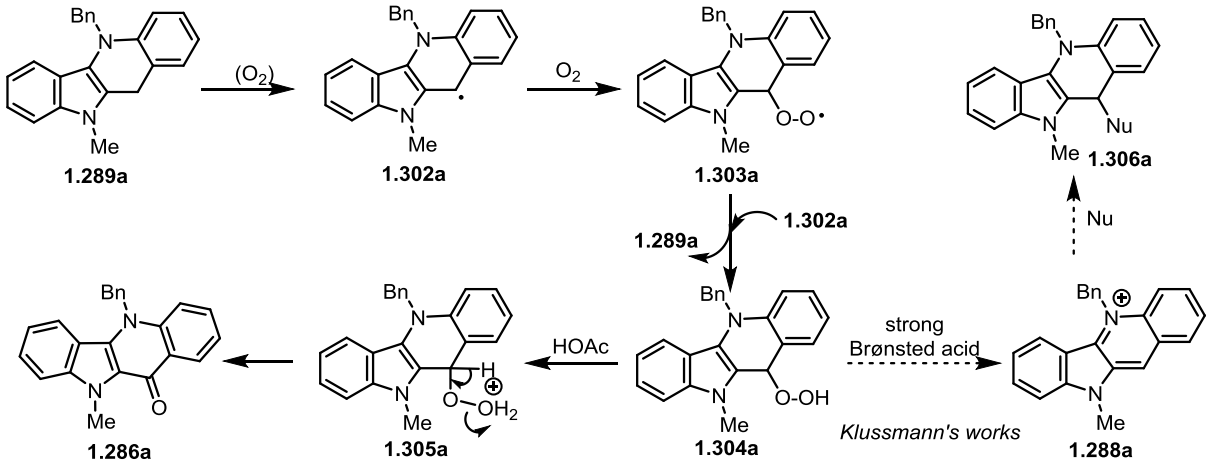
(2) Sequence of reduction by Hantzsch ester and oxidation by oxygen molecule and HOAc

The intermediate **1.288a** would be readily reduced by Hantzsch ester to afford dihydroindolo-quinolinium **1.289a**.[94] A very quick reduction in this case could be a reason for the complete suppression of formation of side product **1.287a**, therefore enhancing the selectivity. To further confirm the role of Hantzsch ester in controlling the selectivity of this transformation, alternative hydride donors such as dihydrobenzothiazoles were examined. Pleasingly, comparable results were obtained when Hantzsch ester was replaced by 2-(4-nitrophenyl)-2,3-dihydrobenzothiazole **1.300** or 2-(4-methoxyphenyl)-2,3-dihydrobenzothiazole **1.301** (Scheme 1.72).




**Scheme 1.72: Alternative hydride donor in double cycliation of 1.284a**

Finally, in the presence of oxygen and HOAc, dihydroindolo-quinolinium **1.289a** would be oxidized to furnish final product **1.296a** (Scheme 1.71). The oxidation of this intermediate could proceed via a benzylic radical **1.302a**, followed by trapping with ground state oxygen to form peroxide radical species **1.303a**. Hydrogen abstraction of **1.303a** from C-H benzylic of **1.289a** would release hydroperoxide **1.304** and regenerate radical species **1.302**. The formation of analogous hydroperoxide has been well-documented by Klussmann and coworkers in Brønsted acid-catalyzed oxidative coupling reactions.[96] However, different from those works, in the presence of milder acid, such as HOAc, hydroperoxide **1.304** would undergo rearrangement to provide desired product **1.286a**.[97] The similar oxidation of acridine derivatives by oxygen molecule was also reported by Pandey et al. using photoredox catalyst as a radical initiator.[98]




**Scheme 1.73: Possible mechanism for oxidation of 1.289a to 1.286a**

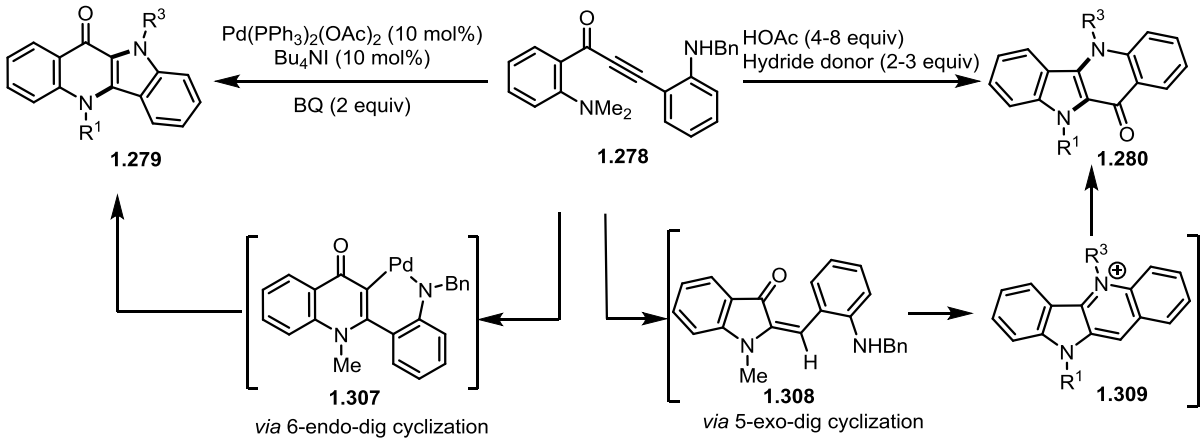
[96] (a) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5004. (b) Pintér, Á.; Klussmann, M. *Adv. Synth. Catal.* **2012**, *354*, 701. (c) Schweitzer-Chaput, B.; Sud, A.; Pintér, Á.; Dehn, S.; Schulze, P.; Klussmann, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 13228.

[97] (a) Kharasch, M.S.; Fono, A.; Nudenberg, W.; Poshkus, A. C. *J. Org. Chem.* **1950**, *15*, 775. For oxidation of acridines in absence of strong Brønsted acid to form ketone see: (b) Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc. Perkin Trans. II* **1989**, 1037.

[98] Pandey, G.; Jadhav, D.; Tiwari, S. K.; Singh, B. *Adv. Synth. Catal.* **2014**, *356* (13), 2813.

## 4.4. Conclusion

In summary, the double cyclization of 1,3-diarylprop-2-yn-1-ones **1.278** bearing *N*,*N*-dialkylated amino and *N*-monoalkylated amino groups at *ortho* positions of aromatic rings has been investigated in two different pathways. In the presence of palladium catalyst, 1,3-diarylprop-2-yn-1-ones underwent 6-endo-dig cyclization to afford indolo[3,2-b]quinolinones **1.279** in moderate yield under oxidative conditions. On the other hand, in the presence of stoichiometric amount of acid such HOAc and hydride donor, it assumedly proceeded via 5-exo-dig cyclization, followed by condensation and oxidation to afford other indolo[3,2-b]quinolinone products **1.280** in good yields (Scheme 1.72).




**Scheme 1.72: Pd-catalyzed and acid-mediated double cyclization of 1,3-diarylprop-1-one-2-ynes**

# PART II

# Copper-Catalyzed Cyanoalkylation of Unactivated Alkenes

# CHAPTER 1

## Introduction

## 1.1. Cyanoalkylation in Catalytic C-C Bond Forming Reactions

Nitriles are important functional group in organic chemistry due to their facile conversion into many other functional groups such as carboxylic acids, esters, amides, amines and ketones.[99] Numbers of nitrile-containing natural products have been found in a variety of plants and animal sources (Figure 2.1). Particularly, they are most commonly present in various glycosides of mandelonitrile which are well-known for causing cyanogenetic toxic (**2.2**, **2.3**).[100] Nitriles are linear, sterically small and metabolically stable functional groups compared to others. Moreover, given the fact that they can act as hydrogen bond acceptors, nitriles are considered as a biosteric functional group to carbonyl in pharmacophore study, and have been employed intensively in medicinal chemistry.[101] Indeed many nitrile-containing compounds have been used as marketed drugs and lead compounds in clinical development (**2.4-2.7**, Figure 2.1).

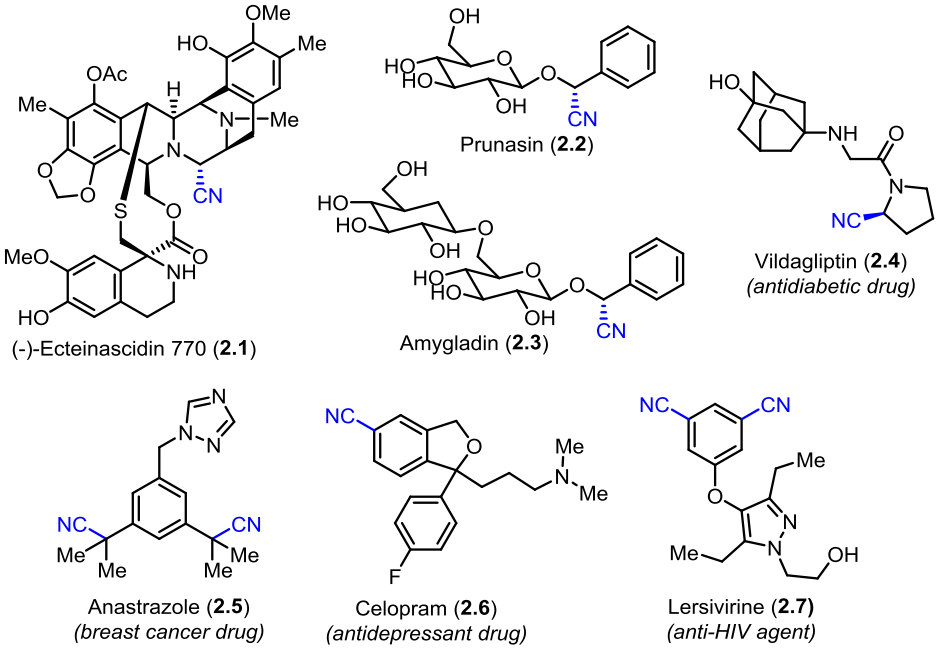



**Figure 2.1: Nitrile-containing natural products and bioactive compounds**

Owing to the synthetic versatility and the potential value in medicinal chemistry of nitriles, plenty of methodologies to this chemical class have been reported. However, development of an efficient, economic and user/environment-friendly synthesis is still a highly attractive topic to organic chemists. Among synthetic approaches to nitriles,[102] catalysed cyanoalkyaltion of organic compounds

[99] Pappoport, Z.; Patai, S. *Chemistry of the Cyano Group*, Wiley & Sons, London, 1970. (b) Fleming, F.F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.
[100] Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189.
[101] Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.
[102] Reviews on nitrile synthesis: (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (c) Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014**, *55*, 1271. (d) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137. (e)

involving introduction of a nitrile moiety via C-C bond-forming reaction from a simple and available alkylnitrile has attracted a great attention.[102f] The utilization of ubiquitous, inexpensive, easy-to-handle alkylnitriles as preinstalled-CN sources to reach highly complex nitriles is economically and practically useful in both chemical and medicinal chemistry. However, different from prefunctionalized substrates such as halonitriles,[103] trimethylsilylacetonitrile,[104] cyanoacetates[105] and cyanomethyltributyltin;[106] direct catalyzed cyanomethylation/cyanoalkylation from unactivated nitriles is more challenging due to the lack of activity of C-H bond at α- position of CN triple bond. In this part of manuscript, we summarized herein the recent advances for activation of alkylnitriles in catalytic C-C bond-forming transformations. Based on the nature of active cyanomethyl intermediate, those reactions can be categorized into two parts as the following.

Bisseret, P.; Duret, G.; Blanchard, N. *Org. Chem. Front.* **2014**, *1*, 825. (f) López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170.

[103] (a) Yang, Y.; Tang, S.; Liu, C.; Zhang, H.; Sun, Z.; Lei, A. *Org. Biomol. Chem.* **2011**, *9*, 5343. (b) Nambo, M.; Yar, M.; Smith, J. D.; Crudden, C. M. *Org. Lett.* **2015**, *17*, 50.

[104] (a) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. (b) Jinzaki, T.; Arakawa, M.; Kinoshita, H.; Ichikawa, J.; Miura, K. *Org. Lett.* **2013**, *15*, 3750.

[105] (a) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912. (b) Shang, R.; Ji, D. S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 4470. (c) (d) Recio, III, A.; Heinzman, J. D.; Tunge, J. a. *Chem. Commun.* **2012**, *48*, 142. (d) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

[106] (a) Kosugi, M.; Kiryu, T. F.; Migita, G. Y.; Sano, H. **1984**, *Chem. Lett.* **1984**, 1511. (b) Kashin, A. N.; Tulchinsky, M. L.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *292*, 205.

### 1.1.1. Cyanoalkyl as Nucleophilic Reagents

α-Cyano carbanions, most commonly generated from deprotonation of alkylnitriles with strong bases such as LiHMDS or LDA, are important synthetic intermediate, particularly for the C-C bond-forming transformations such as alkylation or nucleophilic addition.[107] Due to inductive stabilization of electron-withdrawing nitrile functional group, negative charge is delocalized on either nitrogen atom or adjacent carbon atom. As the result, the nitrile anion species can be divided into *N*-metalated and *C*-metalated either contact or separated ion pair (Figure 2.2). Calculation and NMR experimental analyses revealed that substantial portion of negative charge at α-cyano carbanions is localized on the adjacent carbon atom;[108] resulting in excellent nucleophilic activity of α-cyano carbanions to a wide range of electrophiles.

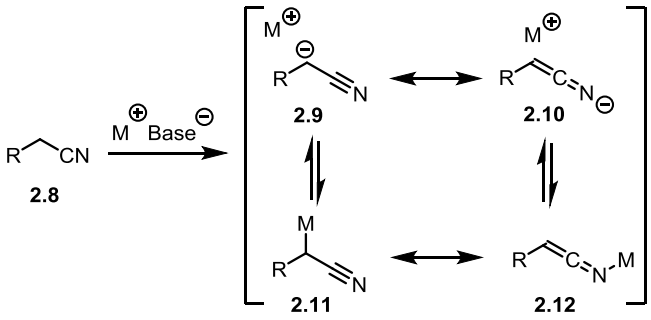
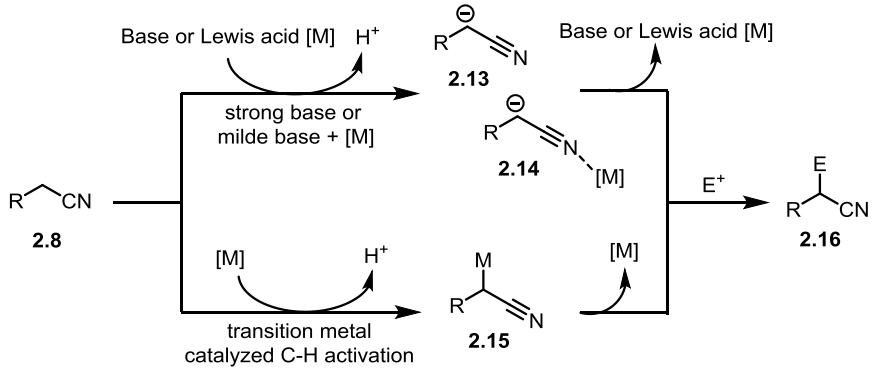



**Figure 2.2: Nitrile-stabilized carbanions**

Although α-cyano carbanions was broadly used in organic chemistry, catalytic activation of nitriles as nucleophiles has been limited to some activated nitriles such as α-cyano esters, malonitriles and α-sulfonyl nitriles ($pK_a$ ~12-13 in DMSO)[109] wherein a mild Brønsted base is enough for deprotonation. In contrast, the in situ generation of carbanions from simple alkylnitriles ($pK_a$ 31.3 in DMSO)[64] requires the utilization of strong bases as mentioned previously, which are usually incompatible with catalytic system or base-sensitive substrates. To overcome the intrinsically low chemoactivity of C-H bond at α-position of simple alkylnitriles, most strategies has focused on the catalytic generation of either nitrile carbanions using appropriate bases or Lewis-acid such as metal salts; or α-cyanoalkyl organometallic intermediate using transition metal catalyst (Scheme 2.1).

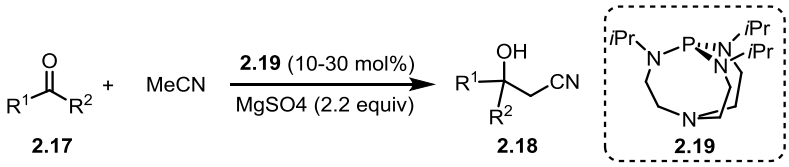
[107] Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* **1984**, *31*, 1.
[108] (a) Bradamante, S.; Pagani, G. A. *J. Chem. Soc. Perkin Trans. II* **1986**, 1035. (b) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327. (c) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (d) Carlier, P. R.; Lo, C. W. S. *J. Am. Chem. Soc.* **2000**, *122*, 12819.
[109] Kumagai, N.; Matsunage, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632.




**Scheme 2.1: General strategy for catalytic C-H activation of alkylnitriles**

### 1.1.1.1. Catalytic base-promoted α-deprotonation

Due to drawback of using strong base in initiating side reactions, there were limited examples for the direct catalytic base-promoted cyanoalkylation in the literature. The first example for this strategy was reported by Verkade and coworkers. The reaction of acetonitrile with ketones or aldehydes **2.17** in the presence of a catalytic amount of strong non-ionic proazaphosphatrane **2.19** ($pK_{aH}$ ~34 in MeCN)[110] and $MgSO_4$ afforded β-hydroxyl nitriles **2.18** in good to excellent yields (Scheme 2.2).[111] In this case, proazaphosphatrane **2.19** was found to be compatible with catalytic generation of cyanomethyl anion without triggering base-sensitive dehydration of **2.18**, whereas $MgSO_4$ was used to activate carbonyl for nucleophilic addition.



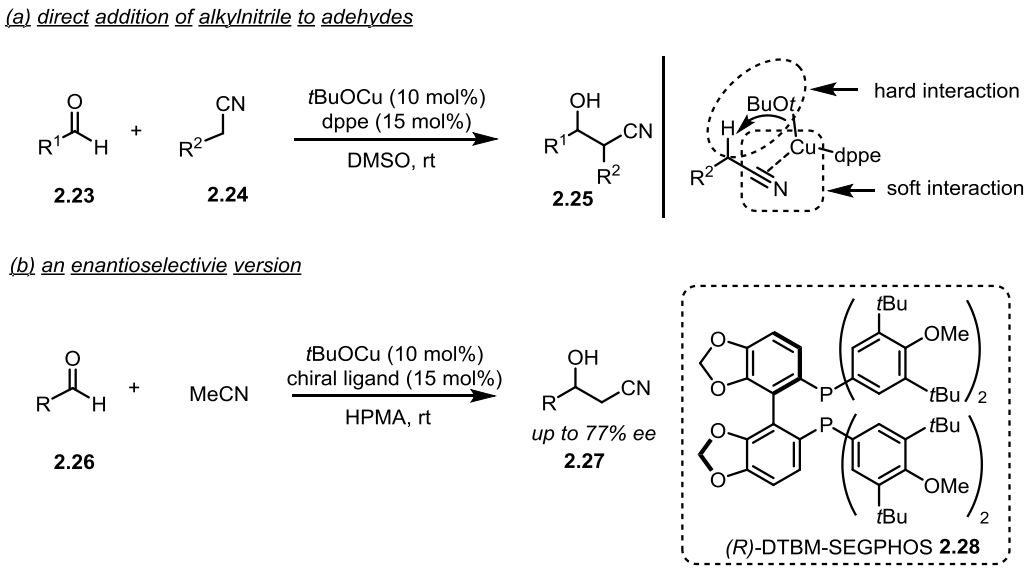

**Scheme 2.2: Proazaphosphatrane-catalyzed synthesis of β-hydroxyl nitriles**

Another example for base-promoted α-deprotonation in cyanoalkylation was reported by Knochel using strong base *t*BuOK ($pK_{aH}$ ~32.2 in DMSO)[112] as a catalyst for addition of nitriles **2.20** to moderately active Michael acceptors such as vinylic silanes, phosphines and thio derivatives **2.21a-c** (Scheme 2.3).[113]


**Scheme 2.3: *t*BuOK-catalyzed cyanoalkylation by Knochel**

[110] Ishikawa, T. *Superbases for Organic Synthesis*, John Wiley & Sons, UK, **2009**.
[111] Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.
[112] Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295.
[113] Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, *8*, 745.

An alternative strategy for α-deprotonation of nitriles was based on the utilization of Lewis-acid such as metal sources to lower the $pK_a$ value of the alkylnitriles through their coordination with nitrogen atom. As the result, a mild base was sufficient for deprotonation to generate nitrile carbanions. Pioneered on this synthetic approach, Shibasaki reported an efficient catalytic direct addition of alkylnitriles **2.24** to aldehydes **2.23** using *t*BuOCu-dppe as a catalyst (Scheme 2.4-a).[114a] The working hypothesis of this reaction was based on the soft interaction between copper center and CN triple bond, facilitating the deprotonation of nitriles by alkoxide via hard interaction. An enantioselective version was later succeeded using combination of *t*BuOCu and chiral phosphines such as (R)-DTBM-SEGPHOS (**2.28**), affording β-hydroxyl nitriles **2.27** in good yields, albeit in moderate enantioselectivity (Scheme 2.4-b).[114b]

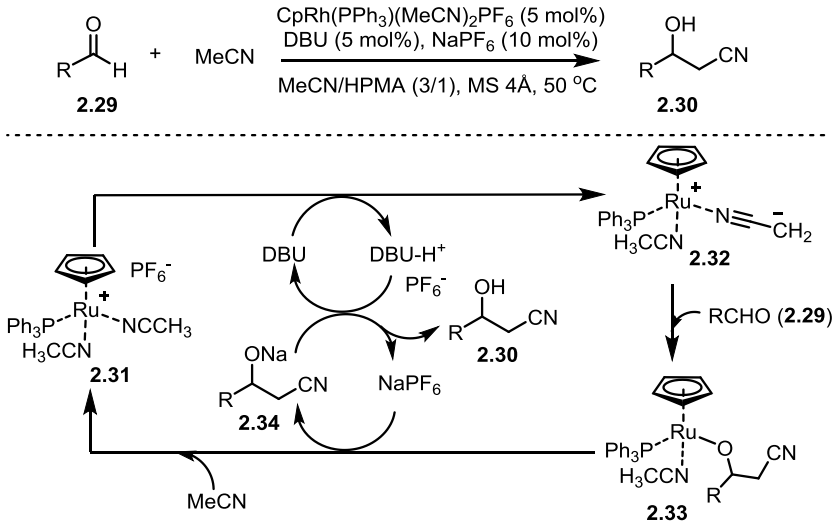



**Scheme 2.4: *t*BuOCu-catalyzed cyanoalkylation of aldehydes by Shibasaki**

Complementary to above work, Shibasaki and coworkers also discovered that cationic ruthenium complexes were also suitable for the catalytic direct cyanomethylation. Cooperative catalytic system of a cationic ruthenium complex, DBU and $NaPF_6$ enabled the activation of acetonitrile as a nucleophile in the reaction with aldehydes **2.29** to afford β-hydroxyl nitriles **2.30** in good to excellent yields (Scheme 2.5).[115] Based on NMR spectroscopy, ESI-MS and kinetic evidences, this aldol-type reaction could proceed through the following steps: (1) formation of ruthenium complex **2.31** through dominant coordination between soft Lewis acid ruthenium and acetonitrile, promoting the deprotonation; (2) deprotonation of acetonitrile by DBU to form metalated nitrile **2.32**; (3) 1,2-insertion of metalated nitrile **2.32** to aldehyde **2.29** to provide alkoxylated ruthenium complex **2.33**; (4) conversion of **2.33** into **2.31** with concomitant release of 3-Na alkoxide nitrile **2.34** which is

[114] (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757.
[115] Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632.

accelerated by $NaPF_6$ via hard interaction between Na cation and alkoxide; (5) protonation of alkoxide **2.34** by DBU-$H^+$ to afford desired product **2.30** and concurrently regenerate both DBU and $NaPF_6$ to close the catalytic cycles.

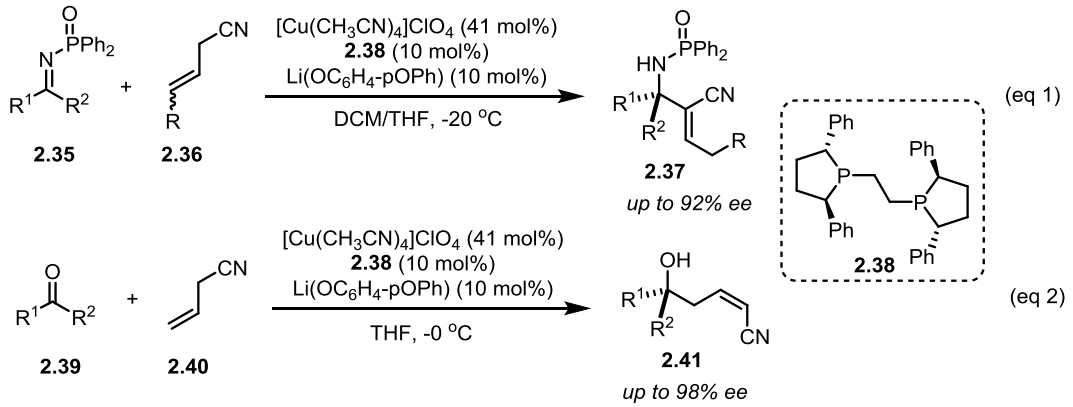



**Scheme 2.5: Ruthenium-catalyzed cyanoalkylation of aldehydes by Shibasaki**

Alternative direct activation of alkylnitriles as nucleophiles in the reaction with aldehydes using different metal complexes such as nickel,[116] palladium[117] was also exploited.

Analogously, less active imines were found to be applicable in Mannich-type reaction with nitriles in the presence of a catalytic amount of Lewis acidic metals to afford corresponding 3-aminonitriles.[114,118] However, in these cases, more active nitriles such as allylic or benzylic cyanides were employed to compensate the activity of imines. Indeed, asymmetric Mannich-type reaction between *N*-diphenylphosphinoylimines **2.35** and allylic cyanides **2.36** in the presence of a copper(I) salt, chiral bidentate phosphine **2.38** and Li($OC_6H_4$-*p*-OPh) was reported by Shibasaki to afford α,β-unsaturated nitriles **2.37**, resulting from nucleophilic addition and isomerization of double bond (eq 1, Scheme 2.6).[118a] Surprisingly, when the same catalytic system was employed in Aldol-type reaction between ketones **2.39** and allylic cyanides **2.40**, δ-hydroxynitriles **2.41**, resulted from γ-addition, were obtained with complete regio-, stereoselectivity and excellent enantioselectivity (eq 2, Scheme 2.6).[119]

[116] Fan, L.; Ozerov, O. V. *Chem Commun* **2005**, *35*, 4450.
[117] Aydin, J.; Conrad, C. S.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 5175.
[118] (a) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195. (c) Hyodo, K.; Nakamura, S.; Tsuji, K.; Ogawa, T.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3385. (d) Hyodo, K.; Nakamura, S.; Shibata, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10337.
[119] Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195.



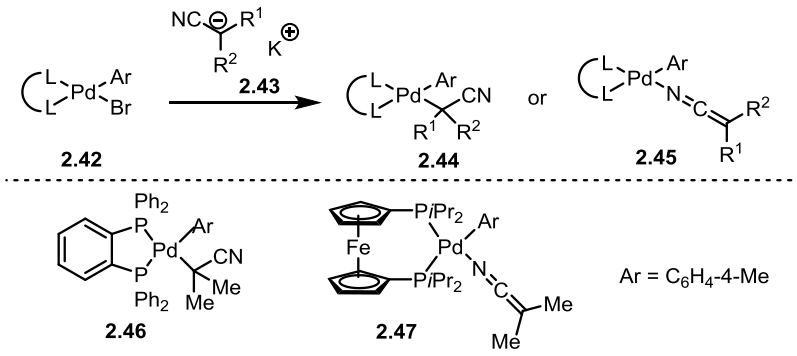

**Scheme 2.6: Asymmetric copper-catalyzed cyanoalkylation of imines/ketones by Shibasaki**

### 1.1.1.2. Catalytic generation of metalated alkylnitriles

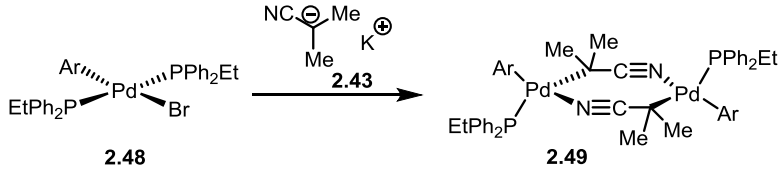
The second strategy for catalytic C-C bond-forming transformation via direct activation of alkylnitriles could be accomplished by transition metal catalysis. Prior to this approach, transition metal-catalyzed methods for the direct coupling of ketone enolates and their derivatives were intensively studied.[120] However, nitriles are less acidic than ketones, but a cyano group is more electron-withdrawing than an acyl group, leading to unpredictable effects during catalysis of alkylnitriles. Moreover, as discussed previously, there are several possible bonding modes of metalated nitriles: nitrile carbanion can coordinate to a metal center through either α-carbon atom (*C*-metalated nitriles) or nitrogen atom (*N*-metalated nitriles). In the context of current topic, the generation of C-metalated nitriles **2.15** might be the crucial step (Scheme 2.1), which is followed by trapping with appropriate electrophile (through reductive elimination or insertion) to furnish C-C bond.

Pioneered in this topic, Hartwig and coworkers implemented an insightful investigation on the structures of arylpalladium cyanoalkyl complexes.[121] Numbers of these complexes was synthetized and characterized by combining NMR, IR spectroscopy techniques with X-ray crystallography. Experimental observation showed that the preferred binding mode for cyanoalkyl group was through α-carbon atom which is in agreement with soft attribution of palladium. For examples, complex **2.46** chelated by 1,2-bis(diphenylphosphino)benzene (DPPBz), was shown to be C-bound by isobutyronitrile (Scheme 2.7). In case of larger and more donating ligands (for example, diisopropylphosphinoferrocene; D*i*PPF), the sterically hindered nitrile carbanion coordinates with palladium center through nitrogen atom (complex **2.47**, Scheme 2.7). Additionally, when a labile ligand was present, the phosphine was displaced by the nitrogen atom and a bridging $\mu^2$-C,N cyanoalkyl complex was formed (complex **2.49**, Scheme 2.8).

[120] (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676.
[121] Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.

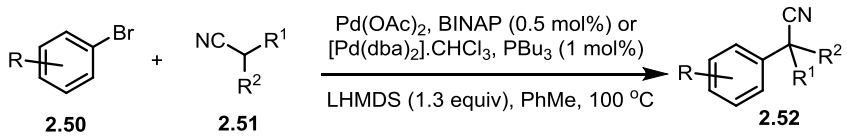



**Scheme 2.7: Synthesis and structures of arylpalladium cyanoalkyl complexes**



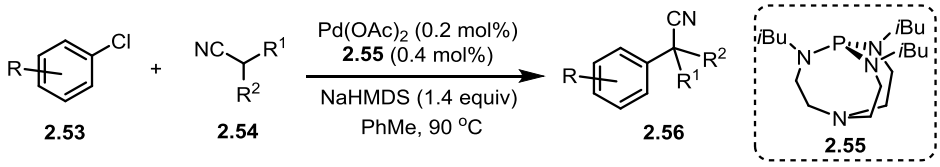

**Scheme 2.8: Formation of $\mu^2$-C,N cyanoalkyl complex**

Based on above results and additional study on reductive elimination of *C*-metalated cyanoalkyl complexes, the catalyzed direct coupling of aryl bromides and alkylnitriles was achieved in the presence of LHMDS, either combined catalytic system of [$Pd(OAc)_2$ and BINAP] or [$Pd_2(dba)_3$ and $PBu_3$] to afford α-arylnitriles in good to excellent yields (Scheme 2.9).




**Scheme 2.9: Palladium-catalyzed α-arylation of nitriles by Hartwig**

As an improvement of Hartwig's work, Verkade reported a useful method for the direct α-arylation of nitriles using combination of $Pd(OAc)_2$ and commercially available proazaphosphatrane **2.55** as the ligand (Scheme 2.10).[122] This condition allowed aryl chlorides which are generally inert to oxidative addition, to participate in the coupling to provide desired product in good yields.

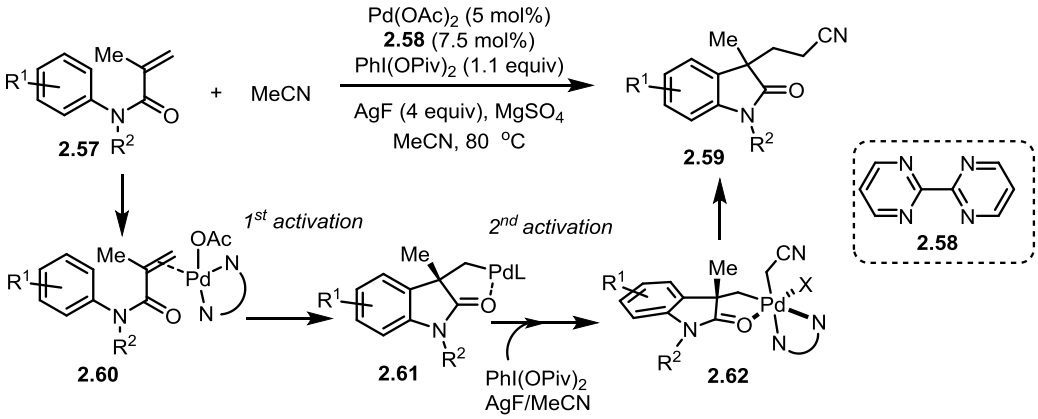



**Scheme 2.10: Palladium-catalyzed α-arylation of nitriles by Verkade**

Liu and coworkers reported a palladium-catalyzed oxidative arylalkylation of activated alkenes for synthesis of cyano-bearing oxindoles involving dual C-H activation of both aniline and acetonitrile

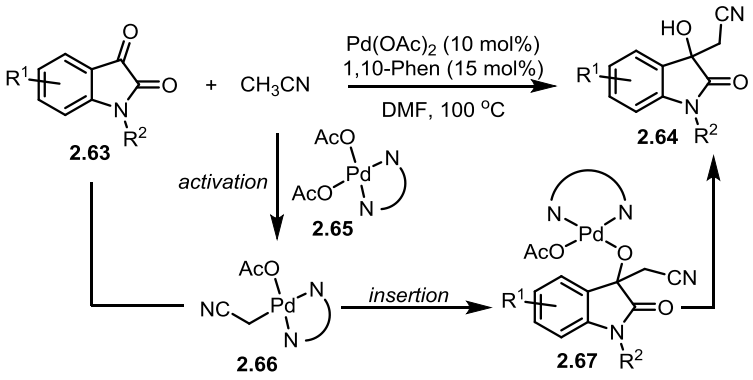
[122] You, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5051.

using $PhI(OPiv)_2$ and AgF as co-promoters (Scheme 2.11).[123] The reaction could be initiated by coordination of the olefin to palladium catalyst, followed by first C-H activation of aniline to form palladium complex **2.61**. The second C-H activation of acetonitrile could take place in the presence of $PhI(OPiv)_2$/AgF, thus generating Pd(IV) complex **2.62** which would undergo reductive elimination to afford cyano-bearing oxindoles **2.59** as final product. Primary mechanistic studies showed that C-H activation of nitrile was the rate determining step.




**Scheme 2.11: Palladium-catalyzed oxidative arylalkylation by Liu**

Palladium-catalyzed C-H activation of acetonitrile in the reaction with isatins **2.63** was reported by Yang to afford Aldol-type products **2.64** in good to excellent yields (Scheme 2.12).[124] Although no experimental evidences for its mechanism, the reaction was proposed to proceed through an activation of acetonitrile by palladium complex **2.65** to form α-cyanomethyl palladium complex **2.66** that could undergo insertion to carbonyl of isatins to furnish 3-hydroxyloxindole products.

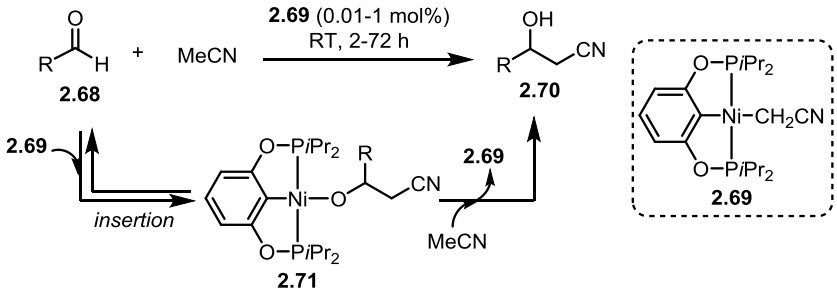



**Scheme 2.12: Palladium-catalyzed cyanomethylation of isatins by Wang**

Alternative to above work, an Aldol-type reaction was reported by Guan using a highly active nickel pincer complex **2.69** as a catalyst (Scheme 2.13).[125] Mechanistic studies indicated that the

[123] Wu, T.; Mu, X.; Liu, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 12578.
[124] Wang, G.; Zhou, A.; Wang, J.; Hu, R.; Yang, S-D. *Org. Lett.* **2013**, *15*, 5270.
[125] Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7523.

reaction was initiated by reversible 1,2-insertion of *N*-metalated acetonitrile to aldehydes, followed by an activation of acetonitrile by the resulting alkoxylated nickel complex **2.71** to release 3-hydroxylnitrile **2.70** in good yield with concurrent regeneration of the catalyst **2.69**. Different from base-promoted Lewis-acidic metal assisted α-deprotonation, no evidence of *N*-metalated acetonitrile involving catalytic cycles was observed.




**Scheme 2.13: Nickel-catalyzed cyanomethylation of aldehydes by Wang**

Similar aldol-type reactions between aldehydes and alkylnitriles were reported using efficient catalytic system of $[Rh(OMe)(cod)]_2$ with either $PPh_3$[126] or NHC ligands.[127] However, mechanism for C-H activation of alkylnitriles was not described in those works.

[126] (a) Goto, A.; Endo, K.; Saito, S. *Chem. Comn.* **2008**, 2212. (b) Goto, A.; Naka, H.; Noyori, R.; Saito, S. *Chem. Asian J.* **2011**, *6*, 1740.
[127] Sureshkumar, D.; Ganesh, V.; Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2014**, *20*, 15723.

### 1.1.2. Cyanoalkyl as Electrophilic Radical Reagents

An alternative method for direct activation of alkylnitriles could be achieved through homolytic cleavage α-C-H bond to generate cyanoalkyl radicals which would be ready to undergo various free radical processes to form C-C bond. Considering bond-dissociation energy (BDE)[128] of the C-H bond, the homolytic cleavage of α-C-H bond of alkylnitriles should be more favourable compared to other C($sp_3$)-H bonds (Figure 2.3). Moreover, due to electro-withdrawing cyano group, radical center on adjacent carbon atom can be stabilized. As the result, selective activation of alkylnitriles to generate electrophilic cyanoalkyl radicals is practically feasible. Owing to high bond-dissociation energy, homolytic cleavage of α-C-H bond of alkylnitriles is nevertheless challenging, thus normally requiring normally hash conditions to generate cyanoalkyl radical.

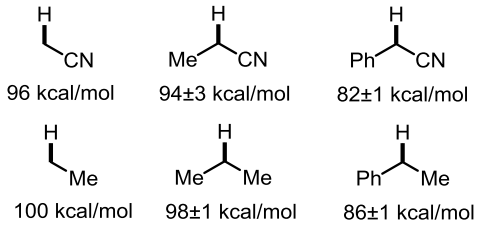


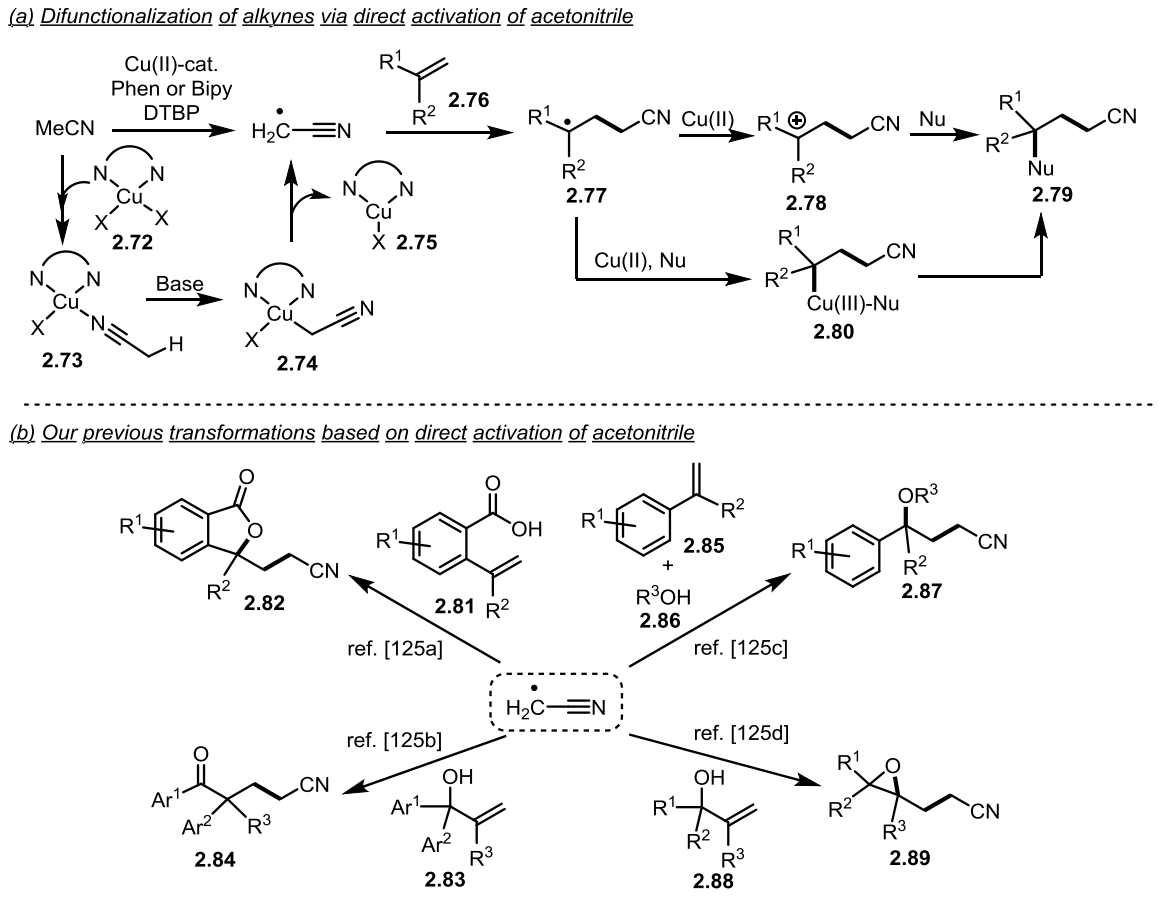

**Figure 2.3: Comparison of BDE of C-H bond in nitriles and alkanes**

Recently, our group have developed an efficient method to activate alkylnitriles using catalytic system of Cu(II)/DTBP. Cyanoalkyl radicals generated in situ from alkylnitriles in the presence of Cu(II) salt, phenanthroline or bipyridine derivative and DTBP, participated in the addition to unactivated alkenes **2.76**, followed by trapping the resulting radical intermediates **2.77** with appropriate partners to complete the difunctionalization of alkenes (Scheme 2.14).[129] Although peroxide itself can abstract proton of alkylnitriles to afford cyanoalkylradical, the formation of desired products were still observed in the absence of DTBP, indicating that copper(II) salts indeed played an important role for generation of cyanomethyl radical. The mechanism was proposed to proceed through a sequence of *N*-activation of nitrile by Cu(II)/*N*,*N*-ligand complex **2.72** and deprotonation to give *C*-chelated nitrile intermediate **2.74**. The resulting copper(II) cyanoalkylnitrile intermediate **2.74** could be spontaneously decomposed to provide cyanomethyl radical and corresponding copper(I) complex **2.75**. Furthermore, copper(II) could participate in a SET process to oxidize radical species **2.77** to the corresponding carbenium **2.78** which was subsequently trapped by suitable nucleophile to form desired product **2.79**. Alternatively, formation of C-Nu bond could result from an reductive

[128] Luo, Y.-R. *Handbook of Bond Dissociation Energy in Organic Compound*, CRC Press, Boca Raton, **2002**
[129] (a) Bunescu, A.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2014**, *20*, 14633. (b) Bunescu, A.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 3132. (c) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5443. (d) Bunescu, A.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1890.

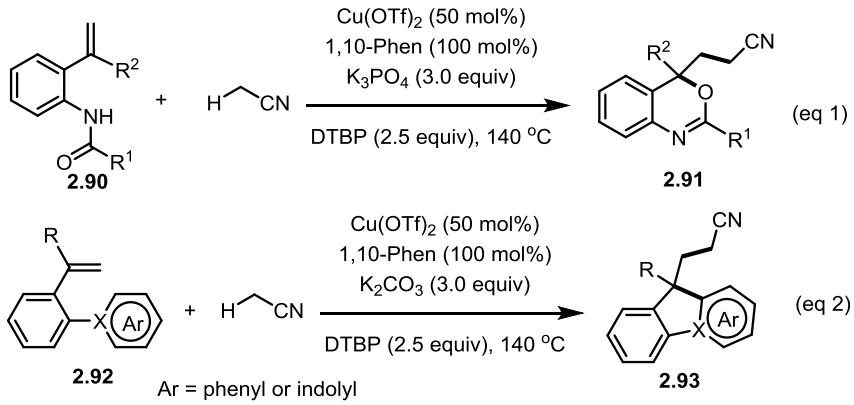
elimination of Cu(III) intermediate **2.80** which was generated by radical recombination of **2.77** and Cu(II) species (Scheme 2.14-a).

Taking advantage of this direct activation of nitriles via the formation of cyanomethyl radical, several copper(II)-catalyzed cyanomethylation of unactivated alkenes were successfully developed by our group, which can be summarized in Scheme 2.14-b. The combination of Cu(II), *N*,*N*-ligand and DTBP was later applied to the synthesis of nitrile-containing heterocycles such as benzoxazines (eq 1, Scheme 2.15),[130] fluorenes[131] and pyrroloindoles (eq 2, Scheme 2.15)[131] by Xu and Ji.



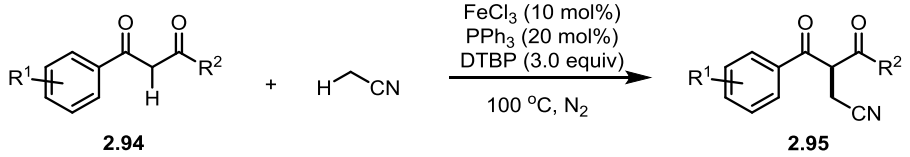

**Scheme 2.14: Copper-catalyzed cyanomethylation by Zhu**

[130] Chu, X.-Q.; Xu, X.-P.; Meng, H.; Ji, S.-J. *RSC Adv.* **2015**, *5*, 67829.
[131] Chu, X.; Xing, Z.; Meng, H.; Xu, X.; Ji, S. *Org. Chem. Front.* **2016**, *3*, 165.




**Scheme 2.15: Copper-catalyzed cyanomethylation by Xu and Ji**

A direct activation of acetonitrile in cross-dehydrogenative-coupling (CDC) reaction between 1,3-dicarbonyls and acetonitrile using Fe(III)/DTBP systems was recently reported by Kim and Wu (Scheme 2.16).[132] A radical mechanism was also proposed based on the experimental observation of cyanomethyl radical formation.

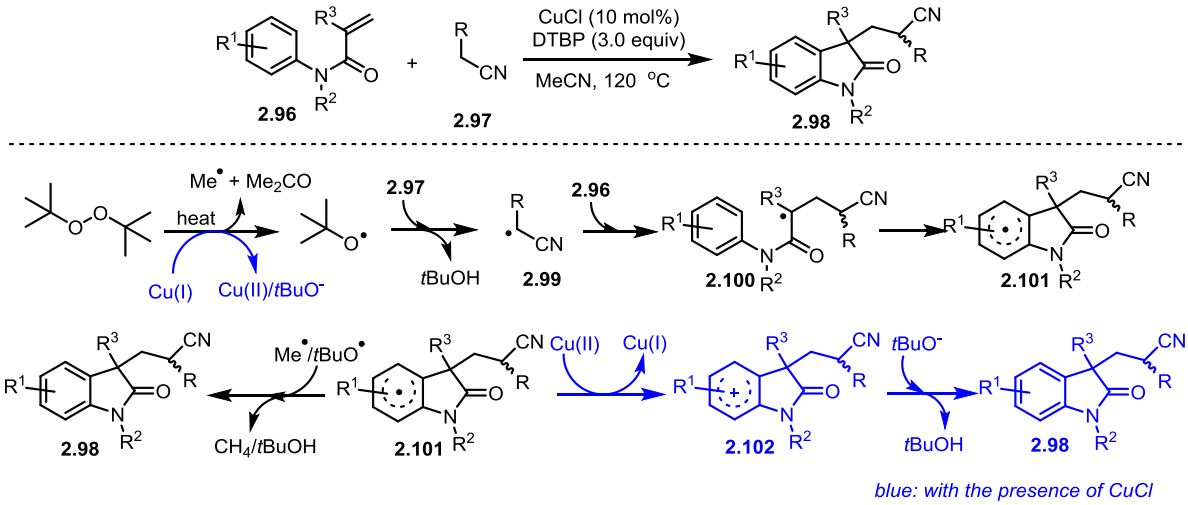



**Scheme 2.16: Iron-catalyzed CDC reaction of 1,3-dicarbonyls and acetonitrile by Kim and Wu**

The simple strategy for the generation of cyanoalkyl radical is hydrogen abstraction of nitriles with a highly active radical species. Regarding to this approach, Gao and You reported a successful activation of alkylnitriles **2.97** by *t*BuO• species derived from di-*tert*-butylperoxide (DTBP). The resulting cyanoalkyl radical **2.99** was applied to a cascade involving alkene addition and cyclization to access oxindole **2.98** (Scheme 2.17).[133] Without the presence of metal salts, the domino process still afforded desired product, albeit in modest yields; a catalytic amount of CuCl (10 mol%) was proven to be important to the efficiency of the transformation. The role of CuCl could be explained by its contribution in Cu(I)/Cu(II) cycle in which Cu(I) facilitates the decomposition of DTBP to provide *t*BuO• species, whereas Cu(II) oxidizes cyclic radical intermediate **2.101** via SET process, followed by deprotonation to restore aromaticity.

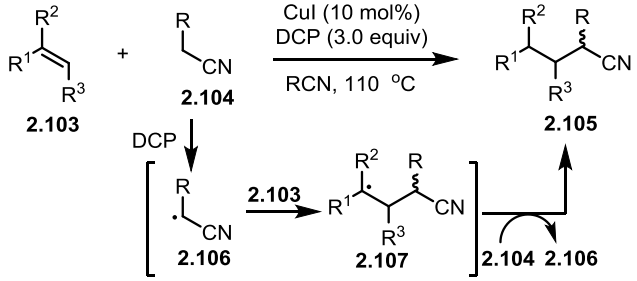
A wide range of alkylnitriles was found to be compatible to catalytic system, including benzyl cyanide and malononitrile. Interestingly, combined system of CuI/DTBP was also applicable for activation of nitroalkanes in the similar transformation.

[132] Wang, C.; Li, Y.; Gong, M.; Wu, Q.; Zhang, J.; Kim, J. K.; Huang, M.; Wu, Y. *Org. Lett.* **2016**, *18*, 4151.
[133] Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. *Chem. Commun.* **2014**, *50*, 15049.




**Scheme 2.17: Copper-catalyzed radical cascade cyanomethylation by Gao and You**

The catalytic system of Cu(I)/peroxide was later exploited by Liu and coworkers in hydrocyanoalkylation of unactivated alkenes with alkylnitriles (Scheme 2.18).[134] The activation of α-C-H bond was succeeded in the presence of CuI (10 mol%) and dicumylperoxide (DCP). Again, a catalytic amount of copper salts is not crucial for the success of this transformation but essential for better outcome. A wide range of disubstituted alkenes with various functional groups was applicable to this hydrocyanoalkylation; but trisubstituted substrates were significantly less active.

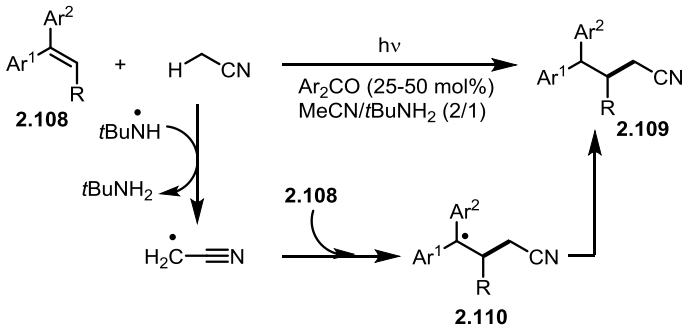



**Scheme 2.18: Copper-catalyzed hydrocyanoalkylation by Liu**

Apart from peroxide chemistry, cyanoalkyl radical was found to be accessible by photomediated transformations. Yamashita and Yasuda reported an hydrocyanomethylation of olefins in the presence of benzophenone derivatives (25-50 mol%) as photosensitizers and *t*BuNH$_2$ under irradiation by mercury lamp (Scheme 2.19).[135] The reaction was proposed to proceed through: (1) the formation of *t*BuNH• from the interaction between excited Ar$_2$CO and *t*BuNH$_2$; (2) hydrogen abstraction of acetonitrile by *t*BuNH• to generate cyanomethyl radical; (3) radical addition to olefins, followed by another hydrogen abstraction to afford hydrocyanomethylated product. However, this cyanomethylation was limited to 1,2-diarylethylenes; other substrates such as simple styrenes were

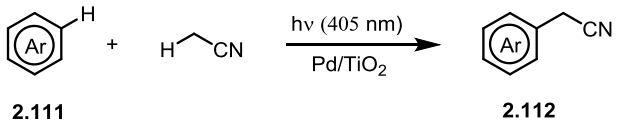
[134] Li, Z.; Xiao, Y.; Liu, Z.-Q. *Chem. Commun.* **2015**, *51*, 9969.
[135] Yamashita, T.; Yasuda, M.; Watanabe, M.; Kojima, R.; Tanabe, K.; Shima, K. *J. Org. Chem.* **1996**, *61*, 6438.

found to be incompatible. Interestingly, the combination of benzophenone derivatives and *t*BuNH$_2$ was applicable for the direct α-C-H bond activation of ketones, esters, amides and sulfoxides in the similar transformations.[136]




**Scheme 2.19: Photosensitized hydrocyanomethylation of alkenes by Yamashita and Yasuda**

Recently, Yoshida and coworkers developed an interesting CDC reaction between an aromatic ring and acetonitrile using heterogeneous palladium catalyst hybridized with a titanium dioxide photocatalyst (Scheme 2.20).[137] The experimental observations clarified the formation of cyanomethyl radical in the presence of hybrid catalyst upon irradiation. Although desired products were obtained in synthetically insignificant yields, the improvement in this direct C-C bond forming transformation is promising for wide application.




**2.111** **2.112**

**Scheme 2.20: Photocatalyzed CDC reaction of aromatic ring and acetonitrile by Yoshida**

[136] Yamashita, T.; Watanabe, M.; Kojima, R.; Shiragami, T.; Shima, K.; Yasuda, M. *J. Photochem. Photobiol. A: Chem.* **1998**, *118*, 165.
[137] Yoshida, H.; Fujimura, Y.; Yuzawa, H.; Kumagai, J.; Yoshida, T. *Chem Commun* **2013**, *49*, 3793.

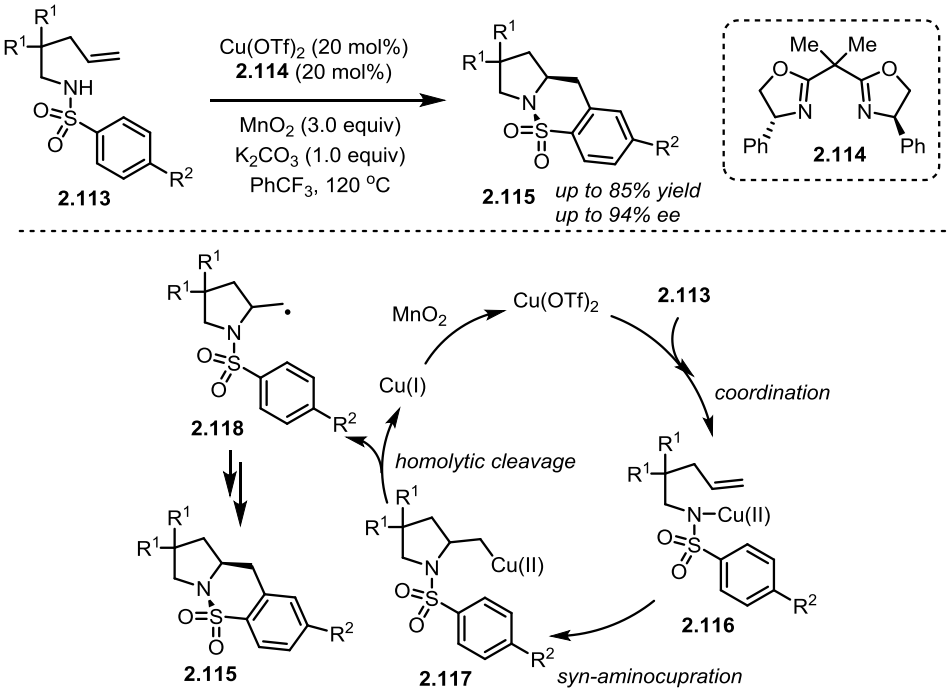
## 1.2. Copper-Catalyzed Carbo-oxygenation/amination of Alkenes

The difunctionalization of alkenes represents a domain of main interest in organic synthesis.[5,6] Recently, numbers of transition-metal-catalyzed difucntionalization of alkenes, particularly palladium-catalyzed transformations,[7] have been reported, providing attractive strategies for the assembly of functionalized organic compounds. Given the fact that carbon-carbon bond formation is a fundamental transformation in organic chemistry, palladium-catalyed carbo-oxygenation or carbo-amination of alkenes has flourished immensely for last decade. However, due to susceptibility for β-hydride elimination of alkylpalladium intermediate, those reactions are sometimes challenging (see part I, chapter 1.2.1). Development of alternative metal-catalyzed carbo-oxygenation or carbo-amination, therefore, has been of great interest.

Copper catalysts, inexpensive and abundant transition metal resources, represent multiple properties in chemical transformations, such as Lewis acid, π-acid, a single-electron mediator and a two-electron mediator.[5g-i] As a result, copper-catalyzed transformation becomes a powerful tool to difunctionalize C-C multiple bonds, especially in carbo-oxygenation and carbo-amination. As related to our research topics, herein we would like introduce some examples in the literature on carbo-oxygenation and carbo-amination of alkynes using copper catalysis. Owing to versatile reactivity of copper complexes, those transformations will be categorized based on mechanism of the first bond-formation step, including: copper-catalyzed difunctionalization via nucleocupration, via electrophilic activation and via radical addition.

### 1.2.1. Copper-Catalyzed Carbo-oxygenation/amination of Alkenes via Nucleocupration

Similar to palladium-catalyzed transformations, copper-catalyzed carbo-oxygenation/amination could be initiated by nucleocupration through nucleophilic attack of oxygen/nitrogen atom to double bonds to form alkylcopper intermediates. However, the resulting organocopper intermediates could act as either nucleophiles or radical precursors. Pioneered in this approach, Chemler has contributed many important works in the field of difunctionalization of alkenes, particularly in copper-catalyzed asymmetric version.[5g] For instance, enantioselective $Cu(OTf)_2$-catalyzed intramolecular oxidative carboamination of alkenylsulfonamides **2.113** was successfully developed to access polycyclic sultams **2.115** in good yields and enantioselectivities (Scheme 2.21).[138] The process is composed of a multi-step sequence involving: (1) *syn*-aminocupration of alkenes to form five-membered organocopper(II) intermediate **2.117**; (2) homolytic cleavage C-Cu(II) bond to generate Cu(I) species and radical species **2.118** which could be trapped by the tethered aromatic group; (3) oxidation of Cu(I) species by $MnO_2$ to regenerate the active Cu(II) catalyst.

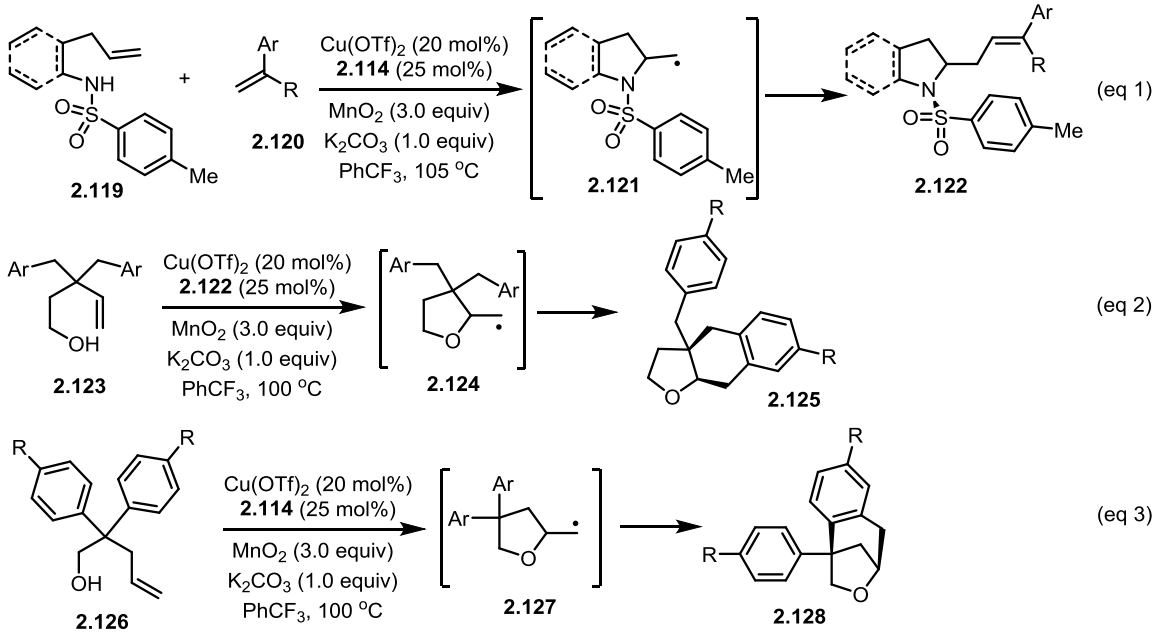



**Scheme 2.21: Enantioselective Cu-catalyzed intramolecular carboamination of alkenes by Chemler**

Copper-catalyzed intermolecular oxidative carboamination of alkenylsulfonamide was further exploited by trapping the putative radical intermediate **2.121** by olefins to provide alkyl Heck-type product **2.122** (eq 1, Scheme 2.22).[139] Lately, copper-catalyzed intramolecular carbooxygenation of 4-

[138] Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948.
[139] Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020.

pentenols **2.123**, **2.126** initiated by oxocupration was described for the construction of fused and bridged-ring tetrahydrofurans **2.125**, **2.128** (eq 2 and eq 3, Scheme 2.22).[140]



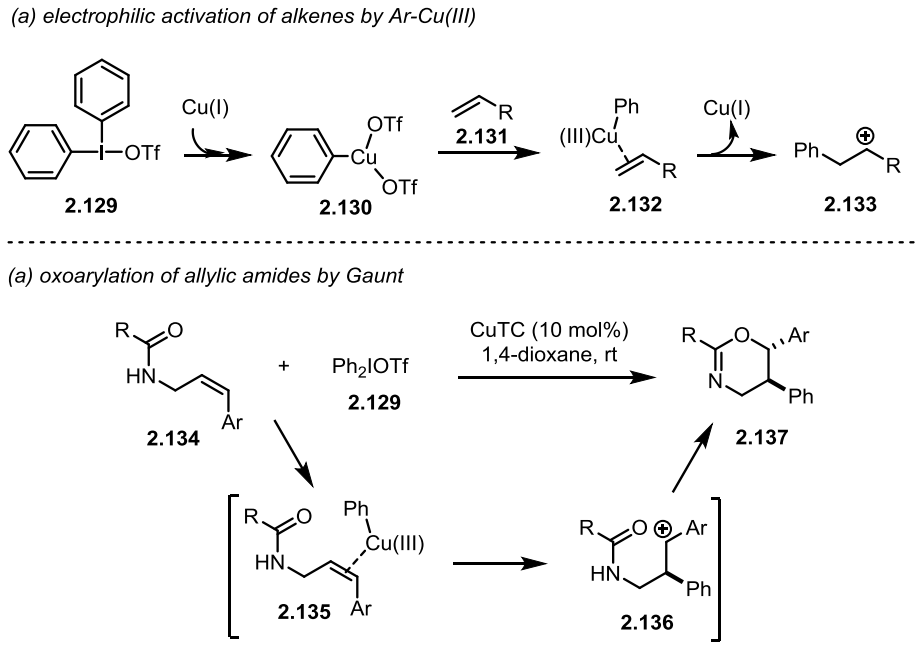

**Scheme 2.22: Chemler's copper-catalyzed carboamination/carbooxygenation of alkenes**

## 1.2.2. Copper-Catalyzed Carbo-oxygenation/amination of Alkenes via Electrophilic Activation

The combination of Cu(I) complexes with diaryliodonium salts results in formation of aryl-Cu(III) species that could be used for electrophilic activation of alkenes to induce their carbo-functionalization. In contrast to nucleocupration, those high oxidation state aryl-Cu(III) species acted as electrophiles, whereas alkenes acted as nucleophiles (Scheme 2.23-a). This C-C bond-forming strategy was demonstrated mainly by Gaunt and coworkers.[141] For examples, in the presence of copper thiophenecarboxylate catalyst, allylic amides **2.134** underwent oxoarylation with diaryliodonium **2.129** to afford oxazine products **2.137** in high yields and excellent diastereoselectivity (Scheme 2.23-b).[142] The reaction was proposed to proceed through an activation of alkenes by organocopper(III) species **2.130**, followed by an nucleophilic attack of alkenes to electrophilic aromatic ring to form a C-C bond

[140] (a) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149. (b) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem, Int. Ed.* **2014**, *53*, 6383.
[141] (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773.
[142] (a) Cahard, E.; Bremeyer, N.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9284. (b) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7986.

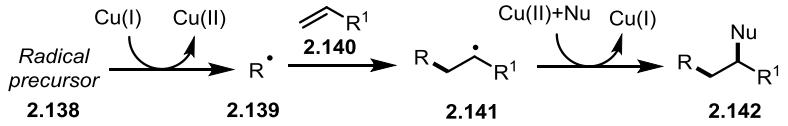
and carbocation intermediate **2.136**. Subsequent intramolecular trapping **2.136** by oxygen atom of amide group could furnish product **2.137**.




**Scheme 2.23: Copper-catalyzed carbooxygenation of alkenes via electrophilic activation**

### 1.2.3. Copper-Catalyzed Carbo-oxygenation/amination of Alkenes via Radical Addition

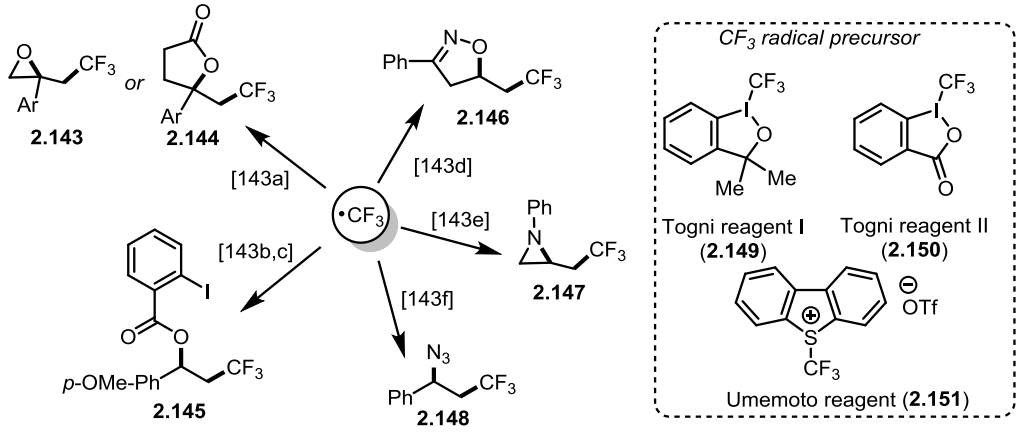
The general approach for this difunctionalization of alkenes could involve the following steps (Scheme 2.24): (1) the generation of carbon radical species **2.139** via a SET process from Cu(I) catalyst to radical precursor **2.138**; (2) subsequent addition into alkenes **2.140** to form a C-C bond and an alkyl radical intermediate **2.141**; (3) trapping **2.141** with suitable nucleophile in the presence of Cu(II) species to form C-Nu bond (Nu = O or N) and regenerate Cu(I) catalyst.




**Scheme 2.24: Copper-catalyzed difunctionalization of alkynes via electrophilic activation**

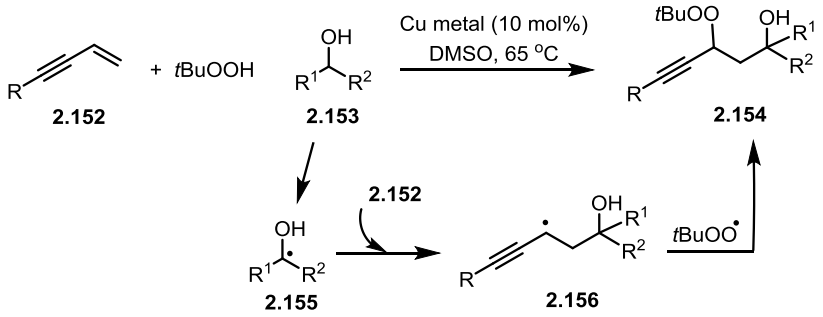
As a demonstration for this synthetic approach, copper-catalyzed trifluoromethylation of double bonds has been developed intensively, and even become a reliable tool for introduction of $CF_3$ into organic molecules. In those transformations, Togni's reagent (**2.149**, **2.150**) and Umemoto's reagent (**2.151**) were employed to generate $CF_3$• radical via single electron reduction. A wide range of nucleophile (Nu= O, N) has been found to be compatible for intramolecular or intermolecular trapping

of radical intermediate **2.141** to afford trifluoromethyl-containing heterocycles such as: epoxides, lactones, isoxazoles, and aziridines (Scheme 2.25).[143]




**Scheme 2.25: Copper-catalyzed trifluoromethylation of alkynes**

Recently, Loh and coworker reported a novel copper-catalyzed three-component oxidative coupling of olefins with hydroperoxide *t*BuOOH and alcohols (Scheme 2.26).[144] The reaction involved an α-C-H activation of alcohols to generate α-hydroxyl carbon radical **2.155**, followed by radical addition to form C-C bond. Subsequent combination of the resulting radical intermediate **2.156** with *t*BuOO• derived from hydroperoxide *t*BuOOH afforded β-peroxy alcohols **2.154** as desired products.




**Scheme 2.26: Copper-catalyzed trifluoromethylation of alkynes**

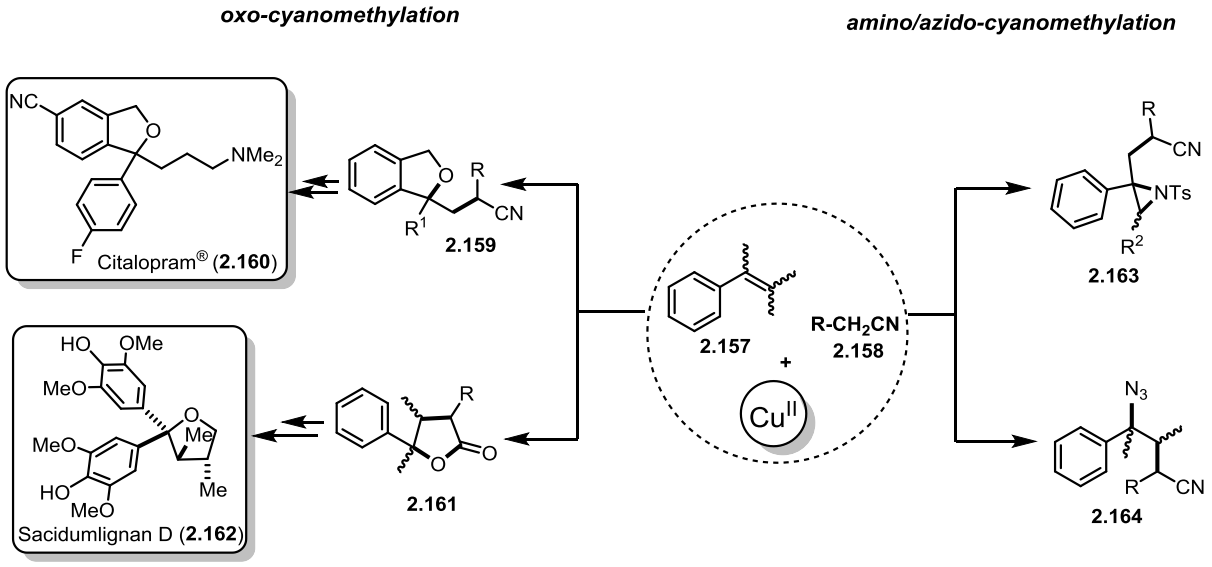
[143] (a) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**. *134*, 12462. (b) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14* , 2882. (c) Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503. (d) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687. (e) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7841. (f) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1881.

[144] Cheng, J. K.; Loh, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 42.

## 1.3. Goals of The Second Part of Thesis

Important advances have been made during the past few years in the copper mediated/catalyzed difunctionalization of unactivated alkenes involving the formation of a C-C and a C-heteroatom bond. Most of the known carbo-oxygenation/carbo-amination reactions were initiated by an intra- or an inter-molecular oxocupration/aminocupration of a C-C double bond followed by the formation of a $C(sp^3)$-$C(sp^2)$ bond (chapter 1.2.1, part II). Although alternative $C(sp^3)$-$C(sp^3)$ bond-forming transformations with participation of $CF_3$• radical were reported (chapter 1.2.3, part II), trifluoromethyl-containing products provide limited rooms for further functionalization to reach complex compounds. The recent success in direct activation of alkylnitriles in difunctionalization of alkenes which is initiated by the formation of a $C(sp^3)$-$C(sp^3)$ bond has been made by our group (see chapter 1.1.2, part II). This initial results prompted us to further exploit the catalytic system of Cu(II)/*N*,*N*-ligand/DTBP to access highly-versatile nitrile compounds.

The second part of my thesis focused on designing new transformations and finding suitable nucleophiles based on general approach outlined in Scheme 2.14. Those works could be divided into two major parts based on the nature of nucleophiles: oxo-cyanomethylation and amino/azido-cyanomethylation (Scheme 2.27). Nitrile-containing/derivative compounds such as 1,3-dihydroisobenzofurans **2.159**, γ-lactones **2.161**, aziridines **2.163** and γ-azidobutyronitriles **2.164** were accessed by using appropriate nucleophiles. Further exploitation of synthetic versatility of nitrile group was implemented to obtain interesting bioactive compound or natural product, including citalopram (**2.160**) and sacidumlignan D (**2.162**).




**Scheme 2.27: Copper-catalyzed cyanomethylation of unactivated alkenes**

# CHAPTER 2

## Copper-Catalyzed Cyanoalkylative Cycloetherification of Alkenes to 1,3-Dihydroisobenzofurans

## 2.1. 1,3-Dihydroisobenzofurans: Application and Synthesis

1,3-Dihydroisobenzofurans (phthalans) are present in a number of natural products which display many interesting biological activities such as antifungal, antibacterial and antioxidant.[145] For examples, pestacin (**2.165**) isolated from an endophytic fungus *Pestalotiopsis microspore*, has been found to exhibit potent antioxidant activity and moderate antifungal properties.[146] The highly active benzylic C-H bond towards reactive oxygen species was postulated to account for its strong antioxidant activity. Moreover, these compounds and their analogues contributed important structural constitutions in pharmaceutical chemistry. Particularly, phenylsubstituted phthalans were found to be highly selective and potent inhibitors of the serotonin transporter (SERT) and the norepinephrine transporter (NET)[147] which are important drug targets for treatment of psychiatric diseases such as depression and anxiety.[148] Indeed, citalopram **2.160** – selective inhibitor of SERT, and talopram **2.170** – selective inhibitor of NET were successfully developed into marketed antidepressant drugs for adults. Alkylidene phthalans were also reported as potential tyrosine kinase inhibitors.[149] Recent primary pharmaceutical studies have showed that these compounds, particularly **2.71** exhibited antidepressant activity comparable to citalopram.[150]

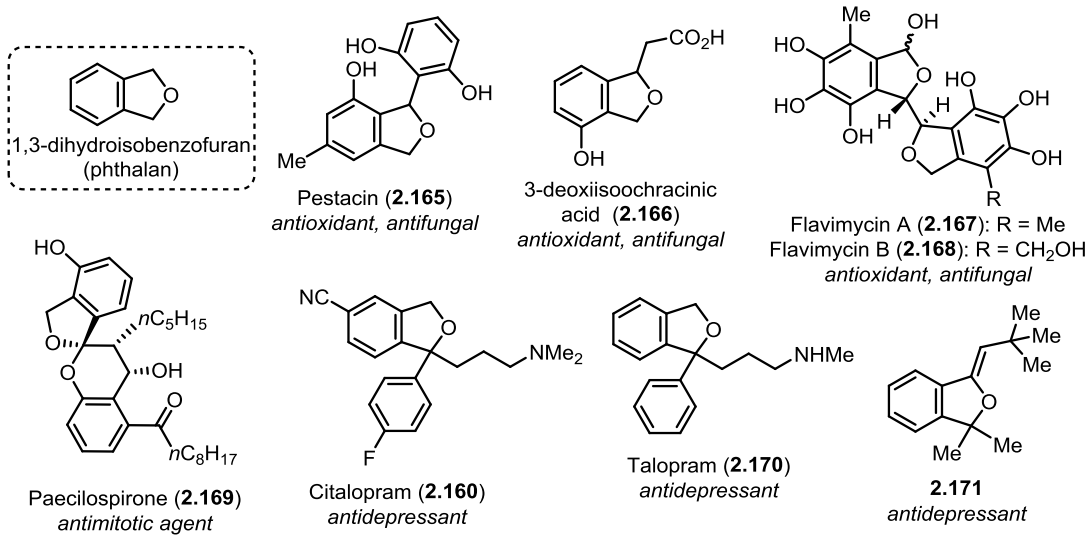



**Figure 2.4: Examples of phthalans in natural products and bioactive compounds**

[145] (a) DeBernardis, J. F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. *J. Med. Chem.* **1987**, *30*, 178. (b) Strobel, G. A.; Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179. (c) X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang and J. Shi, *J. Nat. Prod.* **2004**, *67*, 1661. (d) Y.-J. Kwon, M.-J. Sohn, C.-J. Kim, H. Koshino and W.-G. Kim, *J. Nat. Prod.* **2012**, *75*, 271.

[146] Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. *Tetrahedron* **2003**, *59*, 2471.

[147] Bigler, A. J.; Bøgesø, K. P.; Toft, A.; Hansen, V. *Eur. J. Med. Chem.* **1977**, *12*, 289.

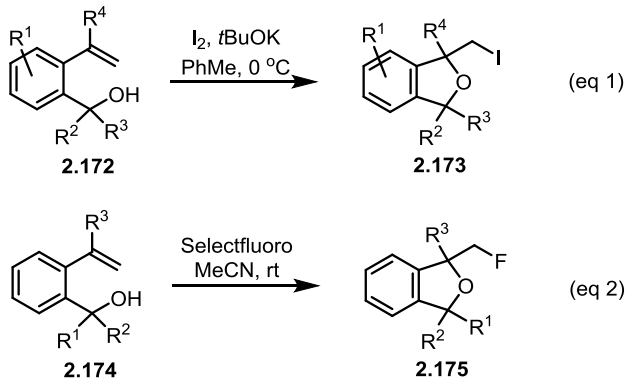
[148] Inoue, T.; Kusumi, I.; Yoshioka, M. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 519.

[149] Andrews, S. W.; Guo, X.; Zhu, Z.; Hull, C. E.; Wurster, J. A.; Wang, S.; Wang, E. H.; Malone, T. *U.S. Pat. Appl. Publ.* **2006**, US 20060004084 A1 20060105.

[150] Praveen, C.; Iyyappan, C.; Girija, K.; Kumar, K. S.; Perumal, P. T. *J. Chem. Sci.* **2012**, *124*, 451.

Besides their important application in medicinal chemistry, 1,3-dihydroisobenzofurans have been used in the agricultural, perfume and colorant industries.[151]

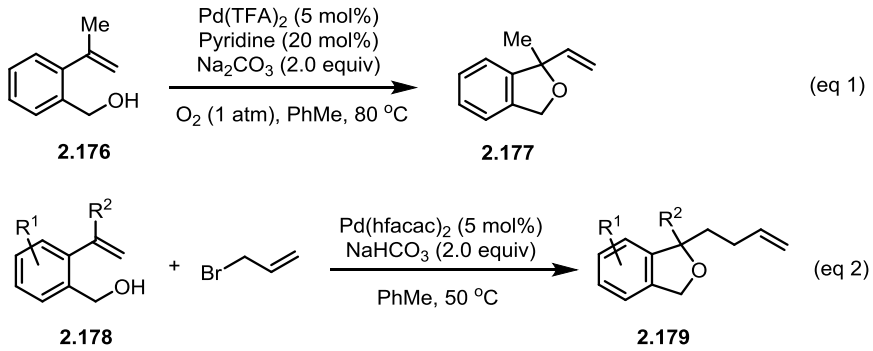
Owing to their valuable bioactivities, a variety of synthetic approaches to 1,3-dihydroisobenzofuran derivatives have been investigated.[152] Among them, electrophile-induced cycloetherification of (2-vinylphenyl)methanol derivatives has been intensively exploited. These resulting oxa-heterocycles can be further derivatized taking advantage of the leaving group aptitude of electrophilic group. For example, Kobayashi reported a simple iodine/*t*BuOK-promoted iodoetherification of 2-vinylbenzyl alcohols **2.172** to give phthalans **2.173** (eq 1, Scheme 2.28).[153] Alternative mild and metal-free fluoroetherifcation was later published by Rueping to access fluoro-containing phthalans **2.175** using Selectfluor as a promoter (eq 2, Scheme 2.28).[154]




**Scheme 2.28: Haloetherification of (2-vinylphenyl)methanol to access phthalans**

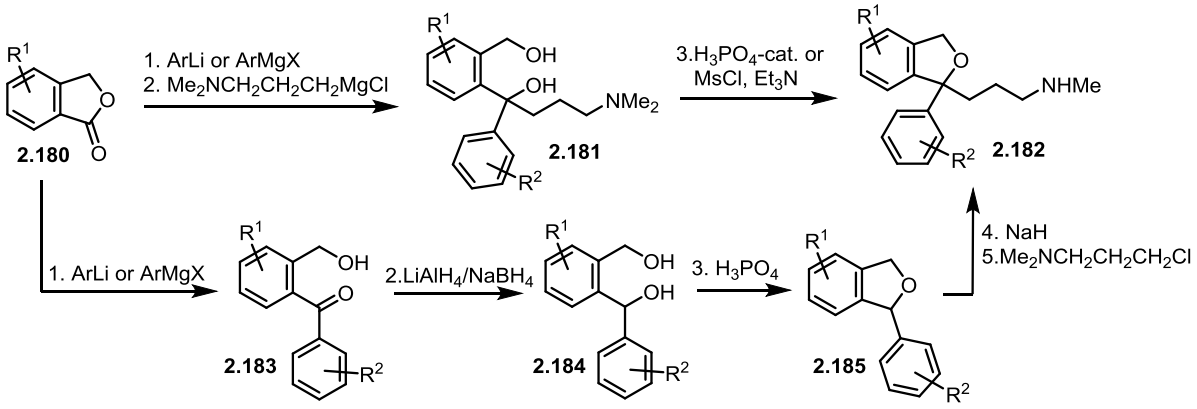
Transition metal-catalyzed transformations were also employed to construct this interesting scaffold. Stoltz and coworkers reported an oxidative cyclization of 2-vinylbenzyl alcohols **2.176** in the presence of $Pd(TFA)_2$, pyridine and $Na_2CO_3$ under oxygen atmosphere to afford 1-vinylphthalans **2.177** (eq 1, Scheme 2.29).[155] This reaction could proceed through a sequence of activation of double bond by Pd(II) catalyst, oxopalladation to alkylpalladium(II) complext and β-hydride elimination. Taking advantage of the formation of alkylpalladium (II) intermediate, a cascade reaction of 2-vinylbenzyl alcohols **2.178** with allyl bromide involving oxopalladation, carbopalladation and β-halide elimination was developed by France to access 1-homoallylated 1,3-dihydroisobenzofurans **2.179** (eq 2, Scheme 2.29).[156] The utility of this heteroallylation was demonstrated in the synthesis of citalopram by a sequence of functional-group interconversions of alkene moiety.

[151] (a) DeBernardis, J. F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. *J. Med. Chem.* **1987**, *30*, 178. (b) Houlihan, W. J.; Nadelson, J. *U.S. Patent* 37,45,165, **1973**. (c) Feichtinger, H.; Linden, H. (Ruhrchemie A.-G.), *U.S. Patent* US31,76,024, **1965**.
[152] Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213.
[153] Kobayashi, K.; Shikata, K.; Fukamachi, S.; Konishi, H. *Heterocycles* **2008**, *75*, 599.
[154] Parmar, D.; Rueping, M. *Chem. Commun.* **2014**, *50*, 13928.
[155] Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.
[156] Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem. Sci.* **2013**, *4*, 3538.




**Scheme 2.29: Pd-catalyzed oxidative cyclization of (2-vinylphenyl)methanol to phthalans**

Cycloetherification to 1,3-dihydroisobenzofurans can be also achieved by employing various starting materials, such as α-hydroxybenzyl quarternary ammonium salts,[157a] *o*-fluoromethylbromo-benzene,[157b] phthalyl alcohols,[157c] α,α'-dihalo-*o*-xylenes.[157d] Particularly, phthalides **2.180** have been exploited as valuable starting materials for the preparation of 1-aryl-1-[3-(diemthylamino)propyl]phthalans **2.182** which is a selective and potent inhibitor of NET and SERT, such as citalopram and talopram.[147,158] The synthesis generally involved the conversion of phthalides **2.180** into diol intermediates **2.181** by two-fold Grignard reaction with aryl organometallic compound and (3-dimethylamino)propylmagnesium chloride. Subsequent acid-catalyzed or MsCl/$Et_3N$-promoted cycloetherfication of the resulting diols afforded bioactive products **2.182**. In an alternative route, phthalides **2.180** could be converted in to 1-arylphathalans **2.185** by a sequence of Grignard reaction, reduction and cycloetherfication. Finally, introduction of aminoalkyl chain was completed through metalation followed by reaction with (3-dimethylamino)propyl chloride (Scheme 2.30).

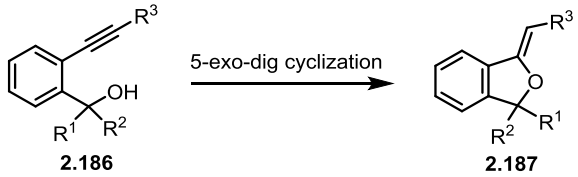



**Scheme 2.30: Two pathways in synthesis of antidepressant-drug candidates**

[157] (a) Demyanovich, V. M.; Shishkina, I. N.; Kuznetsova, A. A.; Potekhin, K. A.; Chesnova, A. V. *Russ. J. Org. Chem.* **2006**, *42*, 986. (b) Zhang, L.; Zhang, W.; Liu, J.; Hu, J. *J. Org. Chem.* **2009**, *74*, 2850. (c) Panda, B.; Sarkar, T. K. *Tetrahedron Lett.* **2008**, *49*, 6701. (d) Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. *Synlett* **2002**, 1526.

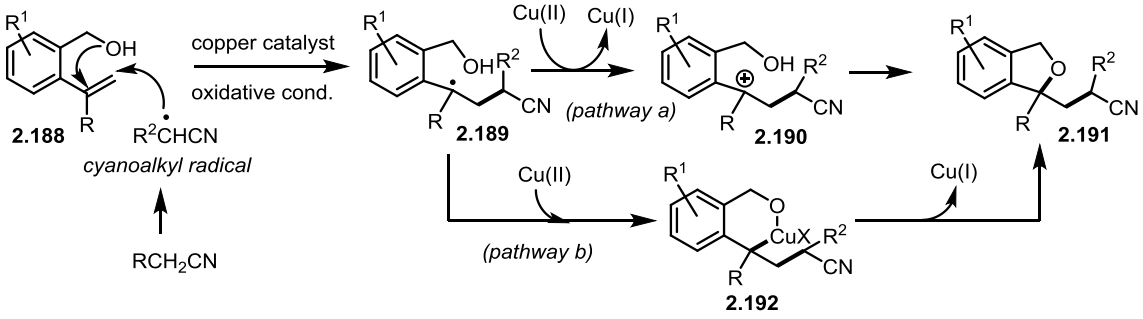
[158] Eildal, J. N. N.; Andersen, J.; Kristensen, A. S.; Jørgensen, A. M.; Bang-Andersen, B.; Jørgensen, M.; Strømgaard, K. *J. Med. Chem.* **2008**, *51*, 3045.

Potentially bioactive alkylidene phthalans **2.186** generally were synthesized via intramolecular 5-exo-dig cyclization of (2-alkylnylphenyl)methanols **2.187**. A number of reagents were found to promote this cyclization, including: copper salts,[159 a] silver salts,[159b] alkaline bis(trimethylsilyl)-amides[159c] (Scheme 2.31).




**Scheme 2.31: Synthesis of alkylidene phthalans via cyclization of (2-alkylnylphenyl)methanols**

In connection with our research program dealing with copper-catalyzed alkylative difunctionalization of alkenes using alkylnitrile as a key reactant (see chapter 1.1.2),[131] we turned our attention on the development of novel synthesis of 1,3-dihydroisobenzofurans using this methodology (Scheme 2.32). The designed reaction might involve the addition of cyanomethyl radical resulting from direct activation of alkyl nitrile, to unactivated double bonds **2.188**, followed by oxidation of benzylic radical intermediate **2.189** by appropriate copper salt to the carbenium ion **2.190** (pathway a, Scheme 2.32). Trapping of the latter **2.190** by the pendant hydroxyl group would afford the desired 1,3-dihydroisobenzofurans **2.191**. Alternatively, radical combination of **2.189** with Cu(II) salt followed by ligand exchange with the tether hydroxyl function would provide **2.192**, which upon reductive elimination, would deliver the product **2.191** with concomitant regeneration of Cu(I) (pathway b). Overall, the reaction would produce a medicinally relevant heterocycle via formation of a C($sp^3$)-C($sp^3$) and a C($sp^3$)-O bonds involving formally a ($sp^3$)-H functionalization step. This transformation provides an alternative synthetic approach to France's palladium-catalyzed alkylative cycloetherification[156] which is initiated by oxometallation process. The utility of cyanoalkylative etherification was further exploited in the syntheses of antidepressant drugs such as citalopram.




**Scheme 2.32: Designed copper-catalyzed cyanoalkylation in synthesis of 1,3-dihydroisobenzofurans**

[159] (a) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767. (b) Lu, D.; Zhou, Y.; Li, Y.; Yan, S.; Gong, Y. *J. Org. Chem.* **2011**, *76*, 8869. (c) Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A.; Reid, S. *Organometallics* **2012**, *31*, 7287.

## 2.2. Results and Discussion

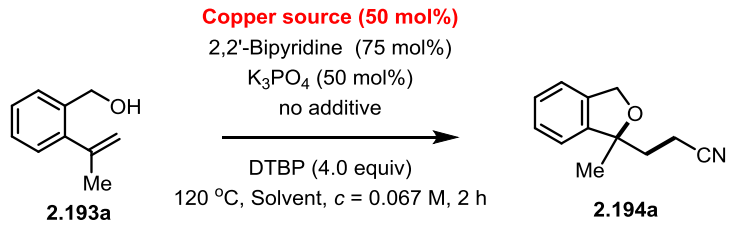
### 2.2.1. Conditions survey

We began the survey of reaction conditions using [2-(prop-1-en-2-yl)phenyl]methanol (**2.193a**) as the benchmark substrate. Condition screening for copper-catalyzed alkylative cycloetherificaion was carried by varying copper sources, ligands, solvents, and additives etc.

#### 2.2.1.1. Screening conditions: Copper sources

Based on our previous works,[129] we decided to apply the typical combinatory system of Cu(II)/*N*,*N*-ligand/DTBP for this alkylative cycloetherificaion. Gratifying, in the presence of $Cu(OTf)_2$ (50 mol%), 2,2'-bipyridine (75 mol%), $K_3PO_4$ (50 mol%), DTBP (4.0 equiv), heating a solution of **2.193a** in MeCN (*c* 0.067 M) at 120 ºC after 2 hours afforded desired phthalan **2.194a** in 20% yield with full conversion (entry 1, Table 2.1).

**Table 2.1: Copper sources screening[(a)]**



**2.193a** **2.194a**

| Entry | Copper source (0.5 equiv) | Solvent | Yield (Conversion)[(b)] |
|---|---|---|---|
| 1 | **$Cu(OTf)_2$** | MeCN | 20% (100% conv.) |
| 2 | **$Cu(OAc)_2$** | MeCN | 22%, (90% conv.) |
| 3 | **$Cu(BF_4)_2.6H_2O$** | MeCN | 24%, (100% conv.) |
| 4 | **$CuCl_2$** | MeCN | Degradation |
| 5 | **$CuF_2$** | MeCN | <10%, (82% conv.) |
| 6 | **$Cu(acac)_2$** | MeCN | 22%, (73% conv.) |
| 7 | **Cu(I) sources** | MeCN | no reaction or degrad. |
| 8 | **$Cu(OTf)_2$** | MeCN/MeOH (4/1) | 33%, (100% conv.) |
| 9 | **$Cu(OAc)_2$** | MeCN/MeOH (4/1) | 25%, (80% conv.) |
| 10 | **$Cu(BF_4)_2.6H_2O$** | MeCN/MeOH (4/1) | 37% (29%)[(c)], (100% conv.) |
| 11 | **$Cu(acac)_2$** | MeCN/MeOH (4/1) | <10%, (84% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.193a** (0.1 mmol), copper source (0.5 equiv), 2,2'-bipyridine (0.75 equiv), DTBP (4.0 equiv) and $K_3PO_4$ (0.5 equiv) in given solvent (*c* 0.067 M) under nitrogen at 120 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield.

Different copper sources were later investigated under the same condition. $Cu(OTf)_2$, $Cu(OAc)_2$, $Cu(BF_4)_26H_2O$ and $Cu(acac)_2$ displayed the similar activities, providing desired product in about 20% NMR yield (entry 1-3, 6). Whereas, $CuCl_2$, $CuF_2$ and copper (I) sources such as $Cu_2O$, CuX (X = Cl, Br, I) were not suitable for this reaction, either giving insignificant yields, or causing degradation of starting material (entry 4, 5, 7).

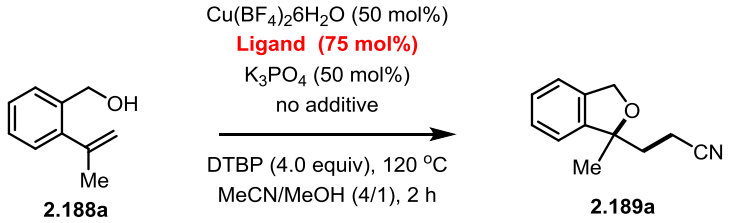
Although it has been demonstrated that the copper salt is mainly responsible for the generation of cyanomethyl radical,[129] the presence of *t*BuO• radical in the reaction mixture could be problematic in the present case. Indeed, the BDE of benzylic CH of benzyl alcohol (87 kcal/mol) is relatively low and it can therefore easily transfer its hydrogen to *t*BuO• (BDE of *t*BuO-H: 106 kcal/mol).[128] Although the BDE of H-$CH_2OH$ (96 kcal/mol) is higher than that of the benzylic CH, we were pleased to find that by using MeOH as a co-solvent, the yield of product **2.194a** was increased significantly (entries 1, 8). With co-solvent system of MeCN/MeOH (v/v 4/1) in hand, $Cu(BF_4)_2.6H_2O$ was found to be the best catalyst to our transformation, furnishing a complete conversion and **2.194a** in 37% NMR or 29% isolated yield (entry 10) after re-examination of copper salts (entry 8-11).

#### 2.2.1.2. Screening conditions: Ligands

The *N,N*-ligand including bipyridines, phenanthrolines and bisoxazoline were next screened in the presence of $Cu(BF_4)_26H_2O$ (50 mol%), $K_3PO_4$ (50 mol%) and DTBP (4.0 equiv) at 120 °C (Table 2.2). Unfortunately, simple pyridine **L3** and *N,N*-ligands bearing substituents at *ortho* positions of nitrogen atoms such as **L2**, **L5** induced the decomposition (entry 2, 3, 5). Phenanthroline **L4** was found to be more productive ligand to the reaction in comparison to bipyridine **L1** and bisoxazoline **L6** (entry 1, 4, 6). After changing substituents on phenanthroline (entry 7, 8) and tuning ligand loading (entry 9-11), the best result was obtained (57% NMR yield, 100% conversion) when bathophenanthroline (4,7-diphenyl-1,10-phenanthroline **L8**) was employed and ½ molar ratio of Cu/Ligand was applied (entry 11).

Gratefully, the combination of $Cu(BF_4)_26H_2O$/bathophenanthroline enabled the reaction to result in comparable yield, albeit slightly drop in conversion when copper loading was decreased to 30 mol% (entry 12).

**Table 2.2: Ligand screening[(a)]**




**2.188a** **2.189a**

| Entry | Ligand (equiv) | Yield (Conversion)[b] |
|---|---|---|
| 1 | **L1 (0.75)** | 37% (29%)[c], (100% conv.) |
| 2 | **L2 (0.75)** | Degradation |
| 3 | **L3 (1.50)** | Degradation |
| 4 | **L4 (0.75)** | 47% (40%)[c], (100% conv.) |
| 5 | **L5 (0.75)** | Degradation |
| 6 | **L6 (0.75)** | 34%, (100% conv.) |
| 7 | **L7 (0.75)** | 19%, (76% conv.) |
| 8 | **L8 (0.75)** | 53% (44%)[c], (100% conv.) |
| 9 | **L8 (0.25)** | 42%, (100% conv.) |
| 10 | **L8 (0.50)** | 50%, (100% conv.) |
| 11 | **L8 (1.00)** | 57% (51%)[c], (100% conv.) |
| 12[d] | **L8 (0.60)** | 52%, (92% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.193a** (0.1 mmol), $Cu(BF_4)_2.6H_2O$ (0.5 equiv), Ligand (0.25-1.00 equiv), DTBP (4.0 equiv) and $K_3PO_4$ (0.5 equiv) in MeCN/MeOH (4/1, *c* 0.067 M) under nitrogen at 120 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield. (d) $Cu(BF_4)_2.6H_2O$ (0.3 equiv), and $K_3PO_4$ (0.25 equiv) were used

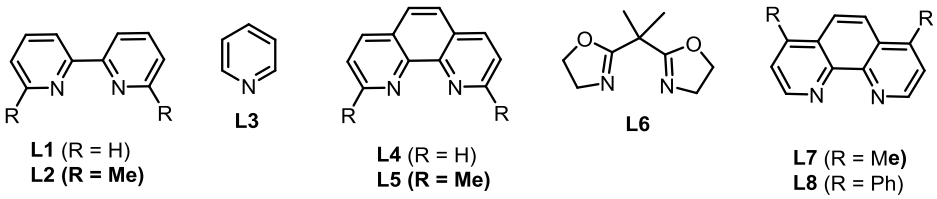
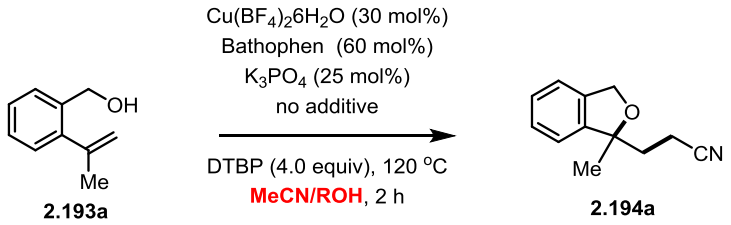



**Figure 2.5: Selected ligands for screening**

### 2.2.1.3. Screening conditions: Solvents

The positive effect of using methanol as co-solvent prompted us to investigate different co-solvent systems (Table 2.3). Unfortunately, no improvement was observed when MeOH was replaced by other ROH solvents (entry 1-6). Further varying the amount of MeOH (entry 7-9) allowed us to conclude that a mixed solvent (MeCN/MeOH v/v = 7/3) is optimum to furnish **2.194a** in 54% NMR yield (entry 8).

**Table 2.3: Solvent screening[(a)]**




**2.193a** **2.194a**

| Entry | Solvents | Yield (Conversion)[(b)] |
|---|---|---|
| 1 | **MeCN/MeOH (4/1)** | 52%, (92% conv.) |
| 2 | **MeCN/EtOH (4/1)** | 40%, (90% conv.) |
| 3 | **MeCN/*i*PrOH (4/1)** | 19%, (96% conv.) |
| 4 | **MeCN/*t*BuOH (4/1)** | 28%, (100% conv.) |
| 5 | **MeCN/$CF_3CH_2OH$ (4/1)** | 26%, (100% conv.) |
| 6 | **MeCN/$H_2O$ (4/1)** | 39%, (78% conv.) |
| 7 | **MeCN/MeOH (9/1)** | 33%, (100% conv.) |
| 8 | **MeCN/MeOH (7/3)** | 54%, (90% conv.) |
| 9 | **MeCN/MeOH (6/4)** | 43%, (83% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.193a** (0.1 mmol), $Cu(BF_4)_2.6H_2O$ (0.3 equiv), bathophenanthroline (0.6 equiv), DTBP (4.0 equiv) and $K_3PO_4$ (0.25 equiv) in MeCN/ROH (*c* 0.067 M) under nitrogen at 120 °C for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield.

### 2.2.1.4. Screening conditions: Oxidants, Additives and Temperature

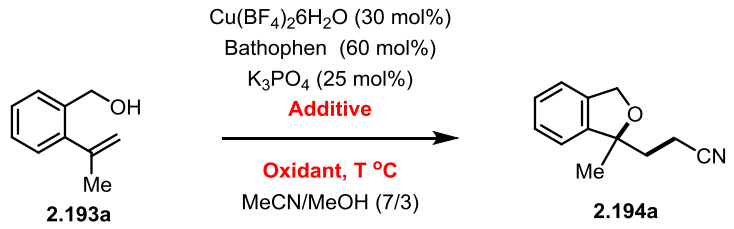
The effect of alternative peroxides to the reaction outcome was later examined (entry 1-4, Table 2.4). Dicumyl peroxide (**O2**) and Luperox® 101, 2,5-bis(*tert*-butylperoxy)-2,5-dimethylhexane (**O3**) displayed the similar activities to DTBP (**O1**), whereas, *tert*-butyl benzoyl peroxide (**O4**) caused the degradation. This result could be reasoned by the fact that **O4** is likely to undergo thermal decomposition at high temperature to generate *t*BuO• radical which is detrimental to the reaction, compared to others **O1-O3**.[160] Lowering DTBP (**O1**) loading led to the decrease in both conversion and yield (entry 5, 6).

Intrigued by the role played by alcoholic solvent, benzyl alcohol, diphenylcarbinol and 1-phenylethanol (1.2 equiv) were added into the reaction mixture (entries 7-9). Gratefully, we were able to obtained **2.194a** in 61% yield when BnOH was introduced as an additive (entry 7). Comparable

[160] Eds. Brandrup, J; Immergut, E.H.; Grulke, E.A. "*Polymer Handbook*", 4th Edition, John Wiley, New York, **1999**, II/2-69.

yield was observed in case of using diphenylcarbinol (entry 8), whereas 1-phenylethanol had no influence (entry 9). Addition of other substituted benzyl alcohols (*p*-$NO_2C_6H_4CH_2OH$, *P*-$ClC_6H_4CH_2OH$, *p*-$MeOC_6H_4CH_2OH$) afforded **2.194a** in reduced yields (entry 10-12). Finally, yield of **2.194a** was slightly increased when the reaction was performed at 100 °C (entry 13).

**Table 2.4: Oxidant, additive and temperature screening[(a)]**

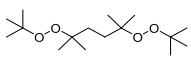



**2.193a** **2.194a**

| Entry | Oxidant (equiv) | Additive (equiv) | Yield (Conversion)[(b)] |
|---|---|---|---|
| 1 | **O1 (4.0)** | None | 54%, (90% conv.) |
| 2 | **O2 (4.0)** | None | 50%, (100% conv.) |
| 3 | **O3 (4.0)** | None | 50%, (94% conv.) |
| 4 | **O4 (4.0)** | None | <10%, (100% conv.) |
| 5 | **O1 (3.0)** | None | 52%, (90% conv.) |
| 6 | **O1 (2.0)** | None | 39%, (80% conv.) |
| 7 | O1 (4.0) | **BnOH (1.2)** | 61%, (94% conv.) |
| 8 | O1 (4.0) | **Diphenylcarbinol (1.2)** | 60%, (89% conv.) |
| 9 | O1 (4.0) | **1-Phenylethanol (1.2)** | 52%, (91% conv.) |
| 10 | O1 (4.0) | ***p*-$NO_2C_6H_4CH_2OH$ (1.2)** | 48%, (90% conv.) |
| 11 | O1 (4.0) | ***p*-Cl $C_6H_4CH_2OH$ (1.2)** | 59%, (93% conv.) |
| 12 | O1 (4.0) | ***p*-MeO $C_6H_4CH_2OH$ (1.2)** | 59%, (91% conv.) |
| 13[(d)] | O1 (4.0) | **BnOH (1.2)** | 69% (65%)[(d)], (100% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.193a** (0.1 mmol), $Cu(BF_4)_2.6H_2O$ (0.3 equiv), bathophenanthroline (0.6 equiv), Oxidant (2-4 equiv), $K_3PO_4$ (0.25 equiv) and additive (1.2 equiv) in MeCN/MeOH (4/1, *c* 0.067 M) under nitrogen at T °C. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield. (d) Reaction performed at 100 °C.

**O1 = DTBP (di-*tert*-butyl peroxide)** **O2 = Dicumyl peroxide**

**O3 =**  **O4 = *tert*-butyl benzoyl peroxide**

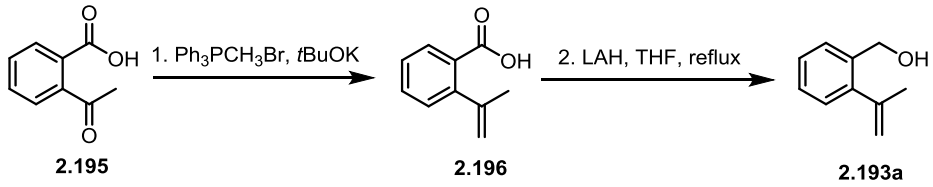
Overall, the optimum conditions consisted of performing the cyanoalkylative etherification of **2.193a** in MeCN/MeOH (v/v 7/3, *c* 0.025 M) at 100 °C in the presence of $Cu(BF_4)_2.6H_2O$ (30 mol%),

bathophenanthroline (60 mol%), $K_3PO_4$ (25 mol%), DTBP (4.0 equiv) and benzyl alcohol (1.2 equiv). Under these conditions, alkyloxigenation of **1.293a** afforded nitrile-containing 1,3-dihydro-isobenzofuran **1.294a** in 65% isolated yield.

## 2.2.2. Substrate scope

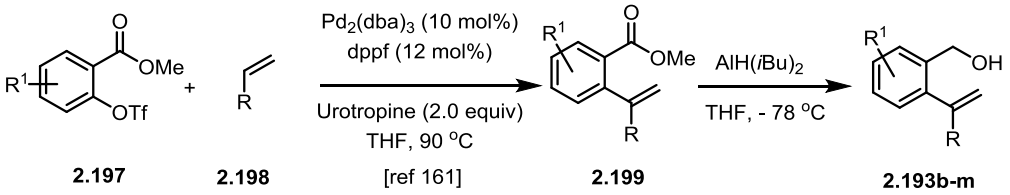
### 2.2.2.1. Synthesis of starting materials

Several approaches were applied for the synthesis of (2-vinylphenyl)methanol derivatives. The first approach leading to the synthesis of **1.293a** is depicted in Scheme 2.33.[156] Commercially available 2-acetylbenzoic acid (**2.195**) was converted into 2-(prop-1-en-2-yl)benzoic acid (**2.196**) by Wittig reaction. Subsequent reduction of **2.196** with LAH afforded **2.193a** in good overall yield.



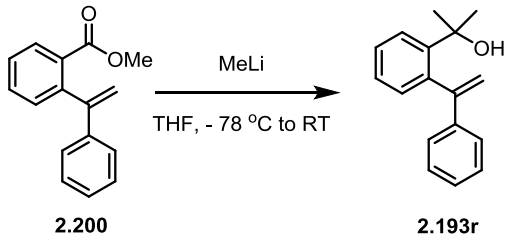

**Scheme 2.33: Synthesis of 2.193a**

The second approach leading to the synthesis of **1.293b-m** is depicted in Scheme 2.34. These starting materials were accessed through 2 steps: (1) Heck reaction of terminal olefins **2.193** with phenol triflates **2.197** using Zhou's conditions to afford 2-aryl-1-alkene **2.199** with high regioselectivity;[161] (2) subsequent reduction of **2.199** by $AlH(iBu)_2$ at low temperature.




**Scheme 2.34: Synthesis of 2.193b-m**

Finally, the third approach leading to the synthesis of **1.293r** is depicted in Scheme 2.35. 1,1-diarylethylene **2.200** which can be prepared by using Zhou's Heck coupling reaction described in the second approach, underwent two-fold Grignard reaction with MeLi to furnish **2.193r** in good yield.

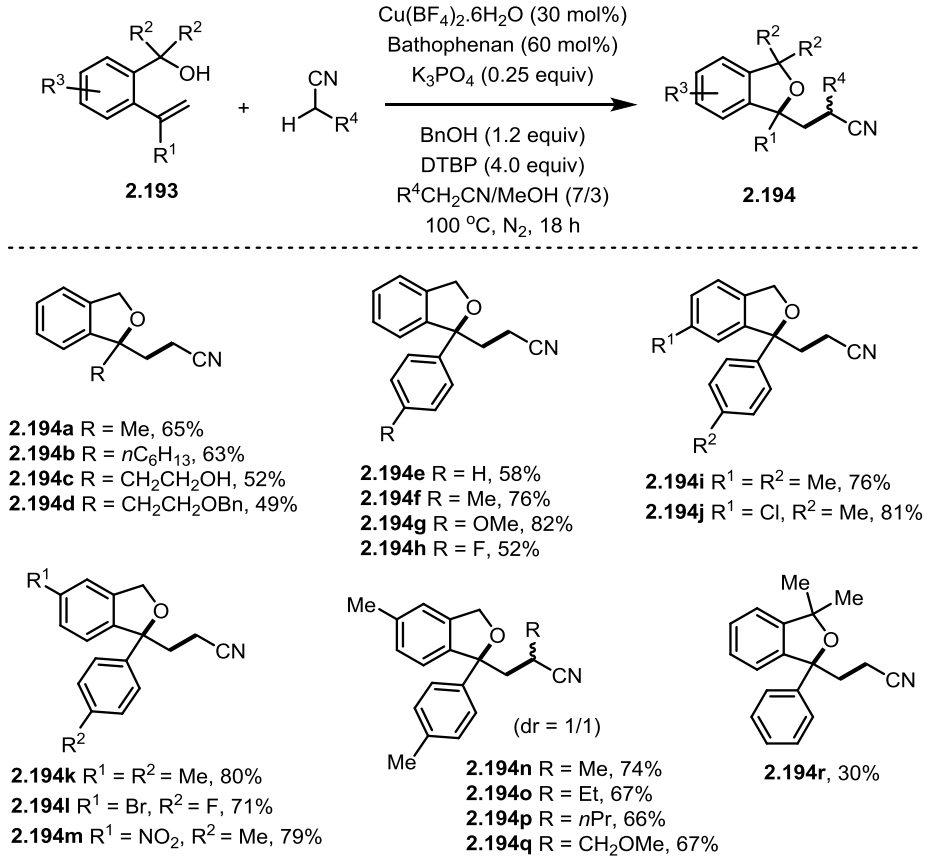



**Scheme 2.35: Synthesis of 2.193r**

[161] (a) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5915. (b) Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Eur. J.* **2013**, *19*, 3504.

### 2.2.2.2. Substrate scope

With the optimized conditions in hand, the scope of the copper-catalysed cyanoalkylative cycloetherification of alkenes was investigated. The results are summarized in Scheme 2.36.




**Scheme 2.36: Scope for copper-catalyzed cyanoalkylative etherification of alkenes**

In addition to α-methyl substituted styrenes **2.193a**, α-hexyl, α-hydroxyethyl and α-benzyloxyethyl substituted styrenes (**2.193b-d**) participated in this reaction to afford the corresponding 1,3-dihydrobenzofurans (**2.194b-d**) in moderate to good yields. Pleasingly, substrates bearing functional groups such as free hydroxyl (**2.193c**) or benzylated hydroxyl (**2.193d**) were found to be tolerated in reaction conditions.

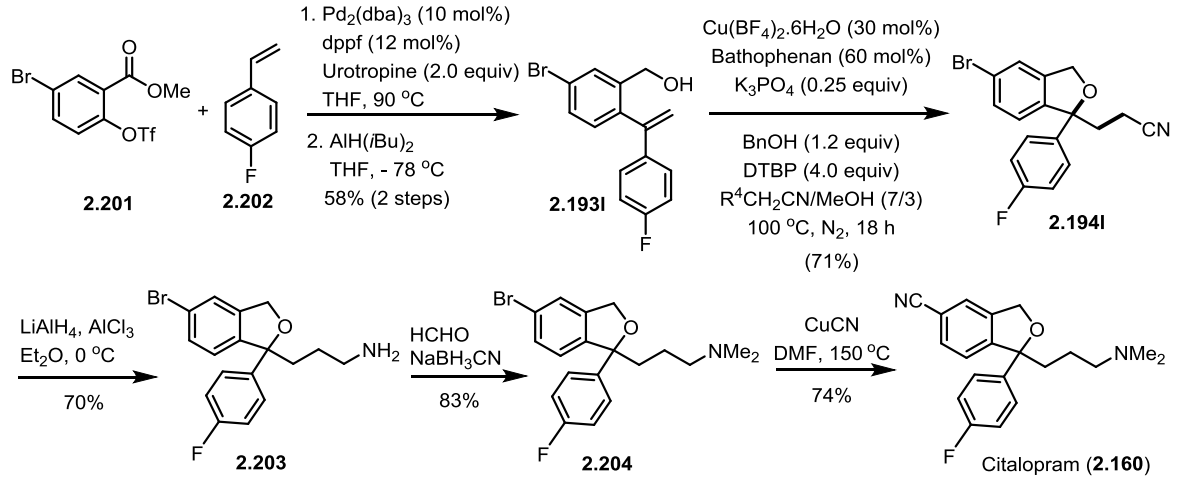
α-Aryl substituted styrenes with electron-donating (Me, MeO) or electron-withdrawing (F, Cl, Br, $NO_2$) substituents on both aryl rings, regardless of their positions, participated well in this reaction (**2.194e-m**). While we expected that substrates with electron-donating substituents would be transformed to 1,3-dihydroisobenzofurans (example **2.194f, 2.194g**) in high yields, we were surprised to observe that substrates with electron-withdrawing groups ($NO_2$, Cl, Br) were also converted to compounds **2.194j, 2.194l, 2.194m** in very good yields. The experimental observation might suggest the reaction mechanism is unlikely to proceed through carbenium intermediate as depicted in pathway a, Scheme 2.32. However, it could not be ruled out that high yields of these substrates may result

simply from their stability toward *t*BuO• radical. The hydrogen abstraction of C-H benzylic alcohol by electrophilic *t*BuO• radical to form the corresponding nucleophilic α-hydroxyl carbon radical is anticipated to be unfavourable in the presence of electro-withdrawing substituents. The presence of halides and nitro group in this bicycles provided obvious handles for post-functionalizations.

Propionitrile, butyronitrile, pentanenitrile and 3-methoxypropionitrile also took part in the reaction leading to the corresponding dihydroisobenzofurans **1.294n-q** as a mixture of two diastereoisomers (dr 1/1), although the reactions were relatively slow and required higher temperature to complete (110 °C) in these cases. Alkene **1.293r** with a pendant tertiary benzylic alcohol function afforded **1.294r** in low yield (30%), most probably due to the instability of the tertiary alcohol under the reaction conditions.

### 2.2.3. Application of Copper-catalyzed cyanoalkylative etherification of alkenes

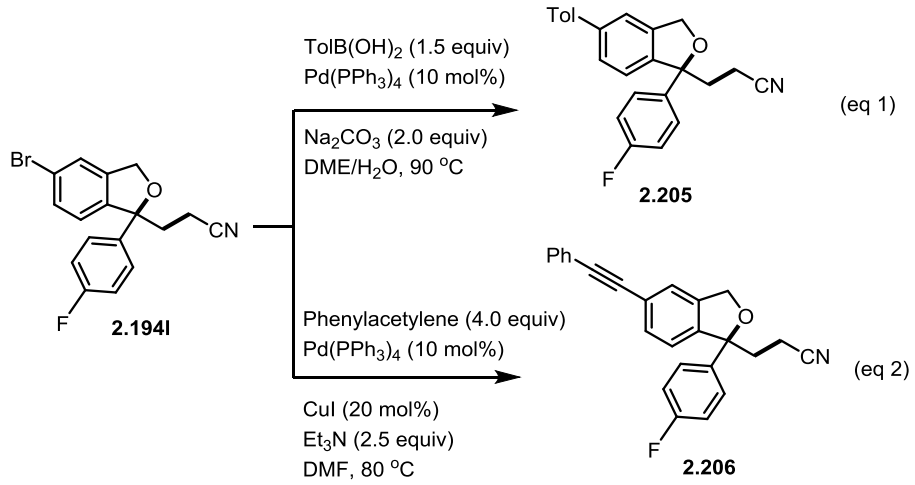
Citalopram (**2.160**), marketed in over 65 countries under different brand names and estimatedly exposed to more than 8 million people, was one of the top-selling antidepressant drugs.[162] To illustrate the synthetic potential of our methodology, synthesis of **2.160** featuring the key cyanoalkylative cycloetherification was undertaken (Scheme 2.37). Regioselective Heck reaction of triflate **2.201** with 4-fluorostyrene (**2.202**) according to Zhou[161] followed by reduction of the methyl ester furnished **2.193l**. Copper-catalysed reaction of **2.193l** with acetonitrile under our optimised conditions afforded dihydroisobenzofuran **2.194l** in 71% yield. The reaction was performed in a gram scale with similar synthetic efficiency. Reduction of the cyano group to primary amine **2.203** followed by reductive *N*,*N*-dimethylation provided **2.204**. Finally, Rosenmund-von Braun reaction of **2.204** (CuCN, DMF, 150 °C) afforded citalopram (**2.160**) in 74% yield.




**Scheme 2.37: Synthesis of citalopram (2.160)**

[162] (a) Baldwin, D.; Johnson, F. N. *Rev. Contemp. Pharmacother.* **1995**, *6*, 315. (b) Keller, M. B. *J. Clin. Psychiatry* **2000**, *61*, 896. (c) Dorell, K.; Cohen, M. A.; Huprikar, S. S.; Gorman, J. M.; Jones, M. *Psychosomatics* **2005**, *46*, 91.

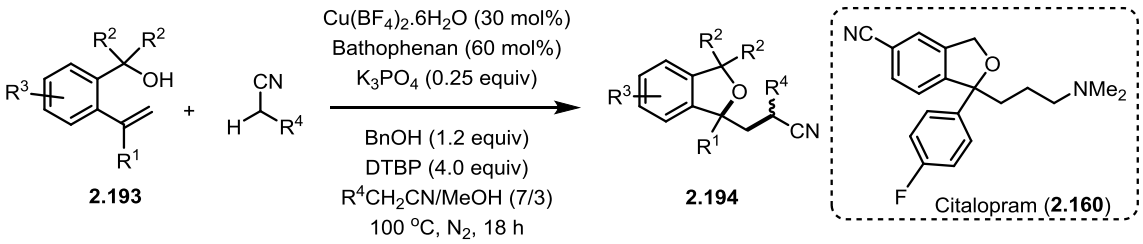
Taking advantage of the aryl bromide function in **1.294l**, a diverse set of substituents can be introduced to the dihydroisobenzofuran framework. For example, Suzuki-Miyaura cross-coupling of **1.194l** with *p*-tolylboronic acid afforded **2.205** (eq 1, Scheme 2.38), while Sonogashira reaction of **2.194l** with ethynylbenzene provided **2.206** (eq 2, Scheme 2.38). Applying the sequence of reduction of nitrile and reductive *N*,*N*-dimethylation of the resulting amine shown in Scheme 2.36 would afford a range of citalopram analogues with structural modification on side chain, aromatic rings and benzylic positions.




**Scheme 2.38: Post-transformation of dihydroisobenzofuran 2.189l**

## 2.3. Conclusion

In summary, we developed a novel copper-catalysed cyanoalkylative cycloetherification of substituted (2-vinylphenyl)methanol using alkylnitriles as alkyl donors. The reaction provided an efficient approach to1,3-dihydroisobenzofurans via the formation of C($sp^3$)-C($sp^3$) and C($sp^3$)-O bond (Scheme 2.39). The synthetic potential of this novel transformation was demonstrated by the development of a concise synthesis of citalopram, a marketed anti-depressant drug.[163]




**Scheme 2.39: Copper-catalyzed cyanoalkylative etherification of alkenes; synthesis of 1,3-dihydroisobenzofurans**

[163] Tu, H. M.; Wang, Q.; Zhu, J. *Chem. Commun.* **2016**, *4*, 11100–11103.

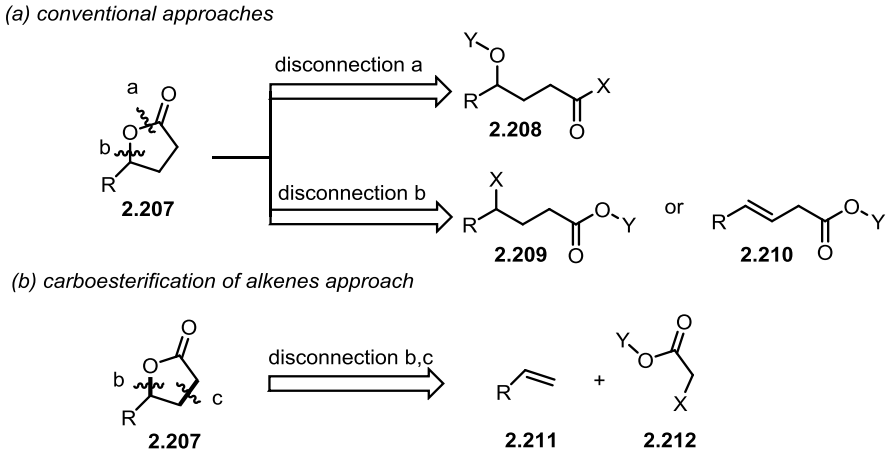
# CHAPTER 3

## Copper-Catalyzed Formal [2+2+1] Heteroannulation of Alkenes, Alkylnitriles, and Water in Synthesis of γ-Lactones

## 3.1. Heteroannulation of Alkenes in Synthesis of γ-Lactones

γ-Butyrolactone is important structural core found in many biologically active natural products[164] and is also a useful synthetic building block in the syntheses of many types of natural products including antibiotics, pheromones, antifungal and flavour components.[165] Consequently, the development of efficient methods for the synthesis of γ-butyrolactone has received considerable attention. Conventionally, γ-butyrolactones could be obtained from either γ-hydroxyl carbonyl compounds **2.208** (disconnection a, Scheme 2.40-a) or carbonyl compounds **2.209**/**2.210** bearing a functional group at γ-position (disconnection b, Scheme 2.40-a).

Transition metal-mediated/catalyzed difunctionalization of alkenes has emerged as a powerful tool in organic synthesis because of their high potential for application in natural products and drugs synthesis.[5] Important progress has been made during the past few years in this research area, particularly carboamination, carbooxygenation and carbohalogenation of alkenes. Among these transformations, carboesterification of alkenes involving the formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-O bond in single step, has become a promising synthetic approach to γ-lactones (Scheme 2.40-b).



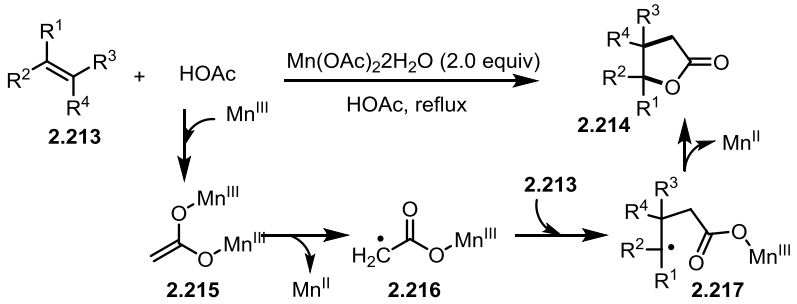

**Scheme 2.40: Synthetic approaches for synthesis of γ-lactones**

As mentioned in chapter 1 - part II, transition metal-catalyzed $C(sp^3)$-$C(sp^3)$ bond-forming difunctionalization of alkenes remained a challenge. Those reactions are limited mainly to the transformations initiated by $CF_3$• radical. The development of novel carboesterification of alkenes for construction of γ-lactones as depicted in Scheme 2.40 therefore is of great interest.

[164] (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, **1991**; Vol. 1, pp 476. (b) Bandichhor, R.; Nosse, B.; Reiser, O. *Top. Curr. Chem.* **2005**, *243*, 43. (c) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426.

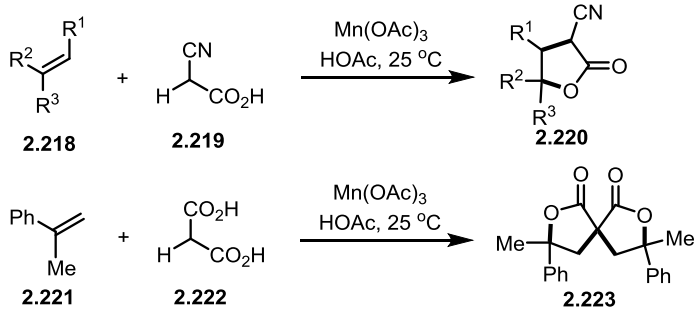
[165] (a) Koch, S. S. C.; Chamberlin, A. R. *J. Org. Chem.* **1993**, *58*, 2725. (b) Koch, S. S. C.; Chamberlin, A. R. *Stud. Nat. Prod. Chem.* **1995**, *16*, 687. (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.

Indeed, Heiba and Bush independently reported manganese(III)-mediated oxidative addition of acetic acid to alkenes **2.213** to afford γ-butyrolactones **2.214** over 40 years ago (Scheme 2.41).[166] The reaction mechanism proceeds through the formation of $Mn^{III}$ enolate **2.215**, followed by a rapid electron transfer to provide free radical **2.216** and concomitantly release $Mn^{II}$ species. Subsequent addition of **2.216** to alkene **2.213** leads to the formation of $C(sp^3)$-$C(sp^3)$ bond and generates alkyl radical **2.217**. The resulting intermediate **2.217** is converted into γ-lactone **2.214** via oxidative electron transfer by another equivalent of $Mn^{III}$. However, the requirement of stoichiometric amount of manganese salt and the employment of corrosive AcOH as solvent under harsh conditions makes this reaction unpractical.




**Scheme 2.41: Manganese-mediated oxidative addition of acetic to alkenes**

As improvement of Heiba and Bush's transformation, the heteroannulation of alkenes with cyanoacetic acid[167] and malonic acid[168] to γ-butyrolactones was reported to proceed smoothly at room temperature (Scheme 2.42). However, malonic acid gives only bis-lactone adducts resulting from the addition to two molecules of alkenes.




**Scheme 2.42: Mn(III)-mediated heteroannulation of alkenes with cyanoacetic acid or malonic acid**

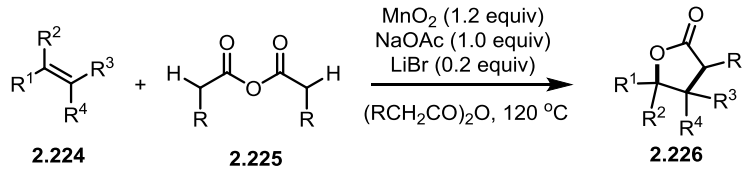
Alternatively, Jiang and coworker recently reported a $MnO_2$-promoted cycloaddition of alkenes with anhydrides involving the formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-O bond to afford a variety of γ-

[166] (a) J. B. Bush, Jr., H. Finkbeiner, *J. Am. Chem. Soc*. **1968**, *90*, 5903. (b) E. I. Heiba, R. M. Dessau, W. J: Koehl, Jr., *J. Am. Chem. Soc*. **1968**, *90*, 5905. (c) E. I. Heiba, R. M. Dessau, P. G: Rodewald, *J. Am. Chem. Soc*. **1974**, *96*, 7977;

[167] Corey, E. J.; Gross, A. W., *Tetrahedron Lett.* **1985**, *26*, 4291.

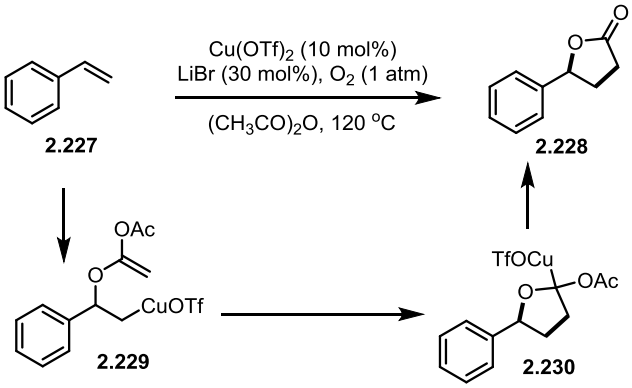
[168] (a) Fristad, W. E.; Hershberger, S. S., *J. Org. Chem.* **1985**, *50*, 3143. (b) Ito, N.; Nishino, H. Kurosawa, K., *Bull. Chem. Soc. Jpn*. **1983**, *56*, 3527.

butyrolactones in good to excellent yields (Scheme 2.43).[169] A wide range of alkenes including styrenes, aliphatic alkenes, internal and terminal alkenes was found to be applicable in this carboesterification.



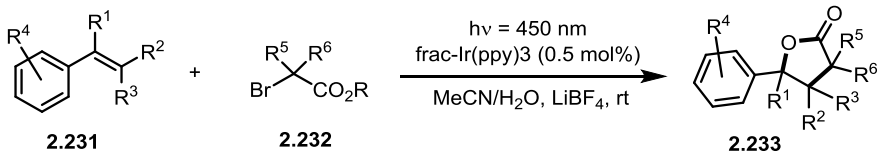

**Scheme 2.43: $MnO_2$-promoted cycloaddition of alkenes with alhydrides by Jiang**

Indeed, copper-catalyzed version of above formal [3+2]-heteroannulation of alkenes with anhydrides was successfully developed by the same group,[170] allowing the simple synthesis of γ-lactones (Scheme 2.44). The proposed mechanism implies *syn*-oxycupration to form intermediate **2.229**, followed by the insertion into the enol to produce the 5-membered intermediate **2.225**. Finally, with the aid of oxygen molecule, **2.230** afforded the product **2.228** and regenerate Cu(II) to complete the catalytic cycles.




**Scheme 2.44: Copper-catalyzed cycloaddition of alkenes with alhydrides by Jiang**

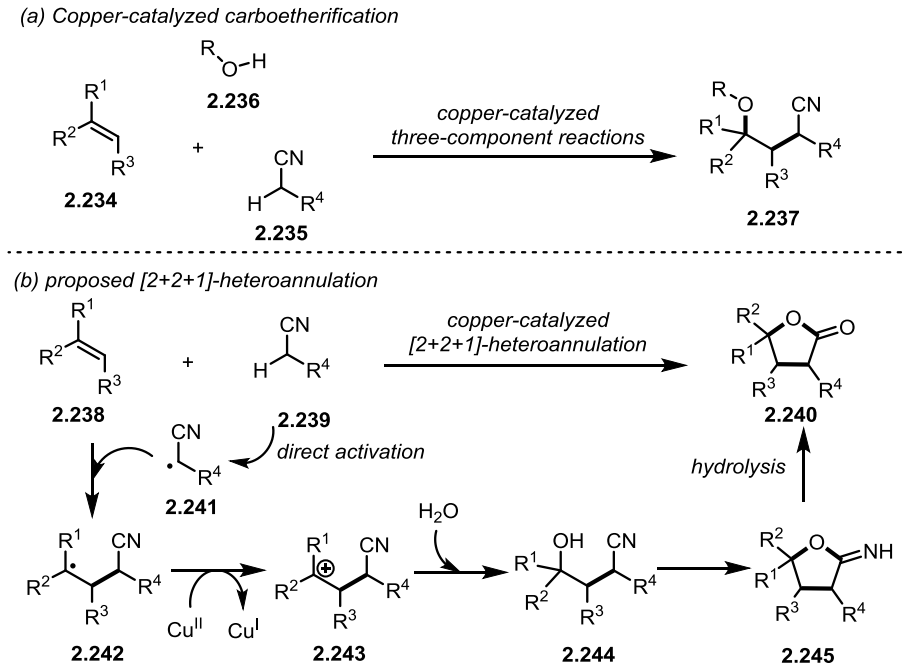
The strategy for $C(sp^3)$-$C(sp^3)$ bond formation via radical addition to alkenes was also exploited in photocatalyzed process. Three-component [2+2+1] heteroannulation of styrenes **2.231**, α-bromoester **2.232** and water was reported by Wu and Liu for the construction of aryl-substituted γ-lactones via visible-light photoredox catalysis (Scheme 2.45).[171]




**Scheme 2.45: Heteroannulation of alkenes to γ-lactones via photoredox catalysis**

[169] Wu, L.; Zhang, Z.; Liao, J.; Li, J. *Chem. Commun.* **2016**, *52*, 2628.
[170] Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652.
[171] Wei, X. J.; Yang, D. T.; Wang, L.; Song, T.; Wu, L. Z.; Liu, Q. *Org. Lett.* **2013**, *15*, 6054.

Inspired by our recent research program aimed at developing copper-catalyzed alkylative difunctionalization of alkenes using alkylnitriles as a key reactant, particularly copper-catalyzed carboetherficaion of unactivated double bonds (Scheme 2.46-a),[129c] we proposed herein a novel synthesis of γ-lactones **2.240** by a copper-catalyzed three-component [2+2+1] heteroannulation of alkenes **2.238**, alkylnitriles **2.2394** and water. The underline principle is outlined in Scheme 2.46-b. Addition of in situ generated α-cyanoalkyl radical **2.241** to alkene **2.238** would afford the adduct radical **2.242** that could be further oxidized to the carbenium ion **2.243**.[172] Trapping of the latter by water would afford γ-hydroxy alkylnitrile **2.244**, which, upon intramolecular cyclization, would provide cyclic imidate **2.245**. Acidic work-up would then convert **2.245** to γ-butyrolactone **2.240**. For the desired domino sequence to proceed towards the formation of **2.240**, the catalytic conditions should satisfy the following mechanistic criteria: a) selective generation of electrophilic α-cyanoalkyl radical **2.241** that adds rapidly to the double bond of alkene **2.238**; b) fast oxidation of the resulting nucleophilic radical **2.242** to carbenium ion **2.243** to avoid the dimerization of the former; c) rapid addition of water to carbenium ion **2.243** to avoid its cationic polymerization with the remaining alkene and d) proper activation of the cyano group to accelerate the lactonization process.




**Scheme 2.46: Proposed difunctionalization of alkenes to γ-lactones: Copper-catalyzed three-component reaction of alkenes, alkylnitriles and water**

[172] a) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc*. **1972**, *94*, 843; b) Zhang, B.; Studer, A. *Org. Lett*. **2014**, *16*, 1790. For a recent review: c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem.* **2011**, *123*, 11256; *Angew. Chem. Int. Ed*. **2011**, *50*, 11062.

Overall, the proposed domino process involving a direct activation of ($sp^3$)-H bond of alkylnitriles, an intermolecular hydroxyl-alkyaltion of olefins and an intramolecular lactonization would produce a γ-lactones via formation of a C($sp^3$)-C($sp^3$), a C($sp^3$)-O and a C($sp^2$)-O bonds.

## 3.2. Results and Discussion

### 3.2.1. Conditions survey

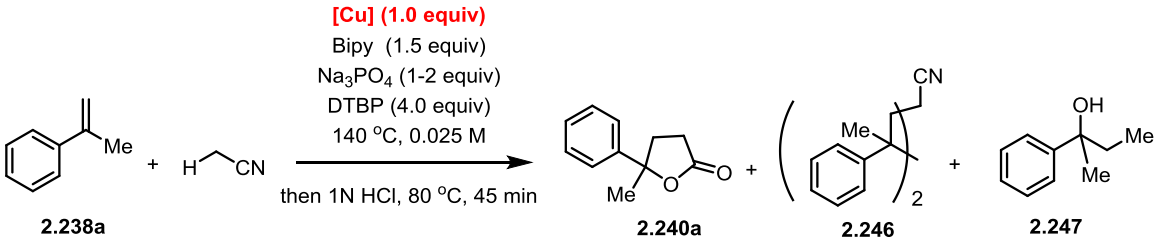
Using α-methyl styrene (**2.238a)** and acetonitrile as test substrates, the reaction conditions were surveyed by varying copper sources, ligands, oxidants, bases and additives.

#### 3.2.1.1. Screening conditions: Copper sources

We started our investigation on three-component reaction by screening the copper sources. Initially, the stoichiometric version was examined when **2.238a** was introduced to our preivous conditions[129c] consisting of copper salts (1.0 equiv), 2,2'-bipyridine (1.5 equiv), $Na_3PO_4$ (1-2 equiv) and DTBP (4.0 equiv) in acetonitrile at 140 ºC for 4 hours. To complete hydrolysis of the possible imidate intermediate **2.245** (see Scheme 2.46), the resulting reaction mixture was treated with aqueous solution of HCl 1N at 80 ºC for 30-45 mins. Gratifyingly, desired product **2.240a** was obtained in significant yields when $Cu(BF_4)_2.6H_2O$, $Cu(ClO_4)_2.6H_2O$ and $Cu(OTf)_2$ were employed (entry 1-4, Table 2.5). The higher yield observed with $Cu(BF_4)_2.6H_2O$ and $Cu(ClO_4)_2.6H_2O$ compared to $Cu(OTf)_2$ may result from hydrated water which could facilitate intermolecular hydroxyl-alkyaltion of **2.238a**. Indeed, introduction of additional amount of water in $Cu(OTf)_2$ conditions afforded higher yield (entry 1,4), albeit still less efficient than $Cu(ClO_4)_2.6H_2O$. Insignificant yield of **2.240a** was observed in case of $Cu(OAc)_2$, $CuF_2$ and $Cu(acac)_2$ with or without water (entry 5-7); while side product **2.246** resulting from radical dimerization was obtained as major product. The influence of anion to redox potential of Cu(II)/Cu(I) might be an explanation to experimental observation. Naked copper(II) species such as $Cu(BF_4)_2$, $Cu(ClO_4)_2$ and $Cu(OTf)_2$ is more powerful oxidants than copper(II) salts with coordinated anion (acetate or fluoride), resulting in fast oxidation of the proposed radical intermediate **2.242** to avoid the formation of dimer.

Given the fact that quantity of water has impact on the outcome of reaction, additional amount of water was introduced to the reaction conditions using $Cu(BF_4)_2.6H_2O$ (entry 8-11). Pleasingly, dramatically increase in yield was achieved (entry 8, 9). However, a side product **2.247** was obtained in significant yield when an excessive amount of water was employed (entry 10, 11). The addition of Me• radical resulting from thermal decomposition of DTBP in the presence of water as a co-solvent, to **2.238a** instead of $•CH_2CN$ might lead to the formation of side product **2.247**.

**Table 2.5: Copper sources screening[(a)]**




| Entry | Cu source (equiv) + $H_2O$ (equiv) | Base (equiv) | Yield[(b)] |
|---|---|---|---|
| 1 | **$Cu(BF_4)_2.6H_2O$ (1)** | $Na_3PO_4$ (2) | 51% |
| 2 | **$Cu(OTf)_2$ (1)** | $Na_3PO_4$ (2) | 16% |
| 3 | **$Cu(ClO_4)_2.6H_2O$ (1)** | $Na_3PO_4$ (2) | 37% |
| 4 | **$Cu(BF_4)_2.6H_2O$ (1) + $H_2O$ (6)** | $Na_3PO_4$ (2) | 37% |
| 5 | **$Cu(OAc)_2$ (1)** w/wo $H_2O$ | $Na_3PO_4$ (2) | Side product **2.246** |
| 6 | **$CuF_2$ (1)** w/wo $H_2O$ | $Na_3PO_4$ (2) | Side product **2.246** |
| 7 | **$Cu(acac)_2$ (1)** w/wo $H_2O$ | $Na_3PO_4$ (2) | Side product **2.246** |
| 8 | $Cu(BF_4)_2.6H_2O$ (1) + **$H_2O$ (10)** | $Na_3PO_4$ (1) | 77% |
| 9 | $Cu(BF_4)_2.6H_2O$ (1) + **$H_2O$ (50)** | $Na_3PO_4$ (1) | 75% + **2.247** (trace) |
| 10 | $Cu(BF_4)_2.6H_2O$ (1) + **$H_2O$ (100)** | $Na_3PO_4$ (1) | 54% + **2.247** (27%) |
| 11 | $Cu(BF_4)_2.6H_2O$ (1) + **$H_2O$ (200)** | $Na_3PO_4$ (1) | 54% + **2.247** (41%) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), copper source (1.0 equiv), 2,2'-bipyridine (1.5 equiv), DTBP (4.0 equiv) and $Na_3PO_4$ (1-2 equiv) in MeCN (*c* 0.025 M) under nitrogen at 140 °C for 4 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

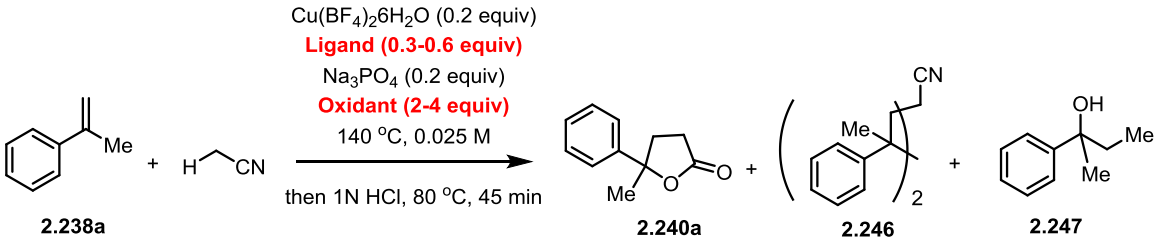
### 3.2.1.2. Screening conditions: Ligands and oxidants

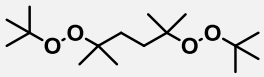
With promising result of stoichiometric version in hand, we next examined three-component reaction using a catalytic amount of $Cu(BF_4)_2.6H_2O$ with 30 equiv of water. Gratefully, desired product **2.240a** was obtained in 57% NMR yield (entry 1, Table 2.6). The investigation of the effect of *N*,*N*-ligands on the outcome of reaction (entry 2-10) revealed that: (1) bipyridine-derived ligands are more compatible to catalytic system than phenanthrolines (entry 2-4 compared to entry 7-9); (2) no significant influence of substituents at 4,4'-positions of bipyridine ring was observed (entry 2-4); while the presence of substituents at 2,2'-positions shut down the reaction (entry 5-6); (3) 1/3 molar ratio of copper/ligand is optimum (entry 11).

Different oxidants were also screened, including organic peroxide and inorganic salts. Dicumyl peroxide which is extremely unstable at high temperature (140 °C) (entry 12), induced the degradation;

while Luperox® 101, 2,5-bis(*tert*-butylperoxy)-2,5-dimethylhexane afforded a comparable yield to DTBP (entry 13). Interestingly, silver carbonate was found to be effective to catalytic cycles, albeit giving lower yield (entry 14).

**Table 2.6: Ligand and oxidant screening[a]**




| Entry | Ligand (equiv) | Oxidant (equiv) | Yield[b] of 2.240 |
|---|---|---|---|
| 1 | **L1** (0.3) | DTBP (4) | 57% |
| 2 | **L2** (0.3) | DTBP (4) | 55% |
| 3 | **L3** (0.3) | DTBP (4) | 48% |
| 4 | **L4** (0.3) | DTBP (4) | 46% |
| 5 | **L5** (0.3) | DTBP (4) | trace |
| 6 | **L6** (0.3) | DTBP (4) | trace |
| 7 | **L7** (0.3) | DTBP (4) | 55% |
| 8 | **L8** (0.3) | DTBP (4) | 42% |
| 9 | **L9** (0.3) | DTBP (4) | 18% |
| 10 | **L10** (0.3) | DTBP (4) | trace |
| 11 | **L1** (0.6) | DTBP (4) | 60% |
| 12 | **L1** (0.3) | **Dicumyl peroxide (4)** | Degradation |
| 13 | **L1** (0.3) |  **(2)** | 56% |
| 14 | **L1** (0.3) | **$Ag_2CO_3$ (2)** | 42% |
| 15 | **L1** (0.3) | **$MnO_2$ (4)** | trace |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(BF_4)_2.6H_2O$ (0.2 equiv), ligand (0.3-0.6 equiv), oxidant (2-4 equiv), $Na_3PO_4$ (0.2 equiv) and water (30 equiv) in MeCN (*c* 0.025 M) under nitrogen at 140 °C for 4 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

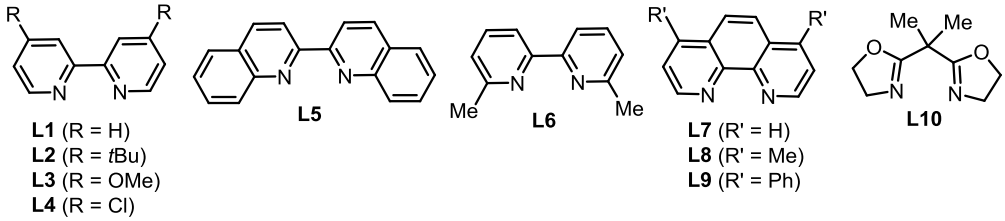
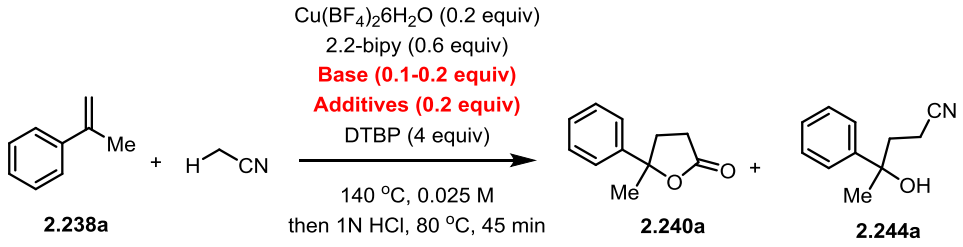



**Figure 2.6: Selected ligands for screening**

### 3.2.1.3. Screening conditions: Bases and additives

Replacing $Na_3PO_4$ by $K_3PO_4$ in the previous condition afforded the same yield of **2.240a** (entry 1, 2, Table 2.7), however, lower loading of $K_3PO_4$ is required. Since intermediate **2.244a** was detected before the acidic treatment, various Lewis acids were tested in order to accelerate the intramolecular lactonization step. Adding lanthanide triflates (entries 3, 4), $Mg(OTf)_2$ (entry 5) to the reaction mixture increased slightly the yield of **2.240a**. A significant improvement was observed by performing the reaction in the presence of a catalytic amount of $Mg(ClO)_4$, $Zn(OTf)_2$ $Ca(ClO_4)_2$ and $Ca(OTf)_2$ (entries 6-10),[173] with the latter furnishing the cleaner reaction. Including $Ca(OTf)_2$ as Lewis acid, the influence of base on the reaction outcome was re-investigated. $Na_3PO_4$ (entry 11), DBN and *N*-methylimidazole (entries 15, 16) were as efficient as $K_3PO_4$ (entry 8), while lower yield of **2.240a** was isolated when KO*t*Bu, LiO*t*Bu and 2,6-lutidine (entries, 12, 13 and 17) were used as bases. Gratefully, a clear improvement of the reaction efficiency was observed when the reaction was performed in the presence of DBU (entry 14).

**Table 2.7: Base and additive screening[(a)]**




| Entry | Base (equiv) | Additive (equiv) | Yield[(b)] of 2.240a |
|---|---|---|---|
| 1 | $Na_3PO_4$ (0.2) | **None** | 60% |
| 2 | $K_3PO_4$ (0.1) | **None** | 60% |
| 3 | $K_3PO_4$ (0.1) | **$In(OTf)_3$ (0.2)** | 66% |
| 4 | $K_3PO_4$ (0.1) | **$Yb(OTf)_3$ (0.2)** | 69% |

[173] Niggemann, M.; Meel, M. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3684.

| | | | |
|---|---|---|---|
| 5 | $K_3PO_4$ (0.1) | **$Mg(OTf)_2$ (0.2)** | 68% |
| 6 | $K_3PO_4$ (0.1) | **$Mg(ClO_4)_2$ (0.2)** | 79% |
| 7 | $K_3PO_4$ (0.1) | **$Zn(OTf)_2$ (0.2)** | 75% |
| 8 | $K_3PO_4$ (0.1) | **$Ca(OTf)_2$ (0.2)** | 81% (69%)[(c)] |
| 9 | $K_3PO_4$ (0.2) | **$Ca(OTf)_2$ (0.2)** | 74% |
| 10 | $K_3PO_4$ (0.1) | **$Ca(ClO_4)_2$ (0.2)** | 65% |
| 11 | **$Na_3PO_4$ (0.2)** | $Ca(OTf)_2$ (0.2) | 75% |
| 12 | **KO*t*Bu (0.1)** | $Ca(OTf)_2$ (0.2) | 56% |
| 13 | **LiO*t*Bu (0.1)** | $Ca(OTf)_2$ (0.2) | 54% |
| 14 | **DBU (0.15)** | $Ca(OTf)_2$ (0.2) | 89% (73%)[(c)] |
| 15 | **DBN (0.15)** | $Ca(OTf)_2$ (0.2) | 75% |
| 16 | ***N*-methylimidazole (0.15)** | $Ca(OTf)_2$ (0.2) | 75% |
| 17 | **2,6-lutidine (0.15)** | $Ca(OTf)_2$ (0.2) | 56% |

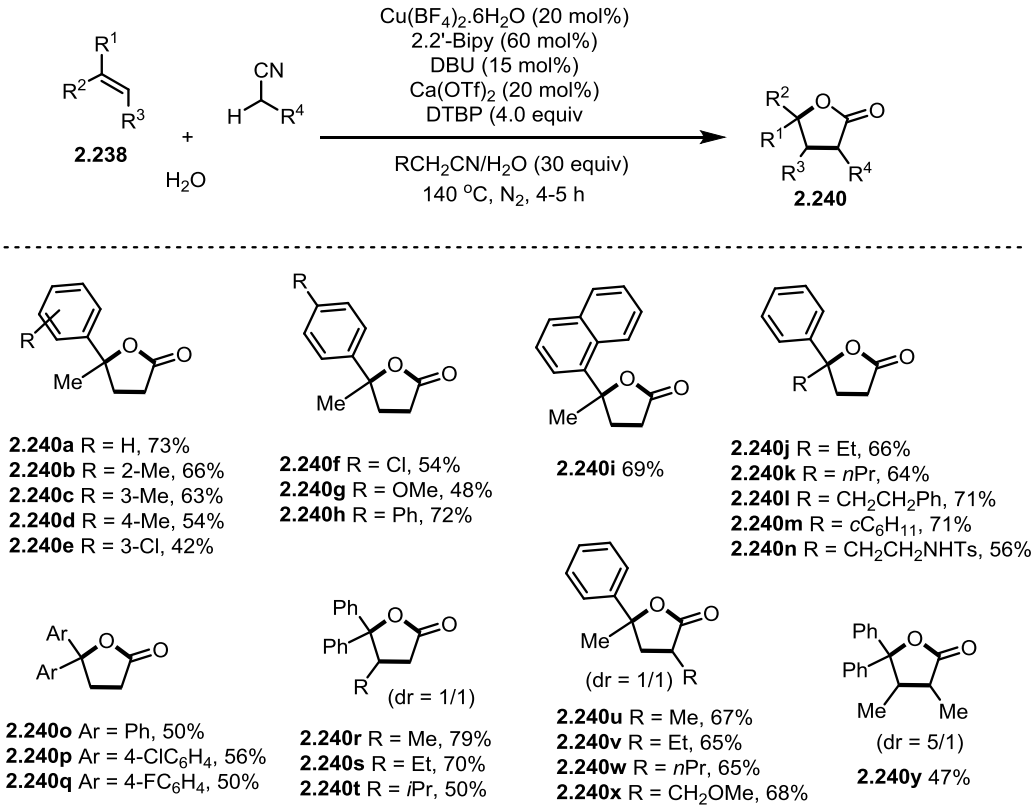
(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(BF_4)_2.6H_2O$ (0.2 equiv), 2,2'-bipyridine (0.6 equiv), DTBP (4 equiv), base (0.1-0.2 equiv), additive (0.2 equiv) and water (30 equiv) in MeCN (*c* 0.025 M) under nitrogen at 140 ºC for 4 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield.

Overall, under optimum conditions [$Cu(BF_4)_2.6H_2O$ (0.2 equiv), 2,2'-bipyridine (0.6 equiv), DTBP (4 equiv), DBU (0.15 equiv) , $Ca(OTf)_2$ (0.2 equiv) and water (30 equiv) in MeCN (*c* 0.025 M) under nitrogen at 140 ºC for 4 h], **2.240a** was isolated in 73% isolated yield. We noted that the reaction proceeded equally well in the dark. Since three chemical bonds were created in this domino process, the average yield per chemical bond formation is around 90%.

### 3.2.2. Substrate scope

With the optimized conditions in hand, the scope of this copper-catalyzed formal [2+2+1] heteroannulation was investigated. The result is summarized in Scheme 2.47.

Firstly, the effect of the substituents on the aromatic ring of α-methyl styrenes **2.238a-i** was examined. The substrates with both electron-donating (Me, OMe) and electron-withdrawing (Cl) substituents on the aromatic ring regardless of their positions afforded γ-butyrolactones **2.240b-i** in moderate to good yields. Surprisingly, electron-donating substituents (Me, OMe) at *para*-position to double bond provided desired products in lower yields (**2.240d**, **2.240g**) even though these groups stabilize the carbenium intermediate. A risk of cationic polymerization could be an explanation in these cases. Indeed, when Me substituent resides at *ortho* position, steric effect might hinder the polymerization process, resulting in the formation of **2.240b** in higher yield compared to **2.240c** and **2.240d**.



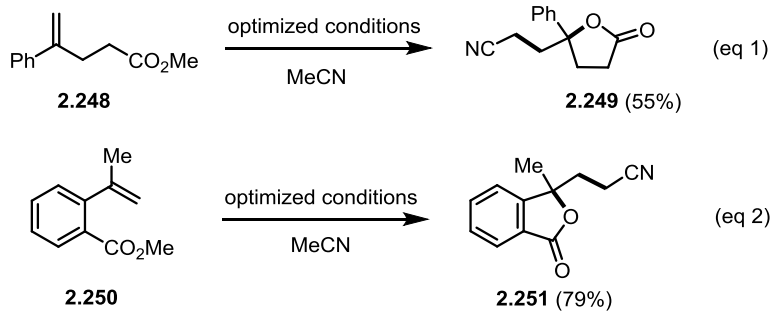

**Scheme 2.47: Substrate scope for Cu-catalyzed [2+2+1]-heteroannulation to γ-lactones**

α-Primary alkyl (methyl, ethyl, isopropyl and (2-phenyl)ethyl), secondary alkyl (cyclohexyl) and functionalized alkyl substituted styrenes also participated in the reaction to provide the corresponding γ-butyrolactones (**2.240j-n**) in good yields. Unfortunately, tertiary alkyl such as R = *t*Bu, did not afford any desired product.

1,1-Diaryl substituted alkenes was found to be compatible to the reaction, leading to the corresponding lactones (**2.240o-q**) in slightly lower yields. Side products resulting from Me• radical addition were observed in these cases. High activity towards radical species of 1,1-diarylethylenes reduces chemoselectivity of radical addition step, wherein both Me• radical and electrophilic •$CH_2CN$ could react with electron-rich double bonds. As a result, the optimum conditions for these substrates were carried out with 2.5 equiv of DTBP instead of 4.0 equiv.

Importantly, trisubstituted alkenes participated in the reaction equally well to give efficiently the 3,4,4-trisubstituted γ-butyrolactones **2.240r-t**. Particularly, **2.240r** was obtained in very good yield indicating Thorpe-Ingold effect in lactonization step.

Propionitrile, butyronitrile, valeronitrile and 2-methoxypropionitrile are competent alkylating agents to initiate the domino process leading to the corresponding γ-butyrolactones **2.240u-x** as a mixture of two diastereoisomers. Pleasingly, reaction of trisubstituted alkenes with propionitrile afforded the 2,3,4,4-tetrasubstituted γ-butyrolactone **2.240y**, albeit in a slightly reduced yield (47%).

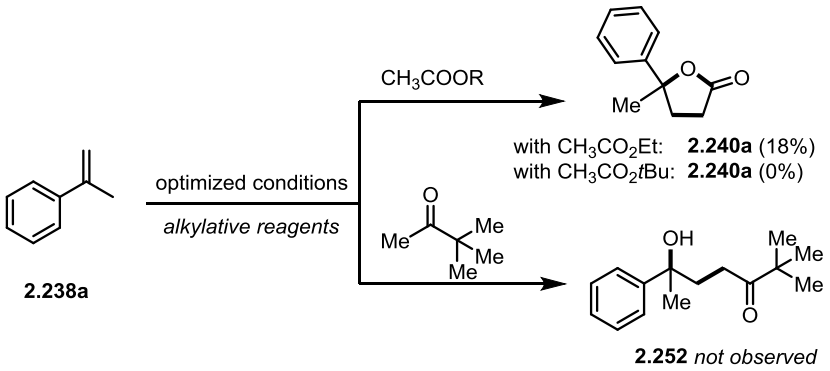



**Scheme 2.48: Additional examples on the synthesis of nitrile-containing γ-lactones**

The reaction of methyl 4-phenylpent-4-enoate (**2.248**) with acetonitrile under standard conditions afforded lactone **2.249** in which the cyano group remained untouched (eq 1, Scheme 2.48). Similarly, methyl 2-(prop-1-en-2-yl)benzoate (**2.250**) was converted under identical conditions to lactone **2.251** (eq 2). The observed high chemo-selective cyclization could be account for by the direct interception of the benzylic cation by the tethered methoxycarbonyl function. Moreover, the efficient formation of phthalide **2.251** suggests these conditions could provide an improvement to our previous method for the synthesis of phthalides, wherein benzoic derivatives are required to the success of catalytic system.[129a]

Unfortunately, aliphatic alkenes, α-monosubstituted styrenes were found to be unsuitable to our reaction conditions, either furnishing γ-lactones in modest yields or undergoing degradation/polymerization.

The attempts for exploring alternative alkylative reagents to alkylnitriles were implemented (Scheme 2.49). Reaction of **2.238a** in ethyl acetate under optimized conditions afforded lactone **2.240a** in 18% isolated yield. On the other hand, the same reaction in *tert*-butyl acetate and in pinacolone led to a complex mixture. This result indicated that it might be possible to generate $EtOOCCH_2$• and to engage it in subsequent domino processes.

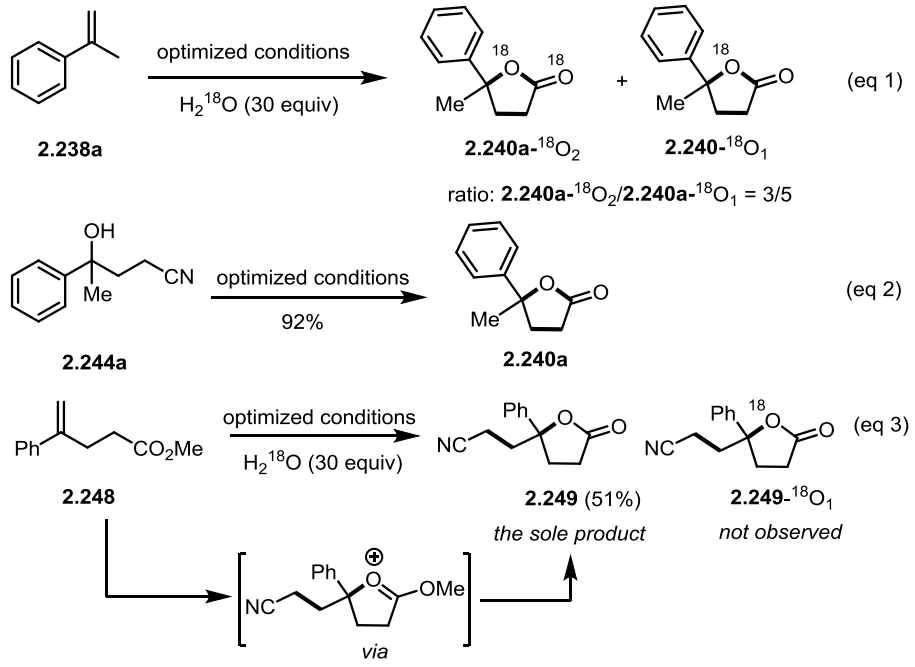



**Scheme 2.49: Initial attempts on finding alternative alkylative reagents**

### 3.2.3. Mechanistic aspect

We turned out attention to the reaction mechanism. Although the mechanism of copper-catalyzed cyanoalkylation of unactivated alkenes has been studied intensively in previous works,[129] a slight change in the reaction conditions might entail the alteration in mechanism.

In the absence of $Cu(BF_4)_2.6H_2O$ or 2,2'-bipyridine, no trace amount of γ-butyrolactone **2.240a** was formed. On the other hand, without DTBP, **2.238a** was converted to lactone **2.240a** in 39% NMR yield in the presence of a stoichiometric amount of $Cu(BF_4)_2.6H_2O$. These observations are in accord with our previous conclusion that the Cu catalyst played a key role in the generation of acetonitrile radical **2.241** and that DTBP served mainly as an oxidant to regenerate the Cu(II) species.[174] In our initial survey of reaction conditions, we have isolated the dimer **1.246**, resulting most probably from the dimerization of the benzylic radical **2.242** due to its inefficient oxidation to carbenium ion **2.243**. Therefore, the copper catalyst played a dual role in this transformation, *ie*, to generate the cyanoalkyl radical and to oxidize selectively the adduct radical to the carbenium ion.




**Scheme 2.50: $^{18}$O-labbeling and control experiments**

Moreover, an isotope labelling experiment was conducted to gain further mechanistic insights. Reaction of alkene **2.238a** with acetonitrile in the presence of $H_2{}^{18}O$ ($^{18}$O content 97%) under otherwise standard conditions afforded double and mono $^{18}$O labelled products **2.240a**-$^{18}O_2$ and **2.240a**-$^{18}O_1$ in a ratio of 3/5 (eq 1, Scheme 2.50). The up-field shift of $^{13}$C NMR signals of C1 and C4

[174] (a) Morris, G. E.; Oakley, D.; Pippard, D. A.; Smith, D. J. H. *J. Chem. Soc. Chem. Commun.* **1987**, 411. (b) Gephart III, R. T.; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 17350.

in **2.240a**-$^{18}O_2$/**2.240a**-$^{18}O_1$ relative to **2.240a** [$\Delta\delta_{(C=O)}$ $^{16}O-^{18}O$ = + 2.5 Hz, [$\Delta\delta_{(C4)}$ $^{16}O-^{18}O$ = + 4.9 Hz] is in agreement with literature reports.[175] The results of these control experiments indicated that the oxygen atoms in lactones **2.240** came from water rather than from adventurous oxygen or DTBP. Furthermore, submitting the authentic sample of tertiary alcohol **2.244a**[176] to the standard reaction conditions afforded γ-lactone **2.240a** in 92% yield (eq 2) indicating that the tertiary alcohol **2.244** could indeed be an intermediate on the way to lactone **2.240** (*cf.* Scheme 2.44). A similar labelling experiment of alkene **2.248** with acetonitrile in the presence of $H_2{}^{18}O$ was also carried out, affording unlabelled **2.249** as the sole product (eq 3). The result further implies that the intermediate benzylic carbocation was exclusively trapped by tethered methoxycarbonyl function rather than water.

### 3.2.4. Synthetic application of Copper-catalyzed [2+2+1]-heteroannulation of alkenes

(±)-Sacidumlignan D (**2.253**) was isolated by Yue and co-workers from the plant *Sarcostemma acidum* (Roxb.) collected from Hainan island, China, where the local people used it for the treatment of chronic cough and postnatal hypogalactia.[177]

To illustrate the synthetic application of our heteroannulation process, a total synthesis of (±)-sacidumlignan D (**2.253**) was undertaken (Scheme 2.51). Lithium-halogen exchange of arylbromide **2.254**, readily synthesized in two steps from 2,6-dimethoxyphenol,[177d] followed by two-fold nucleophilic addition of the resulting aryllithium species to propionyl chloride furnished a tertiary alcohol, which, without purification, was dehydrated under acidic conditions to give alkene **2.255**. The key copper-catalyzed [2+2+1] heteroannulaton of **2.255** with acetonitrile and water under our standard conditions occurred smoothly to afford lactone **2.256** in 60% yield. Treatment of **2.256** with LHMDS followed by methylation of the lithium enolate provided 2,3-*trans* disubstituted lactone **2.257** as an only stereoisomer. Reduction of lactone **2.257** with $LiAlH_4$ afforded tetrahydrofuran **2.258**, which was converted to (±)-sacidumlignan D (**2.253**) in 93% yield under hydrogenolysis conditions. This is the shortest synthesis reported to date.

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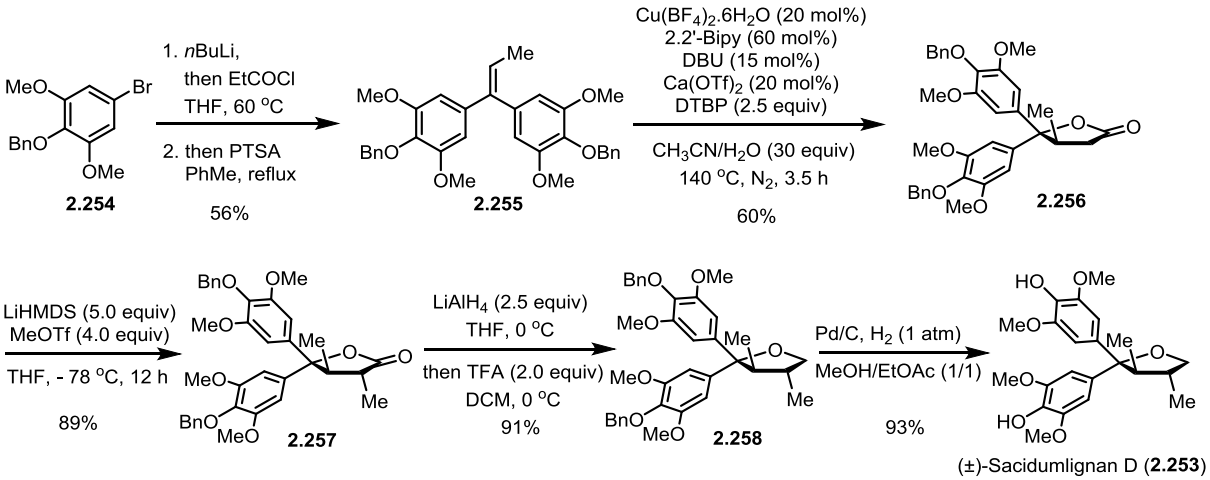
[175] (a) Vederas, J. C. *J. Am. Chem. Soc*. **1980**, *102*, 374. (b) Odabachian, Y.; Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2013**, *52*, 10878. (c) Buyck, T.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc*. **2014**, *136*, 11524.

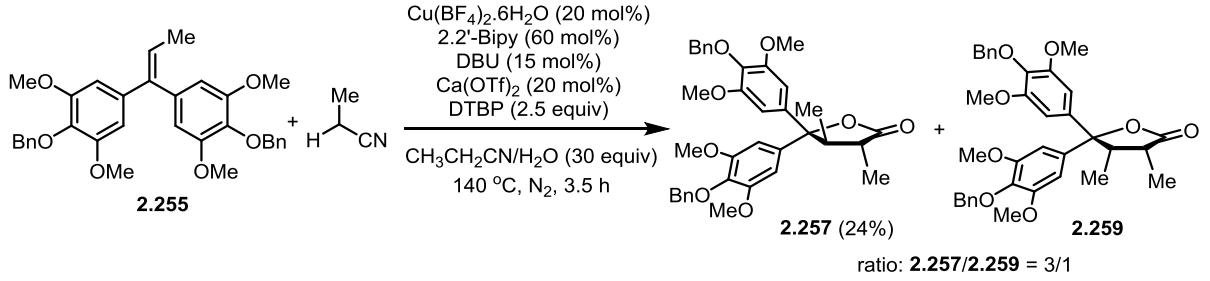
[176] Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624.

[177] (a) Gan, L.-S.; Yang, S.-P.; Fan, C.-Q.; Yue, J.-M. *J. Nat. Prod.* **2005,** *68*, 221. For the synthesis of (±)-Sacidumlignan D: (b) Pandey, D. S. K.; Ramana, C. V. *J. Org. Chem.* **2011**, *76*, 2315. (c) Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 1566. (d) Zhang, J.-J.; Yan, C.-S.; Peng, Y.; Luo, Z.-B.; Xu, X.-B.; Wang, Y.-W. *Org. Biomol. Chem.* **2013**, *11*, 2498. (e) Xie, C.; Bai, D.; Huang, S.-H.; Jia, X.; Hong, R. *Asian J. Org. Chem*. **2014**, *3*, 277.




**Scheme 2.51: Total synthesis of (±)-sacidumlignan D**

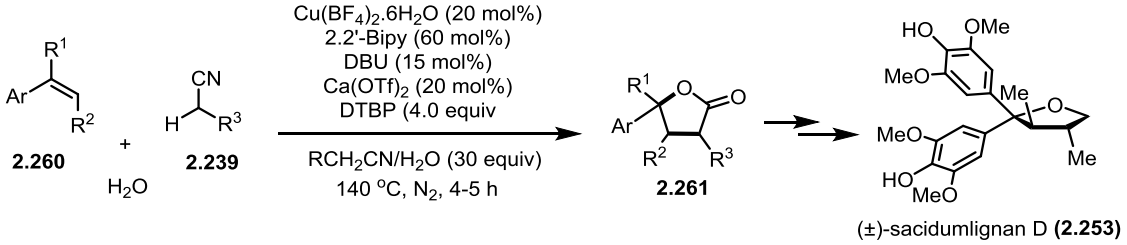
An attempt to improve the synthesis by conducting copper-catalyzed [2+2+1] heteroannulaton of **2.255** with propionitrile to directly access **2.257** was implemented (Scheme 2.52). However, desired 2,3-*trans* disubstituted lactone **2.257** was obtained in 24% yield as major product, accompanying with its 2,3-*cis* isomer in moderate diasteroselectivity (*trans/cis* 3/1). Additional modification of the reaction conditions (copper loading, DTBP loading, temperature…) provided insignificant improvement in yield and diastereoselectivity.




**Scheme 2.52: Heteroannulation of 2.255 with propionitrile**

## 3.3. Conclusion

In summary, we developed a novel copper-catalysed formal [2+2+1]-heteroannulation of styrenes with alkylnitriles and water. The domino process involving direct activation of alkylnitriles, intermolecular hydroxyl-alkylation and intramolecular lactonization, provided an efficient approach to γ-lactone bearing a quaternary carbon center at γ-position via the formation of $C(sp^3)$-$C(sp^3)$, $C(sp^3)$-O and $C(sp^2)$-O bond (Scheme 2.53). The synthetic potential of this novel transformation was demonstrated by the development of a concise total synthesis of (±)-sacidumlignan D.[178]




**Scheme 2.53: Copper-catalyzed [2+2+1]-heteroannulation of alkenes, alkylnitriles and water**

[178] Ha, T. M.; Chatalova-Sazepin, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9249.

# CHAPTER 4

## Copper-Catalyzed Cyanoalkylative Aziridination of Alkenes

## 4.1. Aziridines: Introduction and Synthesis

Aziridine, one of the smallest nitrogen-containing heterocycles, is an important scaffold in organic chemistry. A number of compounds possessing an aziridine ring have been shown to exhibit potent bioactivity, which is usually associated with its ring strain. For example, mitosanes **2.262-2.268**, isolated from soil extracts of *Streptomyces verticillatus*,[179] exhibit both anti-tumor and antibiotic activities:[180] Structure-activity relationship studies have identified that the aziridine ring is an important moiety for such anti-tumor activity. Many synthetic aziridines have also been revealed to exhibit useful biological properties. For instance, aziridine β-D-galactopyranoside **2.270** was evaluated to possess high selectivity against breast cancer.[181] 3-azabicyclo[3.1.0]hexane **2.271** was demonstrated as selective dopamine reuptake inhibitor for treatment of nervous system disorders including inter alia, vasomotor symptoms, chronic pain.[182] Moreover, aziridines are wildly used as versatile synthetic intermediates in organic synthesis. Due to inherent ring strain and the electronegativity of nitrogen atom, aziridines are willing to undergo ring cleavage under relative mild conditions by nucleophiles to access highly complex molecules such as amino alcohols, amino acids and other nitrogen-containing compounds by ring-opening reactions.[183]

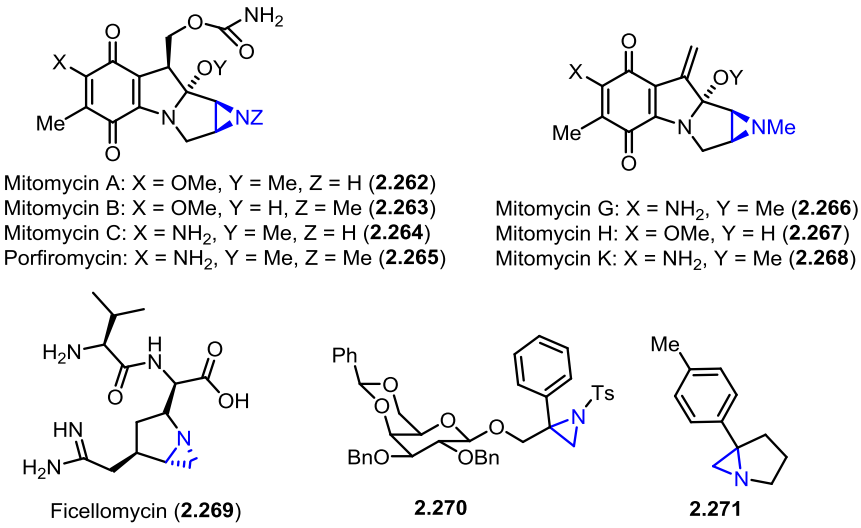


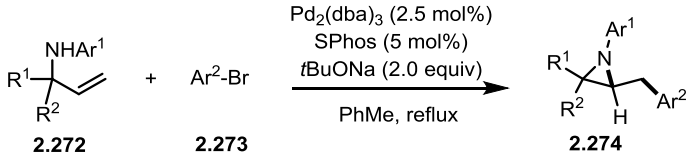

**Figure 2.7: Examples of aziridine-containing natural products and bioactive compounds**

Owing to their importance in bioactivities and synthetic application, the development of methodologies toward aziridines has been of broad interest for at least half a century.[184] Among many

[179] Lefemine, D. V.; Dann, M.; Barbatschi, E.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohnos, N. *J. Am. Chem. Soc.* **1962**, *34*, 3184.
[180] Kasai, M.; Kono, M. *Synlett.* **1992**, 778.
[181] Vega-Pérez, J. M.; Palo-Nieto, C.; Vega-Holm, M.; Góngora-Vargas, P.; Calderón-Montaño, J. M.; Burgos-Morón, E.; López-Lázaro, M.; Iglesias-Guerra, F. *Eur. J. Med. Chem.* **2013**, *70*, 380.
[182] Deecher, D. C; Abou-Gharbia, M. A. *US20060019966A1*.
[183] (a) Tanner, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 599. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
[184] Degenaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881.

efficient synthesis strategies, intramolecular cyclization of 1,2-vicinal haloamines or amino alcohols,[185] addition of nitrenes to alkenes,[186] addition of carbene to imines[187] have been extensively investigated.

Despite of great advances in transition metal-catalyzed difunctionalization of alkenes has been made and applied in various syntheses of five-membered heterocycles such as pyrolidines,[5d] the corresponding methodologies involving the formation of carbon-heteroatom and carbon-carbon bonds for construction of strained three-membered heterocycles such as aziridines remained challenging. To the best of our knowledge, there were limited examples on aziridination of allylic amines via carboamination reported in the literature. For examples, Yorimitsu and Oshima reported a novel method for the synthesis of trisubstituted aziridines **2.274** by palladium-catalyzed reaction of allylic amines **2.272** with aryl halides **2.273** (Scheme 2.54).[188] The reaction was initiated by *syn*-aminopalladation to give C($sp^3$)-N bond, followed by reductive elimination to afford C($sp^3$)-C($sp^2$) bond.

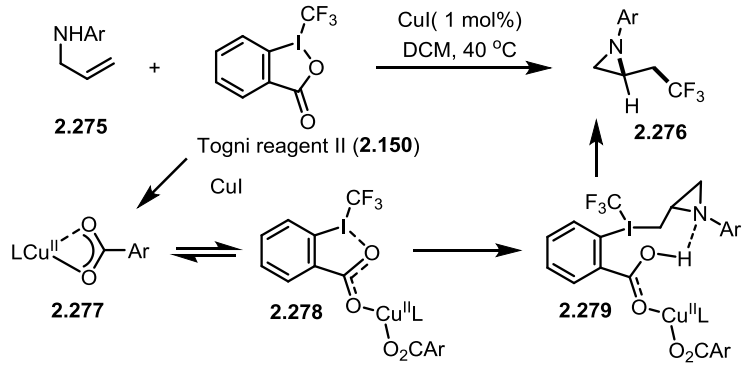



**Scheme 2.54: Palladium-catalyzed carboamination of allylic amines with aryl bromides**

Sodeoka and coworkers reported an efficient aminotrifluoromethylation of allylamines **2.275** with Togni reagent II **2.150** in the presence of CuI catalyst via the sequence of C($sp^3$)-N and C($sp^3$)-C($sp^3$) bond formation, to afford trifluoromethylated aziridines **2.276** in good to excellent yields (Scheme 2.55).[189] The synthetic utility of this method was demonstrated by further functionalization of the products *via* one-pot aziridination and nucleophilic ring-opening. The mechanistic study was recently carried out by the same group, indicating that the reaction was not initiated by the addition of $CF_3$• radical species to allylic amines to form C($sp^3$)-C($sp^3$) bond.[190] Indeed, Cu(II) complex **2.277** generated *in situ* from Cu(I) complex and Togni reagent II, acts as a Lewis acid to activate hypervalent iodane and enhance its electrophilicity. Subsequent intramolecular electrophilic addition

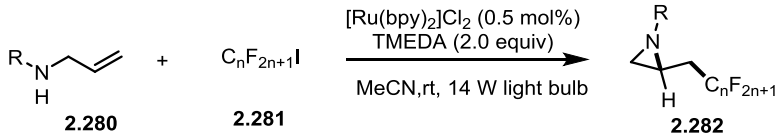
[185] (a) Trost, B. M.; Fleming, J. E. G. I. *Comprehensive Organic Synthesis*, Pergamon, Oxford, **1991**, Vol. 7, p 467; (b) Gribble, G. W.; Gilchrist, T. L. *Progress in Heterocyclic Chemistry*, Pergamon Elsevier Science, Oxford, **2000**; Vol. 12, Chapter 4.1, p.57.
[186] (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (c) Atkinson, R. S. Tetrahedron, **1999**, *55*, 1519. (d) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899.
[187] (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1995**, *34*, 676. (b) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc. Perkin Trans.* 1, **1999**, 2293.
[188] Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 7224.
[189] Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7841.
[190] Kawamura, S.; Egami, H.; Sodeoka, M. *J. Am. Chem. Soc.* **2015**, *137*, 4865.

of nitrogen atom to double bond produces C($sp^3$)-N and intermediate **2.279** which can furnish aziridine **2.276** upon the reductive elimination.




**Scheme 2.55: Copper-catalyzed aminotrifluoromethylation of allylic amines**

An alternative aminotrifluoromethylation of allylic amines and trifluoromethyl iodide was developed by Cho using Ru-bipyridine complexes as photoredox catalyst (Scheme 2.56).[191] Mild conditions enabled a wide range of unactivated alkenes to participate the difunctionalization. Perfluoroalkylation by using perfluoroalkyl iodides such as $C_3F_7I$ and $C_4F_9I$ also proceeded equally well under the same conditions.

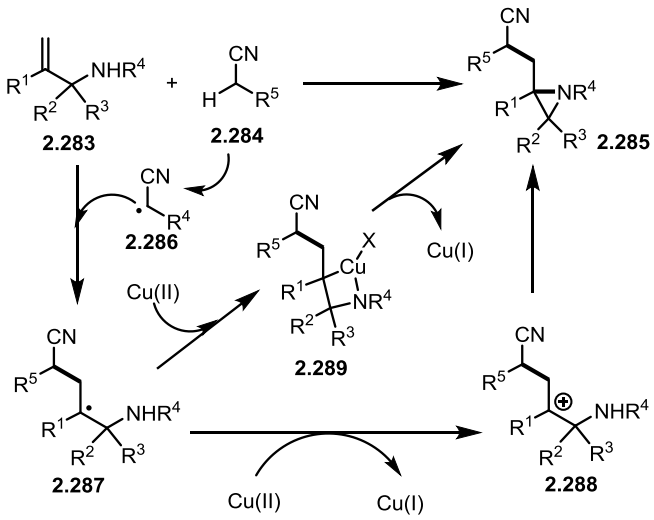



**Scheme 2.56: Copper-catalyzed aminotrifluoromethylation of allylic amines**

Although aminotrifluoromethylation was well-established for construction of trifluoromethylated aziridines which are biologically valuable in medicinal chemistry, the limited chemical modifications with trifluomethyl group offers minimal choices for further transformation. Inspired by our recent research program on difucntionalization of unactivated alkenes using alkylnitrile as alkylating reagents,[129] we turned our attention on the synthesis of aziridines by applying this general strategy. We propose herein an unprecedented copper-catalyzed amino-cyanoalkylation of allylamines **2.283** with alkylnitriles **2.284** to afford nitrile-containing aziridines **2.285**. The working hypothesis of our reaction design is depicted in Scheme 2.57. In situ generation of electrophilic cyanoalkyl radical **2.286** followed by its addition to electron-rich alkene **2.283** would afford adduct radical **2.287** that could be oxidized by a suitable metal salt to the carbenium ion **2.288**. Trapping of the latter by the pendant amino group would afford the desired aziridine **2.285**. Alternatively, radical recombination of **2.287** with Cu(II) salt followed by ligand exchange with the tethered amine would

[191] Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem. Eur. J.* **2013**, *19*, 6209.

provide four-membered metalocycle **2.289**, which would furnish the product **2.285** with concurrent release of Cu(I) salt upon reductive elimination,.



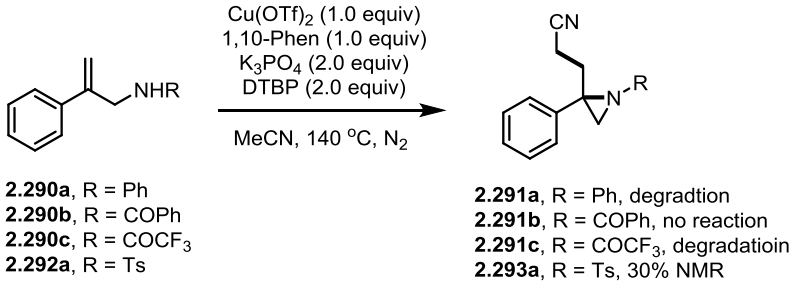

**Scheme 2.57: Our designed copper-catalyzed amino-cyanoalkylation of allylic amines**

Overall, the reaction would provide aziridines bearing a quaternary carbon center *via* formation of a $C(sp^3)$-$C(sp^3)$ and a $C(sp^3)$-N bonds involving a direction activation of C-H bond of alkylnitriles.

## 4.2. Results and Discussion

### 4.2.1. Conditions survey

Primary screening was carried out in order to quickly discover suitable substrates to the proposed cyanoalkylation. Based on above underline principle (Scheme 2.52), key intermediates **2.287** and **2.288** could be stabilized by an aryl group at C-2 position ($R^1$ = aryl) so that 2-arylated allylamines were chosen as models to investigate this transformation. Several *N*-monosubstituted 2-phenylprop-2-en-1-amine were prepared, then introduced to our previous conditions[129] using stoichiometric amount of copper [$Cu(OTf)_2$ (1.0 equiv), 1,10-phenanthroline (1.0 equiv), $K_3PO_4$ (2.0 equiv) and DTBP (2.0 equiv) in acetonitrile at 140 ºC for 2.5 hours] (Scheme 2.58).




**Scheme 2.58: Primary result of copper-mediated amino-cyanoalkylation of alkenes**

*N*-Phenyl and *N*-trifluoroacetyl allylamines (**2.290a**, **2.290c**) led to degradation, while *N*-benzoyl substrate **2.290b** was not reactive in reaction conditions. The instability of *N*-allyl-*N*-phenyl secondary amine to oxidative conditions and the susceptibility of trifluoroacetamide to the hydrolysis in harsh conditions might reason for the experimental outcome of **2.290a** and **2.290c**, respectively. Fortunately, the desired aziridine was observed in 30% NMR, 21% isolated yield when *N*-tosylated allylamine **2.292a** was employed. The primary results suggested that $pK_{a(NH)}$ could be a key factor to the success of the cyclization.

Using *N*-tosylated 2-phenylprop-2-en-1-amine (**2.292a**) as test substrates, the reaction conditions were surveyed by varying copper sources, ligands, oxidants, bases and additives.

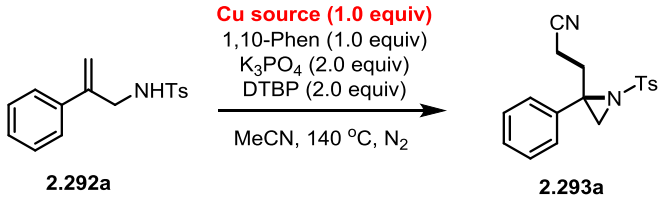
#### 4.2.1.1. Screening conditions: Copper sources

We continued our investigation on the aziridination by screening the copper sources. Initially, the stoichiometric version was examined when **2.292a** was introduced to reaction conditions consisting of copper salts (1.0 equiv), 1,10-phenanthroline (1.0 equiv), $K_3PO_4$ (2.0 equiv) and DTBP (2.0 equiv) in degassed acetonitrile at 140 ºC for 2.5 hours. Gratifyingly, the desired product **2.293a** was obtained in 30% and 52% NMR yields when $Cu(OTf)_2$ and $Cu(BF_4)_2.6H_2O$ were employed, respectively (entry 1, 3, Table 2.8). Only a trace amount of the desired product was observed when other copper(II) salts and copper(I) halides were used. As discussed previously, ionic copper(II)

species such as $Cu(BF_4)_2$ and $Cu(OTf)_2$ are more efficient for oxidation of the proposed radical intermediate **2.287** to carbenium, therefore facilitating intramolecular cyclization to afford aziridine.

It is worthy to note that in the absence of $Cu(BF_4)_2.6H_2O$ or 2,2'-bipyridine, no trace amount of aziridine **2.293a** was formed. On the other hand, without DTBP, **2.292a** was converted to lactone **2.293a** in 18% NMR yield in the presence of a stoichiometric amount of $Cu(BF_4)_2.6H_2O$ with 35% NMR conversion after 1 h. These experimental observations indicated that Cu catalyst played a key role in the generation of acetonitrile radical **2.286**.

**Table 2.8: Copper sources screening[(a)]**




**2.292a** **2.293a**

| Entry | Cu source (1.0 equiv) | Yield[(b)] (conversion) |
|---|---|---|
| 1 | **$Cu(OTf)_2$** | 30% (100% conv.) |
| 2 | **$Cu(OAc)_2$** | trace (100% conv.) |
| 3 | **$Cu(BF_4)_2$. 6H2O** | 52% (100% conv.) |
| 4 | **$CuSO_4$** | trace (100% conv.) |
| 5 | **$Cu(acac)_2$** | trace (42% conv.) |
| 6 | **$CuF_2$** | trace (92% conv.) |
| 7 | **$CuCl_2$** | trace (100% conv.) |
| 8 | **CuX (X = Cl, Br, I)** | trace (100% conv.) |

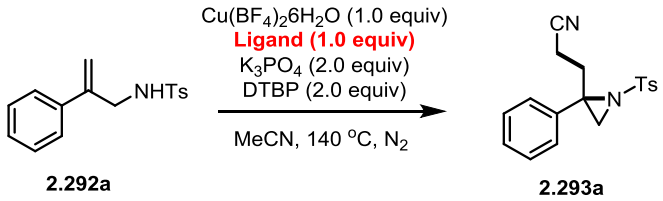
(a) Reaction conditions: The reaction was performed in a sealed tube: **2.292a** (0.05 mmol), copper source (1.0 equiv), 1,10-phenanthroline (1.0 equiv), DTBP (2.0 equiv) and $K_3PO_4$ (2.0 equiv) in MeCN (*c* 0.067 M) under nitrogen at 140 °C for 2.5 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.2.1.2. Screening conditions: Ligands

The influence of *N*,*N*-ligand to the reaction outcome was next examined. Unfortunately, substituted 1,10-phenanthroline ligands were found to be incompatible to the reaction (entry 1-4, Table 2.9). Yield of **2.293a** was slightly increased when phenanthroline (**L1**) was replaced by 2,2'-bipyridine (**L5**). Attempts to modify electron-property of 2,2'-bipyridine by introducing substituents at 4,4' and 2,2'- positions gave no improvement (entry 6-9). Again, in cases of both phenanthrolines and bipyridines as ligands, when substituents locate at *ortho*- positions to nitrogen atoms, the combination of copper/N,N-ligand was inactive to convert allylamine to the desired product (**L4**, **L9**, entry 4, 9).

Terpyridine (**L10**) and 2,2'-bipyrimidine (**L11**) were suitable, albeit, providing the desired product in decreased yields (entry 10, 11).

**Table 2.9: Ligand screening**[a]




**2.292a** **2.293a**

| Entry | Ligand (1.0 equiv) | Yield[b] (conversion) |
|---|---|---|
| 1 | **L1** | 52% (100% conv.) |
| 2 | **L2** | 21% (100% conv.) |
| 3 | **L3** | 0% (100% conv.) |
| 4 | **L4** | 0% (100% conv.) |
| 5 | **L5** | 60% (100% conv.) |
| 6 | **L6** | 38% (100% conv.) |
| 7 | **L7** | 54% (100% conv.) |
| 8 | **L8** | 43% (100% conv.) |
| 9 | **L9** | 0% (100% conv.) |
| 10 | **L10** | 43% (100% conv.) |
| 11 | **L11** | 39% (100% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.292a** (0.05 mmol), $Cu(BF_4)_2 6H_2O$ (1.0 equiv), *N*,*N*-ligand (1.0 equiv), DTBP (2.0 equiv) and $K_3PO_4$ (2.0 equiv) in MeCN (*c* 0.067 M) under nitrogen at 140 °C for 2.5 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

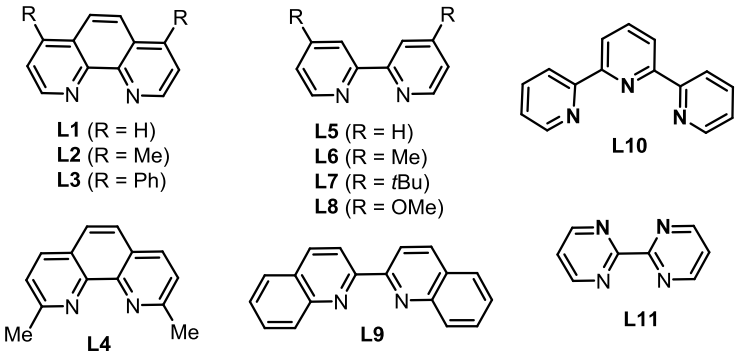


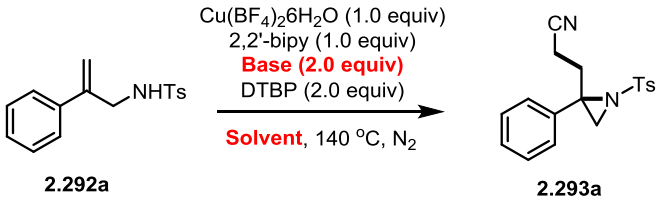

**Figure 2.8: Selected ligands for screening**

#### 4.2.1.3. Screening conditions: Bases and solvents

Primary screening on substituents on nitrogen atom implied that the deprotonation of NH-Ts has impact on the reaction. As the result, we turned our attention on the effect of base to the reaction outcome. Unfortunately, no improvement was achieved when many different inorganic bases were examined. Weaker bases (compared to $K_3PO_4$) such as carbonate or carboxylate provided only trace of the desired product (entry 3, 4, Table 2.10). Stronger bases such as hydroxyl or alkoxide resulted in lower yield or degradation (entry 5, 6). It is worthy to note that in the absence of base, the formation of the desired product was not observed, implying the importance of the deprotonation to the success of reaction.

Co-solvent system which was found to have positive impact on the previous copper-catalyzed cyanomethylation was also investigated. However, the presence of methanol, ethanol and isopropanol were detrimental to the formation of **2.293a** (entry 7, 8). Lewis acid-promoted ring-opening of aziridines by alkoxide could explain for this observation. Indeed, bulky *tert*-butanol that cannot induce nucleophilic attack, had no influence to the outcome of the reaction (entry 9). The presence of additional 10% DMA provided the desired aziridine equally well, while co-solvent of MeCN/DMSO shut down the reaction (entry 10, 11).

**Table 2.10: Base and solvent screening[(a)]**




**2.292a** **2.293a**

| Entry | Base | Solvent | Yield[(b)] (Conversion) |
|---|---|---|---|
| 1 | **$K_3PO_4$** | MeCN | 60% (100% conv.) |
| 2 | **$Na_3PO_4$** | MeCN | 25% (100% conv.) |
| 3 | **$K_2CO_3$, $Na_2CO_3$** | MeCN | <20% (100% conv.) |
| 4 | **KOAc, CsOPiv** | MeCN | <20% % (100% conv.) |
| 5 | **KOH** | MeCN | 30% (100% conv.) |
| 6 | **KO*t*Bu** | MeCN | 0% (100% conv.) |
| 7 | $K_3PO_4$ | **MeCN/MeOH (19/1)** | 0% (100% conv.) |
| 8 | $K_3PO_4$ | **MeCN/*i*PrOH (19/1)** | 40% (100% conv.) |
| 9 | $K_3PO_4$ | **MeCN/*t*BuOH (19/1)** | 60% (100% conv.) |
| 10 | $K_3PO_4$ | **MeCN/DMA (9/1)** | 56% (100% conv.) |

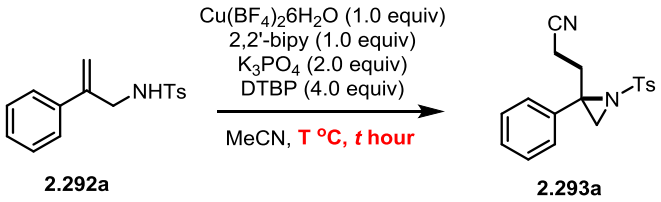
| | | | |
|---|---|---|---|
| 11 | $K_3PO_4$ | **MeCN/DMSO (9/1)** | 0% (100% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.292a** (0.05 mmol), $Cu(BF_4)_26H_2O$ (1.0 equiv), 2,2'-bipyridine (1.0 equiv), DTBP (2.0 equiv) and Base (2.0 equiv) in given solvent (*c* 0.067 M) under nitrogen at 140 ºC for 2.5 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.2.1.4. Screening conditions: Time and Temperature

The degradation of the desired product in the presence of MeOH by mostly possible ring-opening reaction implied that aziridine **2.293a** could be degraded during reaction by the moisture in MeCN. Careful monitoring reaction time was performed. Indeed, the reaction was complete after 30 min, at 140 ºC, affording **2.2293a** in 79% NMR yield (entry 2, Table 2.11). Slightly better yield was obtained when the reaction was conducted at reduced temperature 130 ºC for 1 h (entry 3). Further decreasing temperature to 120 ºC gave comparable yield.

**Table 2.11: Time and Temperature[(a)]**




**2.292a** **2.293a**

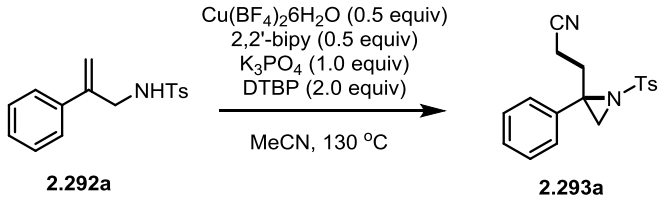
| Entry | Time (h) | Temperature (ºC) | Yield[(b)] (Conversion) |
|---|---|---|---|
| 1 | 2.5 | 140 | 60% (100% conv.) |
| 2 | 0.5 | 140 | 79% (100% conv.) |
| 3 | 1.0 | 130 | 82% (100% conv.) |
| 4 | 0.5 | 130 | 75% (87% conv.) |
| 5 | 2.0 | 120 | 77% (100% conv.) |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.292a** (0.05 mmol), $Cu(BF_4)_26H_2O$ (1.0 equiv), 2,2'-bipyridine (1.0 equiv), DTBP (2.0 equiv) and $K_3PO_4$ (2.0 equiv) in MeCN (*c* 0.067 M) under nitrogen at T ºC for t h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard.

#### 4.2.1.5. Screening conditions: Copper loading and final tuning

With promising result of stoichiometric version in hand, we further explored the amino-cyanoalkylation of **2.292a** at reduced copper loading. When 50 mol% of copper was employed, **2.293a** was obtained in 67% NMR yield (entry 1, Table 2.12). Significant improvement was achieved when ratio of copper/ligand was changed from 1/1 to 1/2 (entry 2), and $K_3PO_4$ loading was reduced to 0.5 equiv (entry 3). Finally, by increasing amount of DTBP and decreasing temperature, aziridine **2.293a** was obtained in 88% isolated yield (entry 4). Gratefully, further reducing copper loading to 20 mol%, yield of the desired product was only slightly reduced to 84% (entry 5).

**Table 2.12: Copper loading screening[(a)]**




**2.292a** **2.293a**

| Entry | Variation | Yield[(b)] (Conversion) |
|---|---|---|
| 1 | none | 67% (100% conv.) |
| 2 | [Cu]/bipy/$K_3PO_4$ = 0.5/1.0/1.0 (equiv) | 78% (100% conv.) |
| 3 | [Cu]/bipy/$K_3PO_4$ = 0.5/1.0/0.5 (equiv) | 85% (100% conv.) |
| 4 | [Cu]/bipy/$K_3PO_4$ = 0.5/1.0/0.5 (equiv), DTBP (4.0 equiv), 120 ºC | 92% (88%)[(c)] (100% conv.) |
| 5 | [Cu]/bipy/$K_3PO_4$ = 0.2/0.45/0.3 (equiv) DTBP (4.0 equiv), 120 ºC | 88% (84%)[(c)] (100% conv.) |

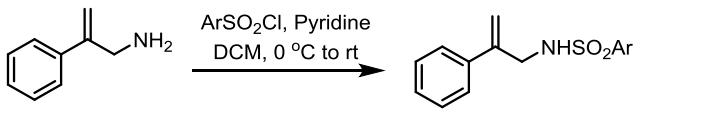
(a) Reaction conditions: The reaction was performed in a sealed tube: **2.292a** (0.05 mmol), $Cu(BF_4)_26H_2O$ (0.5 equiv), 2,2'-bipyridine (0.5 equiv), DTBP (2.0 equiv) and $K_3PO_4$ (1.0 equiv) in MeCN (*c* 0.067 M) under nitrogen at 130 ºC for 1 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_2Br_2$ as an internal standard. (c) Isolated yield.

Overall, under optimum conditions [$Cu(BF_4)_2.6H_2O$ (0.2 equiv), 2,2'-bipyridine (0.45 equiv), DTBP (4.0 equiv) and $K_3PO_4$ (0.3 equiv) in MeCN (*c* 0.067 M) under nitrogen at 120 ºC for 1 h, *N*-tosylated 2-phenylprop-2-en-1-amine (**2.292a**) was converted into nitrile-containing aziridine **2.293**a in 84% isolated yield.

## 4.2.2. Substrate scope

### 4.2.2.1. Synthesis of starting materials

Several approaches were applied for the synthesis of *N*-sulfonylated 2-arylprop-2-en-1-amine derivatives. The first approach leading to the synthesis of **2.292b-d** is depicted in Scheme 2.59. 2-phenylprop-2-en-1-amine (**2.294**)[192] was sulfonylated with the corresponding sulfonyl chloride in the presence of pyridine (Scheme 2.59).



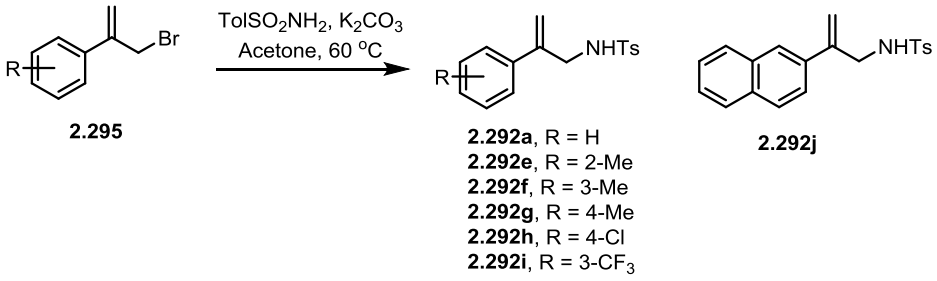

**2.294**

**2.292b**, Ar = Ph
**2.292c**, Ar = 2,4,6-(*i*Pr)$_3$C$_6$H$_2$
**2.292d**, Ar = 4-NO$_2$-C$_6$H$_4$

**Scheme 2.59: Synthesis of 2.292b-d**

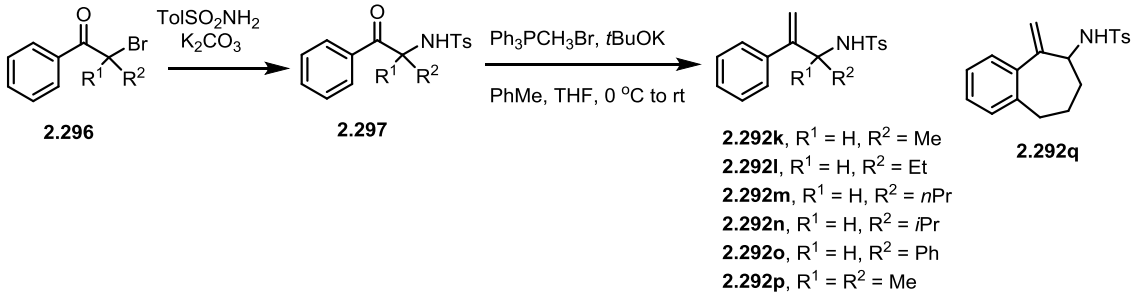
[192] Fort, D. A.; Woltering, T. J.; Nettekoven, M.; Knust, H.; Bach, T. *Chem Commun* **2013**, *49*, 2989.

The second approach leading to the synthesis of **2.292a**, **2.292e-j** is depicted in Scheme 2.60. Nucleophilic substitution of 2-aryl-3-bromoprop-2-en-1 **2.295** with tosylamine in the presence of $K_2CO_3$ in acetone at 60 °C afforded the corresponding *N*-tosylated allylamines (Scheme 2.60).




**Scheme 2.60: Synthesis of 2.292a and 2.292e-j**

The third approach leading to the synthesis of **2.292k-q** is depicted in Scheme 2.61. Allylamines **2.292k-q** with substituents at α-position of nitrogen atom were accessed through a sequence of amination of α-bromoketones **2.296** with tosylamine, followed by Wittig reaction.




**Scheme 2.61: Synthesis of 2.292k-q**

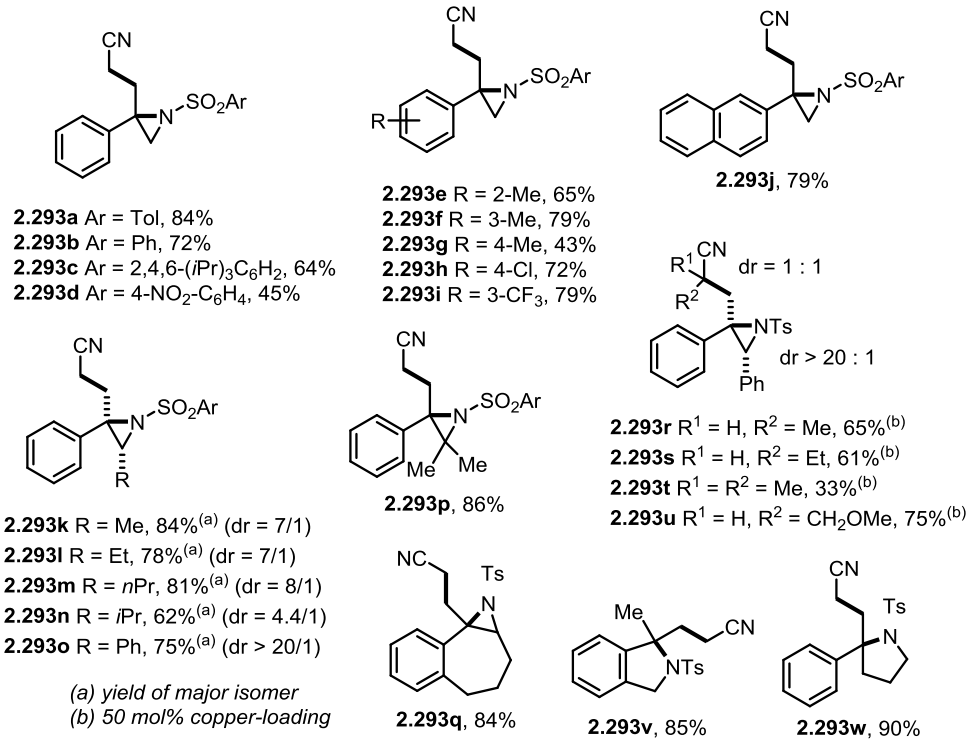
### 4.2.2.2. Substrate scope

With the optimized conditions in hand, the scope of this copper-catalyzed amino-cyanoalkylation of allylamines **2.292** was investigated. The result is summarized in Scheme 2.62.

Different *N*-tosylated 2-phenylprop-2-en-1-amines **2.292b-d** participated in the amino-cyanoalkylation with MeCN to provide the corresponding aziridines in good yields. Gratefully, arylsulfonylated substrate with bulkyl substituents such as **2.292c** gave a reasonable yield. While slower carboamination was observed in case of **2.292d**, producing the desired aziridine **2.293d** in slightly lower yield. Although the deprotonation is facile, the lack of nucleophilicity due to electron-conjugating effect of $NO_2$ might account for this experimental observation.

The effect of the substituents on the aromatic ring of 2-arylprop-2-en-1-amines **2.292e-i** was next examined. The substrates with both weak electron-donating (Me) and electron-withdrawing (Cl) substituents on the aromatic ring regardless of their positions afforded aziridines **2.293e-i** in moderate to good yields. Surprisingly, when Me substituent resided at *para*- or *ortho*- position, the desired

products were obtained in lower yields (**2.293e**, **2.293g**). Particularly, MeO-substituted substrates regardless of its position, gave a mixture of complex products. The stability of the carbenium intermediate **2.288** due to conjugation with Me and MeO on aromatic ring, not only facilitates the nucleophilic trapping by the pendant amino group (see Scheme 2.57), but also triggers cationic polymerization and particularly $Cu(BF_4)_2$ Lewis-acid promoted ring opening of strained aziridines, leading to the degradation.




**Scheme 2.62: Substrate scope for Cu-catalyzed amino-cyanoalkylation of alkenes**

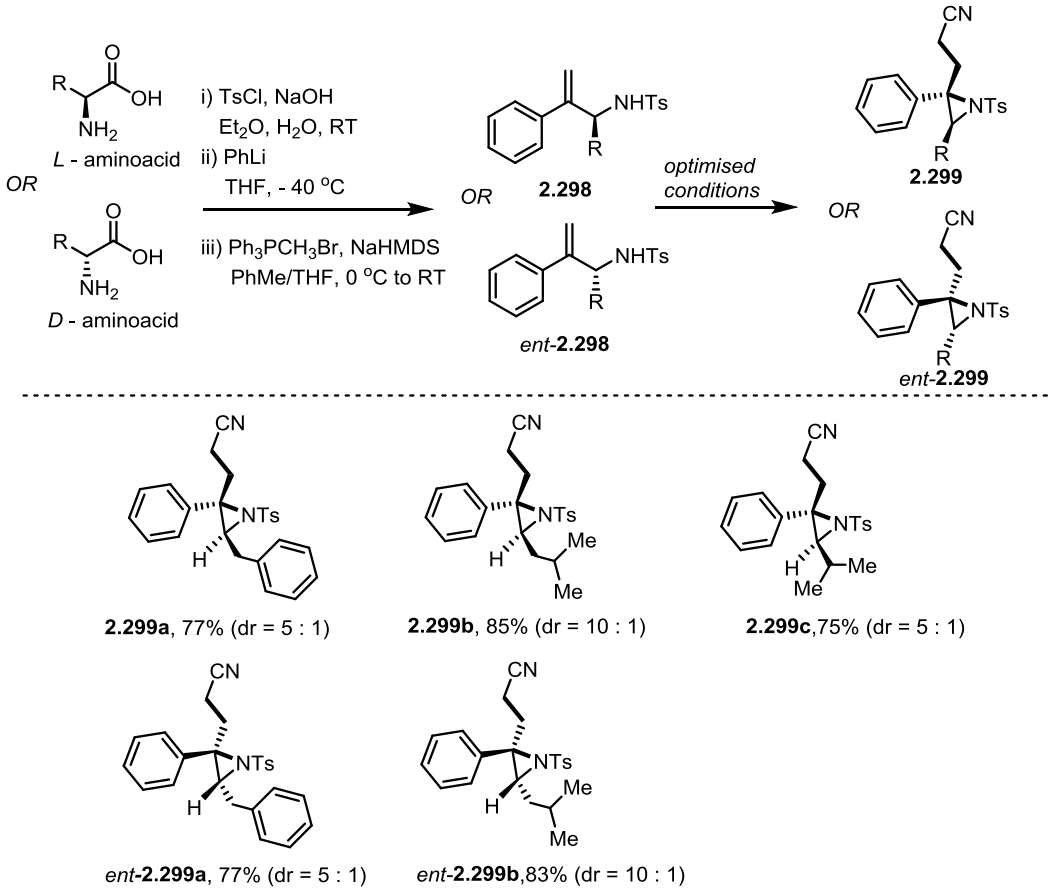
1-Monosubstituted 2-phenylprop-2-en-1-amines **2.292k-o** also participated in the reaction to provide the corresponding 2,2,3-trisubstituted aziridines **2.293k-o** in excellent overall yields (>90% yield), indicating that Thorpe-Ingold effect might involve in cyclization step. Good to excellent diastereoselectivity was observed in these cases, wherein the diastereoisomers with substituent and phenyl group locating on the different sides of aziridine ring, were major isomers (determined by ROESY experiments). Gratifyingly, tetrasubstituted aziridine **2.293p** which is typically challenging target to synthesize was also accessed in excellent yield from 3,3-disubstituted 2-phenylprop-2-en-1-amine **2.292p**.

Propionitrile, butyronitrile, *iso*-butyronitrile and 2-methoxypropionitrile are competent alkylating agents to initiate the domino process with **2.292o** leading to the corresponding aziridines **2.293r-u**, albeit higher cooper loading (50 mol%) was needed.

Pleasingly, the optimized reaction conditions can be applied to the synthesis of nitrile-containing pyrrolidines **2.293v** and **2.293w** from the corresponding starting materials in excellent yields.

### 4.2.3. Synthetic application

To illustrate the synthetic application of our amino-cyanoalkylation of alkenes, synthesis of enantiorich aziridines bearing a quaternary carbon via chiral pool approach was implemented (Scheme 2.63). Enantiorich 1-monosubstituted 2-phenylprop-2-en-1-amines **2.298**, ***ent*-2.298** were accessed from the corresponding commercially available *L*/*D*-amino acids through three-step sequence including: (1) protection of amino group by tosyl chloride; (2) reaction with organoaryl lithium to form enantiorich *N*-tosylated α-aminoketones; (3) subsequent Wittig reaction of these intermediates to afford chiral 1-monosubstituted 2-phenylprop-2-en-1-amines **2.298**, ***ent*-2.298**. Gratefully, copper-catallyzed amino-cyanoalkylation of these chiral alkenes under the optimized conditions led to the formation of enantiorich (>96% ee) aziridines **2.299**, ***ent*-1.299** bearing two chiral carbon centers in high yield and enantioselectivity. Overall, starting from simple *L*/*D*-phenylalanine, leucine and valine, enantiorich aziridines with benzyl, isobutyl, and isopropyl substituent at C-3 respectively, were successfully prepared.

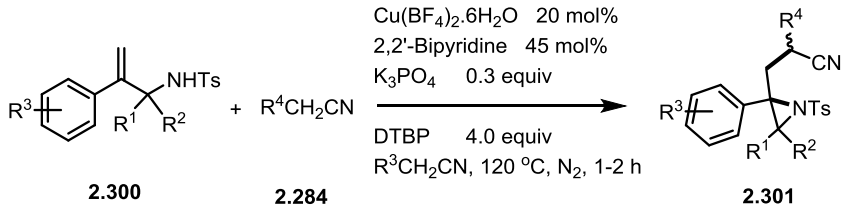



**Scheme 2.63: Synthesis of chiral trisubstituted aziridines by Cu-catalyzed cyanoalkylative aziridination**

With a wide range of chiral natural and synthetic aminoacis, this synthetic approach could provide efficiently various enantiorich 2,2,3-trisubstituted aziridines which are challenging targets for organic synthesis, especially asymmetric synthesis. Moreover, as versatile synthetic building blocks, these aziridines could be further transformed to many useful scaffolds with the pre-installed enantiorich carbon centers.

## 4.3. Conclusion

In summary, we developed a novel copper-catalysed amino-cyanoalkyation of 2-arylprop-2-en-1-amines with alkylnitriles. The domino process involving direct activation of alkylnitriles, intermolecular cyanoalkylation and intramolecular aziridination, provided an efficient approach to aziridines bearing a quaternary carbon center *via* the formation of C($sp^3$)-C($sp^3$), and C($sp^3$)-N (Scheme 2.64). The synthetic potential of this novel transformation was demonstrated by the development of an efficient synthesis to chiral 2,2,3-trisubstituted aziridines through chiral pool approach.




**Scheme 2.64: Copper-catalyzed amino-cyanoalkylation of alkynes to aziridines**

# CHAPTER 5

# Copper-Catalyzed Carboazidation of Alkenes with Acetonitrile and Sodium Azide

*Note: This project was realized in collaboration with Dr. Ala Bunescu*

## 5.1. Carboazidation of Alkynes to Synthesis of Organoazides

Organoazides are important class of organic compounds, which are widely used as valuable intermediates and building blocks in synthesis.[193] Azido group can undergo various transformations such as reduction, cycloaddition and rearrangement.[194] Particularly, azides are well-known for copper-catalyzed 1,3-dipolar addition with terminal alkynes (Click chemistry) which are extensively applied in medicinal chemistry, combinatorial chemistry, polymer chemistry.[195] Furthermore, azido group was found in many bioactive compounds and has been used for designing lead compounds for drug discovery (Figure 2.9). For instance, azidothymidine (AZT, **2.302**) is highly potent nucleoside analogue reverse-transcriptase inhibitor which is used to prevent and treat HIV/AIDS.[196] Besides their importance in medicinal chemistry, organic azides have found broad applications in other research areas such as polymer chemistry, material science.[191,197]

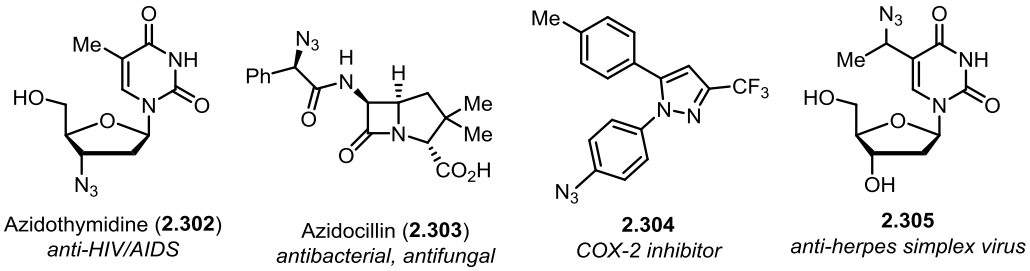


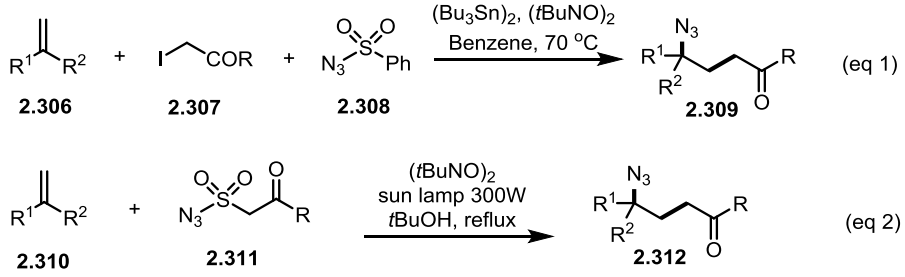

**Figure 2.9: Examples of biologically active organoazides**

Owing to their highly valuable application, the development of an efficient and convenient synthesis of organoazides has become an active research area for organic chemists. In the light of recent advances in difunctionalization, the establishment of novel methodologies involving difuntionalization of alkenes with the introduction of azido group has attracted a great attention. Despite diazidation,[198] azidocyanation,[199] azidophosphonation,[200] oxyazidation[198b] and haloazidation[201]

[193] Wu, K.; Liang, Y.; Jiao, N., *Molecules* **2016,** *21*, 352
[194] (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.
[195] (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128. (b) Meldal, M.; Tomøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.
[196] Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.
[197] Bräse, S.; Banert, K. *Organic Azides*, Wiley-VCH, Weinheim, **2010**.
[198] (a) Chen, Z.-M.; Zhang, Z.; Tu, Y.-Q.; Xu, M.-H.; Zhang, F.-M.; Li, C.-C.; Wang, S.-H. *Chem. Commun.* **2014**, *50*, 10805. (b) Lu, M. Z.; Wang, C. Q.; Loh, T. P. *Org. Lett.* **2015**, *17*, 6110. (c) Yuan, Y. A.; Lu, D. F.; Chen, Y. R.; Xu, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 534.
[199] (a) Online, V. A.; Xu, L.; Mou, X.; Chen, Z.; Wang, S. *Chem. Commun.* **2014**, *50*, 10676. (b) Wu, Z.; Ren, R.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10821.
[200] Xu, J.; Li, X.; Gao, Y.; Zhang, L.; Chen, W.; Fang, H.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 11240.
[201] (a) Valiulin, R. A.; Mamidyala, S.; Finn, M. G. *J. Org. Chem.* **2015**, *80*, 2740. (b) Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *J. Org. Chem.* **2016**, *81*, 4020. (c) Chen, L.; Xing, H.; Zhang, H.; Jiang, Z.-X.; Yang, Z. *Org. Biomol. Chem.* **2016**, *14*, 7463.

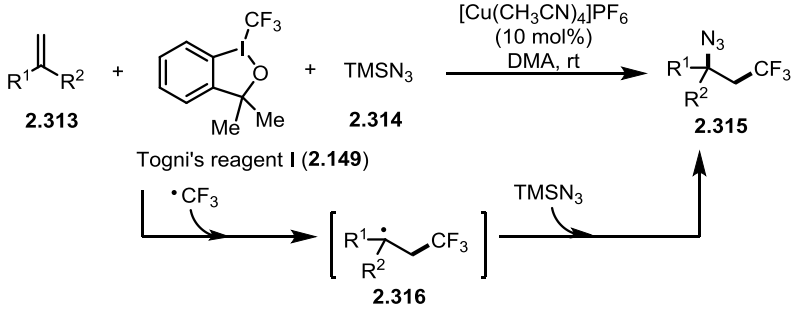
of alkenes have been extensively studied recently, alternative carboazidation with the formation of $C(sp^3)$-$C(sp^3)$ bond is restricted to few examples.

Among those, Renaud group developed carboazidation reaction of unactivated terminal alkenes **2.306** employing an α-iodocarbonyl **2.307** and arenesulfonyl azide **2.308** as the alkyl and the azide sources, respectively (eq 1, Scheme 2.65).[202a] This transformation requires stoichiometric amount of hexabutylditin as a chain-transfer agent. The same group developed very elegant, tin-free desulfonylative carboazidation reaction employing alkanesulfonyl azides **2.311** as source for both alkyl and azide groups (eq 2).[202b] Those approaches were efficiently applied to the synthesis of a series of alkaloids, demonstrating the utility of the formed azido-containing products.[203]




**Scheme 2.65: Renaud's carboazidation of alkenes**

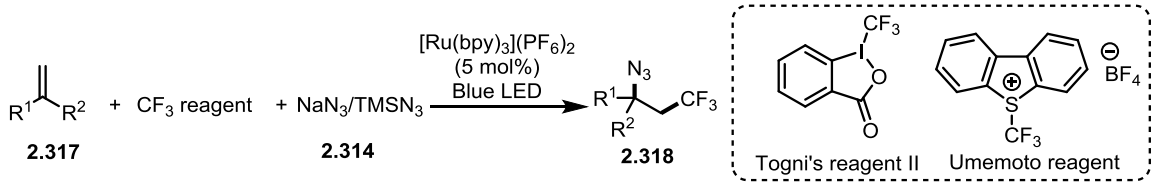
Recently, Liu and coworker reported a novel copper-catalyzed three-component azidotrifluoromethylation of alkenes under mide conditions, in which Togni reagent I was employed as an oxidant as well as a $CF_3$ source, while trimethylsilylazide was employed as azide source (Scheme 2.66).[204] The transformation was postulated to proceed through radical addition of $CF_3$• to alkenes, followed by trapping the radical intermediate with $TMSN_3$ to afford triflouromethyl-containing organozides. Both activated and unactivated alkenes with a wide range of functional groups were suitable to this reaction.




**Scheme 2.66: Copper-catalyzed azidotrifluoromethylation of alkenes by Liu**

[202] (a) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3460. (b) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511.
[203] Lapointe, G.; Kapat, A.; Weidner, K.; Renaud, P. *Pure Appl. Chem.* **2012**, *84*, 1633.
[204] Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1881.

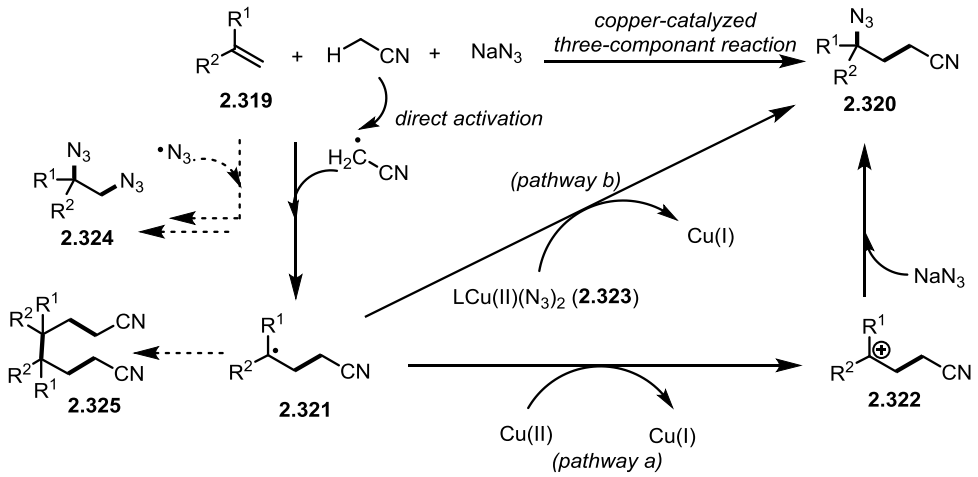
A similar azidotrifluoromethyl of alkenes was developed by Magnier and Masson using photoredox catalysis (Scheme 2.67).[205] Difunctionalization of alkenes involving the formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-N bond was achieved in the presence of ruthenium-pyridine complex, Togni's[205a] or Umemoto's[205b] reagent and $Na_3/TMSN_3$ as photocatalyst, $CF_3$ source and azido source, respectively. However, these transformations were only limited to styrenes and enamines derivatives.




**Scheme 2.67: Photoredox-catalysed azidotrifluoromethylation of alkenes by Magnier and Masson**

As a continuation of our recent research program aimed at developing copper-catalyzed alkylative difunctionalization of alkenes using alkylnitriles as a key reactant,[129] we propose herein a novel synthesis of γ-cyanoazides **2.320** by a copper-catalyzed three-component carboazidation reaction of alkenes **2.319** with acetonitrile and sodium azide. The working hypothesis of this transformation was postulated as the following (Scheme 2.68). Addition of *in situ* generated α-cyanomethyl radical to alkene **2.319** would afford the adduct radical **2.321** that could be further oxidized to the carbenium ion **2.322**. Trapping of the latter by azide anion would afford γ-cyanoazide **2.320** (pathway a). Alternatively, the radical adduct **2.321** would undergo azide transfer with copper(II)-azide complex **2.323** to furnish γ-cyanoazides **2.320** with concurrent release of copper(I) species (pathway b). For the desired domino sequence to proceed towards the formation of **2.320**, the catalytic conditions should satisfy the following mechanistic criteria: a) selective suppression of alternative process of azide radical resulting from oxidation of azide anion by metal salt, leading to the formation of diazide adduct **2.324**;[206] b) fast conversion of the resulting nucleophilic radical **2.321** to carbenium ion **2.322** or Cu(III) complex **2.323** to avoid the formation of dimer side product **2.325**.

[205] (a) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240. (b) Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 4340.
[206] (a) Fristad, W.; Brandvold, T.; Peterson, J.; Thompson, S. *J. Org. Chem.* **1985**, *50*, 3647. (b) Snider, B. B.; Lin, H. *Synth. Commun.* **1998**, *28*, 1913.




**Scheme 2.68: Proposed copper-catalyzed azidocyanomethylation of alkenes**

## 5.2. Results and Discussion

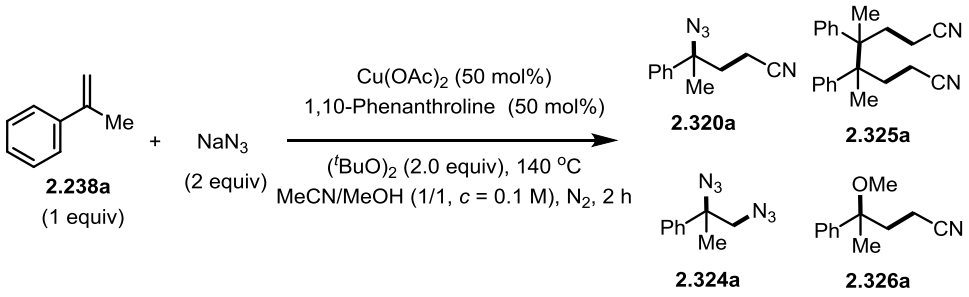
### 5.2.1. Conditions survey

Using α-methyl styrene (**2.238a)** and acetonitrile as test substrates, the reaction conditions were surveyed by varying copper sources, ligands, oxidants, bases and additives.

#### 5.2.1.1. Primary screening

Primary screening was carried out by applying our reported conditions.[131] In the presence of $Cu(OAc)_2$ (50 mol%), 1,10-Phenanthroline (50 mol%), DTBP (2.0 equiv) and sodium azide (2.0 equiv) in mixed solvent MeCN/MeOH, at 140 ºC after 2 h, γ-cyanoazide **2.320a** was obtained in 63% NMR, 56% isolated yield together with a trace amount of side product **2.325a** resulting from dimerization of radical intermediate **2.321** (entry 1, Table 2.13). Interestingly, alkylative etherification product **2.326a**[129c] was not observed even though reaction was performed in MeOH as a co-solvent. Significant improvement was observed when a stoichiometric amount of copper was used, affording 75% isolated yield **2.320a** (entry 2). In the absence of MeOH as co-solvent (entry 3-5), the reaction was less efficient, giving a mixture of products. Particularly, in the absence of 1,10-phenanthroline, diazide **2.324a** became a major product (entry 4). Lowering the temperature gave the similar result, albeit affording less clean reaction with the formation of **2.326a** (entry 6). Moreover, the reduction of $NaN_3$ loading disfavoured the selectivity of **2.320a** over **2.324a** (entry 7). Surprisingly, azidocyanomethylation was found to be cleaner and more efficient under aerobic atmosphere, contrasting to our precedent works wherein oxygen was detrimental to the catalytic system (entry 8, 9).

**Table 2.13: Primary screening[a]**




| Entry | Variation from above conditions | Ratio<br>**2.320a : 2.325a : 2.324a : 2.326a** | Yield[b] |
|---|---|---|---|
| 1 | **None** | 9.2 : 1.0 : - : - | 63 (56)[c] |
| 2 | **$Cu(OAc)_2$ (1.0 equiv)** | >20 : 1.0 : - : - | 88 (75) [c] |
| 3 | **MeCN only** | 4.2 : 1.0 : - : - | 35 |
| 4 | **No Phen, MeCN only** | 1.2 : 1.0 : 2.4 : - | 26 |
| 5 | **No ($^t$BuO)$_2$, MeCN only** | 2.1 : 1.0 : - :- | 17 |
| 6 | **110 $^o$C** | 16.5 : - : - : 1.0 | 66 |
| 7 | **$NaN_3$ (1.2 equiv)** | 8.8 : 2.7 : - : 1.0 | 35 |
| 8 | **Under air** | >20 : 1.0 : - : - | 65 (59)[c] |
| 9 | **Under $O_2$** | >20 : 1.0 : - : - | 68 (61)[c] |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(OAc)_2$ (0.5 equiv), 1,10-phenanthroline (0.5 equiv), DTBP (2.0 equiv) and $NaN_3$ (2.0 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under nitrogen at 140 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_3NO_2$ as an internal standard. (c) Isolated yield.

Overall, according to the primary screening, we could conclude that (1) using MeOH as co-solvent is important to suppression of the formation of dimer **2.325a** and to the efficacy of azidocyanomethylation; (2) ligands and equivalence of $NaN_3$ have strong impact on the formation of diazide product **2.324a**; (3) the formation of alkylative etherification **2.326a** generally is not favourable over the desired product **2.320a** at high temperature.

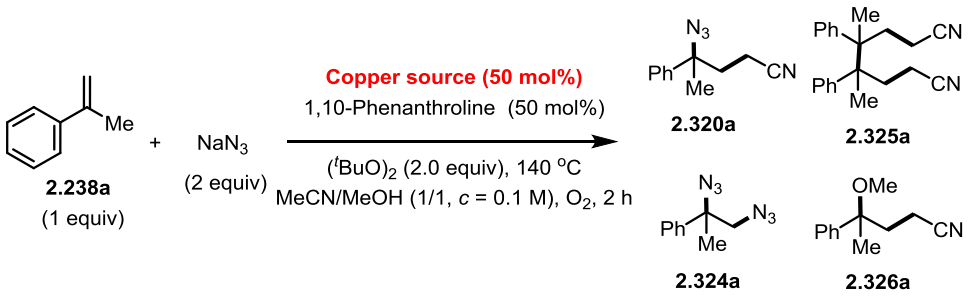
#### 5.2.1.2. Screening conditions: Copper sources

With above promising result in hand, we next investigated the influence of copper sources on the outcome of the reaction (Table 2.14). In contrast to our previous works, $Cu(OTf)_2$ and $Cu(BF_4)_26H_2O$ were less efficient than $Cu(OAc)_2$, providing slightly decrease in yield of **2.320a** along with a trace amount of **2.325a** (entry 2, 3). Significant decrease in yield was observed when other copper(II) sources were used such as $CuF_2$ and $CuSO_4$ (entry 4, 5). Copper(I) and iron sources were

not suitable to the catalytic system, giving dimer **2.325a** as a major product (entry 6, 7). The addition of inorganic and organic bases gave no improvement in yield, but decreased the selectivity of **2.320a**/**2.325a** (entry 8, 9).

The reaction evolution with time was monitored by $^{1}$H-NMR spectroscopy. The reaction was stopped after 20 min before full conversion (TLC). Analysis of the crude mixture showed that the carboamination product **2.320a** was formed in 64% yield and that only a trace amount of dimer was produced (**2.320**/**2.325a** >20/1) (entry 10). After 2 h at 140 °C, the amount of desired compound did not increase, however the dimer **2.325a** was formed in 7% yield. This experimental observation indicated that at certain point the copper catalyst was deactivated and unable to transfer the azide to benzyl radical **2.321** (*cf.* Scheme 2.68). Subsequently, the benzyl radical would dimerize to yield the octanedinitrile **2.325a.** We assumed that the copper (I) species generated at the end of catalytic cycle is not efficiently reoxidized to copper (II).

**Table 2.14: Copper source screening**[(a)]




| Entry | Cu source | Ratio<br>**2.320a : 2.325a : 2.324a : 2.326a** | Yield[(b)] |
|---|---|---|---|
| 1 | **$Cu(OAc)_2$** | >20 : 1.0 : - : - | 68 (61)[(c)] |
| 2 | **$Cu(OTf)_2$** | 6.5 : 1.0 : - : - | 59 |
| 3 | **$Cu(BF_4)_2.6H_2O$** | 6.2 : 1.0 : - : - | 56 |
| 4 | **$CuF_2$** | 7.0 : 1.0 : - : 1.2 | 42 |
| 5 | **$CuSO_4$** | 0.8 : 1.0 : - : - | <30 |
| 6 | **Cu(I) sources** | 0.6-0.9 : 1.0 : - : - | <30 |
| 7 | **$Fe(OAc)_2$** | 1.1 : 1.0 : - : - | <10 |
| 8 | **$Cu(OAc)_2$ + $K_3PO_4$/CsOPiv 20 mol%** | 15-18 : 1.0 : - : - | 66 |
| 9 | **$Cu(OAc)_2$ + DBU 20 mol%** | 13 : 1.0 : - : - | 50 |
| 10[(d)] | **$Cu(OAc)_2$** | >20 : 1.0 : - : - | 64 |

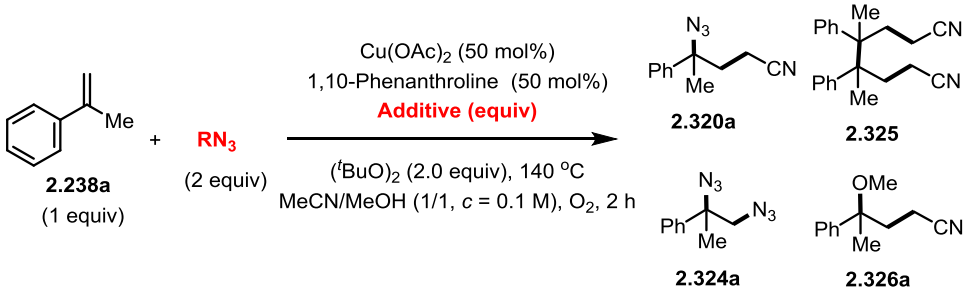
(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), copper source (0.5 equiv), 1,10-phenanthroline (0.5 equiv), DTBP (2.0 equiv)

and $NaN_3$ (2.0 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under $O_2$ atmosphere at 140 °C for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_3NO_2$ as an internal standard. (c) Isolated yield. (d) Reaction time: 20 min.

### 5.2.1.3. Screening conditions: Additive and Azide sources

Based on above hypothesis, different additives such as manganese(III) salts which could act as cooxidants were next screened (Table 2.15). Addition of a catalytic amount of $Mn(OAc)_3$ or $Mn(acac)_3$ provided no improvement, but increased the formation of diazide product **2.324a**[206] (entry 2, 3). Fortunately, in the presence of $MnF_3$ (15 mol%), **2.320a** was obtained in slightly increasing yield (71% NMR and 66% isolated yield), accompanying with minor amount of diazide (entry 4). Applying these conditions, replacing $NaN_3$ by different inorganic or organic azides (entry 5-7), however, afforded the desired product with decreased yields. Gratefully, significant improvement in yield and selectivity (**2.320a**/**2.324a** >20/1) was obtained when additional amount of 1,10-phenanthroline was employed (entry 8), implying that $MnF_3$ coordinates with this *N*,*N*-ligand as well. Finally, after quick screening DTBP loading, the best result for substoichiometric version of azidocyanomethylation was achieved. In the presence of $Cu(OAc)_2$ (50 mol%), 1,10-Phenanthroline (90 mol%), DTBP (2.5 equiv), sodium azide (2.0 equiv) and $MnF_3$ (15 mol%) in mixed solvent MeCN/MeOH (1/1, *c* 0.1 M), at 140 °C after 2 h, γ-cyanoazide **2.320a** was obtained in 84% NMR, 78% isolated yield (entry 9).

**Table 2.15: Additive and azide source screening[(a)]**




| Entry | Additive (equiv) and Azide (equiv) | Ratio<br>**2.320a : 2.325a : 2.324a : 2.326a** | Yield[(b)] |
|---|---|---|---|
| 1 | **No additive, $NaN_3$ (2)** | >20 : 1.0 : - : - | 68 (61)[(c)] |
| 2 | **$Mn(OAc)_3$ (0.15), $NaN_3$ (2)** | 7 : - : 1.0 : - | 68 (61)[(c)] |
| 3 | **$Mn(acac)_3$ (0.15), $NaN_3$ (2)** | 12 : - : 1.0 : - | 39 |
| 4 | **$MnF_3$ (0.15), $NaN_3$ (2)** | 11 : - : 1.0 : - | 72 (66)[(c)] |
| 5 | **$MnF_3$ (0.15), $KN_3$ (2)** | 12 : - : 1.0 : - | 64 |
| 6 | **$MnF_3$ (0.15), $CsN_3$ (2)** | 14 : - : 1.0 : - | 64 |
| 7 | **$MnF_3$ (0.15), $Bu_4NN_3$ (2)** | 12 : - : 1.0 : - | 60 |

| | | | |
|---|---|---|---|
| 8[(d)] | **$MnF_3$ (0.15), $NaN_3$ (2)** | >20 : - : 1.0 : - | 77 (70)[(c)] |
| 9[(d,e)] | **$MnF_3$ (0.15), $NaN_3$ (2)** | >20 : - : 1.0 : - | 84 (78)[(c)] |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(OAc)_2$ (0.5 equiv), 1,10-phenanthroline (0.5 equiv), DTBP (2.0 equiv), $RN_3$ (2.0 equiv) and additive (0.15 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under $O_2$ atmosphere at 140 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_3NO_2$ as an internal standard. (c) Isolated yield. (d) 0.9 equiv of 1,10-phenanthreoline was used. (e) 2.5 equiv of DTBP was used.

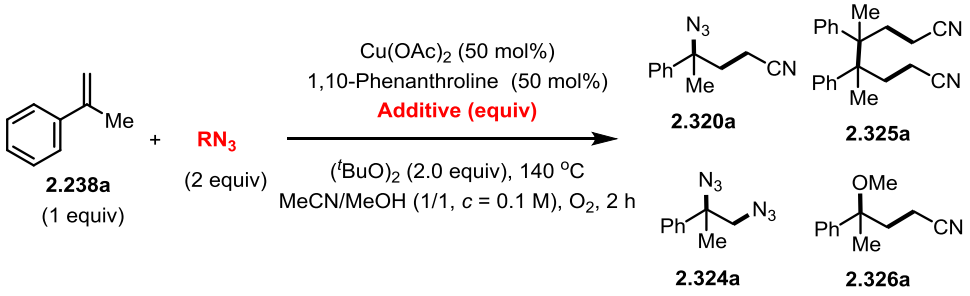
### 5.2.1.4. Screening conditions: Copper loading, ligands and additive loading

Carboazidation was then examined with catalytic copper loading. In the presence of $Cu(OAc)_2$ (20 mol%), 1,10-Phenanthroline (55 mol%), DTBP (2.0 equiv), sodium azide (2.0 equiv) and $MnF_3$ (10 mol%) in mixed solvent MeCN/MeOH (1/1, *c* 0.1 M), at 140 ºC after 2 h, **2.320a** was obtained in 49% NMR yield, along with 10% of dimer **2.325a** (entry 1, Table 2.16).

The impact of *N*,*N*-ligand including 1,10-phenanthrolines, 2,2'-bipyridine, bisoxazoline on the reaction outcome was investigated. Introduction of both electron-donating and electron-withdrawing substituents on 1,10-phenanthroline (**L2**, **L3**) increased the selectivity, but decreased the yield of the desired product (entry 2, 3). Moreover, 2,2'-bipyridine derivatives and bioxazoline (**L4**-**7**, entry 4-7) were found to be less effective compared to 1,10-phenanthroline (**L1**). As a result, 1,10-phenanthroline was chosen for further condition screening.

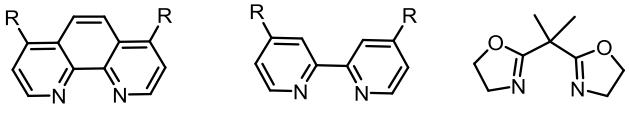
Gratefully, important improvement was observed when additional amount of $MnF_3$ (0.3 equiv) was employed, affording the desired product **2.320a** in 68% NMR, 64% isolated yield (entry 8). The formation of dimer was suppressed completely, however, diazide **2.324a** was observed as a minor product. Finally, increasing 1,10-phenanthroline loading (65 mol%) provided **2.320a** in slightly increased yield (entry 9). It is worth noting that the similar result was obtained when carboazidation was performed under air instead of oxygen atmosphere (entry 9, 10). For the convenience, the following screening was then implemented under air.

**Table 2.16: Ligand and $MnF_3$ loading screening[(a)]**



| Entry | Ligand (equiv) | Ratio 2.320a : 2.325a : 2.324a : 2.326a | Yield[b] |
|---|---|---|---|
| 1 | **L1 (0.55)** | 4.5 : 1.0 : - : - | 49 |
| 2 | **L2 (0.55)** | 10.4 : 1.0 : - : - | 34 |
| 3 | **L3 (0.55)** | 8.7 : 1.0 : - : - | 33 |
| 4 | **L4 (0.55)** | 5.9 : 1.0 : - : - | 36 |
| 5 | **L5 (0.55)** | 5.1 : 1.0 : - : - | 40 |
| 6 | **L6 (0.55)** | 4.0 : 1.0 : - : - | 16 |
| 7 | **L7 (0.55)** | 1.7 : 1.0 : - : - | 31 |
| 8[d] | **L1 (0.55)** | 6.1 : - : 1.0 : - | 68 (64)[c] |
| 9[d] | **L1 (0.65)** | 6.1 : - : 1.0 : - | 71 (66)[c] |
| 10[d,e] | **L1 (0.65)** | 6.5 : - : 1.0 : - | 71 (66)[c] |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(OAc)_2$ (0.2 equiv), ligand (0.55 equiv), DTBP (2.0 equiv), $NaN_3$ (2.0 equiv) and additive (0.15 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under $O_2$ atmosphere at 140 ºC for 2 h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_3NO_2$ as an internal standard. (c) Isolated yield. (d) 0.3 equive of $MnF_3$ was used. (e) Under air atmosphere.




**L1** (R = H)
**L2** (R = OMe)
**L3** (R = Cl)

**L4** (R = H)
**L5** (R = *t*Bu
**L6** (R = Me)

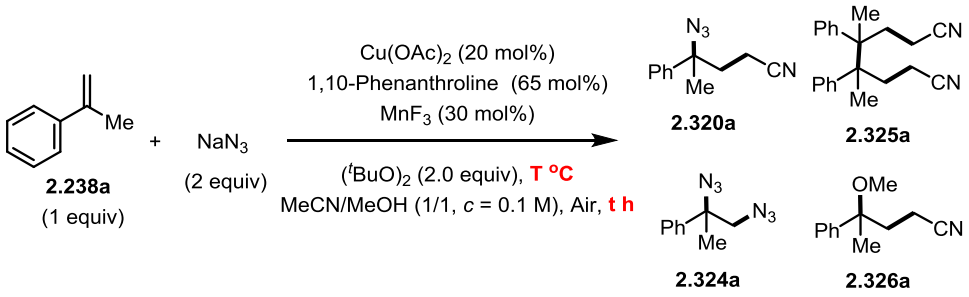
**L7**

**Figure 2.10: Selected ligand for condition screening**

### 5.2.1.5. Screening conditions: Temperature, time and control experiments

Better outcome was observed when slight increase of DTBP peroxide was made, affording **2.320a** in 74% NMR yield (entry 2, Table 2.17). Moreover, lowering temperature of the action was found to be beneficial to the reaction (entry 3, 4). The best result was obtained at 100 ºC, after 10 h, carboazidation product was obtained in 80% NMR, 72% isolated yield (entry 4). However, the undesired diazide **2.324a** was observed in all cases, remaining in the reaction mixture as minor product in around 10% yield.

**Table 2.17: Temperature and time screening[a]**




| Entry | Temperature and Time | Ratio<br>2.320a : 2.325a :<br>2.324a : 2.326a | Yield[b] |
|---|---|---|---|
| 1 | **140 °C, 2 h** | 6.5 : - : 1.0 : - | 71 (66)[c] |
| 2[d] | **140 °C, 2 h** | 6.5 : - : 1.0 : - | 74 (69)[c] |
| 3[d] | **120 °C, 7 h** | 6.5 : - : 1.0 : - | 78 (71)[c] |
| 4[d] | **110 °C, 10 h** | 6.5 : - : 1.0 : - | 80 (72)[c] |

(a) Reaction conditions: The reaction was performed in a sealed tube: **2.238a** (0.1 mmol), $Cu(OAc)_2$ (0.2 equiv), 1,10-phenanthroline (0.65 equiv), DTBP (2.0 equiv), $NaN_3$ (2.0 equiv) and $MnF_3$ (0.3 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under air atmosphere at T °C for t h. (b) Yields determined by $^1$H-NMR spectroscopy with $CH_3NO_2$ as an internal standard. (c) Isolated yield. (d) 2.5 equiv of DTBP was used.

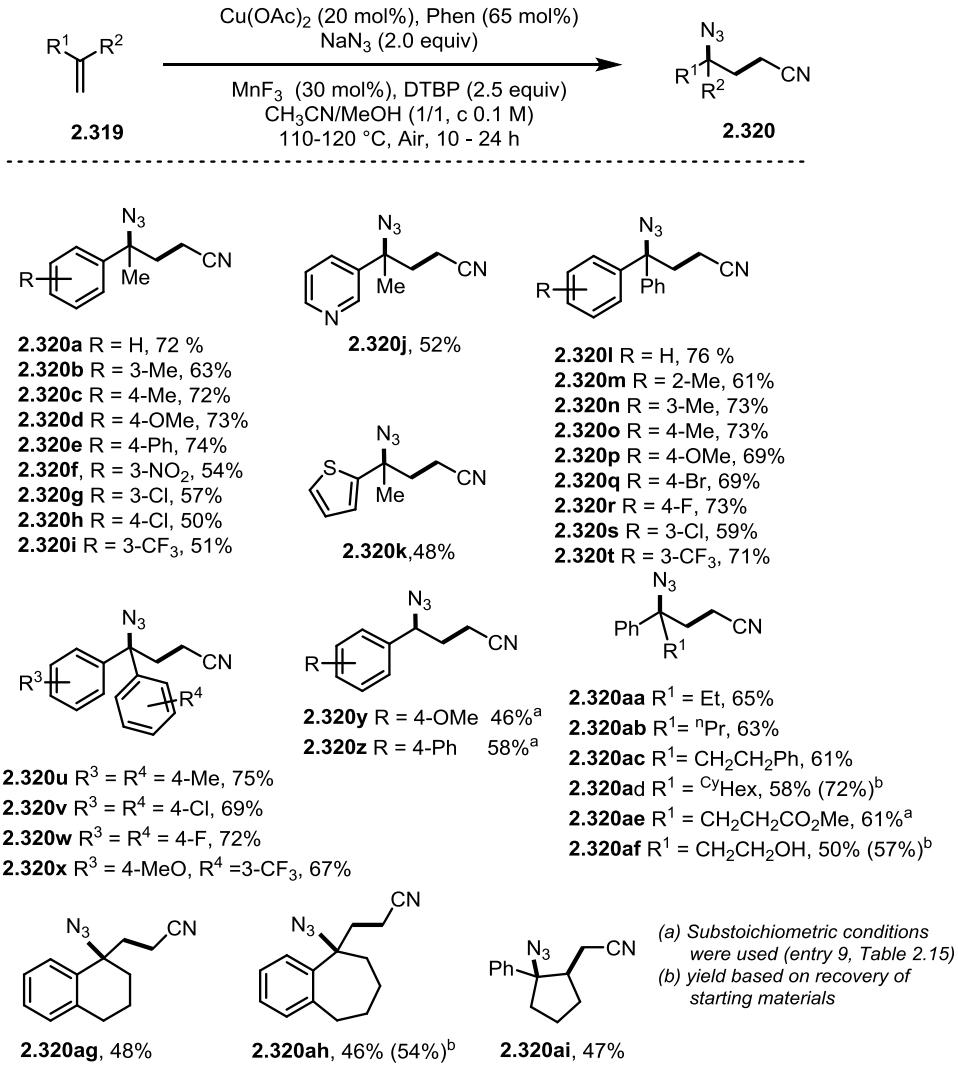
Overall, under optimum conditions [$Cu(OAc)_2$ (0.2 equiv), 1,10-phenanthroline (0.65 equiv), DTBP (2.0 equiv), $NaN_3$ (2.0 equiv) and $MnF_3$ (0.3 equiv) in MeCN/MeOH (1/1, *c* 0.1 M) under air at 110 °C for 10 h], the azidocyanomethylation of alkene **2.238a** furnished **2.320a** in 72% isolated yield.

### 5.2.2. Substrate scope

With the optimized conditions in hand [$Cu(OAc)_2$ (20 mol%), 1,10-phenantroline (0.65 equiv), $MnF_3$ (30 mol%), DTBP (2.5 equiv), air, 110-120 °C, $CH_3CN$/MeOH (1/1, c 0.1 M)], the generality of the carboazidation process was investigated. The result was summarized in Scheme 2.69.

Firstly, the effect of the substituents on the aromatic part of α-methyl styrene derivative was examined. Substrates with weak (*p*-Me) and strong electron donating groups (*p*-OMe) are well-tolerated under the reaction conditions, delivering the carboazidation product in 72% (**2.320c**) and 73% (**2.320d**) yield, respectively. Olefin with electron poor aromatics containing withdrawing functionalities such us $–NO_2$, -Cl, $-CF_3$ are also suitable substrates for difunctionalization, providing the γ-cyanoazide **2.320f-i** in yields ranging from 54-57%, albeit longer reaction time was required. Electro-deficient property of double bonds in these cases might account for slow addition of electrophilic radical $•CH_2CN$. Importantly, α,α-heteroarylmethyl ethylene such as 3-(prop-1-en-2-

yl)pyridine and 2-(prop-1-en-2-yl)thiophene equally undergo the carboazidation reaction furnishing the difunctionalized products **2.320j** and **2.320k** in 52% and 48% yield, respectively.




**Scheme 2.69: Substrate scope for azidocyanomethylation of alkenes**

Symmetric and asymmetric 1,1-diaryl ethylenes were next examined (**2.320l-x**). Reaction of 1,1-diphenylethylene with MeCN provide the γ-cyanoazide **2.320l** in 76% yield, albeit the higher temperature (120 ºC) was required. Good yields for carboazidation products were obtained regardless of the electronic nature and the position of substitution on the aromatic ring (*p*-Cl, *p*-Br, *o*-F, *p*-$CF_3$, *p*-OMe, *o*-Me, *m*-Me, *p*-Me).

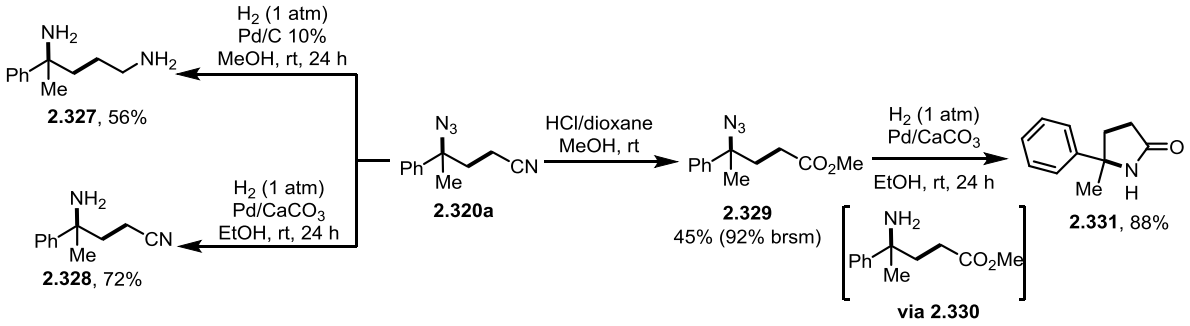
Gratefully, monosubstituted styrene derivatives such as *p*-methoxyvinylbenzene or *p*-phenylvinylbenzene are transformed into 4-azido-4-arylbutanenitriles **2.320y** and **2.320z** in 46% and 58% yield respectively. According to our precedent works, these substrates which readily undergo the radical-initiated polymerization, are not compatible to catalytic system of Cu(II)/*N*,*N*-ligand/DTBP.

Next, the effects of variation in the aliphatic part of 1,1-arylalkylethylene were studied. Substrates with primary alkyl (-Et, -*n*Pr, -$CH_2CH_2Ph$) groups underwent carboazidation reaction and delivered the corresponding desired compounds in 61-65 % yield (**2.320aa-ac**). When (1-cyclohexylvinyl)benzene was subjected to standard reaction conditions the reaction did not reach total conversion. In this case the γ-cyanoazidation product **2.320ad** was obtained in 58% yield (72% based on recovered starting material). Importantly, ester and free alcohol are well tolerated under alkylazidation conditions (**2.320ae** and **2.320af**). Exocyclic disubstituted alkenes and endocyclic trisubstituted alkenes can undergo the difunctionalization process, affording the desired γ-cyanoazidation products in 46 to 48 % yield (**2.320ag-i**).

Unfortunately, other alkylnitriles such as propionitrile, butyronitrile were found to be inactive to the reaction conditions. The carboazidation of α-methyl styrene, 1,1-diphenylethylene and *p*-phenylvinylbenzene afforded no desired product even though stoichiometric amount of copper, higher temperature and modification of $MnF_3$ and sodium azide loading were applied.

### 5.2.3. Synthetic application of carboazidation

To demonstrate the utility of carboazidation process, the formed γ-cyanoazidation products were transformed to different motifs depicted in Scheme 2.70. In the presence of Pd/C in methanol under $H_2$ atmosphere (1 atm), γ-cyanoazide **2.320a** can be reduced to δ-diamine **2.327**. Selective reduction of azide group of compound **2.320a** using $Pd/CaCO_3$ as a catalyst afforded γ-aminonitrile **2.328** in 72% yield. Finally, γ-cyanoazide **2.320a** was converted to the γ-lactam **2.331** through a sequence of two steps: (a) conversion of nitrile into ester group using HCl/MeOH, and (b) reductive cyclization of the resulting intermediate using $Pd/CaCO_3$ under $H_2$ atmosphere.

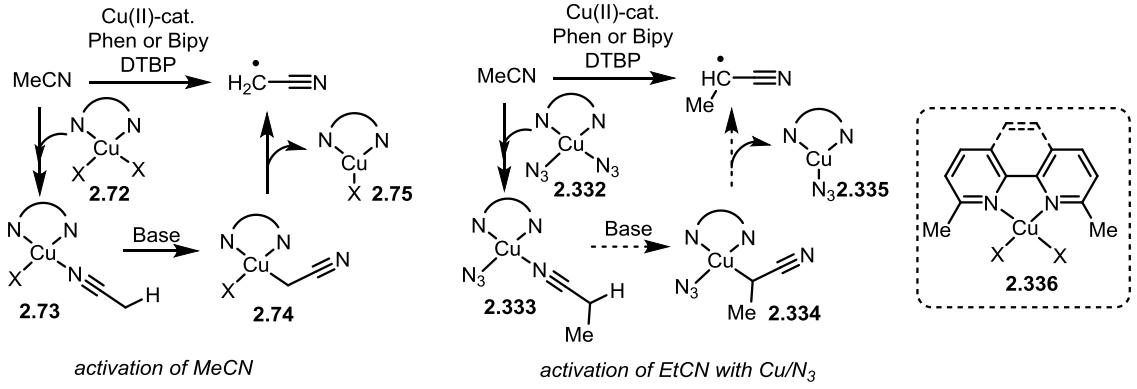



**Scheme 2.70: Post-transformation reactions of γ-cyanoazidation 2.320a**

### 5.2.4. Mechanistic aspect

Control experiments were performed to gain insights on the reaction mechanism. The reaction of **2.238a** with MeCN took place in the absence of DTBP to afford **2.320a** in 15% NMR yield with low conversion. Interestingly, no γ-cyanoazide was detected when the same reaction was performed in the absence of $Cu(OAc)_2$, suggesting that the copper is essential for the acetonitrile activation and $C(sp^3)$-azide bond formation.

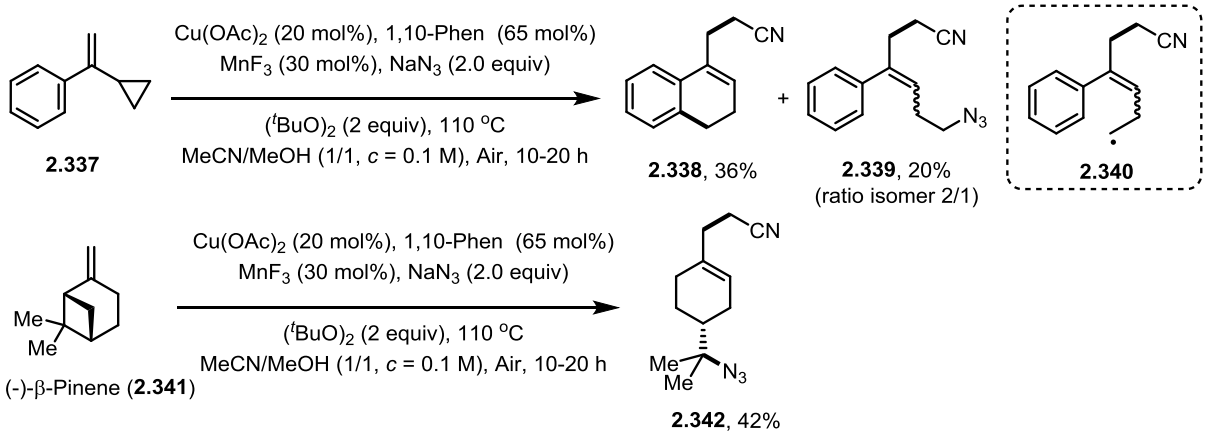
Moreover, given the fact that propionitrile (with BDE of **H-C**H(Me)CN 94±3 kcal.mol$^{-1}$ compared to BDE **H-C**$H_2$CN ~96 kcal.mol$^{-1}$)[128] could not undergo carboazidation suggests that the generation of cyanoalkyl radical may not be mediated by DTBP but copper catalyst. The inactivity of propionitrile could be explained by two factors: (1) steric hindrance and (2) the coordination of azide to copper complex. Different from the precedent work wherein activation of MeCN in catalytic system of Cu(II)/*N*,*N*-ligand/DTBP undergoes smoothly, the activation of EtCN in the presence of azide anion resulting from similar sequence of (a) unfavourable ligand exchanging of azide with EtCN to form *N*-metalated complex **2.333** due to strong coordination of azide to copper and (b) unfavourable rearrangement to form *C*-metalated complex **2.334** due to steric effect of Me group, could be more challenging. Arguably steric effect of Me group could be bolstered by our experimental observation that combination of copper with *N*,*N*-ligands bearing methyl substituents at *ortho*- positions of nitrogen atoms (eg. **2.336**) failed to activate alkylnitriles (Scheme 2.71).




**Scheme 2.71: The activation of MeCN and EtCN without or without azide inion**

As a probe for cyanomethyl radical generation, 1-(1-cyclopropylvinyl)benzene (**2.337**) and β-pinene (**2.341**) were subjected to carboazidation conditions (Scheme 2.72). In both cases rearranged compounds **2.338** and **2.342** were isolated as the major product. In the case of α-cyclopropyl styrene (**2.337**), the formed product is likely the result of cyclopropane ring opening after the addition of cyanomethyl radical to the double bond followed by intramolecular oxidative cyclization of carbo

radical **2.340**.[129c,207] Surprisingly, the intermediate **2.340** was able to undergo azidation to provide allylic azide **2.339** in non-negligible yield. In the second case, the β-pinene underwent the addition/fragmentation/C-$N_3$ bond formation sequence to deliver cyanoazide **2.342** in 42% yield.[208] These radical-clock experiments clearly imply that the proposed radical **2.321** is indeed an intermediate in the catalytic cycles (*cf.* Scheme 2.68).




**Scheme 2.72: Radical-clock experiments**

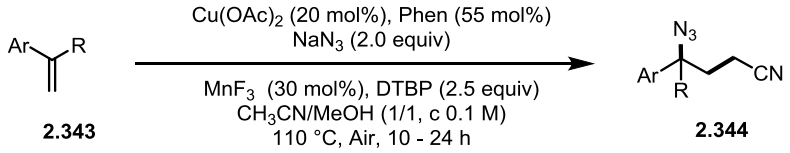
The formation of **2.339** probably results from direct azide transfer of radical **2.340** instead of oxidation by copper(II) to the corresponding carbenium intermediate (which is unstable), followed by trapping with azide anion. This suggests that, the formation of C-$N_3$ bond might proceed through copper-catalyzed azide transfer (pathway b, Scheme 2.68). The suppression of the formation of **2.326a** during optimization further supports for this hypothesis. In MeCN/MeOH (1/1) solvent mixture, the formation of carbenium **2.322** should have led to the formation of **2.326a** as a major product. Additionally, methyl 4-phenylpent-4-enoate (**2.248**) under the optimized conditions underwent selectively carboazidation to form γ-cyanoazide **2.230ae** without the formation of **2.249** resulting from oxycyanomethylation (see Scheme 2.48), giving a clear evidence for the preference of azide-transfer (pathway b, Scheme 2.68) over carbenium/nucleophilic trapping (pathway a, Scheme 2.68).

There is no experimental evidence for the role of $MnF_3$ in the catalytic cycles. We assumed that $MnF_3$ might participate in both regeneration of Cu(II) from Cu(I) species and azide-transfer process of radical intermediate **2.321**.

[207] Liwosz, T. W.; Chemler, S. R., *Chem. Eur. J.* **2013,** *19*, 12771.
[208] Li, Y.; Studer, A., *Angew. Chem. Int. Ed.* **2012**, *51*, 8221.

## 5.3. Conclusion

In conclusion, we developed a novel copper-catalyzed three-component reaction of alkenes with acetonitrile and sodium azide allowing the one-step formation of both $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-N bonds. The reaction is applicable to a wide range of styrene derivatives. The provided γ-cyanoazide can be easily converted to an array of motifs such us γ-lactams, γ-aminonitriles or 1,4-diamines, which are otherwise difficult to access.

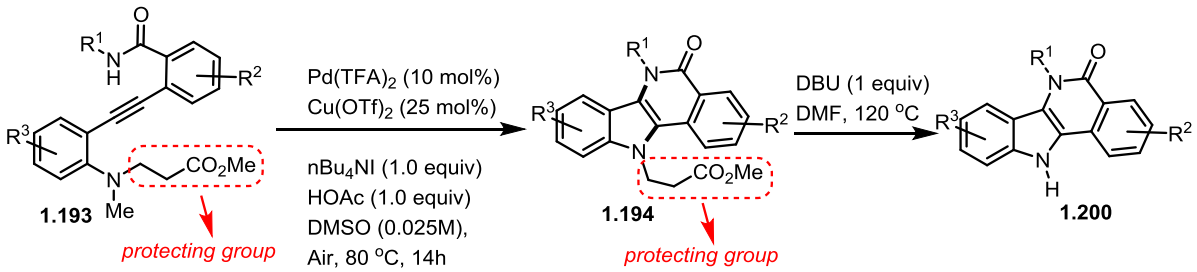



**Scheme 2.73: Copper-catalyzed carboazidation of styrenes**

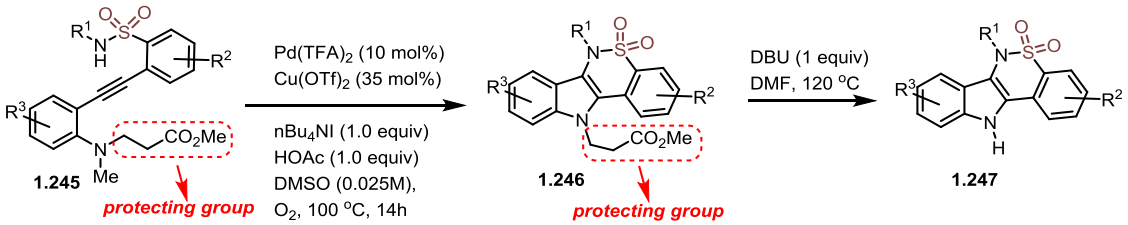
# General Conclusion

In summary, we developed several transition metal-catalyzed difunctionalization of carbon-carbon multiple bonds during my PhD study. These works can be categorized into two major parts: (1) palladium-catalyzed diamination of alkynes to access tetracycles; (2) copper-catalyzed difunctionalization of olefins using alkylnitrile as a key component for the synthesis of value-added molecules.

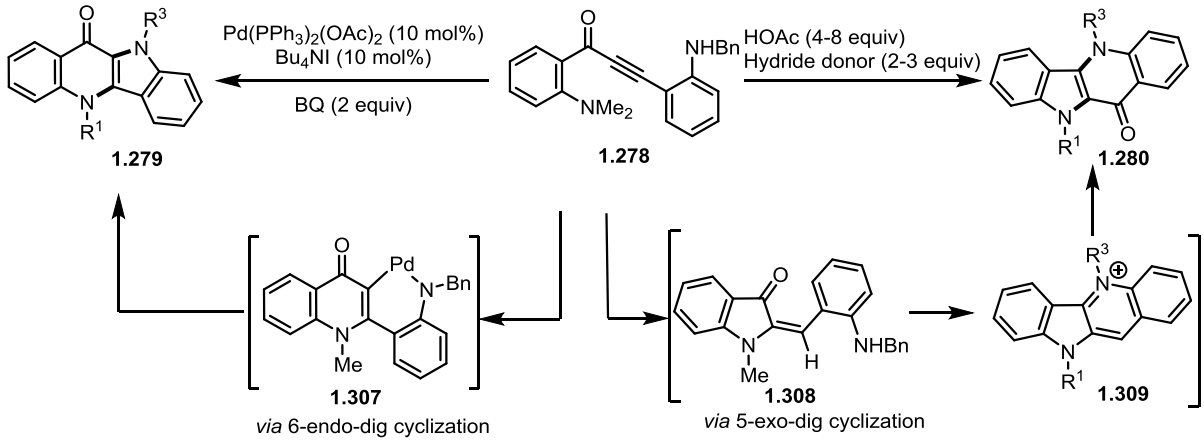
The first part of this thesis aimed at developing a synthesis of free NH tetracyclic indoles by palladium-catalyzed diamination of 1,2-diarylethynes. The reaction has previously been developed in our group. However, it required the use of *N*,*N*-dimethylaniline as one of the nucleophiles which inevitably led to *N*-methylated products. This drawback prompted us to find a suitable *N*-alkyl group that is compatible with the transformation, yet readily removable after cyclization. Indeed, we found that simple 2-(methoxy-carbonyl)ethyl group satisfied these criteria. Pd(II)-catalyzed double cyclization of 1,2-diarylethynes **1.193** bearing an *N*-methyl-*N*-[2-(methoxy-carbonyl)ethyl]amino and an aminocarbonyl group at the *ortho* positions of the two aromatic rings proceeded smoothly to afford the tetracyclic *N*-[2-(methoxycarbonyl)-ethyl]indoloisoquinolinones **1.194** in good to excellent yields. The *N*-[2-(methoxycarbonyl)-ethyl] group is readily removed under basic conditions (DBU, DMF, 120 °C) to afford the corresponding tetracycles **1.200** with a free indolyl nitrogen. The utility of 2-(methoxycarbonyl)ethyl as a removable *N*-protecting group was subsequently illustrated in other literature-reported Pd(II)- and Pd(0)-catalyzed and selenium-mediated transformations.




The similar strategy was later exploited in the synthesis of free NH tetracyclic indolobenzothiazine *S*,*S*-dioxides. Pd(II)-catalyzed oxidative double cyclization of the 1,2-diarylethynes **1.245** bearing an *N*-methyl-*N*-(2-methoxycarbonyl)ethylamino and an aminosulfonyl group afforded indolobenzothiazine *S*,*S*-dioxides **1.246**. The 2-(methoxycarbonyl)ethyl group attached to the indolyl nitrogen is readily removed under basic conditions (DBU, DMF, 120 °C) to provide the corresponding free indolyl NH tetracycles **1.247**.



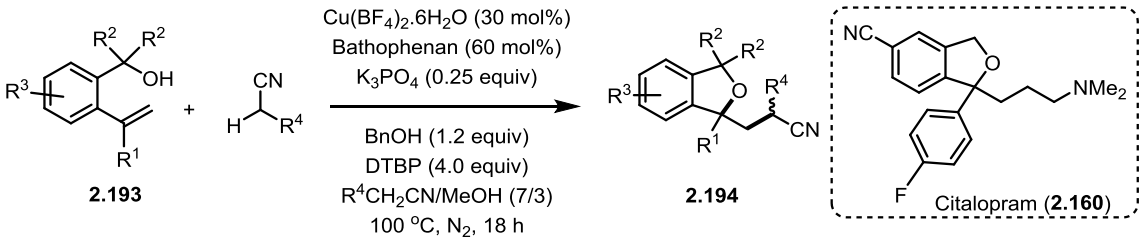

Inspired by early works, the double cyclization of 1,3-diarylprop-2-yn-1-ones **1.278** bearing *N*,*N*-dialkylated amino and *N*-monoalkylated amino groups at *ortho* positions of aromatic rings was then investigated. We developed two sets of conditions allowing access selectively to two types of biologically active quindolinones. In the presence of palladium catalyst under oxidative conditions, 1,3-diarylprop-2-yn-1-ones **1.278** underwent 6-*endo*-dig cyclization to afford indolo[3,2-*b*]quindolinones **1.279** in moderate yield. On the other hand, in the presence of a stoichiometric amount of HOAc and a hydride donor (Hantzsch's ester), a domino process initiated by a 5-*exo*-dig cyclization took place to afford, after intramolecular condensation and oxidation, a regioisomeric indolo[3,2-*b*]quindolinone **1.280** in good yields.



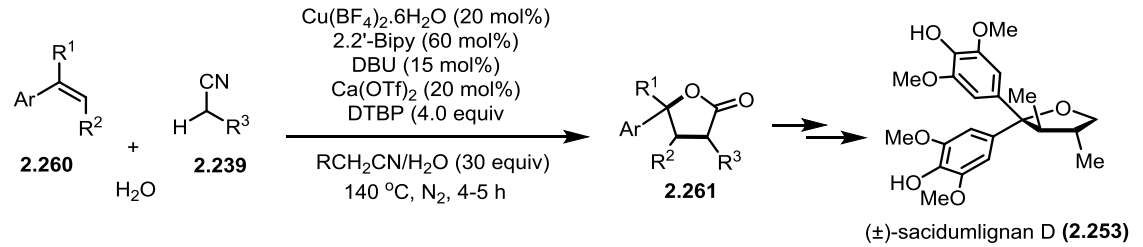

The second part of this thesis was a continuation of our previous research program aimed at developing copper-catalyzed alkylative difunctionalization of alkenes using alkylnitriles as alkylative reagents. The general synthetic strategy is based on the radical addition of cyanoalkyl radical species generated in situ from alkylnitriles followed by oxidation of the resulting radical adduct to carbenium and trapping with an appropriate nucleophile. These transformations allow the consecutive formation of $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-X (X = N, O) bonds to afford value-added molecules from simple starting materials.

Firstly, a copper-catalyzed cyanoalkylative cycloetherification of substituted (2-vinylphenyl)methanol was developed providing an efficient approach to1,3-dihydroisobenzofurans via the formation of a $C(sp^3)$-$C(sp^3)$ and a $C(sp^3)$-O bond. The synthetic potential of this novel

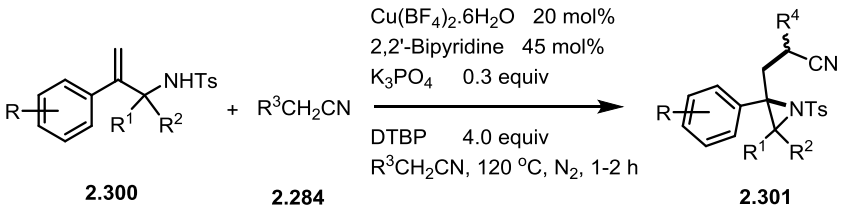
transformation was demonstrated by the development of a concise synthesis of citalopram (**2.160**), a marketed anti-depressant drug.




Secondly, a novel copper-catalyzed three-component reaction of styrenes with alkylnitriles and water was developed. The domino process involved a) generation of alkylnitriles; b) its addition to unactivated double bond; c) oxidation of the resulting radical adduct to carbenium; d) trapping of the carbocation by water and e) lactonization. It provided an efficient approach to γ-lactone bearing a quaternary carbon center at γ-position via the formation of a C($sp^3$)-C($sp^3$), a C($sp^3$)-O and a C($sp^2$)-O bonds. The synthetic potential of this novel transformation was demonstrated by the development of a concise total synthesis of (±)-sacidumlignan D.

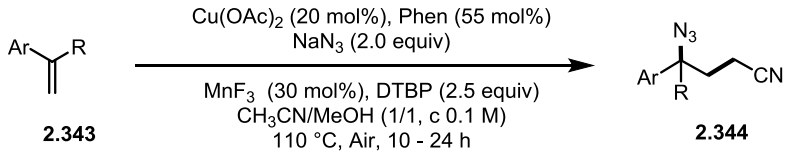



Thirdly, a cyanoalkylative aziridination of alkenes was developed. A wide range of aziridines bearing a quaternary carbon center was synthesized by copper-catalyzed domino process involving direct activation of alkylnitriles, intermolecular cyanoalkylation and intramolecular aziridination. The synthetic potential of this novel transformation was illustrated by the development of an efficient synthesis of enantioenriched 2,2,3-trisubstituted aziridines staring from readily accessible chiral amino acids.




Finally, a novel copper-catalyzed three-component reaction of alkenes with acetonitrile and sodium azide allowing the one-step formation of both C($sp^3$)-C($sp^3$) and C($sp^3$)-N bonds was established. The reaction is applicable to a wide range of styrene derivatives. The so-formed γ-

cyanoazides can be easily converted to an array of important structural motifs such us γ-lactams, γ-aminonitriles or 1,4-diamines that are otherwise difficultly accessible.




**2.343** **2.344**

# PART III

# Experimental Data

# General Information

All reactions were carried out in oven dried glasswares. All chemicals were purchased from Acros, Aldrich, Fluka, VWR, Aplichem or Merck and used directly unless stated otherwise. $CH_3CN$, toluene, DCM, THF and DMF were dried by passage over activated alumina under nitrogen atmosphere ($H_2O$ content < 30 ppm, Karl-Fischer titration).

Chromatographic purification was conducted with technical grade solvents and silica gel 40-63 μm. TLC was performed on Merck silica gel 60 $F_{254}$ TLC aluminium plates and visualized with UV light (254 nm), permanganate stain, Phosphomolyblic acid stain, CAN stain or anisaldehyde stain.

Melting points were measured on a Stuart SMP30 melting point apparatus using open glass capillaries (uncorrected).

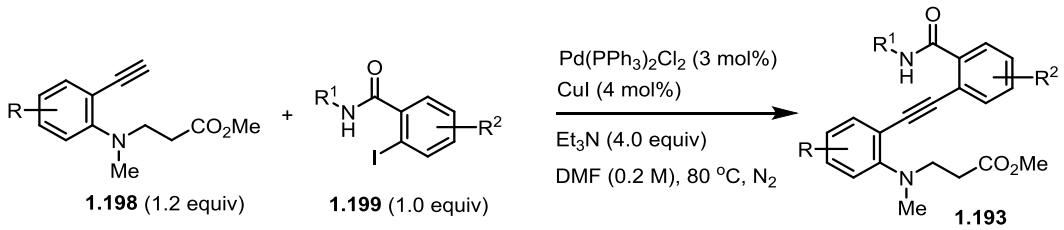
NMR spectra were recorded on a Brüker AvanceIII-400, Brüker Avance-400 at room temperature, $^{1}H$ frequency is at 400.13 MHz, $^{13}C$ frequency is at 100.62 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: $CHCl_3$[1H: 7.26,13C: 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. When needed, a COSY, HSQC and/or HMBC experiments were carried out to confirm the attribution.

IR spectra were recorded in a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacle$^{TM}$ 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.

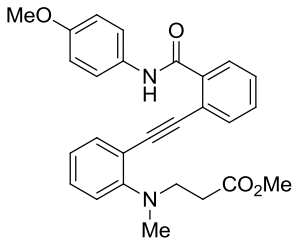
## 3.1. Synthesis of Indoloisoquinolinones by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes. 2−(Methoxycarbonyl)ethyl as a Removable *N*−Protecting Group

### 3.1.1. Preparation of starting materials 1.193



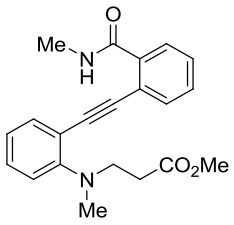

To a solution of 2-iodobenzamide (**1.199**) (0.5 mmol) in 2.5 mL DMF were added bis(triphenylphosphine)palladium(II) dichloride (10.50 mg, 3.0 mol%), CuI (3.82 mg, 4 mol%) and triethylamine (0.28 mL, 2.0 mmol), successively, under argon. After being stirred for 10 min, *o*-alkynylanline **1.198** (0.6 mmol) was added and the reaction mixture was heated with stirring at 80 ºC or 60 ºC until the disappearance of 2-iodobenzamide (**1.199**) (monitored by TLC). The reaction mixture was cooled down, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **1.193**.

Methyl 3-((2-((2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.193a**)




Yield: 162.0 mg (73%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.37 (s, 1H), 8.15 – 8.13 (m, 1H), 7.68 – 7.61 (m, 1H), 7.56 (d, *J* = 8.9 Hz, 2H), 7.51 – 7.41 (m, 3H), 7.34 – 7.25 (m, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.69 – 3.58 (m, 2H), 3.49 (s, 3H), 2.78 (s, 3H), 2.56 – 2.46 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.7, 164.3, 156.5, 153.6, 135.5, 134.4, 133.2, 131.3, 130.7, 130.3, 130.2, 128.8, 122.2, 121.2, 120.0, 118.5, 114.4, 114.1, 95.8, 92.2, 55.5, 51.6, 51.2, 40.0, 32.3; **ATR-IR** *v*1733 (w), 1658 (w), 1511 (s), 1240 (s), 1174 (m), 1034 (w), 829 (m), 754 (s); **HRMS (ESI)** calcd for $C_{27}H_{27}N_2O_4^+$ $[M+H]^+$ 443.1965; found 443.1955.

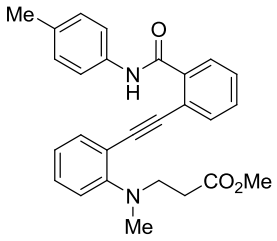
Methyl 3-(methyl(2-((2-(methylcarbamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.193b**)



Yield: 45.6 mg (26%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.18 – 8.02 (m, 1H), 7.70 (s, 1H), 7.62 – 7.55 (m, 1H), 7.49 – 7.45 (m, 1H), 7.44 – 7.41 (m, 2H), 7.34 – 7.28 (m, 1H), 7.03 – 6.92 (m, 2H), 3.71 (t, *J* = 7.5 Hz, 2H), 3.53 (s, 3H), 3.04 (d, *J* = 4.8 Hz, 3H), 2.92 (s, 3H), 2.58 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.7, 164.0, 153.4, 135.3, 134.3, 133.2, 130.6, 130.3, 130.2, 128.8, 121.7, 120.0, 119.0, 115.4, 94.8, 92.7, 51.8, 51.5, 40.5, 32.2, 27.0;

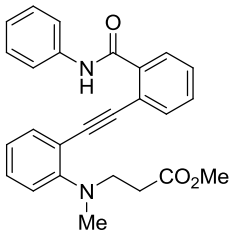
**ATR-IR** *v* 3387 (w), 3386 (w), 3385 (w), 3309 (w), 3308 (w), 3304 (w), 3303 (w), 3302 (w), 3062 (w), 3061 (w), 2949 (w), 2209 (w), 1732 (s), 1731 (s), 1649 (s), 1534 (s), 1493 (s), 1439 (s), 1314 (m), 1285 (s), 1284 (s), 1169 (s); **HRMS (ESI)** calcd for $C_{21}H_{23}N_2O_3^+$ $[M+H]^+$ 351.1703; found 351.1706.

Methyl 3-(methyl(2-((2-(p-tolylcarbamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.193c**)



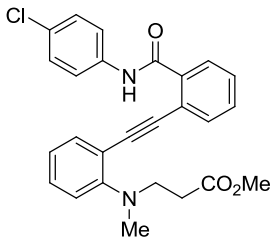
Yield: 149.3 mg (70%), dark yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.37 (s, 1H), 8.18-8.16 (m, 1H), 7.66 – 7.64 (m, 1H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.49 – 7.47 (m, 2H), 7.45 – 7.43 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 (td, *J* = 7.7, 1.6 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 2H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 3.64 (t, *J* = 7.5 Hz, 2H), 3.49 (s, 3H), 2.79 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.31 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.2, 153.6, 135.4 (2C), 134.4, 134.0, 133.2, 130.7, 130.4, 130.2, 129.4, 128.8, 121.1, 120.4, 119.9, 118.4, 114.3, 95.9, 92.1, 51.5, 51.2, 39.9, 32.3, 20.9; **ATR-IR** ν 3340 (w), 2951 (w), 2206 (w), 1732 (s), 1666 (s), 1598 (s), 1537 (s), 1494 (s), 1440 (s), 1321 (s), 1250 (s), 1174 (m), 1045 (m); **HRMS (ESI)** calcd for $C_{27}H_{27}N_2O_3^+$ $[M+H]^+$ 427.2016; found 427.2022.

Methyl 3-(methyl(2-((2-(phenylcarbamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.193d**)



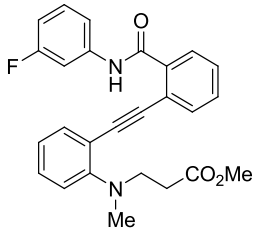
Yield: 163.9 mg (80%), yellow solid; mp: 69 – 70 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.40 (s, 1H), 8.18 – 8.16 (m, 1H), 7.67 – 7.63 (m, 3H), 7.52-7.46 (m, 2H), 7.44 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.89 (td, *J* = 7.5, 1.0 Hz, 1H), 3.65 (t, *J* = 7.5 Hz, 2H), 3.49 (s, 3H), 2.79 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.4, 153.6, 138.0, 135.4, 134.4, 133.2, 130.8, 130.4, 130.2, 128.9, 128.8, 124.4, 121.1, 120.4, 120.0, 118.5, 114.2, 96.0, 92.0, 51.5, 51.2, 39.8, 32.3; **ATR-IR** ν 3340 (w), 2951 (w), 2206 (w), 1732 (s), 1666 (s), 1598 (s), 1537 (s), 1494 (s), 1440 (s), 1321 (s), 1250 (s), 1174 (m); **HRMS (ESI)** calcd for $C_{26}H_{25}N_2O_3^+$ $[M+H]^+$ 413.1859; found 413.1862.

Methyl 3-((2-((2-((4-chlorophenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.193e**)



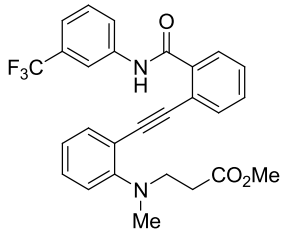
Yield: 163.0 mg (73%), light yellow solid; mp: 71 – 73 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.49 (s, 1H), 8.17 – 8.15 (m, 1H), 7.67 – 7.65 (m, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.51 – 7.48 (m, 2H), 7.43 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 (td, *J* = 7.7, 1.7 Hz, 1H), 7.27 – 7.25 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 3.64 (t, *J* = 7.6 Hz, 2H), 3.49 (s, 3H), 2.79 (s, 3H), 2.52 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.3, 153.7, 136.6, 135.0, 134.4, 133.3, 131.1, 130.4, 130.3, 129.3, 128.9 (2C), 121.5, 121.2, 119.9, 118.5, 114.1, 96.1, 92.0, 51.6, 51.3, 39.8, 32.3; **ATR-IR** ν 2953 (w), 2924 (s), 2853 (m), 1736 (m), 1735 (m), 1672 (w), 1596 (w), 1529 (w), 1493 (m), 1316 (w), 1090 (w), 756 (w); **HRMS (ESI)** calcd for $C_{26}H_{24}ClN_2O_3^+$ $[M+H]^+$ 447.1469; found 447.1483.

Methyl 3-((2-((2-((3-fluorophenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.193f**)



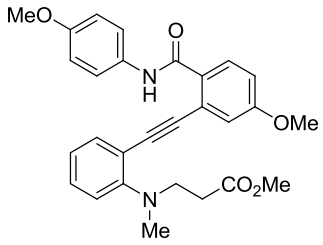
Yield: 170.2 mg (79%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.53 (s, 1H), 8.16 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.67 (dd, *J* = 6.8, 2.5 Hz, 1H), 7.62 (d, *J* = 11.0 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.45 (dd, *J* = 7.7, 1.6, 1H), 7.33 – 7.19 (m, 3H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.81 (ddd, *J* = 9.8, 5.7, 2.0 Hz, 1H), 3.66 (t, *J* = 7.5 Hz, 2H), 3.48 (s, 3H), 2.80 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.4, 163.0 (d, *J* = 244.7 Hz), 153.7, 139.6 (d, *J* = 10.5 Hz), 134.9, 134.5, 133.4, 131.1, 130.5, 130.4, 130.0 (d, *J* = 9.3 Hz), 129.0, 121.2, 120.0, 118.5, 115.6 (d, *J* = 3.0 Hz), 114.1, 111.1 (d, *J* = 21.3 Hz), 107.8 (d, *J* = 26.2 Hz), 96.2, 91.9, 51.6, 51.4, 39.7, 32.3; **ATR-IR** ν 3343 (w), 3332 (w), 3331 (w), 2951 (w), 2919 (w), 2853 (w), 2209 (w), 1735 (m), 1674 (m), 1549 (m), 1493 (m), 1444 (m), 1333 (s), 1271 (m), 1168 (m), 1124 (s), 756 (m); **HRMS (ESI)** calcd for $C_{26}H_{24}FN_2O_3^+$ $[M+H]^+$ 431.1765; found 431.1776.

Methyl 3-(methyl(2-((2-((3-(trifluoromethyl)phenyl)carbamoyl)phenyl)ethynyl)phenyl)amino)-propanoate (**31.193g**)



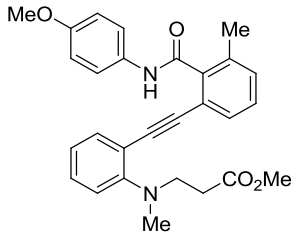
Yield: 158.0 mg (66%), light yellow solid; mp: 58 – 59 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.67 (s, 1H), 8.18 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.89 (s, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.67 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.53-7.49 (m, 2H), 7.44 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.38 – 7.33 (m, 1H), 7.34 – 7.29 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 3.66 (t, *J* = 7.5 Hz, 2H), 3.47 (s, 3H), 2.78 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.6, 153.7, 138.6, 134.8, 134.3, 133.3, 131.3 (q, *J* = 32 Hz), 131.2, 130.5, 130.4, 129.5, 129.0, 123.8 (q, *J* = 273 Hz), 123.3, 121.3, 120.9 (q, *J* = 3.8 Hz), 120.0, 118.5, 117.0 (q, *J* = 4.0 Hz), 113.9, 96.3, 91.9, 51.6, 51.4, 39.7, 32.3; **ATR-IR** ν 3343 (w), 3332 (w), 2951 (w), 2919 (w), 2853 (w), 2209 (w), 2195 (w), 1735 (m), 1674 (m), 1549 (m), 1493 (m), 1444 (m), 1333 (s), 1168 (m), 1124 (s), 756 (m); **HRMS (ESI)** calcd for $C_{27}H_{24}N_2O_3F_3^+$ $[M+H]^+$ 481.1734; found 481.1731.

Methyl 3-((2-((5-methoxy-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)-amino)-propanoate (**31.193h**)




Yield: 177.5 mg (75%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.43 (s, 1 H), 8.18 (d, *J* = 8.8, 1H), 7.52 (d, *J* = 9.0, 2H), 7.46 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.14 (d, *J* = 2.7, 1H), 7.01 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.93 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H), 3.79 (s, 3H), 3.63 (t, *J* = 7.6, 2H), 3.51 (s, 3H), 2.77 (s, 3H), 2.51 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 163.7, 161.2, 156.2, 153.7, 134.4, 132.6, 131.4, 130.3, 127.6, 122.2, 121.3, 121.2, 118.6, 117.8, 115.1, 114.2, 114.0 , 95.7, 92.3, 55.6, 55.4, 51.4, 51.3, 39.9, 32.2; **ATR-IR** ν 3627 (w), 3350 (w), 3349 (w), 2987 (m), 2970 (m), 2902 (m), 1734 (m), 1662 (m), 1534 (m), 1512 (s), 1245 (s), 1045 (m), 829 (w); **HRMS (ESI)** calcd for $C_{28}H_{29}N_2O_5^+$ $[M+H]^+$ 473.2071; found 473.2076.

Methyl 3-((2-((2-((4-methoxyphenyl)carbamoyl)-3-methylphenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.193i**)

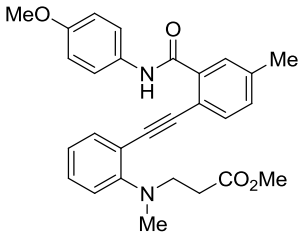



Yield: 191.7 mg (84%), yellow oil;

**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.89 (s, 1H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 7.7, 1H), 7.28 (t, *J* = 7.7, 1H), 7.27 (d, *J* = 7.5, 1H), 7.22-7.17 (m, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.84 (dd, *J* = 8.2, 1.1 Hz, 2H), 6.77 (td, *J* = 7.5, 1.1 Hz, 1H), 3.79 (s, 3H), 3.60 (t, *J* = 7.5, 2H), 3.46 (s, 3H), 2.79 (s, 3H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.46 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.1, 166.7, 156.5, 153.3, 139.0, 136.0, 134.7, 131.2, 130.3, 129.42, 129.40 , 129.0, 121.9, 120.7, 120.6, 117.7, 114.5, 114.1, 92.6, 91.8, 55.5, 51.5, 51.2, 39.7, 32.9, 19.5; **ATR-IR** ν 3290 (w), 2987 (m), 2972 (m), 2902 (m), 1733 (m),

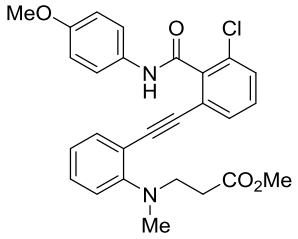
1653 (m), 1511 (s), 1245 (m), 1040 (m); **HRMS (ESI)** calcd for $C_{28}H_{29}N_2O_4^+$ $[M+H]^+$ 457.2122; found 457.2114.

Methyl 3-((2-((2-((4-methoxyphenyl)carbamoyl)-4-methylphenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.193j**)




Yield: 190.3 mg (84%), yellow solid; mp: 78 – 80 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.36 (s, 1H), 8.11 – 7.86 (m, 1H), 7.57 – 7.51 (m, 3H), 7.43 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.32 – 7.26 (m, 2H), 6.95 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.90 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.63 (t, *J* = 7.6, 2H), 3.50 (s, 3H), 2.77 (s, 3H), 2.51 (t, *J* = 7.6 Hz, 2H), 2.43 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 164.3, 156.4, 153.5, 139.2, 135.0, 134.3, 133.2, 131.6, 131.2, 130.9, 130.0, 122.1, 121.2, 118.5, 116.9, 114.6, 114.0, 95.0, 92.3, 55.4, 51.5, 51.2, 39.9, 32.2, 21.4; **ATR-IR** ν 3627 (w), 3350 (w), 3349 (w), 2987 (m), 2970 (m), 2902 (m), 1734 (m), 1662 (m), 1534 (m), 1512 (s), 1245 (s), 1045 (m), 829 (w); **HRMS (ESI)** calcd for $C_{28}H_{29}N_2O_4^+$ $[M+H]^+$ 457.2122; found 457.2115.

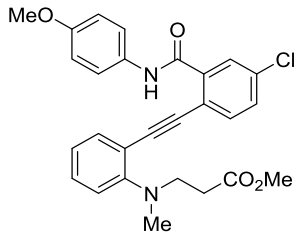
Methyl 3-((2-((3-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.193k**)




Yield: 185.0 mg (78%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.89 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.47 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.39 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.21 (ddd, *J* = 8.4, 7.6, 1.2 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.84 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.79 (td, *J* = 7.6, 1.2 Hz, 1H), 3.79 (s, 3H), 3.60 (t, *J* = 7.5, 2H), 3.47 (s, 3H), 2.79 (s, 3H), 2.59 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.1, 163.9, 156.7, 153.5, 138.5, 134.9, 131.6, 130.9, 130.3, 130.0, 129.8, 129.4, 123.2, 122.1, 120.6, 117.7, 114.2, 114.0, 93.8, 90.4, 55.5, 51.6, 51.2, 39.7, 32.9; **ATR-IR** ν

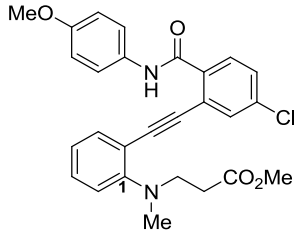
3302 (w), 3290 (w), 3280 (w), 2969 (w), 2969 (w), 2953 (w), 2902 (w), 1732 (m), 1658 (m), 1541 (m), 1511 (s), 1453 (m), 1247 (m), 1037 (w); **HRMS (ESI)** calcd for $C_{27}H_{26}ClN_2O_4^+$ $[M+H]^+$ 477.1576; found 477.1587.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl) (methyl)amino)-propanoate (**1.193l**)




Yield: 212.8 mg (89%), light yellow solid; mp: 71 – 73 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.35 (s, 1H), 8.16 (d, *J* = 2.3 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (td, *J* = 7.8, 7.3, 2.0 Hz, 2H), 7.30 (td, *J* = 8.7, 1.7 Hz, 1H), 6.95 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.61 (t, *J* = 7.5, 2H), 3.50 (s, 3H), 2.77 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 162.8, 156.7, 153.7, 136.8, 135.1, 134.4, 134.4, 130.9, 130.8, 130.5, 130.4, 122.2, 121.3, 118.6, 118.3, 114.1, 113.9, 96.7, 91.2, 55.4, 51.6, 51.3, 39.9, 32.2; **ATR-IR** ν 3342 (w), 3302 (w), 2998 (w), 2951 (w), 2836 (w), 1734 (m), 1659 (m), 1538 (m), 1512 (s), 1247 (m), 1177 (w), 1035 (w), 829 (w); **HRMS (ESI)** calcd for $C_{27}H_{26}ClN_2O_4^+$ $[M+H]^+$ 477.1576; found 477.1569.

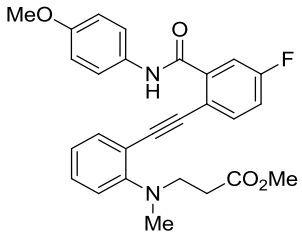
Methyl 3-((2-((5-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.193m**)




Yield: 227.0 mg (95%), light yellow solid; mp: 81 – 83 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.32 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.45 – 7.42 (m, 2H), 7.31 (ddd, *J* = 8.8, 7.4, 1.7 Hz, 1H), 6.96 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.91 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.62 (t, *J* = 7.5, 2H), 3.52 (s, 3H), 2.77 (s, 3H), 2.51 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 163.2, 156.6, 153.8, 136.8, 134.5, 133.7, 132.6, 132.0,

130.9, 130.6, 129.1, 122.2, 121.5, 121.3, 118.6, 114.1, 113.8, 97.0, 90.9, 54.4, 51.6, 51.3, 39.9, 32.2; **ATR-IR** ν 3340 (w), 3300 (w), 3290 (w), 2997 (w), 2997 (w), 2951 (w), 1734 (m), 1650 (m), 1538 (m), 1512 (s), 1442 (w), 1245 (m), 1177 (w), 1035 (w); **HRMS (ESI)** calcd for $C_{27}H_{26}ClN_2O_4^+$ $[M+H]^+$ 477.1576; found 477.1598.

Methyl 3-((2-((4-fluoro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**3n**)




Yield: 198.0 mg (86%), yellow oil;

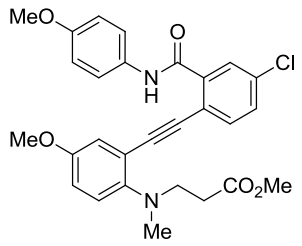
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.49 (s, 1H), 7.91 (dd, *J* = 9.7, 2.8 Hz, 1H), 7.65 (dd, *J* = 8.6, 5.4 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.31 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.20 (ddd, *J* = 8.6, 7.6, 2.8 Hz, 1H), 6.96 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.62 (t, *J* = 7.5, 2H), 3.50 (s, 3H), 2.76 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H);

**$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 162.6, 162.5 (d, *J* = 252.5 Hz), 156.7, 153.7, 137.6 (d, *J* = 7.5 Hz) , 135.3 (d, *J* = 7.8 Hz), 134.3, 130.8, 130.3, 122.2, 121.3, 118.6, 118.3 (d, *J* = 22.3 Hz) , 117.6 (d, *J* = 24.2 Hz), 116.0 (d, *J* = 3.6 Hz), 114.3, 114.1, 95.6, 91.2, 55.4, 51.6, 51.3, 39.9, 32.2;

**ATR-IR** ν 3348 (w), 3347 (w), 3336 (w), 2987 (m), 2971 (m), 2902 (w), 1734 (m), 1662 (m), 1601 (w), 1512 (s), 1246 (s), 1046 (m), 830 (m);

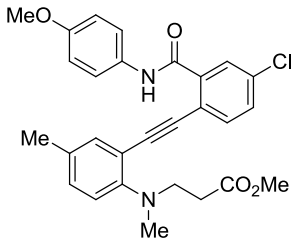
**HRMS (ESI)** calcd for $C_{27}H_{26}FN_2O_4^+$ $[M+H]^+$ 461.1871; found 461.1869.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)-4-methoxyphenyl)(methyl)-amino)propanoate (**1.193o**)



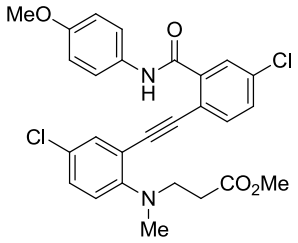
Yield: 196.0 mg (78%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.32 (s, 1H), 8.19 – 8.10 (m, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.45 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.97 – 6.91 (m, 2H), 6.90 – 6.87 (m, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.52 (s, 3H), 3.44 (t, *J* = 7.5 Hz, 2H), 2.67 (s, 3H), 2.45 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.7, 162.9, 156.8, 154.5, 147.8, 136.9, 135.2, 134.5, 130.9, 130.8 , 130.5, 122.5, 120.7, 118.2, 117.6, 117.3, 116.6, 114.1, 96.2, 90.9, 55.5, 55.5, 51.9, 51.6, 40.9, 32.2; **ATR-IR** ν l3324 (w), 3306 (w), 3305 (w), 3293 (w), 2951 (w), 2835 (w), 2202 (w), 1733 (m), 1651 (m), 1603 (w), 1511 (s), 1237 (s), 1179 (m), 1035 (m), 828 (m), 806 (w); **HRMS (ESI)** calcd for $C_{28}H_{28}ClN_2O_5^+$ $[M+H]^+$ 507.1681; found 507.1687.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)-4methylphenyl)(methyl)-amino)propanoate (**1.193p**)



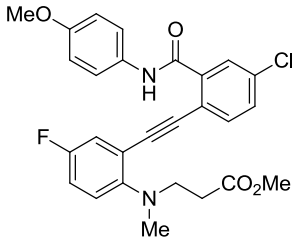

Yield: 199.0 mg (91%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.36 (s, 1H), 8.24 – 8.02 (m, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.9 Hz, 2H), 7.44 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 – 7.06 (m, 1H), 6.93 – 6.79 (m, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 3.52 (t, *J* = 7.5, 2H), 2.73 (s, 3H), 2.47 (t, *J* = 7.5 Hz, 2H), 2.21 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 162.8, 156.7, 151.5, 136.8, 135.1, 134.6, 134.4, 131.2, 130.9, 130.5, 122.3, 122.0, 118.8, 118.4, 114.5, 114.1, 113.9, 96.9, 90.9, 55.5, 51.6, 51.5, 40.2, 32.1, 20.2; **ATR-IR** ν 3288 (w), 2951 (w), 2914 (w), 1734 (m), 1650 (m), 1605 (m), 1511 (s), 1243 (s), 1175 (m), 1106 (w), 1035 (w), 829 (m), 805 (w); **HRMS (ESI)**calcd for $C_{28}H_{28}ClN_2O_4^+$ $[M+H]^+$ 491.1732; found 491.1740.

Methyl 3-((4-chloro-2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)phenyl)(methyl)-amino)propanoate (**1.193q**)



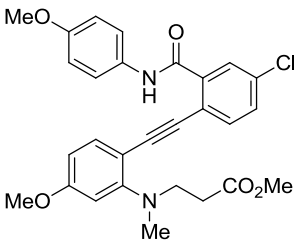
Yield: 187.0 mg (73%), light yellow solid; mp: 117 – 119 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.04 (s, 1H),8.10 (d, *J* = 2.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.46 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.37 (d, *J* = 2.6 Hz, 1H), 7.23 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.97 – 6.85 (m, 3H), 3.80 (s, 3H), 3.58 (t, *J* = 7.5 Hz, 2H), 3.51 (s, 3H), 2.73 (s, 3H), 2.47 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.4, 162.9, 156.8, 152.2, 137.4, 135.5, 134.3, 133.6, 130.9, 130.7, 130.4, 130.2, 126.0, 122.1, 119.7, 117.9, 115.5, 114.2, 94.9, 92.0, 55.5, 51.7, 51.2, 34.0, 32.2; **ATR-IR** ν 3296 (w), 3290 (w), 3277 (w), 2989 (w), 2952 (w), 2910 (w), 1734 (m), 1651 (m), 1540 (m), 1512 (s), 1492 (m), 1247 (s), 1177 (m), 1108 (w), 1035 (w), 828 (m); **HRMS (ESI)** calcd for $C_{27}H_{25}Cl_2N_2O_4^+$ $[M+H]^+$ 511.1186; found 511.1185.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)-4-fluorophenyl)-(methyl)-amino)-propanoate (**1.193r**)



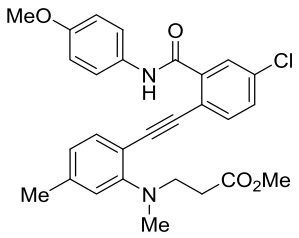

Yield: 157.5 mg (64%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.12 (s, 1H), 8.20 – 8.06 (m, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.46 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.13 (dd, *J* = 8.6, 2.9 Hz, 1H), 7.02 (ddd, *J* = 10.7, 7.8, 3.1 Hz, 1H), 6.97 – 6.91 (m, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.50 (s, 3H), 3.52 – 3.47 (m, 2H), 2.69 (s, 3H), 2.44 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.4, 162.9, 157.3 (d, *J* = 244.6 Hz), 156.8, 150.4 (d, *J* = 3.8 Hz), 137.3, 135.5, 134.5, 130.9, 130.7, 130.4, 122.3, 120.4 (d, *J* = 9.7 Hz), 120.2 (d, *J* = 25.5 Hz), 117.9, 117.2 (d, *J* = 22.1 Hz), 116.6 (d, *J* = 9.0 Hz), 114.2, 94.8, 91.8, 55.5, 51.7, 51.6, 40.6, 32.1; **ATR-IR** *ν* 3055 (w), 2952 (w), 2925 (w), 2869 (w), 2853 (w), 1735 (m), 1681 (m), 1650 (m), 1506 (s), 1463 (m), 1247 (s), 1163 (s), 1035 (s), 994 (s); **HRMS (ESI)** calcd for $C_{27}H_{25}ClFN_2O_4^+$ $[M+H]^+$ 495.1481; found 495.1493.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)-5-methoxyphenyl)(methyl)-amino)propanoate (**1.193s**)



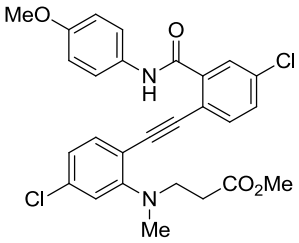
Yield: 215.0 mg (85%), light yellow solid; mp: 100 – 102 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.44 (s, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 7.60 – 7.48 (m, 3H), 7.43 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.35 (d, *J* = 9.2 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.62 – 6.39 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 3.63 (t, *J* = 7.5 Hz, 2H), 3.52 (s, 3H), 2.76 (s, 3H), 2.50 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 162.7, 161.5, 156.6, 155.2, 136.4, 135.7, 134.7, 134.2, 130.9, 130.9, 130.5, 122.1, 118.7, 114.1, 106.2, 106.1, 105.0, 97.2, 90.0, 55.5, 55.4, 51.6, 51.1, 39.7, 32.1; **ATR-IR** ν 2989 (w), 2952 (w), 2911 (w), 2910 (w), 2836 (w), 2199 (w), 1734 (m), 1660 (w), 1601 (m), 1512 (s), 1298 (w), 1238 (s), 1175 (w), 1092 (w), 1037 (m), 1037 (m), 829 (w); **HRMS (ESI)** calcd for $C_{28}H_{28}ClN_2O_5^+$ $[M+H]^+$ 507.1681; found 507.1677.

Methyl 3-((2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl)-5-methylphenyl)-(methyl)-amino)-propanoate (**1.193t**)



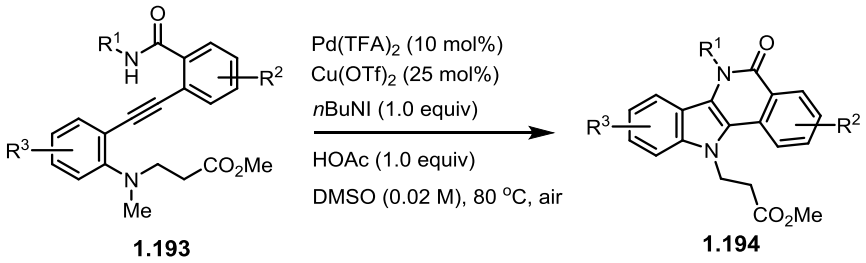

Yield: 231.0 mg (94%), light yellow solid; mp: 93 – 94 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.44 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.76 – 6.71 (m, 2H), 3.80 (s, 3H), 3.60 (t, *J* = 7.5 Hz, 2H), 3.51 (s, 3H), 2.75 (s, 3H), 2.49 (t, *J* = 7.5 Hz, 2H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 162.7, 156.6, 153.7, 141.0, 136.5, 134.9, 134.4, 134.2, 130.9, 130.6, 122.3, 122.2, 119.3, 118.5, 114.1, 111.1, 97.1, 90.6, 55.5, 51.6, 51.3, 39.9, 32.2, 21.9; **ATR-IR** ν 3347 (w), 3338 (w), 2951 (w), 2920 (w), 2203 (w), 1734 (m), 1660 (m), 1602 (m), 1539 (m), 1512 (s), 1469 (m), 1413 (m), 1246 (s), 1176 (m), 1035 (w), 828 (m); **HRMS (ESI)** calcd for $C_{28}H_{28}ClN_2O_4^+$ $[M+H]^+$ 491.1732; found 491.1742.

Methyl 3-((5-chloro-2-((4-chloro-2-((4-methoxyphenyl)carbamoyl)phenyl)ethynyl) phenyl)(methyl)-amino)propanoate (**1.193u**)




Yield: 219.5 mg (86%), light yellow solid; mp: 90 – 91 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.11 (s, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.51 (d, *J* = 9.0 Hz, 2H), 7.45 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 6.91 – 6.86 (m, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 3.65 (t, *J* = 7.5 Hz, 2H), 3.51 (s, 3H), 2.77 (s, 3H), 2.51 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.3, 162.9, 156.7, 154.3, 137.2, 136.0, 135.3, 135.3, 134.2, 130.9, 130.8, 130.4, 122.0, 121.2, 118.7, 118.1, 114.2, 111.9, 95.4, 91.9, 55.5, 51.7, 51.0, 39.7, 32.2; **ATR-IR** ν 3346 (w), 3332 (w), 3296 (w), 2951 (w), 2910 (w), 2865 (w), 2836 (w), 2205 (w), 1735 (m), 1655 (m), 1655 (m), 1585 (w), 1543 (m), 1512 (s), 1494 (m), 1468 (w), 1412 (w), 1246 (s), 1178 (m), 1106 (w), 1036 (w), 829 (m); **HRMS (ESI)** calcd for $C_{27}H_{25}Cl_2N_2O_4^+$ $[M+H]^+$ 511.1186; found 511.1194.

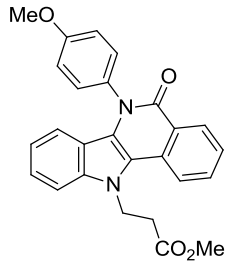
### 3.1.2. Substrate scope for Pd(II)-catalyzed oxidative diamination of alkenes




**1.193** **1.194**

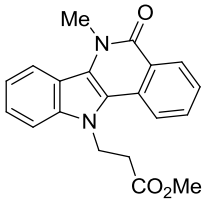
A 5-mL-vial was charged with **1.193** (0.1 mmol), $Pd(TFA)_2$ (10 mol%), $Cu(OTf)_2$ (25 mol%), $n$$Bu_4NI$ (1.0 equiv), acetic acid (1.0 equiv) together with 4 mL DMSO and heated at 80 ºC under air atmosphere (1 atm) for 13 – 15 hours. The reaction mixture was quenched with ice and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Then the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **1.194**.

Methyl 3-(6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194a**)



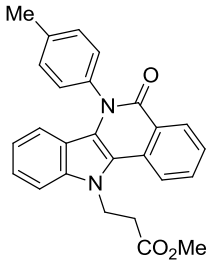

Yield: 30.2 mg (71%), brown solid; mp: 166 – 167 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.73 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.84 (td, *J* = 7.7, 1.5 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.86 (t, *J* = 7.7 Hz, 1H), 6.19 (d, *J* = 8.3 Hz, 1H), 5.01 (t, *J* = 7.7, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 2.97 (t, J = 7.7 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.4, 161.6, 160.1, 138.2, 133.02, 131.9, 131.0, 130.0, 129.3, 126.3, 125.4, 124.8, 123.1, 120.5, 120.3, 120.0, 118.6, 117.3, 115.3, 109.4, 55.8, 52.3, 41.5, 34.7; **ATR-IR** ν 2954 (w), 2925 (w), 2841 (w), 2360 (w), 1736 (m), 1634 (s), 1608 (s), 1511 (s), 1248 (s), 1171 (s), 1029 (s); **HRMS (ESI)** calcd for $C_{26}H_{23}N_2O_4^+$ $[M+H]^+$ 427.1652; found 427.1644.

Methyl 3-(6-methyl-5-oxo-5H-indolo[3,2-*c*]isoquinolin-11(6H)-yl)propanoate (**1.194b**)



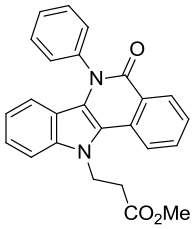

Yield: 26.1 mg (78%), yellow solid; mp: 112 – 113 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$):** δ 8.73 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.79 (m, 1H), 7.58 – 7.54 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 5.00 (t, *J* = 7.8, 2H), 4.20 (s, 3H), 3.71 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 160.9, 138.2, 132.4, 130.6, 128.3, 126.1, 124.76, 124.71,122.5, 120.8, 120.2, 120.0, 118.5, 117.5, 109.7, 52.1, 41.3, 34.4, 32.5; **ATR-IR** ν 2987 (w), 2972 (w), 2902 (w), 1733 (m), 1632 (s), 1610 (m), 1371 (w), 1075 (w), 1067 (w), 1052 (w), 739 (w); **HRMS (ESI)** calcd for $C_{20}H_{19}N_2O_3^+$ $[M+H]^+$ 335.1390; found 335.1385.

Methyl 3-(5-oxo-6-(p-tolyl)-5H-indolo[3,2-*c*]isoquinolin-11(6H)-yl)propanoate (**1.194c**)



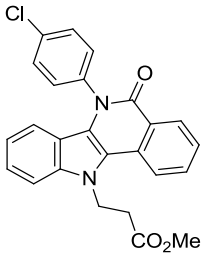

Yield: 31.1 mg (76%), yellow solid; mp: 188 – 189 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.73 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.29 (ddd, *J* = 8.3, 7.0, 1.1 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 8.3 Hz, 1H), 5.00 (t, *J* = 7.8, 2H), 3.73 (s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H), 2.54 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 161.3, 139.1, 138.0, 136.4, 132.8, 130.8, 130.6, 129.1, 128.5, 126.1, 125.3, 124.6, 122.7, 120.3, 120.1, 119.7, 118.4, 117.1, 109.2, 52.1, 41.2, 34.5, 21.4; **ATR-IR** ν 2971 (w), 2922 (w), 1734 (w), 1638 (m), 1609 (w), 1514 (w), 1374 (w), 1353 (w), 1206 (w), 1175 (w), 732 (s); **HRMS (ESI)** calcd for $C_{26}H_{23}N_2O_3^+$ $[M+H]^+$ 411.1703; found 411.1709.

Methyl 3-(5-oxo-6-phenyl-5H-indolo[3,2-*c*]isoquinolin-11(6H)-yl)propanoate (**1.194d**)



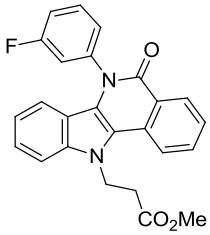

Yield: 28.1 mg (71%), yellow solid; mp: 127 – 129 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.73 (dd, *J* = 8.1, 1.5 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.85 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.67 – 7.57 (m, 4H), 7.51 – 7.47 (m, 3H), 7.32 – 7.27 (m, 1H), 6.82 (t, *J* = 7.6 Hz, 1H), 6.03 (d, *J* = 8.2 Hz, 1H), 5.01 (t, *J* = 7.8, 2H), 3.71 (s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.4, 161.3, 139.2, 138.2, 133.1, 131.0, 130.1, 129.33, 129.29, 129.0, 126.4, 125.5, 124.8, 122.7, 120.4, 120.3, 120.0, 118.6, 117.2, 109.4, 52.3, 41.4, 34.7; **ATR-IR** ν 2987 (m), 2972 (m), 2902 (w), 1733 (m), 1644 (s), 1610 (w), 1535 (w), 1375 (m), 1355 (m), 1355 (m), 1251 (w), 1213 (w), 1178 (w), 1066 (m), 1058 (m), 740 (m); **HRMS (ESI)** calcd for $C_{25}H_{21}N_2O_3^+$ $[M+H]^+$ 397.1547; found 397.1550.

Methyl 3-(6-(4-chlorophenyl)-5-oxo-5H-indolo[3,2-*c*]isoquinolin-11(6H)-yl)propanoate (**1.194e**)



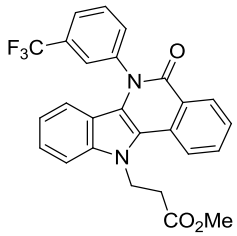

Yield: 31.0 mg (72%), light yellow solid; mp: 173 – 175 ºC; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.71 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.85 (t, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.31 (t, *J* = 8.4 Hz, 1H); 6.89 (t, *J* = 7.6 Hz, 1H), 6.18 (d, *J* = 8.2 Hz, 1H), 5.02 (t, *J* = 7.8, 2H), 3.73 (s, 3H), 2.97 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.3, 161.3, 138.2, 137.7, 135.2, 133.3, 130.9, 130.5, 130.4, 129.3, 126.5, 125.3, 124.9, 122.2, 120.4, 120.2, 120.1, 118.8, 116.9, 109.5, 52.3, 41.4, 34.7; **ATR-IR** ν 2952 (w), 2951 (w), 2925 (w), 2854 (w), 2853 (w), 1744 (m), 1635 (s), 1534 (m), 1493 (m), 1470 (w), 1469 (w), 1383 (w), 1374 (w), 1206 (w), 1175 (w), 827 (w), 740 (m); **HRMS (ESI)** calcd for $C_{25}H_{20}ClN_2O_3^+$ $[M+H]^+$ 431.1157; found 431.1153.

Methyl 3-(6-(3-fluorophenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194f**)



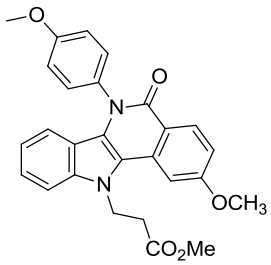

Yield: 30.7 mg (74%), light yellow solid; mp: 171 – 173 ºC; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.71 (d, *J* = 7.8, Hz, 1H), 8.19 (d, *J* = 8.2 Hz, 1H), 7.86 (t, *J* = 7.6 Hz, 1H), 7.68 – 7.57 (m, 2H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.27 – 7.24 (m, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.13 (d, *J* = 8.2 Hz, 1H), 5.02 (t, *J* = 7.8, 2H), 3.74 (s, 3H), 2.98 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.3, 163.5 (d, *J* = 249.1 Hz), 161.2, 140.5 (d, *J* = 9.8 Hz), 138.2, 133.3, 131.3 (d, *J* = 8.8 Hz), 130.9, 129.3, 126.5, 125.3, 125.1 (d, *J* = 3.3 Hz), 124.9, 122.1, 120.3 (d, *J* = 22.0 Hz), 120.0, 118.7, 117.0, 116.9, 116.8, 116.6 (d, *J* = 20.8 Hz), 109.5, 52.3, 41.4, 34.7; **ATR-IR** ν 3062 (w), 2951 (w), 1733 (m), 1646 (s), 1608 (m), 1535 (m), 1488 (m), 1373 (m), 1355 (m), 1177 (m), 738 (s); **HRMS (ESI)** calcd for $C_{25}H_{20}FN_2O_3^+$ $[M+H]^+$ 415.1452; found 415.1448.

Methyl 3-(5-oxo-6-(3-(trifluoromethyl)phenyl)-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194g**)



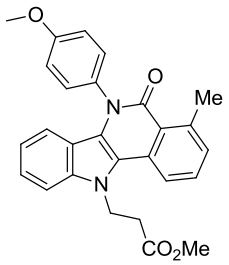

Yield: 30.6 mg (66%), light yellow solid; mp: 97 – 98 °C; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.71 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.92 – 7.76 (m, 4H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.00 (d, *J* = 8.3 Hz, 1H), 5.02 (t, *J* = 7.8, 2H), 3.73 (s, 3H), 2.98 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.3, 161.3, 139.7, 138.2, 133.4, 132.9, 132.9, 132.6 (q, *J* = 33.2 Hz), 130.9, 130.7, 129.4, 126.6, 126.5 (q, *J* = 3.7 Hz), 126.2 (q, *J* = 3.6 Hz), 125.2, 125.0, 120.4, 120.2, 119.7, 116.8, 110.3 109.6, 52.3, 41.4, 34.7 ($CF_3$ not detected); **ATR-IR** *ν* 2957 (w), 2922 (w), 1734 (m), 1650 (s), 1610 (w), 1331 (s), 1169 (s), 1127 (s), 1068 (m), 741 (m); **HRMS (ESI)** calcd for $C_{26}H_{20}F_3N_2O_3^+$ $[M+H]^+$ 465.1421; found 465.1418.

Methyl 3-(2-methoxy-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194h**)



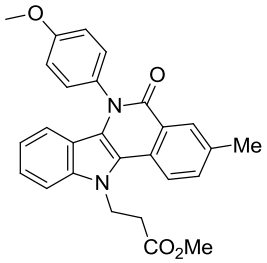

Yield: 36.0 mg (79%), brown solid; mp: 178 – 180 °C; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.64 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.29 (ddd, *J* = 8.5, 6.9, 1.2 Hz, 1H), 7.15 – 7.12 (m, 3H), 6.85 (t, *J* = 7.5 Hz, 1H), 6.18 (d, *J* = 8.1 Hz, 1H), 4.98 (t, *J* = 8.0, 2H), 4.01 (s, 3H), 3.95 (s, 3H), 3.73 (s, 3H), 2.98 (t, *J* = 7.9 Hz, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.4, 163.3, 161.5, 160.0, 138.3, 133.0, 131.9, 130.9, 130.0, 124.9, 123.7, 120.6, 119.9, 119.2, 118.4, 117.3, 115.3, 114.1, 109.3, 103.5, 55.8 (2C), 52.3, 41.4, 34.9; **ATR-IR** ν 2971 (m), 2902 (m), 1732 (w), 1644 (s), 1609 (s), 1512 (s), 1473 (m), 1249 (s), 1037 (m); **HRMS (ESI)** calcd for $C_{27}H_{25}N_2O_5^+$ $[M+H]^+$ 457.1758; found 457.1776.

Methyl 3-(6-(4-methoxyphenyl)-4-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194i**)



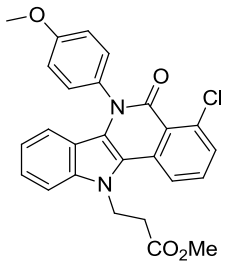
Yield: 36.1 mg (82%), brown solid; mp: 119 – 120 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.85 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1H), 6.17 (dd, *J* = 8.2 Hz, 1H), 4.98 (t, *J* = 7.8, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 3.00 (s, 3H), 2.94 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 162.5, 159.8, 144.8, 138.7, 132.1, 131.9, 130.9, 130.0, 129.9, 124.6, 123.6, 123.2, 120.3, 119.8, 118.8, 118.2, 117.0, 115.2, 109.3, 55.6, 52.1, 41.5, 34.5, 25.2; **ATR-IR** ν 2953 (w), 2953 (w), 2929 (w), 2838 (w), 1735 (m), 1645 (s), 1607 (m), 1601 (m), 1512 (s), 1366 (m), 1354 (m), 1292 (m), 1248 (s), 1031 (w), 741 (m); **HRMS (ESI)** calcd for $C_{27}H_{25}N_2O_4^+$ $[M+H]^+$441.1809; found 441.1793.

Methyl 3-(6-(4-methoxyphenyl)-3-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl) propanoate (**1.194j**)



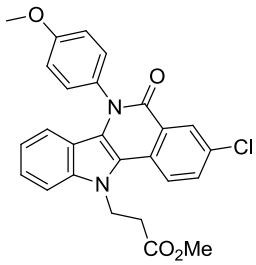
Yield: 26.8 mg (61%), light brown crystal; mp: 157 – 159 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.53 – 8.50 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.66 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.27 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.14 (d, *J* = 8.9 Hz, 2H), 6.85 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 6.16 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.99 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.55 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 161.4, 159.8, 137.8, 136.3, 134.2, 131.9, 130.5, 129.8, 126.7, 125.3, 124.3, 122.1, 120.12, 120.09, 119.7, 118.6, 117.2, 115.1, 109.1, 55.6, 52.1, 41.1, 34.5, 21.3; **ATR-IR** ν 3290 (w), 2987 (m), 2972 (m), 2902 (m), 1733 (m), 1653 (m), 1511 (s), 1245 (m), 1040 (m); **HRMS (ESI)** calcd for $C_{27}H_{24}N_2O_4Na^+$ $[M+Na]^+$ 463.1628; found 463.1638.

Methyl 3-(4-chloro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194k**)



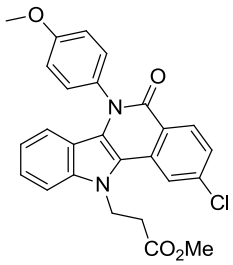

Yield: 22.1 mg (48%); yellow solid; mp: 142 – 143 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.08 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.31 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.86 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.17 (d, *J* = 8.2, Hz, 1H), 4.96 (t, *J* = 7.8, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 160.0, 159.9, 138.9, 138.5, 132.2 (2C), 131.6, 129.9 (2C), 125.3, 124.1, 121.4, 120.7, 120.1, 119.0, 117.7, 116.8, 115.2, 109.4, 55.6, 52.2, 41.6, 34.4; **ATR-IR** ν 2953 (w), 2953 (w), 2839 (w), 1734 (m), 1650 (s), 1596 (m), 1512 (s), 1354 (m), 1248 (s), 1030 (w), 742 (m); **HRMS (ESI)** calcd for $C_{26}H_{21}ClN_2O_4Na^+$ $[M+Na]^+$ 483.1082; found 483.1086.

Methyl 3-(3-chloro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194l**)



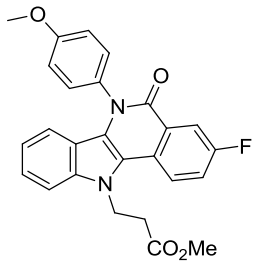

Yield: 39.1 mg (85%), light yellow solid; mp: 147 – 149 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.30 (ddd, *J* = 8.4, 7.0, 1.2 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.87 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1H), 6.17 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.97 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 2.93 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 160.5, 160.0, 138.2, 133.1, 132.1, 131.4, 130.3, 129.7, 127.4, 126.6, 125.0, 123.1, 121.7, 120.4, 120.0, 117.8, 117.0, 115.2, 109.2, 55.6, 52.2, 41.2, 34.4; **ATR-IR** ν 2987 (w), 2970 (w), 2902 (w), 1735 (m), 1646 (s), 1523 (m), 1512 (s), 1375 (w), 1355 (m), 1249 (s), 1034 (w), 742 (w); **HRMS (ESI)** calcd for $C_{26}H_{21}ClN_2O_4Na^+$ $[M+Na]^+$ 483.1082; found 483.1089.

Methyl 3-(2-chloro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194m**)




Yield: 31.3 mg (68%), brown solid; mp: 205 – 206 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.64 (d, *J* = 8.6 Hz, 1H), 8.15 (d, *J* = 1.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.32 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.87 (ddd, *J* = 8.1, 7.0, 0.9 Hz, 1H), 6.17 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.98 (t, *J* = 7.8 Hz, 2H), 3.95 (s, 3H), 3.74 (s, 3H), 2.96 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.9, 161.0, 160.0, 139.4, 138.3, 132.5, 131.4, 130.1, 129.7, 126.4, 125.2, 124.1, 123.5, 120.5, 120.0, 119.9, 117.2, 116.9, 115.2, 109.3, 55.6, 52.2, 41.1, 34.6; **ATR-IR** ν 2998 (w), 2953 (w), 2839 (w), 1735 (m), 1648 (s), 1601 (s), 1511 (s), 1463 (m), 1351 (m), 1249 (s), 1213 (m), 1179 (m), 1030 (w), 906 (w), 833 (w), 741 (m); **HRMS (ESI)** calcd for $C_{26}H_{21}ClN_2O_4Na^+$ $[M+Na]^+$ 483.1082; found 483.1076.

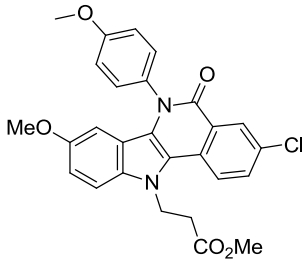
Methyl 3-(3-fluoro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194n**)




Yield: 33.3 mg (75%), light yellow solid; mp: 191 – 192 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.38 (dd, *J* = 9.5, 2.9 Hz, 1H), 8.18 (dd, *J* = 9.1, 4.7 Hz, 1H), 7.57 (ddd, *J* = 9.1, 7.7, 2.9 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.30 (ddd, *J* = 8.3, 7.0, 1.2 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.87 (t, *J* = 7.6, Hz, 1H), 6.18 (dd, *J* = 8.2, 1.0 Hz, 1H), 4.98 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.73 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 160.8 (d, *J* = 247.8 Hz), 160.6 (d, *J* = 3.1 Hz), 160.0, 137.9, 131.5, 129.7, 127.4 (d, *J* = 7.5 Hz), 125.8 (d, *J* = 2.5 Hz), 124.6, 122.4 (d, *J* = 7.6 Hz), 122.3 (d, *J* = 2.0 Hz), 121.2 (d, *J* = 23.4 Hz), 120.2, 120.0. 118.0, 117.1, 116.2 (d, *J* = 22.9 Hz), 115.2, 109.2, 55.6, 52.2, 41.2, 34.4; **ATR-IR** ν 2955 (w), 2911 (w), 2903 (w), 1734 (m), 1646 (s),

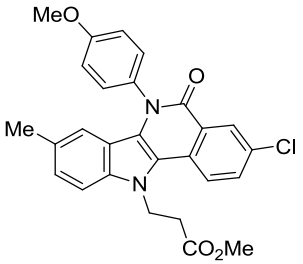
1577 (m), 1538 (m), 1512 (s), 1462 (m), 1443 (m), 1355 (m), 1250 (s), 1181 (m), 742 (w); **HRMS (ESI)** calcd for $C_{26}H_{21}FN_2O_4Na^+$ $[M+Na]^+$ 467.1378; found 467.1389.

Methyl 3-(3-chloro-6-(4-methoxyphenyl)-8-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194o**)




Yield: 40.1 mg (82%), brown solid; mp: 192 – 193 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (d, *J* = 2.3 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 9.1 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.94 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.53 (d, *J* = 2.4 Hz, 1H), 4.92 (t, *J* = 7.8, 2H), 3.92 (s, 3H), 3.71 (s, 3H), 3.45 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 160.3, 160.1, 153.6, 133.6, 133.1, 132.0, 131.4, 130.3, 130.1, 127.5, 126.5, 122.7, 121.6, 118.4, 116.9, 115.7, 115.1, 110.2, 101.2, 55.7, 55.2, 52.2, 41.3, 34.5. **ATR-IR ν** 2952 (w), 2836 (w), 1734 (m), 1644 (s), 1525 (s), 1512 (s), 1458 (m), 1247 (s), 1208 (m), 1033 (m), 835 (w), 799 (w), 733 (w); **HRMS (ESI)** calcd for $C_{27}H_{24}ClN_2O_5^+$ $[M+H]^+$ 491.1368; found 491.1365.

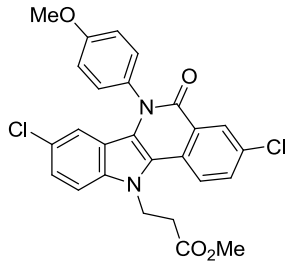
Methyl 3-(3-chloro-6-(4-methoxyphenyl)-8-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194p**)




Yield: 38.0 mg (80%), light yellow solid; mp: 196 – 197 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (d, *J* = 2.3 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.38-7.34 (m, 3H), 7.16-7.12 (m, 3H), 5.91 (s, 1H), 4.93 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.72 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.17 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.3, 160.6, 160.2, 136.9, 133.2, 132.1, 131.7, 130.4, 129.9, 129.3, 127.7, 126.8, 126.6, 122.9, 121.8, 120.1, 118.1, 117.3, 115.3, 109.2, 55.9, 52.3, 41.4, 34.6, 21.7; **ATR-IR** ν 2953 (w), 2921 (w), 2920 (w), 2839 (w), 1734 (m), 1644 (s), 1607 (m), 1528 (s),

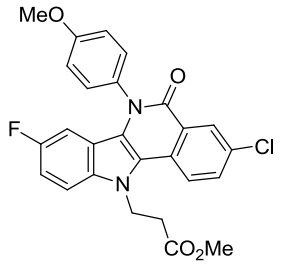
1512 (s), 1462 (m), 1439 (m), 1330 (m), 1248 (s), 1172 (m), 1032 (m), 793 (w), 733 (m); **HRMS (ESI)** calcd for $C_{27}H_{24}ClN_2O_4^+$ $[M+H]^+$ 475.1419; found 475.1420.

Methyl 3-(3,8-dichloro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194q**)




Yield: 30.7 mg (62%), light yellow solid; mp: 218 – 219 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (d, *J* = 2.4 Hz, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.24 (dd, *J* = 8.9, 2.1 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H, 6.07 (d, *J* = 2.0 Hz, 1H), 4.94 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.71 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.9, 160.3, 160.3, 136.4, 133.2, 132.6, 130.9, 130.4, 129.6, 127.1, 126.9, 125.5, 125.1, 122.4, 121.7, 119.7, 118.8, 117.7, 115.4, 110.4, 55.7, 52.2, 41.4, 34.4; **ATR-IR** ν 2953 (w), 2926 (w), 2851 (w), 2841 (w), 1738 (m), 1635 (s), 1607 (m), 1606 (m), 1522 (s), 1459 (m), 1304 (m), 1252 (s), 1033 (w), 830 (m), 772 (m); **HRMS (ESI)** calcd for $C_{26}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$ 495.0873; found 495.0866.

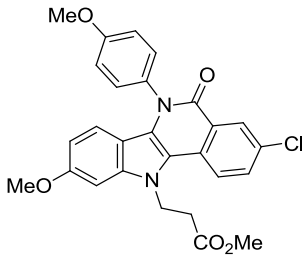
Methyl 3-(3,8-dichloro-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)-propanoate (**1.194r**)




Yield: 33.5 mg (70%), light yellow solid; mp: 225 – 226 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.41 (dd, *J* = 9.1, 4.2 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 7.10 – 6.98 (m, 1H), 5.79 (dd, *J* = 10.1, 2.5 Hz, 1H), 4.95 (t, *J* = 7.8, 2H), 3.95 (s, 3H), 3.72 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 160.3, 160.2, 157.1 (d, *J* = 236.0 Hz), 134.8, 133.2, 132.6, 130.9, 130.4, 129.6, 127.2, 126.8, 122.8 (d, *J* = 4.9 Hz), 121.7, 119.2, 116.8 (d, *J* = 10.6 Hz), 115.3, 113.5 (d, *J* = 26.5 Hz), 110.2 (d, *J* =

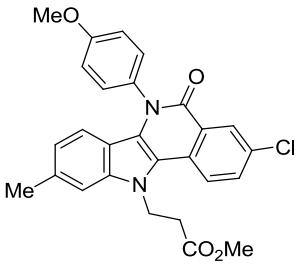
9.3 Hz), 105.3 (d, *J* = 26.3 Hz), 55.6, 52.2, 41.4, 34.4; **ATR-IR** *v* 2987 (w), 2966 (w), 2958 (w), 2902 (w), 1735 (m), 1636 (s), 1526 (m), 1514 (m), 1333 (w), 1253 (m), 1029 (w), 836 (w), 794 (w); **HRMS (ESI)** calcd for $C_{26}H_{21}FClN_2O_4^+$ $[M+H]^+$ 479.1168; found 479.1170.

Methyl 3-(3-chloro-9-methoxy-6-(4-methoxyphenyl)-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194s**)




Yield: 42.6 mg (87%), light yellow solid; mp: 176 – 177 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.64 (d, *J* = 2.4 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 2.2 Hz, 1H), 6.52 (dd, *J* = 9.0, 2.2 Hz, 1H), 6.02 (d, *J* = 9.0 Hz, 1H), 4.89 (t, *J* = 7.8, 2H), 3.94 (s, 3H), 3.86 (s, 3H), 3.73 (s, 3H), 2.92 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 160.5, 160.0, 158.5, 139.6, 133.1, 131.4, 131.3, 130.2, 129.6, 127.5, 125.7, 123.6, 121.3, 121.1, 117.0, 115.2, 111.5, 110.0, 92.5, 55.6, 55.6, 52.2, 41.2, 34.3; **ATR-IR** ν 2952 (w), 2910 (w), 2836 (w), 1734 (m), 1651 (m), 1512 (s), 1492 (m), 1247 (s), 1177 (w), 828 (m); **HRMS (ESI)** calcd for $C_{27}H_{24}ClN_2O_5^+$ $[M+H]^+$ 491.1368; found 491.1365;

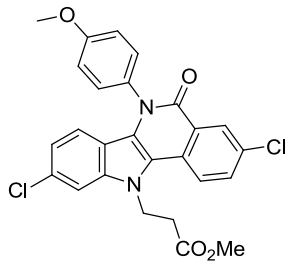
Methyl 3-(3-chloro-6-(4-methoxyphenyl)-9-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194t**)




Yield: 35.5 mg (75%), brown solid; mp: 202 – 203 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.66 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.23 (s, 1H), 7.13 (d, *J* = 8.8 Hz, 2H), 6.70 (dd, *J* = 8.5, 1.4 Hz, 1H), 6.03 (d, *J* = 8.4 Hz, 1H), 4.92 (t, *J* = 7.8, 2H), 3.94 (s, 3H), 3.74 (s, 3H), 2.90 (t, *J* = 7.8 Hz, 2H), 2.45 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 160.4, 160.0, 138.7, 135.4, 133.1, 131.7, 131.5, 130.2, 129.6, 127.5, 126.2, 123.3, 121.9, 121.4, 120.0, 117.4, 115.2, 115.0, 109.0, 55.6, 52.2, 41.1, 34.4, 22.0; **ATR-IR** ν 2987 (m), 2971 (m), 2912

(w), 1639 (s), 1607 (m), 1511 (s), 1436 (m), 1355 (m), 1249 (s), 1036 (m), 911 (w), 830 (w), 801 (w), 733 (w); **HRMS (ESI)** calcd for $C_{27}H_{24}ClN_2O_4^+$ $[M+H]^+$ 475.1419; found 475.1417.

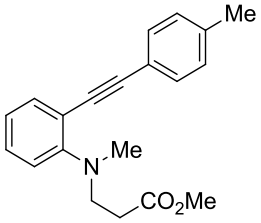
Methyl 3-(3-chloro-6-(4-methoxyphenyl)-9-methyl-5-oxo-5H-indolo[3,2-c]isoquinolin-11(6H)-yl)propanoate (**1.194u**)




Yield: 40.0 mg (81%), yellow solid; mp: 217 – 218 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.66 (d, *J* = 2.4 Hz, 1H), 8.08 (d, *J* = 8.8 Hz, 1H), 7.78 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.40 (s, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.82 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.04 (d, *J* = 8.8 Hz, 1H), 4.91 (t, *J* = 7.8, 2H), 3.94 (s, 3H), 3.74 (s, 3H), 2.93 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.8, 160.4, 160.1, 138.5, 133.2, 132.4, 131.1, 131.1, 130.4, 129.6, 127.2, 126.6, 123.0, 121.6, 121.3, 120.8, 118.2, 115.6, 115.3, 109.3, 55.6, 52.2, 41.4, 34.3; **ATR-IR** ν 2955 (w), 2923 (w), 2855 (w), 2854 (w), 1740 (m), 1607 (m), 1562 (m), 1511 (s), 1253 (s), 1208 (w), 1171 (w), 831 (m); **HRMS (ESI)** calcd for $C_{26}H_{21}Cl_2N_2O_4^+$ $[M+H]^+$ 495.0873; found 495.0875.

### 3.1.3. Selective cyclization of *o*-alkynylaniline 1.201

**Preparation of *o*-alkynylaniline 1.201**



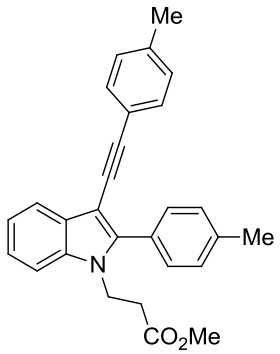

*o*-Alkynylaniline **1.201** was prepared by the Sonogashira reaction of *ortho*-iodoaniline with 4-tolylacetylene according to the procedure reported in our previous publication (Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 12311–12315).

Yield 88%; brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.26 – 7.20 (m, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 6.99 – 6.85 (m, 2H), 3.79 – 3.68 (m, 2H), 3.58 (s, 3H), 2.91 (s, 3H), 2.74 – 2.62 (m, 2H), 2.37 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.9, 153.4,

138.3, 134.5, 131.4, 129.2, 129.1, 121.1, 120.8, 118.3, 116.0, 94.8, 88.0, 51.7, 51.5, 40.0, 32.9, 21.6; **ATR-IR** ν 1735 (s), 1592 (w), 1511 (w), 1489 (m), 1437 (w), 1169 (m), 1046 (w), 818 (m), 756 (m); **HRMS (ESI)** calcd for $C_{20}H_{22}NO_2^+$ $[M+H]^+$ 308.1645; found 308.1658.

**Pd(II)-catalyzed cyclizative alkynylation to form 3-alkynylindole 1.203**

A 5-mL-Vial was charged with **1.201** (0.1 mmol), 4-tolylacetylene (**1.202**) (2 equiv), $Pd(TFA)_2$ (10 mol%), *n*$Bu_4NI$ (1.0 equiv), HOAc (1.0 equiv) together with 1.0 mL DMSO and heated at 50 ºC under air atmosphere (1 atm) for 22 h. The reaction mixture was quenched with ice and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in vacuo. Then the crude product was purified by flash column chromatography on silica gel (petroleum ether/DCM 1: 1) to give compound **1.203**.

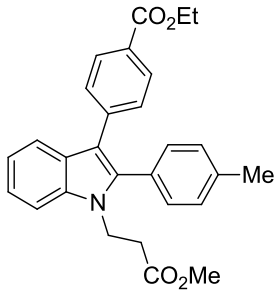



Yield 31.3 mg (77%), brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.31 (m, 4H), 7.31 – 7.22 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.52 (t, *J* = 7.6 Hz, 2H), 3.60 (s, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.3, 143.4, 138.8, 137.4, 136.1, 131.2, 130.0, 129.5, 129.3, 129.1, 127.9, 123.1, 121.5, 121.1, 120.4, 110.0, 98.1, 92.1, 83.1, 52.0, 40.1, 34.3, 21.6; **ATR-IR** ν 2205 (w), 1730 (m), 1419 (m), 1258 (m), 1168 (s), 817 (s), 744 (s); **HRMS (ESI)** calcd for $C_{28}H_{26}NO_2^+$ $[M+H]^+$ 408.1958; found 408.1962.

**Pd(0)-catalyzed arylative cyclization to form 3-arylindole 1.206**

A 5-mL-Vial was charged with **1.201** (0.075 mmol), aryl iodide **1.205** (1.1 equiv), $Pd(PPh_3)_2Cl_2$ (3 mol%), *n*$Bu_4NI$ (0.1 equiv) together with 1.5 mL $CH_3CN$ and flushed with argon for 5 min. Then the reaction mixture was heated by microwave at 90 ºC for 1 h. The reaction mixture was quenched with ice and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Then the crude product was

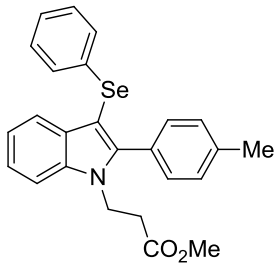
purified by flash column chromatography on silica gel (petroleum ether/DCM 1: 1) to give compound **1.206**.




Yield 29.7 mg (90%), foam; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.94 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.35 (d, *J* = 8.5 Hz, 2H), 7.34 – 7.29 (m, 1H), 7.25 – 7.16 (m, 5H), 4.44 (t, *J* = 7.6 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 3.62 (s, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.41 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.4, 166.9, 140.3, 138.7, 138.2, 136.3, 130.8, 129.7, 129.6, 129.5, 128.4, 127.4, 127.1, 122.7, 120.9, 119.7, 115.1, 110.0, 60.9, 52.0, 39.5, 34.5, 21.5, 14.5; **ATR-IR** ν 1736 (w), 1709 (m), 1606 (w), 1461 (w), 1362 (w), 1270 (s), 1176 (m), 1102 (m), 1020 (w), 776 (w), 744 (m), 711 (m); **HRMS (ESI)** calcd for $C_{28}H_{28}NO_4^+$ $[M+H]^+$ 442.2013; found 442.2013.

**PhSeCl-mediated electrophilic cyclization to form 3-phenylselenylindole 1.209**

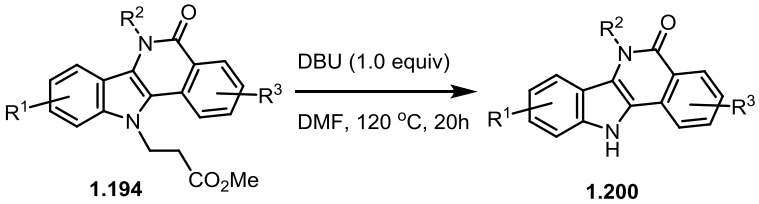
A 5-mL-Vial was charged with **1.201** (0.1 mmol), PhSeCl (**1.208**) (0.2 mmol), *n*$Bu_4NI$ (1.0 equiv) together with DCE (2 mL) and was heated at 70 ºC under nitrogen atmosphere for 6 h. The reaction mixture was quenched with saturated sodium bicarbonate solution and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in vacuo. Then the crude product was purified by flash column chromatography on silica gel (petroleum ether/DCM 2 : 1) to give compound **1.209**.




Yield 30.0 mg (67%), brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.36 – 7.23 (m, 5H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.17 – 7.04 (m, 5H), 4.54 – 4.45 (m, 2H), 3.59 (s, 3H), 2.71 – 2.61 (m, 2H), 2.43 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.3, 145.7, 139.0, 136.7, 134.5, 131.0, 130.6, 130.5, 129.3, 129.0, 128.6, 128.3, 125.4, 123.0, 121.2, 121.0, 110.0, 52.0,

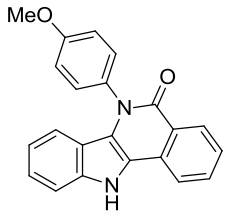
40.4, 34.5, 21.6; **ATR-IR** ν 1735 (m), 1476 (w), 1457 (w), 1436 (w), 1354 (w), 1198 (m), 1166 (m), 1021 (w), 829 (w), 737 (s); **HRMS (ESI)** calcd for $C_{25}H_{24}NO_2Se^+$ $[M+H]^+$ 450.0967; found 450.0974.

### 3.1.4. Synthesis of tetracyclic free NH indoles by retro-Michael reaction



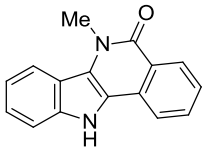

A 5-mL-Vial was charged with **1.194** (0.05 mmol), DBU (1.0 equiv) and DMF (2.5 mL) and was flushed by $N_2$ for 5 minutes. The reaction mixture was then heated at 120 ºC under nitrogen atmosphere for 24 h. The reaction mixture was quenched with ice and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Then the crude product was purified by flash column chromatography on silica gel to give compound **1.200**.

6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200a**)



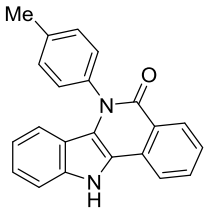
Yield: 16.5 mg (97%), yellow solid; mp: 262 – 263 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.06 (s, 1H), 8.36 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.91 (td, *J* = 7.8, 1.4 Hz, 1H), 7.58 (t, *J* = 7.9 Hz, 1H), 7.50 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.25 – 7.14 (m, 3H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.05 (d, *J* = 8.2 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.4, 159.3, 136.8, 132.8, 131.8, 130.0, 129.0, 128.7, 126.3, 124.0, 123.8, 121.0, 120.8, 118.91, 118.89, 118.6, 117.0, 114.8, 112.0, 55.5; **ATR-IR** ν 3214 (w), 3183 (w), 2953 (w), 2952 (w), 2925 (w), 2853 (w), 2853 (w), 1623 (s), 1610 (s), 1557 (m), 1511 (s), 1461 (m), 1302 (m), 1168 (w), 1029 (m), 752 (s), 741 (m), 733 (m); **HRMS (ESI)** calcd for $C_{22}H_{17}N_2O_2^+$ $[M+H]^+$ 341.1285; found 341.1281.

6-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200b**)



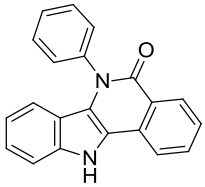

Yield: 10.8 mg (87%), yellow solid; mp: 221 – 222 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.05 (s, 1H), 8.37 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.85 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.33 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.15 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 4.06 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.9, 136.9, 132.3, 128.8, 127.9, 126.1, 123.9, 123.4, 120.8, 120.3, 120.2, 119.3, 118.7, 117.3, 112.1, 31.7; **ATR-IR** ν 3219 (w), 3184 (w), 2953 (m), 2952 (m), 2923 (s), 2853 (m), 1714 (m), 1562 (m), 1464 (s), 1397 (m), 1376 (m), 1254 (m), 1077 (m), 1049 (m), 745 (s); **HRMS (ESI)** calcd for $C_{16}H_{13}N_2O^+$ $[M+H]^+$ 249.1022; found 249.1025.

6-(p-tolyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200c**)




Yield: 15.3 mg (95%), yellow solid; mp: 282 – 283 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.09 (s, 1H), 8.36 (d, *J* = 7.9 Hz, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.91 (t, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.38 (d, *J* = 7.9 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 5.99 (d, *J* = 8.2 Hz, 1H), 2.50 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.8, 138.9, 137.2, 137.0, 133.3, 130.7, 129.4, 129.13, 129.10, 126.9, 124.4, 124.3, 121.4, 120.9, 119.4, 119.3, 119.2, 117.3, 112.5, 21.4; **ATR-IR** *v* 3176 (w), 2954 (w), 2926 (w), 1727 (m), 1612 (s), 1554 (m), 1512 (m), 1457 (m), 1352 (m), 1254 (m), 1168 (m), 752 (s), 731 (s), 695 (s); **HRMS (ESI)** calcd for $C_{22}H_{17}N_2O^+$ $[M+H]^+$ 325.1335; found 325.1332.

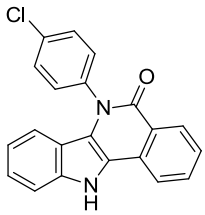
6-phenyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200d**)




Yield: 14.7 mg (95%), yellow solid; mp 304 -305 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.09 (s, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 8.26 (d, *J* = 8.1 Hz, 1H), 7.92 (t, *J* = 7.7 Hz, 1H), 7.70-7.6 4 (m, 3H),

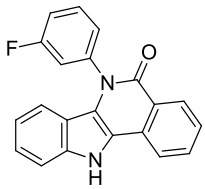
7.60 (t, *J* = 7.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.74 (t, *J* = 7.7 Hz, 1H), 5.90 (d, *J* = 8.3 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.2, 139.2, 136.8, 132.9, 129.8, 129.04, 128.98 (2C), 128.7, 126.4, 124.0, 123.8, 121.0, 120.4, 118.9 (2C), 118.7, 116.8, 112.0; **ATR-IR** ν 3179 (w), 2956 (m), 2922 (s), 2853 (m), 1722 (w), 1622 (m), 1492 (w), 1461 (m), 1352 (w), 1188 (w), 1081 (w), 966 (m), 739 (m), 694 (m); **HRMS (ESI)** calcd for $C_{21}H_{15}N_2O^+$ $[M+H]^+$ 311.1179; found 311.1170.

6-(4-chlorophenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200e**)




Yield: 16.5 mg (96%), yellow solid; mp: 342 - 344 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.15 (s, 1H), 8.35 (d, *J* = 8.0 Hz, 1H), 8.24 (d, *J* = 8.0 Hz, 1H), 7.91 (t, *J* = 7.6 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 6.82 (t, *J* = 7.7 Hz, 1H), 6.04 (d, *J* = 8.2 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.7, 138.4, 137.2, 134.0, 133.5, 131.5, 130.3, 129.4, 129.2, 127.0, 124.4, 124.2, 121.5, 120.4, 119.6, 119.4, 119.0, 117.4, 112.6; **ATR-IR** ν 3179 (w), 3075 (w), 2920 (w), 2907 (w), 2895 (w), 1623 (s), 1613 (s), 1556 (s), 1489 (m), 1353 (m), 1088 (w), 727 (s), 726 (s), 692 (s), 633 (m); **HRMS (ESI)** calcd for $C_{21}H_{14}N_2OCl^+$ $[M+H]^+$ 345.0789; found 345.0777;

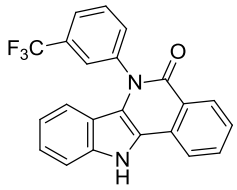
6-(3-fluorophenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200f**)




Yield: 15.9 mg (97%), yellow solid; mp: 273 - 274 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.12 (s, 1H), 8.37 (dd, *J* = 8.1, 1.3 Hz, 1H), 8.26 (d, *J* = 7.7 Hz, 1H), 7.93 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.60 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 7.55-7.51 (m, 3H), 7.45 – 7.38 (m, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.81 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.00 (d, *J* = 8.3 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 162.6 (d, *J* = 245.5 Hz), 160.1, 140.6 (d, *J* = 10.2 Hz), 136.7, 133.0, 131.3 (d, *J* = 9.1 Hz), 129.0, 128.8, 126.5, 125.5 (d, *J* = 3.2 Hz), 123.9 (2C), 121.1, 120.0, 119.1, 118.8, 118.5, 116.7 (d, *J* = 23.3 Hz), 116.6, 116.1 (d, *J* = 20.7 Hz), 112.1; **ATR-IR** ν 3224 (w), 3075 (w), 3067 (w), 2924 (w), 2923 (w), 2922 (w), 1625 (s), 1563 (m), 1489 (w), 1453 (w), 1452 (w), 1374 (w), 1349 (w),

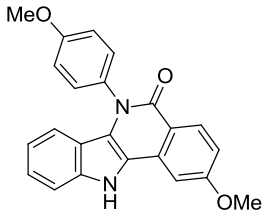
1254 (w), 1178 (w), 741 (m), 694 (w); **HRMS (ESI)** calcd for $C_{21}H_{14}FN_2O^+$ $[M+H]^+$ 329.1085; found 329.1084.

6-(3-(trifluoromethyl)phenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200g**)



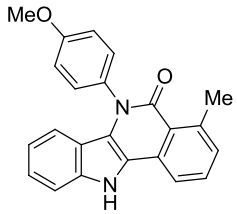

Yield: 18.3 mg (97%), yellow solid; mp: 259 – 260 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.16 (s, 1H), 8.37 (dd, *J* = 8.1, 1.2 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 8.09 – 8.01 (m, 2H), 7.98 – 7.87 (m, 3H), 7.61 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.19 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.79 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 5.89 (d, *J* = 8.2 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.3, 139.8, 136.8, 133.6, 133.1, 131.0, 130.5 (q, *J* = 32.3 Hz), 129.0, 128.8, 126.5, 126.3 (q, *J* = 3.7 Hz), 125.8 (q, *J* = 4.1 Hz), 123.9 (2C), 123.8 (q, *J* = 272.0 Hz), 121.1, 119.8, 119.1, 119.0, 118.1, 116.6, 112.2; **ATR-IR** ν 3253 (w), 3227 (w), 2956 (w), 2924 (w), 2853 (w), 1623 (s), 1555 (m), 1450 (m), 1348 (m), 1329 (s), 1300 (m), 1168 (s), 1126 (s), 1093 (m), 1068 (s), 739 (s), 697 (s); **HRMS (ESI)** calcd for $C_{22}H_{14}F_3N_2O^+$ $[M+H]^+$ 379.1053; found 379.1052.

6-(4-methoxyphenyl)-3-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200h**)




Yield: 16.1 mg (85%), yellow solid; mp: 290 – 291 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.97 (s, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 7.73 (s, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.10 (m, 4H), 6.78 (t, *J* = 7.7 Hz, 1H), 6.04 (d, *J* = 8.3 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 162.7, 160.3, 159.3, 136.7, 131.8, 131.1, 130.6, 130.1, 123.8, 121.3, 119.0, 118.9, 118.7, 117.7, 117.0, 115.2, 114.7, 111.9, 102.8, 55.7, 55.5; **ATR-IR** *v* 3137 (w), 2959 (w), 2835 (w), 1630 (s), 1620 (s), 1511 (s), 1247 (s), 1023 (s), 1000 (s), 743 (s); **HRMS (ESI)** calcd for $C_{23}H_{19}N_2O_3^+$ $[M+H]^+$ 371.1390; found 371.1395.

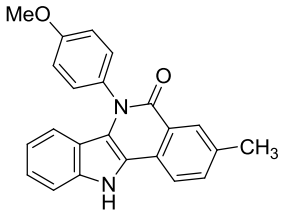
6-(4-methoxyphenyl)-4-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200i**)




Yield: 17.1 mg (97%), yellow solid; mp: 270 - 271 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.89 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.72 (td, *J* = 7.7, 2.7 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.6 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.20-7.16 (m, 3H), 6.77 (t, *J* = 7.7 Hz, 1H), 6.18 (dt, *J* = 6.6, 3.1 Hz, 1H), 3.90 (s, 3H), 2.84 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 161.4, 159.2, 142.4, 136.9, 132.1, 132.1, 130.2, 130.1, 129.7, 123.8, 122.1, 120.8, 119.1, 118.9, 118.9, 118.8, 116.8, 114.8, 111.9, 55.5, 24.0; **ATR-IR** *v* 3175 (w), 2926 (w), 2852 (w), 1707 (w), 1615 (s), 1561 (s), 1510 (s), 1248 (s);

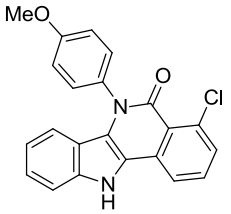
**HRMS (ESI)** calcd for $C_{23}H_{19}N_2O_2^+$ $[M+H]^+$ 355.1441; found 355.1442.

6-(4-methoxyphenyl)-3-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200j**)



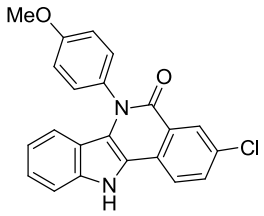

Yield: 17.0 mg (96%), yellow solid; mp: 318 - 320 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.99 (s, 1H), 8.17 (d, *J* = 1.6 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.16 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 6.78 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.04 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 3H), 2.51 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.4, 159.3, 136.5, 135.9, 134.0, 131.9, 130.0, 128.6, 126.4, 124.1, 123.5, 121.0, 120.1, 118.84, 118.80, 118.7, 117.1, 114.8, 111.9, 55.5, 21.2; **ATR-IR** *v* 3293 (w), 2968 (s), 2967 (s), 2923 (s), 1623 (m), 1614 (m), 1613 (m), 1512 (s), 1464 (m), 1378 (m), 1249 (s), 1075 (s), 1057 (s); **HRMS (ESI)** calcd for $C_{23}H_{19}N_2O_2^+$ $[M+H]^+$ 355.1441; found 355.1452.

4-chloro-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200k**)



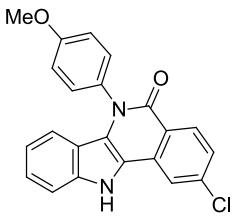
Yield: 16.7 mg (89%), yellow solid; mp: 266 – 267 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.08 (s, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.81 (t, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.41 (dd, *J* = 8.6, 2.1 Hz, 2H), 7.25 – 7.12 (m, 3H), 6.79 (t, *J* = 7.7 Hz, 1H), 6.02 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.4, 159.3, 136.5, 135.9, 134.0, 131.9, 130.0, 128.6, 126.4, 124.1, 123.5, 121.0, 120.1, 118.84, 118.80, 118.7, 117.1, 114.8, 111.9, 55.5; **ATR-IR** *v* 3172 (w), 2928 (w), 2927 (w), 2926 (w), 1637 (s), 1610 (m), 1510 (s), 1249 (s), 1026 (s), 1007 (s), 739 (s); **HRMS (ESI)** calcd for$C_{22}H_{16}ClN_2O_2^+$ $[M+H]^+$ 375.0895; found 375.0891.

6-(4-methoxyphenyl)-4-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200l**)




Yield: 16.7 mg (89%), yellow solid; mp: 337 - 339 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.08 (s, 1H), 8.29 (s, 1H), 8.28 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.20 – 7.19 (m, 1H), 6.80 (t, *J* = 7.6 Hz, 1H), 6.04 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.4, 136.9, 133.0, 131.5, 130.7, 129.9, 128.0, 127.4, 125.5, 125.3, 124.2, 123.3, 121.2, 119.1, 119.0, 118.0, 116.8, 114.9, 112.0, 55.5; **ATR-IR** ν 3276 (w), 3248 (w), 3247 (w), 2927 (w), 2926 (w), 2853 (w), 1715 (m), 1714 (m), 1621 (s), 1579 (m), 1562 (m), 1512 (s), 1458 (m), 1372 (m), 1351 (w), 1302 (m), 1249 (s), 1172 (m), 1172 (m), 1171 (m), 1171 (m), 1106 (w), 1031 (m), 831 (m), 745 (m); **HRMS (ESI)** calcd for $C_{22}H_{16}ClN_2O_2^+$ $[M+H]^+$ 375.0895; found 375.0909.

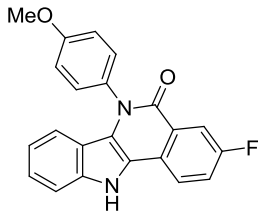
2-chloro-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200m**)




Yield: 17.8 mg (95%), yellow solid; mp: 300 – 301 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.07 (s, 1H), 8.36 (d, *J* = 2.1 Hz, 1H), 8.34 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.31 – 7.10 (m, 3H), 6.81 (ddd, *J* = 8.0, 7.0, 0.9 Hz, 1H), 6.05 (d, *J* = 8.3 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.9, 159.4, 137.9, 137.0, 131.5,

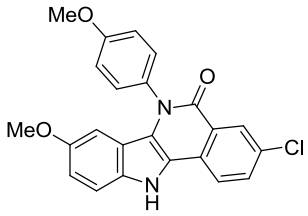
131.4, 130.0, 129.9, 126.2, 124.4, 122.5, 122.0, 120.4, 119.1 (2C), 117.5, 116.7, 114.9, 112.1, 55.5; **ATR-IR** ν 3213 (w), 2960 (w), 2959 (w), 2923 (w), 1614 (s), 1557 (m), 1510 (s), 1460 (m), 1438 (w), 1375 (m), 1249 (s), 1032 (m), 837 (w), 742 (s); **HRMS (ESI)** calcd for $C_{22}H_{16}ClN_2O_2^+$ $[M+H]^+$ 375.0895; found 375.0881.

3-fluoro-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200n**)




Yield: 17.4 mg (97%), yellow solid; mp: 329 – 331 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.10 (s, 1H), 8.32 (dd, *J* = 8.9, 5.1 Hz, 1H), 8.02 (dd, *J* = 9.7, 2.8 Hz, 1H), 7.85 (td, *J* = 8.7, 2.8 Hz, 1H), 7.50 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.17 (m, 1H), 6.80 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1H), 6.04 (d, *J* = 8.2 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 160.5 (d, *J* = 244.1 Hz), 59.6 (d, *J* = 3.3 Hz), 159.4, 136.6, 131.5, 129.9, 125.8 – 125.7 (2C), 123.9 (d, *J* = 8.2 Hz), 123.8, 121.4 (d, *J* = 23.6 Hz), 120.3, 119.0, 118.8, 118.3, 116.9, 114.8, 114.0 (d, *J* = 22.9 Hz), 112.0, 55.5; **ATR-IR** ν 3246 (w), 3234 (w), 2987 (m), 2958 (s), 2923 (s), 2857 (m), 1626 (w), 1625 (w), 1611 (w), 1610 (w), 1512 (w), 1462 (w), 1462 (w), 1378 (w), 1250 (w), 1076 (w), 1066 (m), 1058 (w); **HRMS (ESI)** calcd for $C_{22}H_{16}FN_2O_2^+$ $[M+H]^+$ 359.1190; found 359.1185.

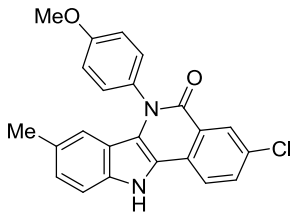
3-chloro-8-methoxy-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200o**)




Yield:19.2 mg (95%), yellow solid; mp: 306 – 308 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.93 (s, 1H), 8.28 (d, *J* = 2.2 Hz, 1H), 8.23 (d, *J* = 8.6 Hz, 1H), 7.96 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.39 (d, *J* = 2.4 Hz, 1H), 3.89 (s, 3H), 3.40 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.6, 159.2, 152.6, 132.9, 132.2, 131.4, 130.6, 130.2, 128.0, 127.5, 125.2, 123.2, 121.0, 118.8, 116.7, 114.8, 114.3, 112.8, 100.5, 55.6, 54.6; **ATR-IR** ν 3417 (w), 3410 (w), 3277 (w), 2956 (w), 2927 (w), 2855 (w), 1725 (w), 1620

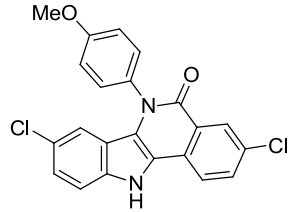
(w), 1549 (w), 1510 (w), 1455 (w), 1248 (m), 1026 (s), 1006 (s); **HRMS (ESI)** calcd for $C_{23}H_{18}ClN_2O_3^+$ $[M+H]^+$ 405.1000; found 405.1006.

3-chloro-6-(4-methoxyphenyl)-8-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200p**)



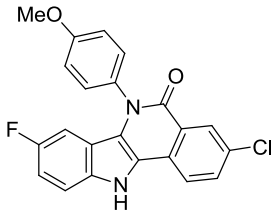

Yield: 18.4 mg (95%), yellow solid; mp: 349 – 351 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.00 (s, 1H), 8.27 (d, *J* = 2.3 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 7.96 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.42 – 7.38 (m, 3H), 7.21 (d, *J* = 8.8 Hz, 2H), 7.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.79 (d, 1.6 Hz, 1H), 3.91 (s, 3H), 2.10 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.5, 159.4, 135.4, 132.9, 131.5, 130.5, 129.9, 128.0, 127.5, 127.4, 125.8, 125.1, 123.3, 120.9, 118.5, 118.2, 116.9, 114.8, 111.8, 55.6, 21.3; **ATR-IR** ν 3295 (w), 3294 (w), 3252 (w), 3251 (w), 3250 (w), 2957 (w), 2922 (w), 2921 (w), 2857 (w), 2856 (w), 1620 (s), 1560 (s), 1510 (s), 1453 (m), 1305 (m), 1304 (m), 1250 (s), 1031 (m), 1031 (m), 834 (m), 801 (s); **HRMS (ESI)** calcd for $C_{23}H_{18}ClN_2O_2^+$ $[M+H]^+$ 389.1057; found 389.1061.

3-chloro-6-(4-methoxyphenyl)-8-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200q**)



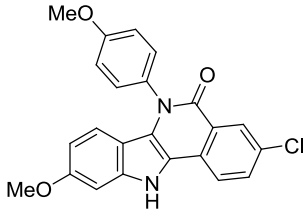

Yield: 18.8 mg (92%), yellow solid; mp: 309 – 311 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.37 (s, 1H), 8.29 (d, *J* = 2.4 Hz, 1H), 8.28 (d, *J* = 8.8 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.20 (dd, *J* = 8.6, 2.1 Hz, 1H), 5.92 (d, *J* = 1.9 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.6, 159.3, 135.2, 133.1, 131.3, 131.1, 129.9, 128.1, 127.1, 125.7, 123.9, 123.5, 123.4, 120.5, 119.4, 118.0, 117.5, 115.0, 113.7, 55.7; **ATR-IR** ν 3444 (w), 3437 (w), 3429 (w), 3422 (w), 2923 (w), 2852 (w), 2851 (w), 1649 (w), 1052 (s), 1025 (s), 1006 (s), 823 (m), 761 (m); **HRMS (ESI)** calcd for $C_{22}H_{15}Cl_2N_2O_2^+$ $[M+H]^+$ 409.0505; found 409.0496.

3-chloro-8-fluoro-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200r**)



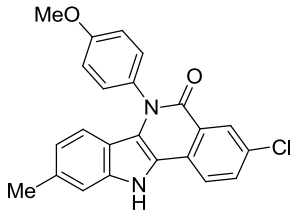

Yield:18.8 mg (96%), yellow solid; mp: 314 – 315 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.25 (s, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.52 (dd, *J* = 9.0, 4.6 Hz, 1H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.08 (td, *J* = 9.0, 2.6 Hz, 1H), 5.61 (dd, *J* = 10.4, 2.6 Hz, 1H), 3.91 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.6, 159.3, 156.1 (d, *J* = 232.0 Hz), 133.5, 133.1, 131.2, 131.0, 130.0, 128.1, 127.2, 125.6, 123.5, 121.1 (d, *J* = 5.0 Hz), 119.8, 116.4 (d, *J* = 10.7 Hz), 114.9, 113.4 (d, *J* = 9.6 Hz), 112.5 (d, *J* = 26.7 Hz), 103.4 (d, *J* = 25.6 Hz), 55.6; **ATR-IR ν** 3310 (w), 3302 (w), 3299 (w), 2960 (w), 2925 (w), 2916 (w), 2842 (w), 2841 (w), 1624 (s), 1560 (s), 1549 (s), 1510 (s), 1454 (m), 1252 (s), 1106 (m), 1034 (m), 832 (m), 799 (s), 794 (s), 748 (m); **HRMS (ESI)** calcd for $C_{22}H_{15}ClFN_2O_2^+$ $[M+H]^+$ 393.0801; found 393.0807.

3-chloro-9-methoxy-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200s**)



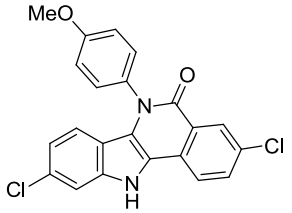

Yield: 19.2 mg (95%), yellow solid; mp: 304 – 306 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.92 (s, 1H), 8.25 (d, *J* = 2.3 Hz, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 7.93 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 2.3 Hz, 1H), 6.49 (dd, *J* = 9.0, 2.3 Hz, 1H), 5.91 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.4 (2C), 157.5, 138.3, 132.9, 131.4, 129.8 (2C), 128.0, 127.4, 124.3, 122.9, 121.7, 119.8, 117.0, 114.9, 111.3, 109.8, 94.4, 55.5, 55.2, **ATR-IR** ν 3235 3228 (w), 3227 (w), 2852 (w), 1723 (w), 1722 (w), 1616 (s), 1510 (s), 1461 (m), 1444 (m), 1443 (m), 1380 (m), 1246 (s), 1203 (s), 1166 (s), 811 (s), 798 (s); **HRMS (ESI)** calcd for $C_{23}H_{18}ClN_2O_3^+$ $[M+H]^+$ 405.1000; found 405.1015.

3-chloro-6-(4-methoxyphenyl)-9-methyl-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200t**)



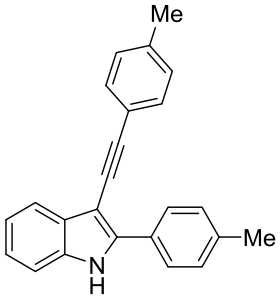

Yield: 18.0 mg (93%), yellow solid; mp: 313 – 315 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 11.94 (s, 1H), 8.26 (d, *J* = 2.3 Hz, 1H), 8.24 (d, *J* = 8.6 Hz, 1H), 7.95 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.29 – 7.25 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 2H), 6.63 (dd, *J* = 8.5, 1.4 Hz, 1H), 5.93 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 2.36 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.4 (2C), 137.4, 133.8, 132.9, 131.5, 130.3, 129.9, 128.0, 127.5, 124.9, 123.2, 121.4, 121.0, 118.7, 117.5, 114.8 (2C), 111.6, 55.5, 21.4; **ATR-IR** ν 3310 (w), 3309 (w), 3308 (w), 2953 (w), 2952 (w), 2951 (w), 2950 (w), 2925 (w), 2924 (w), 2856 (w), 2855 (w), 2854 (w), 2853 (w), 1621 (s), 1557 (s), 1556 (s), 1543 (s), 1508 (s), 1458 (m), 1248 (s), 1025 (m), 827 (s), 826 (s), 798 (s), 741 (m); **HRMS (ESI)** calcd for $C_{23}H_{18}ClN_2O_2^+$ $[M+H]^+$ 389.1051; found 389.1045.

3,9-dichloro-6-(4-methoxyphenyl)-6,11-dihydro-5H-indolo[3,2-c]isoquinolin-5-one (**1.200u**)



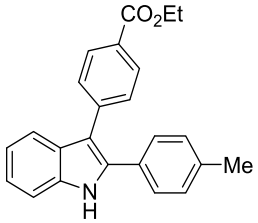

Yield: 19.6 mg (96%), yellow solid; mp: 336 – 338 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.32 (s, 1H), 8.29 (d, *J* = 2.3 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.54 (d, *J* = 1.9 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.00 (d, *J* = 8.8 Hz, 1H), 3.90 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.5, 159.4, 137.1, 133.1, 131.14, 131.09, 129.9, 128.7, 128.1, 127.1, 125.4, 123.4, 121.1, 120.2, 119.6, 118.8, 115.7, 115.0, 111.6, 55.5; **ATR-IR** ν 3308 (w), 2959 (w), 2919 (w), 2918 (w), 2850 (w), 1627 (s), 1573 (s), 1560 (s), 1559 (s), 1509 (s), 1461 (m), 1249 (s), 1105 (m), 1105 (m), 1067 (m), 1022 (s), 834 (s), 834 (s), 827 (s), 827 (s), 801 (s), 801 (s), 780 (m), 748 (m); **HRMS (ESI)** calcd for $C_{22}H_{15}Cl_2N_2O_2^+$ $[M+H]^+$ 409.0505; found 409.0508.

2-(*p*-Tolyl)-3-(*p*-tolylethynyl)-1H-indole (**1.204**)



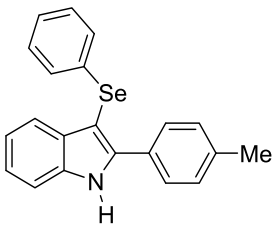

Yield 12.1 mg (75%), foam; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.31 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 7.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.38 (dd, *J* = 6.8, 1.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H), 2.39 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.7, 138.6, 137.7, 135.4, 131.3, 130.5, 129.8, 129.2, 128.9, 126.5, 123.4, 121.5, 121.0, 120.2, 111.0, 95.8, 93.7, 83.6, 21.6, 21.5; **ATR-IR** *v* 3413 (w), 2919 (w), 2203 (w), 1495 (w), 1442 (m), 1260 (m), 816 (s), 741 (s); **HRMS (ESI)** calcd for $C_{24}H_{20}N^+$ $[M+H]^+$ 322.1590; found 322.1581.

Ethyl 4-(2-(p-tolyl)-1H-indol-3-yl)benzoate (**1.207**)




Yield 17.6 mg (99%), foam; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.31 (s, 1H), 8.09 – 8.00 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.49 (m, 2H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.19 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 167.0, 140.5, 138.2, 136.0, 135.3, 130.0, 129.9, 129.7, 129.5, 128.43, 128.37, 128.1, 122.9, 120.9, 119.5, 113.7, 111.1, 61.0, 21.4, 14.5; **ATR-IR** *v* 3353 (w), 1693 (m), 1606 (m), 1455 (m), 1275 (s), 1108 (m), 1021 (m), 822 (m), 745 (m); **HRMS (ESI)** calcd for $C_{24}H_{22}NO_2^+$ $[M+H]^+$ 356.1645; found 356.1660.

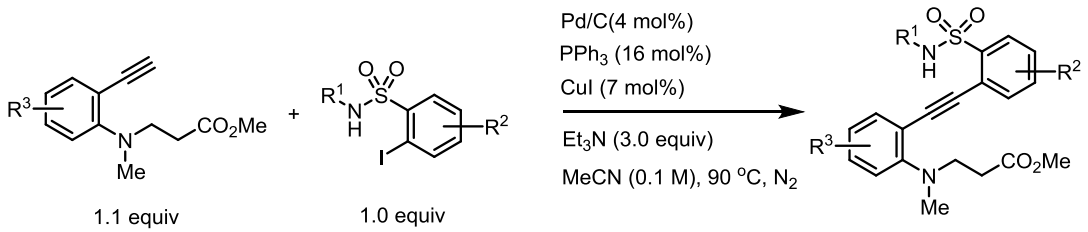
3-(Phenylselanyl)-2-(p-tolyl)-1H-indole (**1.210**)



Yield 9.4 mg (52%), brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.46 (s, 1H), 7.63 – 7.50 (m, 3H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.15 (m, 3H), 7.15 – 6.96 (m, 6H), 2.32 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 142.4, 138.8, 136.2, 134.3, 132.3, 129.5, 129.3, 129.2, 128.5, 128.4, 125.5, 123.2, 121.2, 121.0, 111.0, 95.6, 21.5; **ATR-IR** *v* 3405 (w), 3404 (w), 3403 (w), 3402 (w), 2921 (w), 2921 (w), 2852 (w), 1280 (w), 1280 (w), 1265 (w), 820 (m), 734 (s); **HRMS (ESI)** calcd for $C_{21}H_{18}NSe^{+}$ $[M+H]^{+}$ 363.0526; found 363.0534.

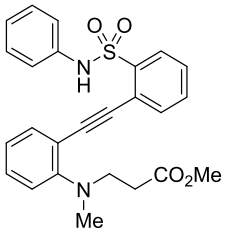
## 3.2. Synthesis of Tetracyclic Indolobenzothiazine S,S−Dioxides by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes

### 3.2.1. Preparation of starting materials 1.245



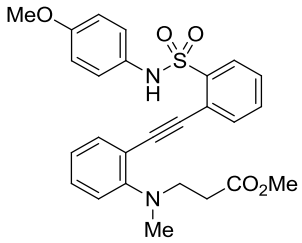

To a solution of 2-iodobenzensulfonamide (**1.251**) (0.4 mmol) in 4.0 mL MeCN were added Pd/C 10% (17.10 mg, 4 mol%), $Ph_3P$ (17.10 mg, 16 mol%), CuI (54.4 mg, 7 mol%) and triethylamine (0.16 mL, 1.2 mmol), successively, under argon. After being stirred for 30 min, *o*-alkynylanline **1.248** (0.44 mmol) was added and the reaction mixture was heated with stirring at 80 ºC for 1.5 – 2.0 hours. The reaction mixture was cooled down, filtered through a short bed of celite and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **1.245**.

Methyl 3-((2-((2-(N-benzylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245a**)



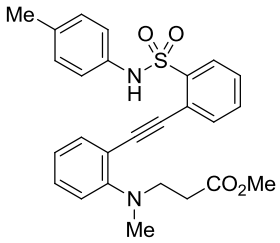
Yield: 144.0 mg (80%), yellow solid; 80 – 81 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.69 (s, 1H), 8.00 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.62 (ddd, *J* = 9.1, 7.6, 1.5 Hz, 2H), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.35 (td, *J* = 7.7, 1.3 Hz, 1H), 7.23 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.17 (td, *J* = 7.5, 1.1 Hz, 1H), 7.15 – 7.09 (m, 4H), 7.02 – 6.87 (m, 1H), 3.60 (t, *J* = 7.5 Hz, 2H), 3.52 (s, 3H), 2.84 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 153.6, 140.2, 136.7, 133.8, 133.8, 132.2, 130.4, 129.9, 129.1, 128.3, 125.2, 124.5, 122.0, 121.3, 120.9, 118.9, 96.0, 90.5, 52.1, 51.6, 43.4, 31.0; **ATR-IR** ν 3119 (w), 3078 (w), 2948 (w), 2859 (w), 1724 (s), 1598 (w), 1490 (m), 1345 (m), 1336 (m), 1160 (s), 1040 (m), 928 (w); **HRMS (ESI)** calcd for $C_{25}H_{25}N_2O_4S^+$ $[M+H]^+$ 449.1530; found 449.1538.

Methyl 3-((2-((2-(N-(4-methoxyphenyl)sulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245b**)



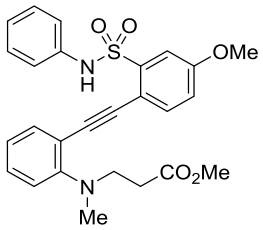

Yield: 162.4 mg (85%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.53 (s, 1H), 7.92 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1H), 7.39 (td, *J* = 7.8, 1.6 Hz, 1H), 7.33 (td, *J* = 7.7, 1.3 Hz, 1H), 7.22 (d, *J* = 8.2 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.11 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 3.68 (s, 3H), 3.53 – 3.49 (m, 5H), 2.79 (s, 3H), 2.49 (t, *J* = 7.7 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.4, 157.7, 153.5, 140.3, 133.7, 132.0, 130.3, 129.8, 129.1, 128.3, 125.5, 125.4, 124.6, 121.4, 120.8, 119.3, 114.3, 96.1, 90.3, 55.3, 51.9, 51.6, 44.1, 31.1; **ATR-IR** ν 3066 (w), 2952 (w), 2951 (w), 2840 (w), 2839 (w), 2215 (w), 1736 (m), 1510 (m), 1337 (m), 1250 (m), 1164 (s), 1035 (w), 1034 (w), 763 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_5S^+$ $[M+H]^+$ 479.1635; found 479.1646.

Methyl 3-(methyl(2-((2-(*N*-(*p*-tolyl)sulfamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.245c**)



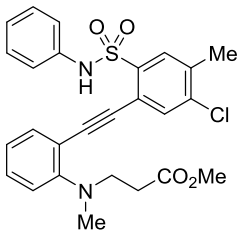

Yield: 147.8 mg (80%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.57 (s, 1H), 7.97 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42-7.37 (m, 1H), 7.34 (td, *J* = 7.7, 1.3 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.16 (td, *J* = 7.5, 1.1 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.57 (d, *J* = 7.6 Hz, 2H), 3.52 (s, 3H), 2.83 (s, 3H), 2.52 (t, *J* = 7.6 Hz, 2H), 2.18 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 153.7, 140.4, 135.2, 134.0, 133.9, 133.8, 132.2, 130.5, 130.0, 129.8, 128.4, 124.6, 122.8, 121.5, 121.0, 119.2, 96.1, 90.6, 52.2, 51.7, 43.7, 31.1, 20.9; **ATR-IR** ν 3065 (w), 3060 (w), 3059 (w), 3058 (w), 2950 (w), 2858 (w), 2857 (w), 2856 (w), 2214 (w), 2213 (w), 1732 (m), 1510 (m), 1437 (m), 1337 (m), 1161 (s); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_4S^+$ $[M+H]^+$ 463.1686; found 463.1693.

Methyl 3-((2-((2-(N-benzylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245d**)



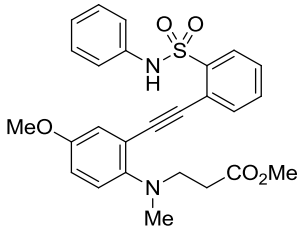

Yield: 78.5 mg (41%), brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.77 (s, 1H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.39 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.24 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.21 – 7.13 (m, 5H), 7.07 – 7.02 (m, 1H), 6.99 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.83 (s, 3H), 3.61 (d, *J* = 7.6 Hz, 2H), 3.55 (s, 3H), 2.85 (s, 3H), 2.53 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.7, 159.4, 153.3, 141.9, 136.7, 135.3, 133.5, 130.0, 129.3, 125.4, 124.7, 122.5, 121.5, 119.7, 118.7, 114.9, 112.8, 94.4, 90.6, 55.9, 52.2, 51.7, 43.6, 31.1; **ATR-IR** ν 3232 (w), 3223 (w), 3067 (w), 3057 (w), 3056 (w), 2952 (w), 2853 (w), 1734 (m), 1600 (m), 1495 (m), 1228 (m), 1160 (s); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_5S^+$ $[M+H]^+$ 479.1635; found 479.1634.

Methyl 3-((2-((5-chloro-4-methyl-2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.245e**)



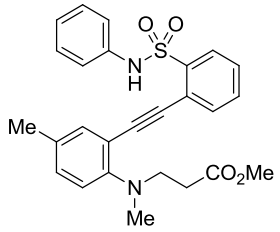

Yield: 105.2 mg (53%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.65 (s, 1H), 7.85 (s, 1H), 7.61 – 7.58 (m, 2H), 7.44 – 7.38 (m, 1H), 7.24 – 7.13 (m, 6H), 7.06 – 7.02 (m, 1H), 3.58 (t, *J* = 7.8 Hz, 2H), 3.52 (s, 3H), 2.83 (s, 3H), 2.51 (t, *J* = 7.7 Hz, 2H), 2.36 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 153.7, 138.7, 138.5, 137.3, 136.6, 133.9, 133.9, 132.2, 130.7, 129.4, 125.5, 124.8, 122.4, 121.6, 119.7, 118.9, 96.3, 89.5, 52.3, 51.8, 43.6, 31.1, 20.2; **ATR-IR** ν 3070 (w), 3069 (w), 2951 (w), 2854 (w), 1735 (m), 1596 (w), 1493 (m), 1472 (m), 1344 (w), 1162 (s), 954 (m); **HRMS (ESI)** calcd for $C_{26}H_{26}ClN_2O_4S^+$ $[M+H]^+$ 497.1296; found 497.1299.

Methyl 3-((4-methoxy-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.245f**)



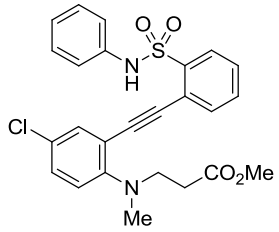

Yield: 95.7 mg (50%), light yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 10.06 (s, 1H), 7.98 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.46 (td, *J* = 7.6, 1.3 Hz, 1H), 7.34 (td, *J* = 7.7, 1.3 Hz, 1H), 7.21 – 7.09 (m, 6H), 7.04 – 6.99 (m, 1H), 6.97 (dd, *J* = 8.9, 3.0 Hz, 1H), 3.85 (s, 3H), 3.53 (s, 3H), 3.44 (t, *J* = 7.8 Hz, 2H), 2.75 (s, 3H), 2.51 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 156.5, 140.4, 136.7, 133.7, 132.1, 129.9, 129.1, 128.41, 128.37, 125.3, 123.0, 122.5, 120.8, 120.7, 117.4, 116.8, 95.7, 90.0, 55.6, 52.8, 51.6, 44.5, 31.0; **ATR-IR** ν 3073 (w), 2987 (m), 2970 (m), 2901 (m), 2213 (w), 2212 (w), 1735 (m), 1600 (w), 1599 (w), 1496 (m), 1343 (m), 1342 (m), 1225 (m), 1224 (m), 1165 (s), 1065 (m), 1037 (m), 919 (w), 760 (m), 730 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_5S^+$ $[M+H]^+$ 479.1635; found 479.1639.

Methyl 3-(methyl(4-methyl-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.245g**)



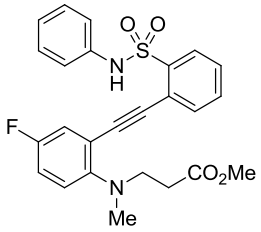

Yield: 97.9 mg (53%), light yellow solid; mp: 86 – 88 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.87 (s, 1H), 7.99 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.69 – 7.56 (m, 1H), 7.46-7.42 (m, 2H), 7.34 (td, *J* = 7.8, 1.3 Hz, 1H), 7.21 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.18 – 7.08 (m, 5H), 7.00 (m, 1H), 3.53-3.49 (m, 5H), 2.80 (s, 3H), 2.51 (t, *J* = 7.7 Hz, 2H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 151.1, 140.2, 136.7, 134.5, 134.0, 133.7, 132.1, 131.2, 129.9, 129.1, 128.2, 125.1, 122.2, 121.4, 121.0, 119.1, 96.1, 90.0, 52.4, 51.6, 43.8, 30.9, 20.6; **ATR-IR** ν 3073 (w), 3041 (w), 3027 (w), 2951 (w), 2921 (w), 2920 (w), 2880 (w), 2207 (w), 1736 (m), 1599 (w), 1496 (m), 1346 (m), 1165 (s), 759 (w); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_4S^+$ $[M+H]^+$ 463.1686; found 463.1689.

Methyl 3-((4-chloro-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245h**)



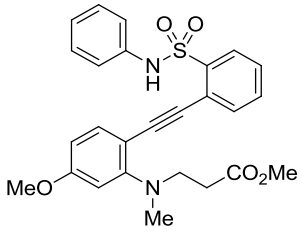
Yield: 133.3 mg (69%), light yellow solid; mp: 110 – 112 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.43 (s, 1H), 8.01 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.58 (d, *J* = 2.5 Hz, 1H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.39 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.17 – 7.09 (m, 5H), 7.05 – 6.97 (m, 1H), 3.61 (d, *J* = 7.5 Hz, 2H), 3.53 (s, 3H), 2.84 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.4, 152.1, 140.3, 136.5, 134.0, 133.2, 132.3, 130.3, 130.0, 129.2 (2C), 128.7, 125.2, 122.5, 121.8, 120.4, 120.3, 94.3, 91.4, 52.0, 51.7, 43.3, 30.9; **ATR-IR** ν 3127 (w), 3117 (w), 3072 (w), 3030 (w), 3029 (w), 2951 (w), 2845 (w), 2219 (w), 2211 (w), 1732 (m), 1597 (w), 1489 (m), 1345 (m), 1162 (s), 911 (m), 756 (m), 730 (s), 695 (m); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_4S^+$ $[M+H]^+$ 483.1140; found 483.1146.

Methyl 3-((4-fluoro-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245i**)



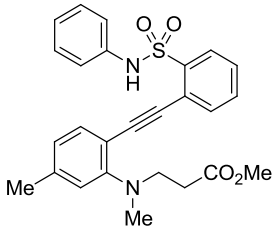
Yield: 123.1 mg (66%), white solid; mp: 110 – 111 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 9.70 (s, 1H), 7.99 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.64 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.48 (td, *J* = 7.6, 1.3 Hz, 1H), 7.37 (td, *J* = 7.7, 1.4 Hz, 1H), 7.31 (dd, *J* = 8.6, 3.0 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.17 – 7.07 (m, 4H), 7.12 – 7.08 (m, 1H), 7.05 – 6.99 (m, 1H), 3.53 (s, 3H), 3.53 – 3.50 (m, 2H), 2.79 (s, 3H), 2.52 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.4, 159.2 (d, *J* = 244.7 Hz), 149.7, 140.4, 136.6, 133.9, 132.2, 129.9, 129.2, 128.7, 125.3, 123.2 (d, *J* = 9.2 Hz), 122.2, 121.0 (d, *J* = 10.0 Hz), 120.3, 119.8 (d, *J* = 23.6 Hz), 117.4 (d, *J* = 22.2 Hz), 94.4, 91.0, 52.5, 51.6, 44.1, 30.9; **ATR-IR** ν 3115 (w), 3075 (w), 2952 (w), 2886 (w), 2885 (w), 2208 (w), 1734 (m), 1494 (m), 1345 (m), 1202 (m), 1164 (s), 921 (w), 759 (m); **HRMS (ESI)** calcd for $C_{25}H_{24}FN_2O_4S^+$ $[M+H]^+$ 467.1435; found 467.1438.

Methyl 3-((5-methoxy-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)-propanoate (**1.245j**)



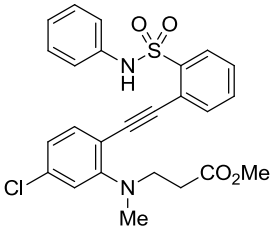
Yield: 151.6 mg (79%), yellow solid; mp: 115 – 117 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.50 (s, 1H), 7.99 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.59 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.44 (td, *J* = 7.6, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1H), 7.12 (d, *J* = 4.3 Hz, 4H), 7.02 – 6.97 (m, 1H), 6.73 – 6.71 (m, 1H), 6.69 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.86 (s, 3H), 3.61 (t, *J* = 7.6 Hz, 2H), 3.54 (s, 3H), 2.85 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 161.4, 155.2, 139.6, 136.7, 135.0, 133.3, 132.2, 129.8, 129.1, 127.7, 125.0, 121.7, 121.3, 110.7, 109.3, 107.7, 96.4, 89.5, 55.5, 51.9, 51.6, 43.0, 30.9; **ATR-IR** ν 2987 (w), 2971 (m), 2901 (w), 2209 (w), 1734 (m), 1600 (m), 1496 (m), 1345 (m), 1298 (m), 1232 (s), 1163 (s), 1079 (m), 1065 (m), 1039 (m), 915 (w), 759 (m), 730 (w), 696 (w); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_5S^+$ $[M+H]^+$ 479.1635; found 479.1645.

Methyl 3-(methyl(5-methyl-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)amino)propanoate (**1.245k**)



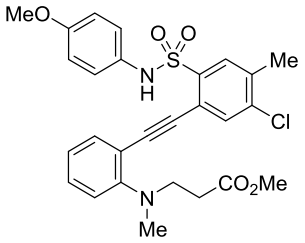
Yield: 138.0 mg (75%), white solid; mp: 80 – 81 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.68 (s, 1H), 7.99 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.61 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.45 (td, *J* = 7.6, 1.4 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.16 – 7.09 (m, 4H), 7.03 – 6.94 (m, 3H), 3.58 (t, *J* = 7.7 Hz, 2H), 3.53 (s, 3H), 2.83 (s, 3H), 2.54 (t, *J* = 7.7 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 153.5, 141.0, 140.0, 136.7, 133.6, 133.5, 132.1, 129.8, 129.1, 128.0, 125.4, 125.0, 122.0, 121.9, 121.1, 115.9, 96.2, 89.9, 52.1, 51.6, 43.4, 30.9, 21.8; **ATR-IR** ν 3070 (w), 3063 (w), 2950 (w), 2845 (w), 2211 (w), 1734 (m), 1601 (w), 1495 (m), 1467 (w), 1436 (w), 1346 (m), 1164 (s), 916 (w), 758 (m), 730 (w), 730 (w), 696 (w); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_4S^+$ $[M+H]^+$ 463.1686; found 463.1695.

Methyl 3-((5-chloro-2-((2-(N-phenylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245l**)



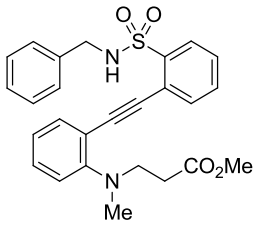
Yield: 142.7 mg (74%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.14 (s, 1H), 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.62 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.47 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (td, *J* = 7.7, 1.3 Hz, 1H), 7.18 – 7.07 (m, 6H), 7.03 – 6.97 (m, 1H), 3.68 (t, *J* = 7.5 Hz, 2H), 3.54 (s, 3H), 2.88 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.3, 154.5, 140.0, 136.5, 136.1, 134.7, 133.8, 132.3, 129.9, 129.1, 128.4, 125.1, 124.1, 121.5, 121.3, 120.6, 116.3, 95.0, 91.3, 51.7, 42.5, 30.9; **ATR-IR** ν 3074 (w), 2951 (w), 2861 (w), 2844 (w), 2843 (w), 2814 (w), 2813 (w), 2211 (w), 1732 (m), 1582 (w), 1492 (m), 1401 (w), 1346 (m), 1162 (s), 1125 (w), 911 (m), 756 (m), 729 (s), 694 (m); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_4S^+$ $[M+H]^+$ 483.1140; found 483.1136.

Methyl 3-((2-((5-chloro-2-(N-(4-methoxyphenyl)sulfamoyl)-4-methylphenyl)ethynyl)phenyl)-(methyl)amino)propanoate (**1.245m**)



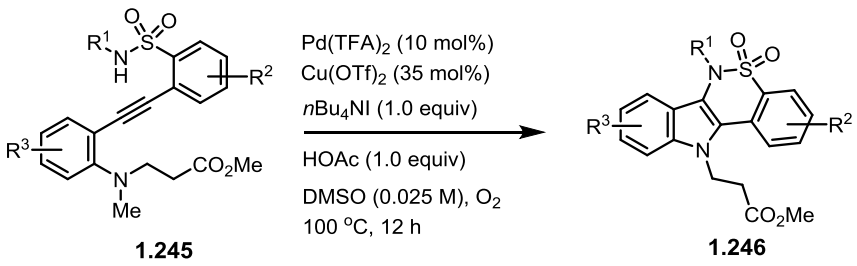
Yield: 116.0 mg (55%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 9.56 (s, 1H), 7.77 (s, 1H), 7.64 (s, 1H), 7.60 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.42 – 7.36 (m, 1H), 7.24 – 7.15 (m, 2H), 7.11 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 3.70 (s, 3H), 3.53 (s, 3H), 3.49 (t, *J* = 7.7 Hz, 2H), 2.77 (s, 3H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.6, 158.0, 153.8, 138.7, 138.5, 137.3, 133.8, 133.8, 132.1, 130.7, 129.0, 125.9, 124.9, 121.7, 119.7, 119.3, 114.5, 96.4, 89.4, 55.5, 52.1, 51.8, 44.4, 31.3, 20.2; **ATR-IR** ν 3000 (w), 2952 (w), 2836 (w), 1734 (m), 1644 (s), 1525 (s), 1512 (s), 1458 (m), 1247 (s), 1208 (m); **HRMS (ESI)** calcd for $C_{27}H_{28}ClN_2O_5S^+$ $[M+H]^+$ 527.1402; found 527.1400.

Methyl 3-((2-((2-(N-benzylsulfamoyl)phenyl)ethynyl)phenyl)(methyl)amino)propanoate (**1.245n**)



Yield: 164.8 mg (89%), brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 6.3 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.22 – 7.16 (m, 2H), 7.10 (dt, *J* = 15.4, 6.0 Hz, 4H), 6.96 (d, *J* = 8.2 Hz, 1H), 4.03 (d, *J* = 6.3 Hz, 2H), 3.52 (s, 3H), 3.33 (t, *J* = 7.6 Hz, 2H), 2.46 (s, 3H), 2.32 (t, *J* = 7.6 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.5, 153.5, 140.5, 136.2, 133.7, 133.6, 132.0, 130.1, 129.6, 128.41, 128.37 (2C), 127.6, 123.7, 120.7, 120.6, 118.2, 95.8, 89.9, 51.5, 51.4, 47.2, 42.0, 30.7; **ATR-IR** ν 3065 (w), 2950 (w), 2925 (w), 2854 (w), 2213 (w), 1732 (m), 1492 (w), 1466 (w), 1455 (w), 1437 (m), 1331 (m), 1161 (s), 1066 (m), 761 (s), 701 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_4S^+$ $[M+H]^+$ 463.1686; found 463.1694.

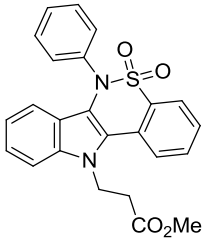
### 3.2.2. Substrate scope for Pd(II)-catalyzed diamination of sulfonamide 2-alkynylanilines




**1.245** **1.246**

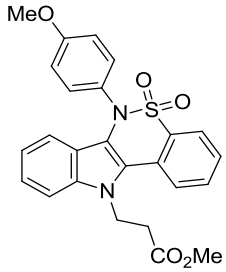
A 5-mL-Vial was charged with **1.245** (0.1 mmol), $Pd(TFA)_2$ (10 mol%), $Cu(OTf)_2$ (35 mol%), $n$$Bu_4NI$ (1.0 equiv), acetic acid (1.0 equiv) together with 4 mL dry DMSO and heated at 100 °C under oxygen (1 atm) for 12 hours. The reaction mixture was quenched with ice and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Then the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **1.246.**

Methyl3-(5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-*b*]indol-11(6H)-yl)propanoate (**1.246a**)



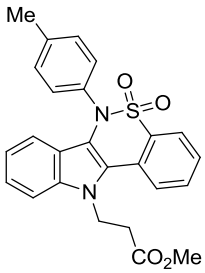
Yield: 32.4 mg (75%), yellow solid; mp: 230 – 232 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.37 – 7.22 (m, 4H), 7.19 (dd, *J* = 7.1, 1.9 Hz, 2H), 7.07 (t, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 4.86 (t, *J* = 7.8, 2H), 3.68 (s, 3H), 2.89 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 138.5, 138.0, 132.7, 132.4, 129.0, 127.7, 127.4, 127.0, 126.1, 125.6, 125.4, 125.0, 123.6, 121.5, 121.2, 120.5, 119.6, 110.2, 52.1, 41.5, 34.3; **ATR-IR** ν 2951 (w), 2924 (w), 2853 (w), 1734 (m), 1593 (w), 1488 (w), 1459 (w), 1350 (s), 1177 (s); **HRMS (ESI)** calcd for $C_{24}H_{21}N_2O_4S^+$ $[M+H]^+$ 433.1217; found 433.1231.

Methyl 3-(6-(4-methoxyphenyl)-5,5-dioxidobenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246b**)



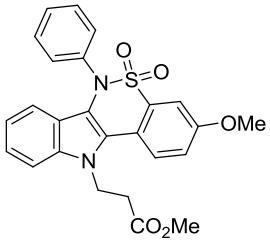
Yield: 18.5 mg (41%), yellow solid; mp: 186 – 187 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.98 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.76 (td, *J* = 7.8, 1.4 Hz, 1H), 7.53 (td, *J* = 7.6, 1.0 Hz, 1H), 7.45 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.3, 7.0, 1.3 Hz, 1H), 7.16 – 7.07 (m, 3H), 7.04 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 1H), 4.85 (t, *J* = 7.8, 2H), 3.76 (s, 3H), 3.67 (s, 3H), 2.88 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 158.8, 138.0, 132.6, 132.0, 131.4, 127.6, 127.0, 125.4, 125.1, 125.0, 123.5, 121.5, 121.1, 121.1, 119.6, 114.2, 110.2, 55.4, 52.1, 41.5, 34.3; **ATR-IR** ν 2987 (w), 2968 (w), 2956 (w), 2902 (w), 1734 (m), 1507 (m), 1507 (m), 1462 (w), 1348 (s), 1251 (m), 1207 (w), 1174 (s), 1032 (w), 746 (m), 735 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_5S^+$ $[M+H]^+$ 463.1322; found 463.1333.

Methyl 3-(5,5-dioxido-6-(p-tolyl)benzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)propanoate (**1.246c**)



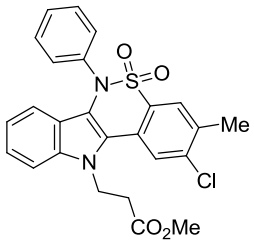

Yield: 31.2 mg (70%), dark brown solid; mp: 192 – 194 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.97 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.76 (td, *J* = 7.8, 1.4 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.48 – 7.43 (m, 1H), 7.32 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.17 – 6.99 (m, 6H), 4.85 (t, *J* = 7.8 Hz, 2H), 3.67 (s, 3H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 138.1, 137.6, 136.1, 132.8, 132.4, 129.8, 127.8, 127.2, 126.2, 125.6, 125.5, 125.1, 123.7, 121.7, 121.3, 121.0, 119.8, 110.3, 52.3, 41.7, 34.5, 21.2; **ATR-IR** ν 2985 (w), 2945 (w), 1738 (s), 1373 (m), 1236 (s), 1045 (s); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_4S^+$ $[M+H]^+$ 447.1373; found 447.1378.

Methyl 3-(3-methoxy-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246d**)



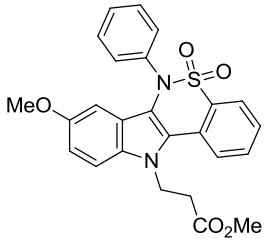

Yield: 34.6 mg (74%), yellow solid; mp: 111 – 112 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.81 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 2.7 Hz, 1H), 7.44 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.32 – 7.24 (m, 5H), 7.21 – 7.16 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.03 (ddd, *J* = 7.9, 6.9, 0.9 Hz, 1H), 4.83 (t, *J* = 7.8 Hz, 2H), 3.88 (s, 3H), 3.68 (s, 3H), 2.89 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 159.3, 138.8, 137.6, 134.1, 129.1, 127.5, 126.2, 126.2, 125.4, 124.5, 121.9, 121.2, 120.3, 119.7, 119.3, 118.6, 110.1, 109.3, 56.0, 52.3, 41.6, 34.5; **ATR-IR** *v* 2955 (w), 2930 (w), 1732 (m), 1605 (w), 1503 (w), 1457 (w), 1348 (s), 1167 (s), 1028 (m), 745 (s), 696 (s); **HRMS (ESI)** calcd for $C_{25}H_{22}N_2O_5SNa^+$ $[M+Na]^+$ 485.1142; found 485.1134.

Methyl 3-(2-chloro-3-methyl-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246e**)



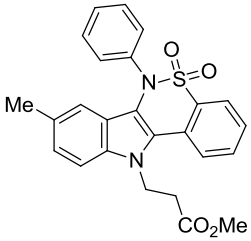

Yield: 34.6 mg (72%), yellow solid; mp: 137 – 138 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 (s, 1H), 7.83 (s, 1H), 7.46 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.36 – 7.23 (m, 4H), 7.21 – 7.15 (m, 2H), 7.10 – 7.02 (m, 2H), 4.84 (t, *J* = 7.7, 2H), 3.68 (s, 3H), 2.88 (t, *J* = 7.7, 2H), 2.48 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 139.3, 138.6, 138.1, 136.5, 130.6, 129.2, 127.6, 127.6, 126.2, 126.1, 125.3, 124.8, 124.1, 121.6, 121.5, 121.0, 119.7, 110.4, 52.3, 41.6, 34.5, 20.2; **ATR-IR** *v* 2966 (w), 2920 (w), 1734 (m), 1595 (w), 1558 (w), 1489 (w), 1458 (w), 1349 (s), 1170 (s), 1081 (m), 745 (m); **HRMS (ESI)** calcd for $C_{25}H_{21}ClN_2O_4SNa^+$ $[M+Na]^+$ 503.0803; found 503.0802.

Methyl 3-(8-methoxy-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246f**)



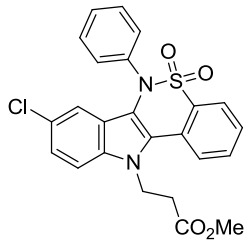

Yield: 35.1 mg (76%), yellow solid; mp: 225 – 226 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.89 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.66 (m, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.24 – 7.14 (m, 3H), 7.11 (dd, *J* = 7.2, 1.8 Hz, 2H), 6.89 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.48 (d, *J* = 2.5 Hz, 1H), 4.74 (t, *J* = 7.8, 2H), 3.60 (s, 3H), 3.57 (s, 3H), 2.79 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.2, 155.0, 138.6, 133.4, 132.8, 132.5, 129.1, 127.8, 127.4, 127.2, 126.4, 126.1, 125.6, 123.7, 122.2, 120.2, 115.7, 111.4, 100.7, 55.8, 52.3, 41.8, 34.5; **ATR-IR** ν 2951 (w), 2924 (w), 2853 (w), 1721 (m), 1496 (m), 1489 (m), 1457 (m), 1346 (s), 1327 (m), 1249 (m), 1210 (m), 1168 (s), 1051 (m), 1021 (m), 803 (m), 761 (m), 737 (m), 698 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_5S^+$ $[M+H]^+$ 463.1322; found 463.1324.

Methyl 3-(8-methyl-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246g**)



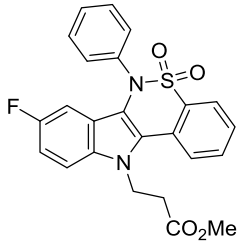

Yield: 32.7 mg (73%), yellow solid; mp: 150 – 151 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.96 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.57 – 7.48 (m, 1H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.18 – 7.13 (m, 3H), 6.88 (s, 1H), 4.82 (t, *J* = 7.8, 2H), 3.67 (s, 3H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.30 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 138.6, 136.4, 132.7, 132.3, 130.8, 129.0, 127.6, 127.3, 127.1, 126.8, 126.0, 125.9, 125.5, 123.6, 121.8, 120.0, 119.0, 109.9, 52.1, 41.5, 34.3, 21.3; **ATR-IR** ν 2952 (w), 2923 (w), 2855 (w), 1736 (m), 1736 (m), 1593 (w), 1489 (m), 1459 (w), 1436 (w), 1353 (s), 1317 (m), 1247 (w), 1237 (w), 1205 (m), 1176 (s), 1138 (w), 737 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_4S^+$ $[M+H]^+$ 447.1373; found 447.1371.

Methyl 3-(8-chloro-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246h**)



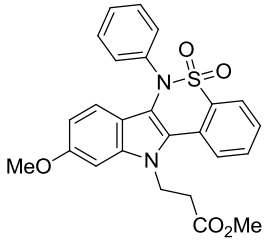

Yield: 24.7 mg (53%), yellow solid; mp: 179 – 180 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.96 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.76 (td, *J* = 7.6, 1.3 Hz, 1H), 7.55 (td, *J* = 7.6, 1.0 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 1H), 7.32 – 7.23 (m, 4H), 7.18 – 7.11 (m, 2H), 7.05 (d, *J* = 2.0 Hz, 1H), 4.82 (t, *J* = 7.8, 2H), 3.68 (s, 3H), 2.86 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 138.4, 136.3, 132.9, 132.8, 129.3, 128.4, 127.8, 127.1, 127.1, 126.7, 126.1, 125.7, 125.5, 123.9, 122.7, 119.8, 118.9, 111.6, 52.4, 41.7, 34.4; **ATR-IR** ν 3067 (w), 3066 (w), 2952 (w), 2926 (w), 2853 (w), 1734 (m), 1488 (m), 1456 (m), 1352 (s), 1302 (m), 1266 (w), 1204 (m), 1174 (s), 736 (s), 694 (m); **HRMS (ESI)** calcd for $C_{24}H_{20}ClN_2O_4S^+$ $[M+H]^+$ 467.0827; found 467.0816.

Methyl 3-(8-fluoro-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246i**)



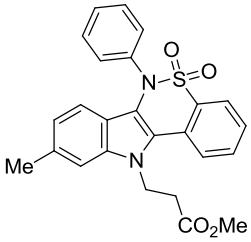

Yield: 28.1 mg (62%), yellow solid; mp: 217 – 219 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.98 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.92 – 7.85 (m, 1H), 77.78 (td, *J* = 7.8, 1.3 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.40 (dd, *J* = 9.1, 4.0 Hz, 1H), 7.41 – 7.35 (m, 3H), 7.16 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.06 (td, *J* = 9.0, 2.5 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.84 (t, *J* = 7.8, 2H), 3.67 (s, 3H), 2.87 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.0, 158.3 (d, *J* = 238.8 Hz), 138.4, 134.6, 132.9, 132.8, 129.3, 128.3, 127.7, 127.3, 126.8, 126.1, 125.6, 123.8, 122.1 (d, *J* = 10.3 Hz), 120.4 (d, *J* = 5.0 Hz), 113.8 (d, *J* = 26.6 Hz), 111.5 (d, *J* = 9.5 Hz), 104.7 (d, *J* = 24.7 Hz), 52.3, 41.8, 34.5; **ATR-IR** ν 3059 (w), 2947 (w), 2929 (w), 2849 (w), 1732 (m), 1490 (m), 1350 (s), 1327 (m), 1243 (m), 1178 (s), 1169 (s), 1158 (s), 1158 (s), 805 (m), 758 (s), 735 (s), 695 (m); **HRMS (ESI)** calcd for $C_{24}H_{20}FN_2O_4S^+$ $[M+H]^+$ 451.1122; found 451.1117.

Methyl 3-(9-methoxy-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246j**)




Yield: 36.0 mg (78%), yellow solid; mp: 133 – 134 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.95 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.73 (td, *J* = 7.7, 1.4 Hz, 1H), 7.48 (td, *J* = 7.6, 1.1 Hz, 1H), 7.31 – 7.25 (m, 3H), 7.19 – 7.16 (m, 2H), 6.92 (d, *J* = 8.8 Hz, 1H), 6.89 (d, *J* = 2.1 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.1 Hz, 1H), 4.80 (t, *J* = 7.8, 2H), 3.86 (s, 3H), 3.68 (s, 3H), 2.87 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 158.7, 139.3, 138.4, 132.6, 131.5, 129.0, 127.4, 127.2, 127.0, 126.1, 125.3, 124.4, 123.0, 120.9, 120.4, 115.7, 111.1, 93.7, 55.7, 52.1, 41.5, 34.1; **ATR-IR** ν 2987 (w), 2953 (w), 2908 (w), 2902 (w), 1735 (m), 1735 (m), 1622 (w), 1593 (m), 1489 (m), 1351 (s), 1252 (m), 1222 (m), 1177 (s), 1028 (w), 759 (w), 736 (w); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_5S^+$ $[M+H]^+$ 463.1322; found 463.1305.

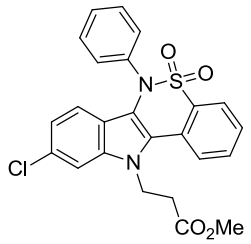
Methyl 3-(9-methyl-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246k**)




Yield: 37.5 mg (80%), yellow solid; mp: 173 – 174 ºC; **$^1$H NMR (400 MHz, CDCl$_3$)** δ 7.96 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.75 (td, *J* = 7.8, 1.4 Hz, 1H), 7.51 (td, *J* = 7.7, 1.1 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.20 – 7.15 (m, 2H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.2 Hz, 1H), 4.82 (t, *J* = 7.8, 2H), 3.69 (s, 3H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.48 (s, 3H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 171.1, 138.5, 138.5, 135.3, 132.6, 132.0, 129.0, 127.4, 127.3, 127.1, 126.0, 125.3, 125.0, 123.4, 123.0, 120.6, 119.4, 119.2, 110.1, 52.1, 41.4, 34.3, 22.1; **ATR-IR** ν 2984 (w), 2952 (w), 2921 (w), 2920 (w), 1735 (m), 1593 (w), 1489 (m), 1458 (w), 1349 (s), 1199 (w), 1177 (s), 758 (w), 736 (m);

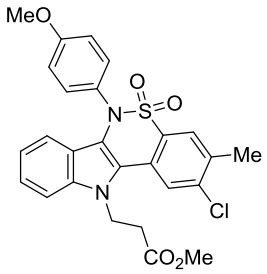
**HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_4S^+$ $[M+H]^+$ 447.1373; found 447.1384.

Methyl 3-(9-chloro-5,5-dioxido-6-phenylbenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)-propanoate (**1.246l**)



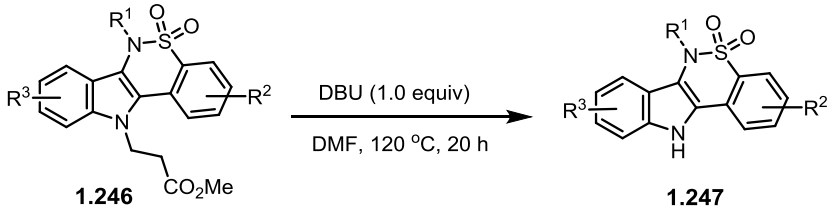

Yield: 22.8 mg (49%), white solid; mp: 191 – 192 ºC; **$^1$H NMR (400 MHz, CDCl$_3$)** δ 7.98 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.46 (s, 1H), 7.32 – 7.26 (m, 3H), 7.20 – 7.14 (m, 2H), 7.03 – 6.94 (m, 2H), 4.82 (t, *J* = 7.8, 2H), 3.69 (s, 3H), 2.89 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 170.9, 138.4 (2C), 132.9, 132.5, 131.2, 129.2, 128.2, 127.7, 126.8, 126.3, 126.2, 125.6, 123.7, 122.2, 120.6, 120.1, 110.5 (2C), 52.4, 41.8, 34.4; **ATR-IR** ν 2996 (w), 2995 (w), 2987 (w), 2979 (w), 2972 (w), 2954 (w), 1736 (m), 1489 (w), 1355 (s), 1205 (w), 1204 (w), 1177 (s), 1138 (w), 763 (w), 737 (m), 695 (w); **HRMS (ESI)** calcd for $C_{24}H_{20}ClN_2O_4S^+$ $[M+H]^+$ 467.0827; found 467.0829.

Methyl 3-(2-chloro-6-(4-methoxyphenyl)-3-methyl-5,5-dioxidobenzo[5,6][1,2]thiazino[4,3-b]indol-11(6H)-yl)propanoate (**1.246m**)



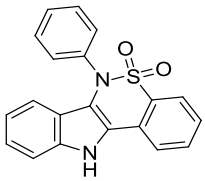

Yield: 22.4 mg (44%), yellow solid; mp: 165 – 166 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.80 (s, 1H), 7.75 (d, *J* = 0.8 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.24 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.08 – 6.93 (m, 4H), 6.73 (d, *J* = 9.0 Hz, 2H), 4.75 (t, *J* = 7.6 Hz, 2H), 3.69 (s, 3H), 3.61 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.40 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 171.1, 159.1, 139.3, 138.1, 136.4, 131.4, 130.3, 127.7, 127.6, 126.1, 125.3, 124.4, 124.1, 121.6, 121.6, 121.4, 119.8, 114.4, 110.4, 55.6, 52.3, 41.6, 34.5, 20.2; **ATR-IR** ν 2987 (w), 2969 (w), 2922 (w), 2909 (w), 2902 (w), 1736 (m), 1507 (s), 1460 (w), 1348 (s), 1251 (s); **HRMS (ESI)** calcd for $C_{26}H_{24}ClN_2O_5S^+$ $[M+H]^+$ 511.1089; found 511.1076.

### 3.2.3. Synthesis of containing-sulfonamide free NH indoles



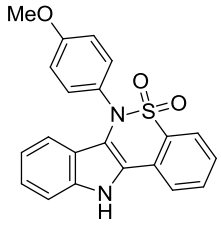

A 5-mL-Vial was charged with **1.246** (0.05 mmol), DBU (1.0 equiv) and DMF (2.5 mL) and was flushed by $N_2$ for 5 minutes. The reaction mixture was then heated at 120 ºC under nitrogen atmosphere for 20 h. The solvent was evaporated directly, then the crude product was purified by flash column chromatography on silica gel to give compound **1.247**.

6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247a**)



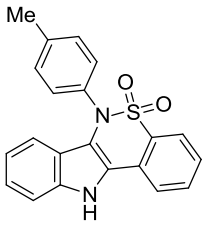
Yield: 16.1 mg (93%), white solid; mp: 273 – 275 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.25 (s, 1H), 8.15 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.91 (td, *J* = 7.7, 1.3 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.63 (td, *J* = 7.7, 1.1 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.25 (ddd, *J* = 8.2, 6.1, 2.1 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.01 – 6.91 (m, 2H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 138.8, 135.8, 133.4, 130.8, 129.2, 128.5, 127.7, 126.8, 126.4, 124.22, 124.15, 124.0, 123.7, 120.5, 120.3, 117.9, 117.8, 112.4; **ATR-IR** ν 3332 (w), 2987 (m), 2974 (m), 2901 (w), 2892 (w), 2884 (w), 1593 (w), 1487 (w), 1335 (m), 1153 (s), 1074 (s), 1068 (s), 1053 (s), 741 (s), 732 (m), 693 (m); **HRMS (ESI)** calcd for $C_{20}H_{15}N_2O_2S^+$ $[M+H]^+$ 347.0849; found 347.0848.

6-(4-methoxyphenyl)-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247b**)




Yield: 15.6 mg (84%), light yellow solid; mp: 242 – 244 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.21 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.24 (ddd, *J* = 8.4, 6.2, 1.9 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.01 – 6.95 (m, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 158.6, 135.8, 133.3, 131.6, 130.6, 128.4, 127.9, 126.8, 124.1, 124.0, 123.8, 123.6, 120.6, 120.2, 118.5, 118.0, 114.4, 112.4, 55.3; **ATR-IR** ν 3346 (w), 3345 (w), 3340 (w), 2957 (w), 2925 (w), 2925 (w), 2925 (w), 2853 (w), 1505 (s), 1337 (s), 1337 (s), 1301 (m), 1248 (s), 1160 (s), 1032 (m), 739 (s); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_3S^+$ $[M+H]^+$ 377.0954; found 377.0952.

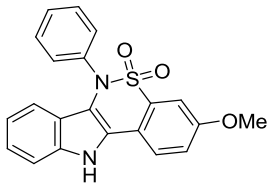
6-(p-tolyl)-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247c**)




Yield: 15.1 mg (84%), white solid; mp: 303 – 305 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.21 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.62 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.00 – 6.96 (m, 4H), 2.27 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 137.3, 136.3, 135.8, 133.3, 130.7, 129.7, 128.4, 126.8,

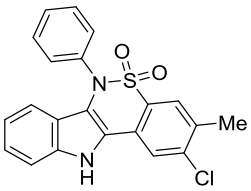
126.2, 124.1, 124.04, 123.97, 123.6, 120.6, 120.2, 118.0, 117.9, 112.4, 20.6; **ATR-IR** ν 3344 (w), 2959 (w), 2958 (w), 2922 (w), 2853 (w), 1592 (w), 1506 (w), 1442 (w), 1332 (s), 1155 (s), 741 (s), 728 (s); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_2S^+$ $[M+H]^+$ 361.1005; found 361.1010.

3-methoxy-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247d**)



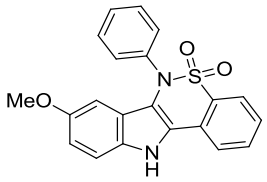

Yield: 17.4 mg (93%), yellow solid; mp: 290 – 291 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.14 (s, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.40 – 7.26 (m, 4H), 7.21 (ddd, *J* = 8.2, 4.6, 3.6 Hz, 1H), 7.12 – 7.09 (m, 2H), 6.98 – 6.92 (m, 2H), 3.88 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 159.2, 139.0, 135.4, 132.2, 129.2, 127.6, 126.3, 125.5, 124.7, 123.5, 120.8, 120.2, 120.1, 119.6, 117.4, 116.0, 112.2, 108.0, 55.9; **ATR-IR** ν 3345 (w), 2956 (w), 2926 (w), 2925 (w), 2854 (w), 2853 (w), 1734 (w), 1717 (w), 1595 (w), 1457 (m), 1342 (s), 1237 (m), 1154 (s), 758 (s), 747 (s); **HRMS (ESI)** calcd for $C_{21}H_{16}N_2NaO_3S^+$ $[M+Na]^+$ 399.0774; found 399.0768.

2-Chloro-3-methyl-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247e**)




Yield: 16.4 mg (83%), yellow solid; mp: 280 – 281 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$):** δ 12.23 (s, 1H), 8.26 (s, 1H), 7.88 (s, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.41 – 7.29 (m, 3H), 7.25 (ddd, *J* = 8.3, 5.8, 2.5 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.02 – 6.93 (m, 2H), 2.46 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 139.2 (2C), 138.9, 136.9, 136.2, 129.7, 128.3, 127.0, 126.9, 126.6, 124.8, 124.3, 123.8, 120.9, 120.9, 118.7, 118.4, 113.0, 20.0; **ATR-IR** *v* 3363 (w), 2923 (w), 2853 (w), 1595 (w), 1488 (m), 1488 (m), 1455 (w), 1355 (m), 1329 (s), 1320 (s), 1263 (m), 1152 (s), 942 (m), 868 (m), 741 (s); **HRMS (ESI)** calcd for $C_{21}H_{15}ClN_2NaO_2S^+$ $[M+Na]^+$ 417.0435; found 417.0441.

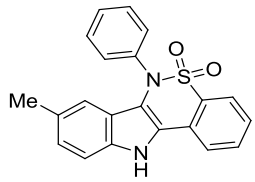
8-methoxy-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247f**)




Yield: 17.5 mg (94%), yellow solid; mp: 271 – 273 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.13 (s, 1H), 8.12 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.91 (td, *J* = 7.6, 1.7 Hz, 1H), 7.85 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.9 Hz, 1H), 7.46 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.41 – 7.27 (m, 3H), 7.14 (dd, *J* = 7.6, 2.4 Hz, 2H), 6.92 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 3.59 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 153.8, 138.7, 133.3, 131.0, 130.8, 129.2, 128.3, 127.6, 126.9, 126.3, 124.8, 124.0, 123.5, 120.9, 117.5, 114.5, 113.4, 99.0, 55.2; **ATR-IR** ν 3335 (w), 2954 (w), 2922 (w), 2853 (w), 1492 (w), 1454 (w), 1341 (s), 1261 (m), 1168 (m), 1154 (s), 1028 (m), 768 (m), 732 (m), 622 (m); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_3S^+$ $[M+H]^+$ 377.0954; found 377.0956.

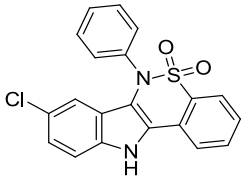
.

8-methyl-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247g**)




Yield: 15.7 mg (87%), yellow solid; mp: 275 – 277 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.13 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.38 – 7.23 (m, 3H), 7.10 – 7.06 (m, 3H), 6.76 (s, 1H), 2.24 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 139.0, 134.3, 133.4, 130.7, 129.2, 129.1, 128.4, 127.6, 127.0, 126.2, 125.9, 124.5, 124.1, 123.6, 120.9, 117.3, 117.1, 112.2, 21.1; **ATR-IR** ν 3335 (m), 2957 (w), 2920 (w), 2853 (w), 1593 (m), 1493 (m), 1342 (s), 1149 (s), 766 (s), 735 (s); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_2S^+$ $[M+H]^+$ 361.1005; found 361.1010.

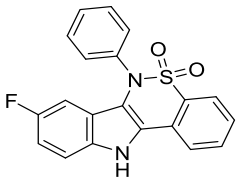
8-chloro-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247h**)




Yield: 17.1 mg (90%), light yellow solid; mp: 279 – 281 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.52 (s, 1H), 8.15 (d, *J* = 7.7, 1H), 7.93 (td, *J* = 7.7, 1.3 Hz, 1H), 7.87 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.66 (td, *J* = 7.7, 1.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.26 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.16 –

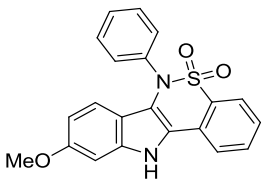
7.10 (m, 2H), 6.92 (d, *J* = 2.1 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 138.6, 134.2, 133.6, 131.1, 129.4, 129.0, 127.9, 126.4, 126.4, 125.8, 124.7, 124.2, 124.1, 123.9, 121.5, 117.2, 116.7, 114.3; **ATR-IR** ν 3326 (w), 2923 (w), 2853 (w), 1594 (w), 1487 (w), 1487 (w), 1471 (w), 1471 (w), 1455 (w), 1455 (w), 1329 (s), 1292 (s), 1154 (s), 762 (s), 745 (m), 696 (m); **HRMS (ESI)** calcd for $C_{20}H_{14}ClN_2O_2S^+$ $[M+H]^+$ 381.0459; found 381.0461.

8-fluoro-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247i**)



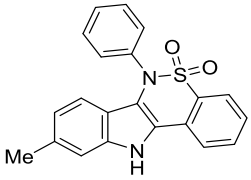

Yield: 17.0 mg (93%), yellow solid; mp: 245- 247 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.41 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.93 (td, *J* = 7.7, 1.3 Hz, 1H), 7.86 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.70 – 7.62 (m, 1H), 7.56 (dd, *J* = 8.9, 4.4 Hz, 1H), 7.43 – 7.25 (m, 3H), 7.17 – 6.98 (m, 3H), 6.65 (dd, *J* = 9.2, 2.5 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 157.0 (d, *J* = 235.1 Hz), 138.6, 133.5 (2C), 132.5, 131.0, 129.3, 128.9, 127.9, 126.5, 126.4, 126.1, 124.0 (d, *J* = 23.8 Hz), 120.7 (d, *J* = 10.5 Hz), 117.8 (d, *J* = 4.9 Hz), 114.0 (d, *J* = 9.7 Hz), 112.7 (d, *J* = 26.3 Hz), 102.4 (d, *J* = 24.6 Hz); **ATR-IR** ν 3409 (w), 2958 (w), 2922 (w), 2874 (w), 2873 (w), 2854 (w), 1490 (m), 1344 (s), 1304 (m), 1254 (m), 1169 (s), 1151 (s), 946 (m), 756 (s), 693 (s); **HRMS (ESI)** calcd for $C_{20}H_{14}FN_2O_2S^+$ $[M+H]^+$ 365.0755; found 365.0738.

9-methoxy-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247j**)



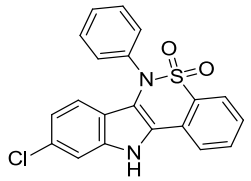

Yield: 16.3 mg (87%), yellow solid; mp: 253 – 255 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.05 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 1H), 7.88 (t, *J* = 7.7 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.37-7.30 (m, 3H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 157.6, 138.7, 137.1, 133.3, 129.9, 129.2, 127.7 (2C), 127.0, 126.4, 123.9, 123.1, 122.9, 118.7, 118.2, 114.8, 110.9, 94.9, 55.3; **ATR-IR** ν 3359 (w), 2957 (w), 2924 (w), 2924 (w), 2904 (w), 1594 (m), 1359 (m), 1326 (s), 1326 (s), 1274 (s), 1149 (s), 1025 (m), 815 (m), 752 (s), 742 (m); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_2S^+$ $[M+H]^+$ 377.0954; found 377.0961.

9-methyl-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247k**)



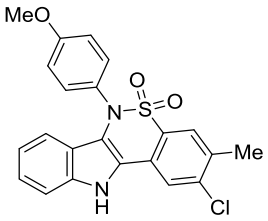

Yield: 16.5 mg (92%), yellow solid; mp: 289 – 291 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.08 (s, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 7.91 (t, *J* = 7.7 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.44 – 7.30 (m, 4H), 7.12 (d, *J* = 7.6 Hz, 2H), 6.83 – 6.79 (m, 2H), 2.41 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 138.8, 136.3, 133.8, 133.3, 130.5, 129.2, 128.1, 127.6, 127.0, 126.3, 123.9, 123.6, 123.4, 122.1, 118.5, 117.9, 117.6, 112.0, 21.5; **ATR-IR** ν 3358 (w), 2957 (w), 2922 (w), 2854 (w), 1592 (m), 1336 (s), 1155 (s), 807 (m), 757 (s), 732 (m), 692 (s); **HRMS (ESI)** calcd for $C_{21}H_{17}N_2O_2S^+$ $[M+H]^+$ 361.1005; found 361.1012.

9-chloro-6-phenyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247l**)



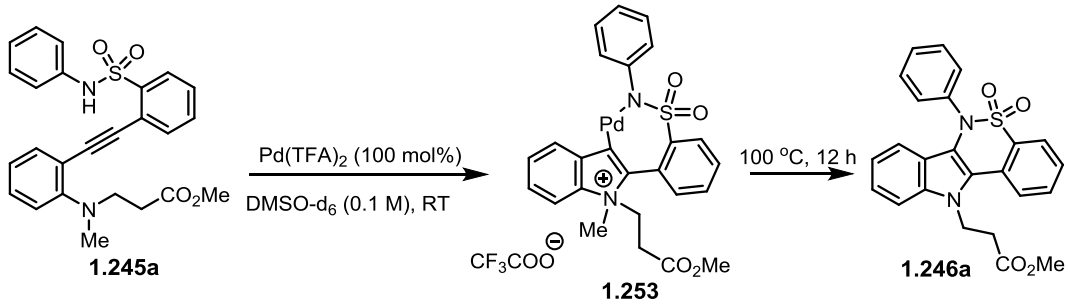

Yield: 16.7 mg (88%), yellow solid; mp: 238 – 239 ºC; **$^1$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.45 (s, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 7.7 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H) ,7.38 – 7.30 (m, 3H), 7.11 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.01 (dd, *J* = 8.6, 1.8 Hz, 1H), 6.93 (d, *J* = 8.5 Hz, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** 138.6, 136.1, 133.5, 130.8, 129.3, 128.9, 128.8, 127.9, 126.42, 126.38, 125.2, 124.0, 123.8, 120.8, 119.33, 119.27, 117.8, 112.0; **ATR-IR** *v* 3344 (w), 2955 (m), 2921 (s), 2853 (m), 1724 (w), 1609 (m), 1596 (m), 1454 (m), 1341 (s), 1158 (s), 1056 (s); **HRMS (ESI)** calcd for $C_{20}H_{13}ClN_2NaO_2S^+$ $[M+Na]^+$ 403.0278; found 403.0283.

2-Chloro-6-(4-methoxyphenyl)-3-methyl-6,11-dihydrobenzo[5,6][1,2]thiazino[4,3-b]indole 5,5-dioxide (**1.247m**)




Yield: 18.6 mg (88%), yellow solid; mp: 295 – 296 ºC; **$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 12.16 (s, 1H), 8.26 (s, 1H), 7.86 (s, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.24 (ddd, *J* = 8.4, 6.4, 2.2 Hz, 1H), 7.11 – 6.95 (m, 4H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.72 (s, 3H), 2.46 (s, 3H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 158.7, 138.3, 136.3, 135.8, 131.5, 129.1, 128.0, 126.4, 126.1, 124.3, 123.7, 122.8, 120.4, 120.3, 118.9, 118.0, 114.4, 112.4, 55.3, 19.5; **ATR-IR** *v* 3319 (w), 3314 (w), 2954 (w), 2929 (w), 2928 (w), 2853 (w), 2836 (w), 1605 (w), 1508 (s), 1460 (m), 1460 (m), 1443 (w), 1319 (s), 1250 (s), 1146 (s), 1035 (s), 748 (s); **HRMS (ESI)** calcd for $C_{22}H_{17}ClN_2NaO_3S^+$ $[M+Na]^+$ 447.0541; found 447.0539.

### 3.2.4. Mechanistic Study



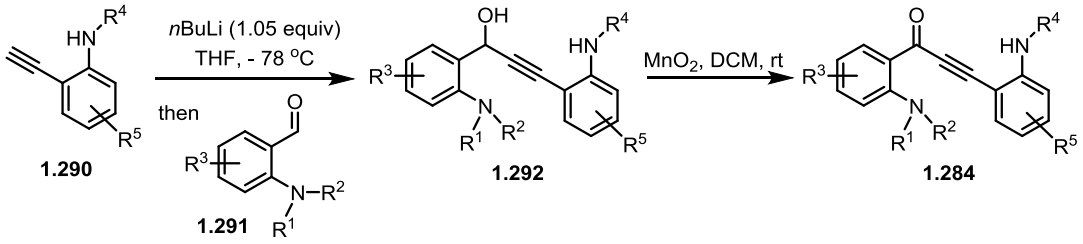

In the glovebox, a NMR tube was charged with **1.245a** (0.1 mmol), $Pd(TFA)_2$ (100 mol%) together with 1 mL DMSO–*d*$_6$ and then sonicated at room temperature. The reaction was monitored by NMR. The starting material was totally consumed after 45 minutes; intermediate **1.253** was observed and characterized by NMR, HRMS. The reaction mixture was further heated to 100 ºC overnight, then quenched with ice and the aqueous phase was extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Then the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **1.246a.**

**$^{1}$H NMR (400 MHz, DMSO-*d*$_6$)** δ 8.23 (d, *J* = 7.9 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.89 - 7.86 (m, 2H), 7.82 - 7.78 (m, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.49 - 7.46 (m, 2H), 7.18 (t, *J* = 7.7 Hz, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 4.68 (t, *J* = 9.0 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 3H), 2.83 (m, 1H), 1.99 – 1.80 (m, 1H); **$^{13}$C NMR (101 MHz, DMSO-*d*$_6$)** δ 170.2, 146.5, 145.0, 138.8 (2C), 137.1, 132.9, 131.8, 130.8, 130.2, 130.1, 129.2, 128.9, 128.5, 128.1 (3C), 128.0,

126.5, 123.5, 117.7, 59.8, 52.3, 50.9, 27.6; **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_4PdS^+$ [M–$CF_3COO^-$] 553.0413; found 553.0432.

## 3.3. Synthetic Approaches to Quindolinones by Palladium-Catalyzed and Acid-Meidated Reactions

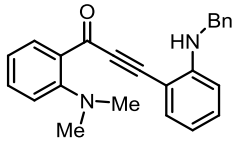
### 3.3.1. Preparation of starting materials 1.245




To a solution of **1.290** (2.2 mmol) in THF (10 mL) was added dropwise a solution of *n*-BuLi in hexane (2.2 mmol, 0.96 mL, 2.3 M) at – 78 °C. The reaction mixture was stirred at this temperature for another 1 h followed by the addition of a solution of **1.291** (2.0 mmol) in THF (10 mL). The resulting mixture was then warmed up to – 40 °C and stirred for additional 2 h. After quenching with aqueous saturated $NH_4Cl$, the reaction mixture was extracted with ethyl acetate, the combined organic phases were dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude propagyl alcohol product **1.292** was dissolved in DCM (20 mL) followed by addition of $MnO_2$ (20 mmol, 1.72 g) in five potions in a period of 3 h. The heterogeneous mixture was allowed to stir at room temperature until **1.292** was totally consumed. The reaction mixture was filtered directly through a short plug of Celite, washed with DCM, and concentrated to afford the crude product. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether) afforded desired product **1.284**.

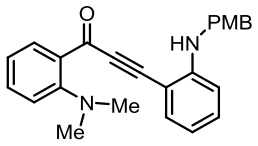
**Characterization Data of Compounds 1.284**

3-(2-(Benzylamino)phenyl)-1-(2-(dimethylamino)phenyl)prop-2-yn-1-one (**1.284a**)



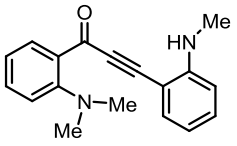
Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.97 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.40 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.36 – 7.27 (m, 5H), 7.23 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 1H), 6.86 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.66 (td, *J* = 7.5, 1.0 Hz, 1H), 6.56 (d, *J* = 8.5 Hz, 1H), 5.52 (t, *J* = 5.8 Hz, 1H), 4.47 (d, *J* = 5.4 Hz, 2H), 2.89 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.1, 152.7, 151.0, 138.7, 134.4, 133.6, 133.0, 132.7, 128.9, 127.7, 127.4, 127.0, 118.8, 116.9, 116.7, 110.5, 104.4, 96.2, 88.8, 47.6, 44.6; **ATR-IR** *v* 2943 (w), 2867 (w), 2173 (m), 1600 (s), 1502 (m), 1159 (s), 995 (m), 747 (s), 698 (s); **HRMS (ESI)** calcd for $C_{24}H_{23}N_2O^+$ $[M+H]^+$ 355.1805; found 355.1805.

1-(2-(Dimethylamino)phenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284b**)



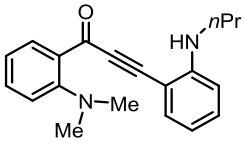

Brown liquid; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.95 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.28 – 7.22 (m, 3H), 6.94 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.89 – 6.81 (m, 3H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.57 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.42 (t, *J* = 5.4 Hz, 1H), 4.39 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H), 2.89 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.1, 159.0, 152.7, 151.1, 134.4, 133.5, 133.0, 132.7, 130.7, 128.3, 127.7, 118.8, 116.8, 116.7, 114.3, 110.5, 104.3, 96.2, 88.8, 55.4, 47.1, 44.6; **ATR-IR** *v* 2935 (w), 2837 (w), 2175 (s), 1612 (s), 1602 (s), 1510 (s), 1324 (m), 1248 (s), 1161 (m), 750 (s); **HRMS (ESI)** calcd for $C_{25}H_{25}N_2O_2^+$ $[M+H]^+$ 355.1911; found 355.1919.

1-(2-(Dimethylamino)phenyl)-3-(2-(methylamino)phenyl)prop-2-yn-1-one (**1.284c**)



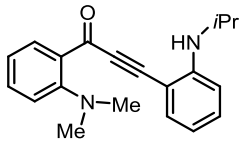

Brown liquid; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.95 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.39 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.28 – 7.22 (m, 3H), 6.94 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.89 – 6.81 (m, 3H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.57 (dd, *J* = 8.5, 1.0 Hz, 1H), 5.42 (t, *J* = 5.4 Hz, 1H), 4.39 (d, *J* = 5.2 Hz, 2H), 3.80 (s, 3H), 2.89 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.1, 159.0, 152.7, 151.1, 134.4, 133.5, 133.0, 132.7, 130.7, 128.3, 127.7, 118.8, 116.8, 116.7, 114.3, 110.5, 104.3, 96.2, 88.8, 55.4, 47.1, 44.6; **ATR-IR** *v* 2935 (w), 2837 (w), 2175 (s), 1612 (s), 1602 (s), 1510 (s), 1324 (m), 1248 (s), 1161 (m), 750 (s); **HRMS (ESI)** calcd for $C_{25}H_{25}N_2O_2^+$ $[M+H]^+$ 385.1911; found 385.1912.

1-(2-(Dimethylamino)phenyl)-3-(2-(propylamino)phenyl)prop-2-yn-1-one (**1.284d**)



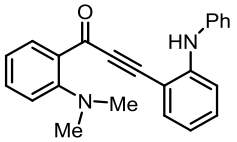
Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.04 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.49 – 7.37 (m, 2H), 7.32 – 7.26 (m, 1H), 7.00 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.90 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.67 – 6.54 (m, 2H), 4.99 – 4.92 (m, 1H), 3.18 (td, *J* = 7.2, 5.7 Hz, 2H), 2.95 (s, 6H), 1.67 (h, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.0, 152.7, 151.4, 134.4, 133.6, 133.3, 132.7, 127.4, 118.4, 116.7, 116.2, 110.0, 104.0, 96.1, 89.2, 45.3, 44.5, 22.7, 11.7; **ATR-IR** *v* 2959 (w), 2932 (w), 2872 (w), 2171 (s), 1616 (m), 1600 (s), 1508 (m), 1189 (m), 1159 (s), 1159 (s), 993 (m), 993 (m), 746 (s); **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O^+$ $[M+H]^+$ 307.1805; found 307.1801.

1-(2-(Dimethylamino)phenyl)-3-(2-(isopropylamino)phenyl)prop-2-yn-1-one (**1.284e**)



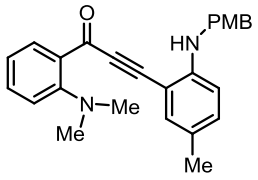

Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.07 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.47 – 7.37 (m, 2H), 7.31 – 7.26 (m, 1H), 6.99 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.89 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.70 – 6.33 (m, 2H), 4.70 (d, *J* = 7.7 Hz, 1H), ), 3.84 – 3.65 (m, 1H), 2.95 (s, 6H), 1.26 (d, *J* = 6.4 Hz, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.9, 152.7, 150.5, 134.5, 133.6, 133.5, 132.7, 127.1, 118.1, 116.6, 116.1, 110.5, 104.1, 96.2, 89.3, 44.3, 44.1, 23.0; **ATR-IR** *v* 2966 (w), 2930 (w), 2170 (s), 1617 (m), 1598 (s), 1506 (m), 1282 (m), 1189 (m), 1175 (s), 1157 (s), 995 (s), 746 (s); **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O^+$ $[M+H]^+$ 307.1805; found 307.1806.

1-(2-(Dimethylamino)phenyl)-3-(2-(phenylamino)phenyl)prop-2-yn-1-one (**1.284f**)



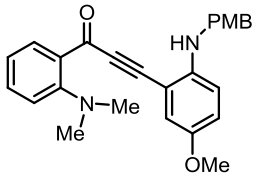

Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.01 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.53 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.41 (ddd, *J* = 8.7, 7.1, 1.8 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.28 – 7.18 (m, 3H), 7.14 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.97 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.92 – 6.86 (m, 1H), 6.79 (td, *J* = 7.5, 1.1 Hz, 1H), 6.74 (s, 1H), 2.89 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.8, 152.9, 147.9, 140.9, 134.6, 133.7, 133.1, 132.2, 129.6, 127.4, 123.8, 122.0, 119.1, 118.8, 116.7, 113.3, 106.6, 96.0, 88.0, 44.7; **ATR-IR** *v* 2987 (w), 2972 (w), 2360 (w), 1594 (w), 1593 (w), 1576 (w), 1265 (m), 733 (s), 699 (s); **HRMS (ESI)** calcd for $C_{23}H_{21}N_2O^+$ $[M+H]^+$ 341.1648; found 341.1450.

1-(2-(Dimethylamino)phenyl)-3-(2-((4-methoxybenzyl)amino)-5-methylphenyl)prop-2-yn-1-one (**1.284g**)



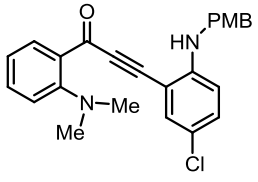

Brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.96 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.32 – 7.19 (m, 3H), 7.11 – 7.02 (m, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.87 – 7.83 (m, 3H), 6.49 (d, *J* = 8.5 Hz, 1H), 5.30 (t, *J* = 5.4 Hz, 1H), 4.37 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 2.88 (s, 6H), 2.21 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.1, 158.9, 152.7, 149.2, 134.4, 133.73, 133.5, 133.0, 130.9, 128.2, 127.7, 125.9, 118.7, 116.7, 114.3, 110.7, 104.2, 96.0, 89.2, 55.4, 47.3, 44.6, 20.2; **ATR-IR** *v* 2968 (w), 2902 (w), 2172 (w), 1614 (m), 1512 (s), 1249 (s), 1169 (w), 1036 (w); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2066.

1-(2-(dimethylamino)phenyl)-3-(5-methoxy-2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284h**)



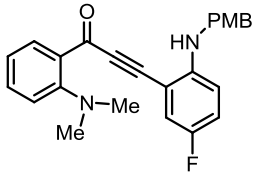

Brown liquid; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.94 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.39 (ddd, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.01 (d, *J* = 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.87 – 6.81 (m, 3H)), 6.53 (d, *J* = 9.0 Hz, 1H), 5.12 (t, *J* = 5.7 Hz, 1H), 4.35 (d, *J* = 5.3 Hz, 2H), 3.80 (s, 3H), 3.73 (s, 3H), 2.88 (s, 6H); **ATR-IR** *v* 2927 (w), 2836 (w), 2169 (m), 1612 (s), 1510 (s), 1246 (s), 1202 (m), 1158 (m), 1021 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2075.

3-(5-Chloro-2-((4-methoxybenzyl)amino)phenyl)-1-(2-(dimethylamino)phenyl)prop-2-yn-1-one (**1.284i**)



Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.38 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 7.26 – 7.19 (m, 2H), 7.16 – 7.11 (m, 1H), 6.94 (t, *J* = 8.0 Hz, 1H), 6.85 (m, 3H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 9.0 Hz, 1H), 5.43 (t, *J* = 5.8 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 2H), 3.78 (s, 3H), 2.87 (s, 6H); **ATR-IR** *v* 2954 (w), 2836 (w), 2177 (w), 1612 (m), 1511 (s), 1496 (s), 1247 (s), 907 (s); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_2^+$ $[M+H]^+$ 419.1521; found 419.1532.

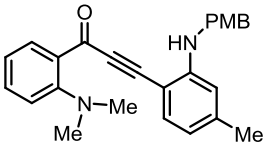
1-(2-(Dimethylamino)phenyl)-3-(5-fluoro-2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284j**)




Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.94 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.38 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H),, 7.26 – 7.20 (

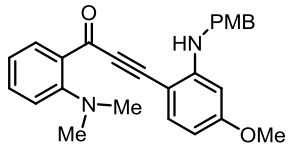
m, 2H), 7.15 (dd, *J* = 8.7, 3.0 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.90 – 6.80 (m, 3H), 6.48 (dd, *J* = 9.2, 4.5 Hz, 1H), 5.28 (t, *J* = 5.4 Hz, 1H), 4.35 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 2.88 (s, 6H); **ATR-IR** *v* 2935 (w), 2836 (w), 2177 (w), 1612 (m), 1510 (s), 1497 (s), 1497 (s), 1247 (s), 1247 (s), 729 (s); **HRMS (ESI)** calcd for $C_{25}H_{24}FN_2O_2^+$ $[M+H]^+$ 403.1816; found 403.1819.

1-(2-(Dimethylamino)phenyl)-3-(2-((4-methoxybenzyl)amino)-4-methylphenyl)prop-2-yn-1-one (**1.284k**)



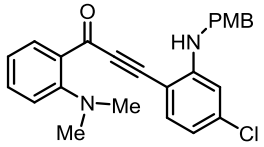

Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.92 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.42 – 7.33 (m, 2H), 7.27 – 7.23 (m, 2H), 6.97 – 6.72 (m, 4H), 6.53 – 6.46 (m, 1H), 6.40 (s, 1H), 5.34 (t, *J* = 5.4 Hz, 1H), 4.37 (d, *J* = 5.4 Hz, 2H), 3.81 (s, 3H), 2.86 (s, 6H), 2.27 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.3, 159.0, 152.6, 151.1, 143.7, 134.4, 133.4, 132.9, 130.8, 128.3, 127.9, 118.7, 118.1, 116.7, 114.3, 111.0, 101.6, 96.2, 89.6, 55.4, 47.1, 44.6, 22.5; **ATR-IR** *v* 2955 (w), 2902 (w), 2168 (s), 1607 (s), 1510 (s), 1246 (s), 1191 (m), 994 (s), 994 (s); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2079.

1-(2-(Dimethylamino)phenyl)-3-(4-methoxy-2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284l**)



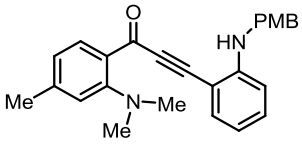

Brown liquid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.91 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.44 – 7.32 (m, 2H), 7.32 – 7.19 (m, 3H), 7.26 (s, 2H), 6.92 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.88 – 6.78 (m, 3H), 6.24 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 5.47 (t, *J* = 5.6 Hz, 1H), 4.37 (d, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 2.87 (s, 6H); **ATR-IR** *v* 2934 (w), 2833 (w), 2170 (m), 1611 (m), 1508 (s), 1243 (s), 1212 (s), 1169 (s), 1159 (s), 1035 (s); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2082.

3-(4-Chloro-2-((4-methoxybenzyl)amino)phenyl)-1-(2-(dimethylamino)phenyl)prop-2-yn-1-one (**1.284m**)




Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.92 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.26 – 7.21 (m, 2H), 6.97 – 6.78 (m, 4H), 6.63 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.57 (d, *J* = 1.9 Hz, 1H), 5.44 (t, *J* = 5.3 Hz, 1H), 4.36 (d, *J* = 5.3 Hz, 2H), 3.81 (s, 3H), 2.88 (s, 6H), 2.86 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.8, 159.2, 152.8, 151.6, 138.9, 135.2, 133.7, 133.0, 129.9, 128.3, 127.4, 118.8, 117.2, 116.7, 114.4, 110.5, 103.0, 96.6, 87.4, 55.5, 47.1, 44.6; **ATR-IR** *v* 2936 (w), 2837 (w), 2176 (m), 1611 (s), 1611 (s), 1595 (s), 1562 (m), 1509 (s), 1429 (m), 1277 (m), 1248 (s); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_2^+$ $[M+H]^+$ 419.1521; found 419.1525.

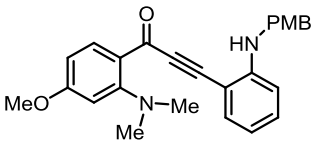
1-(2-(Dimethylamino)-4-methylphenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284n**)




Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.28 – 7.15 (m, 3H), 6.91 – 6.80 (m, 2H), 6.73 (s, 1H), 6.68 – 6.62 (m, 2H), 6.57 (d, *J* = 8.3 Hz, 1H), 5.41 (t, *J* = 5.8 Hz, 1H), 4.39 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 2.87 (s, 6H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.4, 159.0, 153.0, 151.0, 144.6, 134.4, 133.5, 132.6, 130.7, 128.3, 125.2,

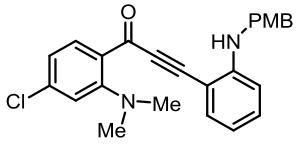
120.0, 117.2, 116.8, 114.3, 110.4, 104.5, 96.2, 88.3, 55.4, 47.1, 44.6, 22.2; **ATR-IR** *v* 2944 (w), 2837 (w), 2173 (s), 1602 (s), 1572 (m), 1510 (s), 1457 (m), 1456 (m), 1247 (s), 1186 (m), 825 (m), 749 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2078.

1-(2-(Dimethylamino)-4-methoxyphenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284o**)



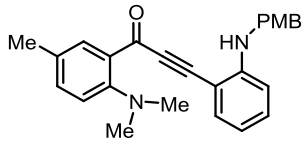

Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.03 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.46 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.15 (m, 3H), 7.00 – 6.78 (m, 2H), 6.65 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 8.7 Hz, 1H), 6.41 – 6.28 (m, 2H), 5.36 (t, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 5.4 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.87 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.9, 164.3, 159.0, 155.1, 150.9, 136.4, 134.2, 132.4, 130.7, 128.4, 121.1, 116.8, 114.3, 110.4, 104.7, 104.6, 102.0, 96.0, 87.9, 55.5, 55.4, 47.2, 44.5; **ATR-IR** *v* 2934 (w), 2837 (w), 2173 (m), 1600 (s), 1510 (s), 1242 (s), 1178 (m), 1110 (m), 827 (m), 749 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2082.

1-(4-Chloro-2-(dimethylamino)phenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284p**)



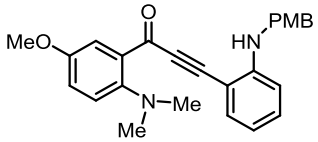

Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.32 – 7.11 (m, 3H), 6.92 – 6.86 (m, 3H), 6.75 (dd, *J* = 8.4, 1.9 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 5.28 (t, *J* = 5.4 Hz, 1H), 4.37 (d, *J* = 5.4 Hz, 2H), 3.81 (s, 3H), 2.87 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.8, 159.1, 153.3, 151.1, 139.7, 134.4, 134.4, 132.9, 130.5, 128.4, 125.6, 118.6, 116.9, 116.6, 114.3, 110.5, 104.1, 95.8, 89.4, 55.45, 47.19, 44.3; **ATR-IR** 2837 (w), 2174 (s), 1614 (s), 1602 (s), 1588 (s), 1510 (s), 1248 (s), 1162 (s), 993 (m), 749 (m); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_2^+$ $[M+H]^+$ 419.1521; found 419.1531.

1-(2-(Dimethylamino)-5-methylphenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284q**)



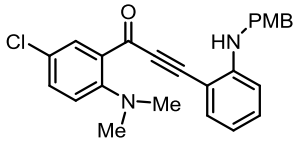

Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.82 – 7.69 (m, 1H), 7.47 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.27 – 7.14 (m, 4H), 6.90 – 6.81 (m, 3H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.52 (t, *J* = 5.7 Hz, 1H), 4.40 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 2.83 (s, 6H), 2.28 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.5, 159.0, 151.1, 151.0, 134.5, 134.4, 132.7 (2C), 130.7, 128.9, 128.5, 128.1, 117.1, 116.8, 114.3, 110.5, 104.4, 96.4, 88.7, 55.4, 47.1, 45.1, 20.4; **ATR-IR** *v* 2947 (w), 2836 (w), 2168 (m), 1619 (m), 1602 (m), 1572 (m), 1510 (s), 1322 (m), 1248 (s), 1171 (s), 1036 (m), 822 (m), 749 (m); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$ 399.2067; found 399.2069.

1-(2-(Dimethylamino)-5-methoxyphenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284r**)




Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.46 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.43 (d, *J* = 3.1 Hz, 1H), 7.29 – 7.17 (m, 3H), 7.02 (dd, *J* = 8.9, 3.1 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.69 – 6.61 (m, 1H), 6.55 (d, *J* = 8.4 Hz, 1H), 5.60 (t, *J* = 5.8 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.79 (s, 6H), 2.78 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.2, 158.9, 153.6, 151.2, 147.7, 134.6, 132.8, 130.6, 130.3, 128.0, 120.7, 119.1, 116.8, 115.3, 114.3, 110.5, 104.3, 96.6, 89.0, 55.9, 55.4, 47.1, 45.7; **ATR-IR** *v* 2934 (w), 2834 (w), 2166 (w), 1572 (m), 1510 (s), 1458 (m), 1244 (s), 1173 (s), 1161 (s), 1028 (s), 821 (m), 749 (s); **HRMS (ESI)** calcd for $C_{26}H_{27}N_2O_3^+$ $[M+H]^+$ 415.2016; found 415.2030.

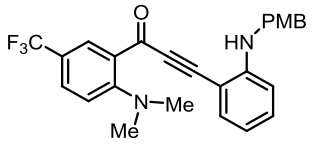
1-(5-Chloro-2-(dimethylamino)phenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284s**)




Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.90 (d, *J* = 2.7 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.31 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.28 – 7.13 (m, 3H), 6.87 – 6.83 (m, 3H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.38 (t, *J* = 5.7 Hz, 1H), 4.39 (d, *J* = 5.5 Hz, 2H), 3.79 (s, 3H), 2.85 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.8, 159.0, 151.2, 151.2, 134.5, 133.1,

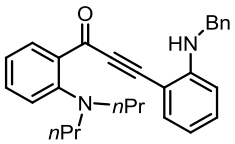
133.0, 132.0, 130.5, 128.5, 128.2, 123.7, 118.2, 116.8, 114.3, 110.6, 103.9, 95.8, 89.8, 55.4, 47.1, 44.6; **ATR-IR** *v* 2936 (w), 2844 (w), 2180 (m), 1611 (s), 1599 (s), 1514 (s), 1492 (m), 1285 (m), 1241 (s), 1163 (s), 826 (s), 760 (s); **HRMS (ESI)** calcd for $C_{25}H_{24}ClN_2O_2^+$ $[M+H]^+$ 419.1521; found 419.1523.

1-(2-(Dimethylamino)-5-(trifluoromethyl)phenyl)-3-(2-((4-methoxybenzyl)amino)phenyl)prop-2-yn-1-one (**1.284t**)



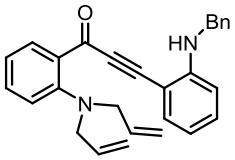

Brown oil; **$^1$H NMR (400 MHz, CDCl$_3$)** δ 8.27 (dd, *J* = 2.1, 1.0 Hz, 1H), 7.56 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.46 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 – 7.11 (m, 3H), 6.95 (d, *J* = 8.9 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.67 (td, *J* = 7.5, 1.0 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.31 (t, *J* = 5.7 Hz, 1H), 4.40 (d, *J* = 5.6 Hz, 2H), 3.80 (s, 3H), 296 (s, 6H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 176.7, 159.0, 153.9, 151.2, 134.5, 133.1, 130.6 (q, *J* = 3.9 Hz), 130.5, 129.7 (q, *J* = 3.4 Hz), 128.2, 125.4, 124.4 (q, *J* = 270 Hz), 119.23 (d, *J* = 33.4 Hz), 116.9, 116.2, 114.3, 110.7, 103.8, 95.5, 90.3, 55.4, 47.1, 44.1; **ATR-IR** *v* 2960 (w), 2959 (w), 2175 (m), 1620 (m), 1603 (m), 1513 (s), 1318 (s), 1158 (s), 1099 (s), 1098 (s), 821 (s), 746 (s); **HRMS (ESI)** calcd for $C_{26}H_{24}F_3N_2O_2^+$ $[M+H]^+$ 453.1784; found 453.1788.

3-(2-(benzylamino)phenyl)-1-(2-(dipropylamino)phenyl)prop-2-yn-1-one (**1.284u**)



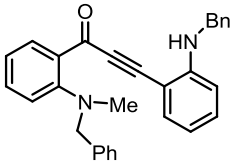

Brown oil; **$^1$H NMR (400 MHz, CDCl$_3$)** δ 7.89 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.45 – 7.15 (m, 8H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.87 (t, *J* = 7.7 Hz, 1H), 6.69 – 6.60 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.39 (t, *J* = 5.9 Hz, 1H), 4.46 (d, *J* = 5.7 Hz, 2H), 3.26 – 2.92 (m, 4H), 1.63 – 1.45 (m, 4H), 0.82 (t, *J* = 7.4 Hz, 6H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 178.5, 151.8, 151.0, 138.7, 133.9, 133.0, 132.54, 132.50, 130.4, 128.9, 127.38, 127.0, 120.3, 119.6, 116.7, 110.4, 104.6, 96.6, 88.2, 55.7, 47.5, 20.4, 11.7; **ATR-IR** *v* 2960 (w), 2930 (w), 2173 (w), 1613 (m), 1602 (m), 1572 (m), 1510 (m), 1453 (m), 746 (s), 697 (s); **HRMS (ESI)** calcd for $C_{28}H_{31}N_2O^+$ $[M+H]^+$ 411.2431; found 411.2445.

3-(2-(Benzylamino)phenyl)-1-(2-(diallylamino)phenyl)prop-2-yn-1-one (**1.284v**)



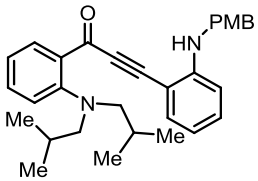

Brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.92 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.48 – 7.43 (m, 1H), 7.42 – 7.19 (m, 7H), 7.02 (d, *J* = 8.3 Hz, 1H), 6.97 – 6.83 (m, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.94 – 5.67 (m, 2H), 5.41 (t, *J* = 5.9 Hz, 1H), 5.26 – 5.03 (m, 4H), 4.46 (d, *J* = 5.6 Hz, 2H), 3.81 (dd, *J* = 6.1, 1.4 Hz, 4H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.5, 151.0, 150.8, 138.7, 134.4, 134.2, 133.1, 132.7, 132.5, 130.5, 128.9, 127.4, 127.0, 120.7, 120.4, 118.22, 116.8, 110.5, 104.3, 96.5, 88.9, 56.4, 47.5; **ATR-IR** *v* 2930 (w), 2848 (w), 2173 (m), 1601 (m), 1322 (m), 1163 (m), 996 (m), 922 (m), 747 (s), 698 (s); **HRMS (ESI)** calcd for $C_{28}H_{27}N_2O^+$ $[M+H]^+$ 407.2118; found 407.2116.

1-(2-(Benzyl(methyl)amino)phenyl)-3-(2-(benzylamino)phenyl)prop-2-yn-1-one (**1.284w**)




Brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.00 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.47 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.42 – 7.15 (m, 12H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H, 6.67 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.41 (t, *J* = 5.8 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 2H), 4.41 (s, 2H), 2.78 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.2, 152.2, 151.0, 138.7, 137.5, 134.3, 133.5, 133.0, 132.8, 128.9, 128.6, 128.4, 128.0, 127.4, 127.3, 127.0, 119.4, 118.6, 116.9, 110.5, 104.3, 96.4, 89.0, 60.5, 47.6, 41.6; **ATR-IR** *v* 2987 (w), 2971 (w), 2902 (w), 2172 (w), 1600 (w), 1451 (m), 1164 (w), 1066 (m), 1052 (m), 747 (s), 731 (s), 697 (s); **HRMS (ESI)** calcd for $C_{30}H_{27}N_2O^+$ $[M+H]^+$ 431.2118; found 431.2119.

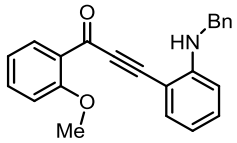
3-(2-(Benzylamino)phenyl)-1-(2-(diisobutylamino)phenyl)prop-2-yn-1-one (**1.284x**)




Brown oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.03 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.35 – 7.18 (m, 4H), 7.09 – 6.96 (m, 1H), 6.91 – 6.82 (m, 2H), 6.76 – 6.71 (m, 1H), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.27 (t, *J* = 5.4 Hz, 1H), 4.39 (d, *J* = 4.5 Hz, 2H), 3.80 (d, *J*

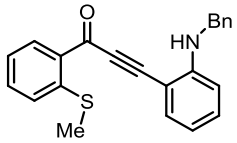
= 1.3 Hz, 3H), 3.03 (d, *J* = 7.2 Hz, 4H), 1.95 (hept, *J* = 6.7 Hz, 2H), 0.81 (d, *J* = 6.6 Hz, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.26, 159.0, 152.3, 150.9, 134.1, 133.9, 133.3, 132.4, 130.7, 128.4, 127.4, 119.5, 117.8, 116.7, 114.3, 110.4, 104.5, 96.1, 88.5, 61.3, 55.4, 47.1, 26.9, 20.6; **ATR-IR** *v* 2957 (w), 2902 (w), 2172 (w), 1602 (m), 1510 (m), 1247 (s), 1151 (m), 1038 (m), 991 (m), 747 (s); **HRMS (ESI)** calcd for $C_{31}H_{37}N_2O_2^+$ $[M+H]^+$ 469.2850; found 469.2845.

3-(2-(Benzylamino)phenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (**1.284y**)



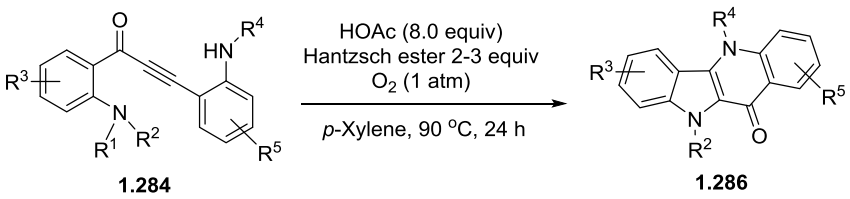

Brown oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.29 – 7.07 (m, 6H), 6.97 – 6.89 (m, 1H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.62 – 6.54 (m, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 5.51 (t, *J* = 5.6 Hz, 1H), 4.38 (d, *J* = 5.6 Hz, 2H), 3.69 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.4, 159.5, 151.2, 138.6, 134.8, 134.5, 132.9, 131.9, 128.9, 127.5, 127.2, 120.9, 116.9, 112.7, 110.4, 104.4, 97.1, 90.4, 56.2, 47.6; **ATR-IR** *v* 2987 (w), 2971 (w), 2902 (w), 2175 (m), 1598 (m), 1453 (m), 1317 (s), 1248 (m), 1008 (s), 747 (s); **HRMS (ESI)** calcd for $C_{23}H_{20}NO_2^+$ $[M+H]^+$ 342.1489; found 342.1492.

3-(2-(Benzylamino)phenyl)-1-(2-(methylthio)phenyl)prop-2-yn-1-one (**1.284z**)




Yellow solid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.30 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.43 – 7.21 (m, 7H), 7.17 – 6.99 (m, 1H), 6.73 – 6.63 (m, 1H), 76.60 (d, *J* = 8.4 Hz, 1H), 5.34 (t, *J* = 5.7 Hz, 1H), 4.47 (d, *J* = 5.6 Hz, 2H), 2.46 (s, 3H), 2.88 (s, 6H), 2.21 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.6, 151.1, 144.5, 138.6, 134.3, 134.1, 133.5, 133.2, 133.0, 128.9, 127.5, 127.3, 124.3, 123.4, 116.9, 110.6, 104.0, 94.6, 91.3, 47.65, 15.69; **ATR-IR** *v* 2987 (m), 2972 (m), 2902 (w), 2180 (w), 1613 (w), 1508 (w), 1315 (w), 1264 (w), 1066 (s), 1048 (s), 732 (s); **HRMS (ESI)** calcd for $C_{23}H_{20}NOS^+$ $[M+H]^+$ 358.1260; found 358.1249.

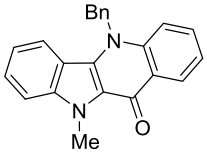
### 3.3.2. Substrate scope of acid-mediated double cyclization




To a solution of **1.284** (0.1 mmol, 1.0 equiv) and Hantzsch ester (2.0-3.0 equiv) in *p*-xylene (*c* = 0.025 M) was added glacial acetic acid (8.0 equiv). The resulting mixture was evacuated and filled back with $O_2$ three times, then connected with balloon of oxygen, warmed up to 90-100 ºC. After stirring for 12-24 h, the reaction mixture was diluted with water, extracted with diethyl acetate. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo.* The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether) to give compound **1.286**.

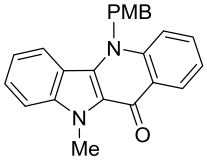
**Characterization Data of Compounds 1.286**

5-Benzyl-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286a**)



Yield: 26.0 mg (77%), yellow solid; mp: 205 – 207 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.73 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.61 (ddd, *J* = 8.5, 6.8, 1.6 Hz, 1H), 7.53 – 7.44 (m, 3H), 7.39 – 7.31 (m, 4H), 7.29 – 7.26 (m, 2H), 7.07 (dt, *J* = 8.2, 3.9 Hz, 1H), 5.98 (s, 2H), 4.47 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.9, 140.9, 140.4, 135.9, 131.8, 131.5, 129.5, 128.1, 127.6, 126.9, 125.9, 125.2, 123.2, 122.5, 121.6, 119.8, 115.2, 114.9, 110.5, 52.8, 31.7; **ATR-IR** *v* 2928 (w), 1618 (s), 1590 (s), 1517 (m), 1461 (m), 1452 (m), 1375 (m), 751 (s), 743 (s), 736 (s), 693 (s); **HRMS (ESI)** calcd for $C_{23}H_{19}N_2O^+$ $[M+H]^+$ 339.1492; found 339.1491.

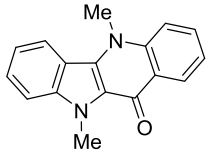
5-(4-Methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286b**)



Yield: 28.3 mg (77%), brown solid; mp: 190 – 192 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.58 (ddd, *J* = 8.6, 6.8, 1.7 Hz, 1H), 7.54 – 7.42 (m, 3H), 7.33 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.21 – 7.12 (m, 2H), 7.07 (ddd, *J* = 8.2, 6.1, 1.9 Hz, 1H), 6.95 –

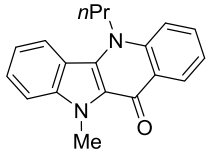
6.80 (m, 2H), 5.87 (s, 2H), 4.43 (s, 3H), 3.76 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.0, 159.3, 140.4, 140.3, 131.7, 131.4, 127.7, 127.5, 127.1, 126.7, 125.2, 123.1, 122.5, 121.4, 119.7, 115.2, 114.9, 114.9, 110.4, 55.4, 52.2, 31.6; **ATR-IR** 2922 (w), 2853 (w), 1615 (m), 1588 (s), 1515 (s), 1459 (m), 1281 (m), 1252 (s), 1033 (m), 746 (s); **HRMS (ESI)** calcd for $C_{24}H_{21}N_2O_2^+$ $[M+H]^+$ 369.1598; found 369.1599.

5,10-Dimethyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286c**)



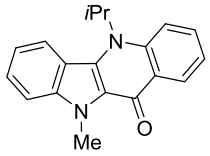

Yield: 12.8 mg (49%), yellow solid; mp: 179 – 181 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.31 – 8.13 (m, 1H), 7.71 (ddd, *J* = 8.5, 6.6, 1.6 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.51 – 7.46 (m, 1H), 7.39 – 7.32 (m, 1H), 7.26 – 7.21 (m, 1H), 4.41 (s, 3H), 4.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.5, 140.3, 140.25, 131.4 (2C), 127.4, 126.8, 125.0, 123.0, 122.7, 121.0, 119.3, 115.8, 114.3, 110.4, 36.1, 31.5; **ATR-IR** *v* 2925 (w), 2853 (w), 1620 (s), 1589 (s), 1517 (m), 1471 (m), 740 (m); **HRMS (ESI)** calcd for $C_{17}H_{15}N_2O^+$ $[M+H]^+$ 263.1179; found 263.1182.

10-Methyl-5-propyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286d**)



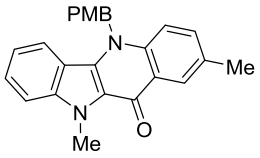

Yield: 18.3 mg (63%), yellow solid; mp: 187 – 188 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.65 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.65 (ddd, *J* = 8.6, 6.8, 1.7 Hz, 1H), 7.58 – 7.48 (m, 2H), 7.46 – 7.39 (m, 1H), 7.30 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H), 7.22 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 4.56 (d, *J* = 8.3 Hz, 2H), 4.35 (s, 3H), 2.13 – 1.96 (m, 2H), 1.18 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.5, 140.3, 139.4, 131.3, 130.4, 127.3, 126.8, 124.9, 123.0, 122.2, 120.9, 119.5, 115.1, 114.1, 110.4, 49.3, 31.5, 21.7, 11.0; **ATR-IR** *v* 2922 (w), 1596 (s), 1513 (s), 1464 (m), 1247 (s), 1173 (m), 1033 (s), 809 (m), 744 (s); **HRMS (ESI)** calcd for $C_{19}H_{19}N_2O^+$ $[M+H]^+$ 291.1492; found 291.1494.

5-Isopropyl-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286e**)



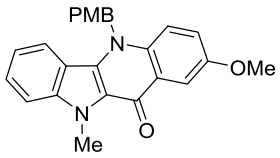

Yield: 19.1 mg (66%), yellow solid; mp: 191 – 193 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.67 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.63 (ddd, *J* = 8.7, 6.7, 1.7 Hz, 1H), 7.58 – 7.45 (m, 2H), 7.35 – 7.31 (m, 1H), 7.29 – 7.19 (m, 1H), 5.71 (hept, *J* = 7.1 Hz, 1H), 4.43 (s, 3H), 1.92 (s, 3H), 1.90 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.1, 140.3, 139.4, 132.2, 130.0, 127.3, 127.1, 126.4, 123.6, 122.5, 121.0, 119.4, 117.6, 115.7, 110.7, 53.9, 31.6, 21.6; **ATR-IR** *v* 2970 (w), 2923 (w), 1617 (m), 1589 (s), 1514 (m), 1461 (m), 1354 (m), 956 (m), 749 (s); **HRMS (ESI)** calcd for $C_{19}H_{19}N_2O^+$ $[M+H]^+$ 291.1492; found 291.1491.

5-(4-Methoxybenzyl)-2,10-dimethyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286g**)




Yield: 23.2 mg (61%), yellow solid; mp: 202 – 204 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.48 – 8.31 (m, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.41 – 7.32 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 2H), 7.06 (ddd, *J* = 8.1, 6.0, 1.9 Hz, 1H), 6.92 – 6.66 (m, 2H), 5.87 (s, 2H), 4.43 (s, 3H), 3.76 (s, 3H), 2.47 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.8, 159.3, 140.4, 138.6, 133.2, 131.3, 131.0, 127.9, 127.4, 127.1, 125.9, 125.1, 123.1, 122.5, 119.5, 115.3, 114.8 (2C), 110.3, 55.4, 52.1, 31.6, 21.0; **ATR-IR** *v* 2929 (w), 1614 (m), 1593 (s), 1515 (s), 1464 (m), 1249 (s), 739 (w); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_2^+$ $[M+H]^+$ 383.1754; found 383.1752.

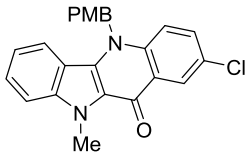
2-Methoxy-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286h**)




Yield: 31.6 mg (79%), yellow solid; mp: 191 – 193 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.13 – 7.97 (m, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.39 (d, *J* = 9.3 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.86 (s, 2H), 4.42 (s, 3H), 3.93 (s, 3H), 3.75 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.9, 159.3, 154.6, 140.5, 135.2, 131.1, 127.7, 127.5, 127.0, 125.9, 122.8, 122.7, 122.5, 119.5, 116.6, 115.2, 114.8, 110.2, 105.2, 55.8, 55.4, 52.2,

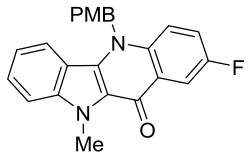
31.6; **ATR-IR** *v* 2933 (w), 2835 (w), 1592 (s), 1514 (s), 1464 (m), 1463 (m), 1278 (m), 1245 (s), 732 (s), 731 (s); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_3^+$ $[M+H]^+$ 399.1703; found 399.1702.

2-Chloro-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286i**)



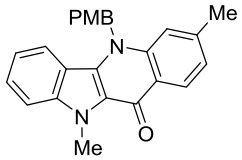

Yield: 24.9 mg (62%), yellow solid; mp: 232 – 234 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.60 – 8.55 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.38 (d, *J* = 9.2 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.11 – 7.04 (m, 1H), 6.94 – 6.76 (m, 2H), 5.87 (s, 2H), 4.37 (d, *J* = 1.2 Hz, 3H), 3.77 (d, *J* = 1.2 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.7, 159.4, 140.5, 138.6, 131.8, 131.4, 127.8, 127.5, 127.2, 127.0, 126.1, 125.9, 123.1, 122.5, 119.9, 116.7, 115.1, 114.9, 110.4, 55.4, 52.3, 31.6; **ATR-IR** *v* 2932 (w), 2836 (w), 1620 (s), 1588 (s), 1514 (s), 1463 (m), 1249 (s), 1249 (s); **HRMS (ESI)** calcd for $C_{24}H_{20}ClN_2O_2^+$ $[M+H]^+$ 403.1208; found 403.1210.

2-Fluoro-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286j**)



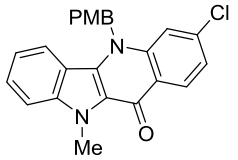

Yield: 27.0 mg (70%), yellow solid; mp: 201 – 203 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.16 (dd, *J* = 9.4, 3.0 Hz, 1H), 7.71 (dt, *J* = 8.4, 0.9 Hz, 1H), 7.43 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 7.34 – 7.26 (m, 2H), 7.24 – 7.14 (m, 1H), 7.12 – 7.05 (m, 2H), 7.02 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 6.86 – 6.72 (m, 2H), 5.77 (s, 2H), 4.19 (s, 3H), 3.70 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 168.5 (d, *J* = 2.9 Hz), 159.3, 157.7 (d, *J* = 242.5 Hz), 140.3, 136.6, 131.3, 127.6, 127.3, 127.0, 126.0 (d, *J* = 6.6 Hz), 122.4, 120.0 (d, *J* = 25.4 Hz), 119.7, 116.9 (d, *J* = 7.7 Hz), 114.9, 114.8, 110.6 (d, *J* = 22.6 Hz), 110.2, 55.3, 52.3, 31.3; **ATR-IR** *v* 2957 (w), 2934 (w), 1598 (s), 1513 (s), 1463 (s), 1269 (s), 1249 (s), 1174 (m), 907 (m), 733 (s); **HRMS (ESI)** calcd for $C_{24}H_{20}FN_2O_2^+$ $[M+H]^+$ 387.1503; found 387.1504.

5-(4-Methoxybenzyl)-3,10-dimethyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286k**)



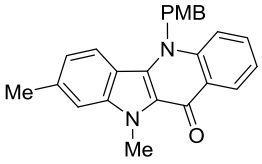

Yield: 24.4 mg (64%), light yellow solid; mp: 242 – 244 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.58 (d, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.60 – 7.37 (m, 2H), 7.22 – 7.15 (m, 4H), 7.06 (ddd, *J* = 8.0, 5.7, 2.4 Hz, 1H), 6.95 – 6.76 (m, 2H), 5.87 (s, 2H), 4.43 (s, 3H), 3.77 (s, 3H), 2.45 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.9, 159.3, 142.5, 140.6, 140.3, 131.3, 127.8, 127.4, 127.1, 126.7, 123.4, 123.2, 123.0, 122.5, 119.6, 115.3, 114.9, 114.4, 110.3, 55.4, 52.1, 31.7, 22.5; **ATR-IR** *v* 2958 (w), 2924 (w), 2841 (w), 1628 (m), 1601 (s), 1510 (s), 1470 (m), 1457 (m), 1290 (s), 1244 (s), 1034 (m), 815 (m), 754 (s); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_2^+$ $[M+H]^+$ 383.1754; found 383.1758.

3-Chloro-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286m**)




Yield: 25.3 mg (63%), yellow solid; mp: 248 – 250 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.58 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.41 (d, *J* = 1.7 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.19 – 7.14 (m, 2H), 7.08 (ddd, *J* = 8.1, 6.6, 1.3 Hz, 1H), 6.96 – 6.84 (m, 2H), 5.84 (s, 2H), 4.39 (s, 3H), 3.78 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.4, 159.5, 140.9, 140.3, 138.0, 131.3, 128.4, 127.7, 127.1, 127.0, 123.6, 123.1, 122.4, 122.1, 120.0, 115.1, 115.0, 114.5, 110.5, 55.4, 52.3, 31.6; **ATR-IR** *v* 2924 (w), 1728 (w), 1619 (s), 1586 (s), 1512 (s), 1465 (m), 1244 (s), 728 (s); **HRMS (ESI)** calcd for $C_{24}H_{20}ClN_2O_2^+$ $[M+H]^+$ 403.1208; found 403.1209.

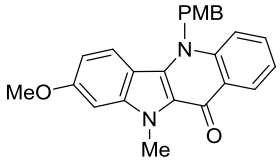
5-(4-Methoxybenzyl)-8,10-dimethyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286n**)




Yield: 29.4 mg (77%), yellow solid; mp: 242 – 244 ºC; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.58 (ddd, *J* = 8.6, 6.9, 1.7 Hz, 1H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.33 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.26 (s, 1H), 7.21 – 7.09 (m, 2H), 6.95 – 6.80 (m, 3H), 5.87

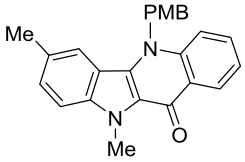
(s, 2H), 4.43 (s, 3H), 3.76 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.8, 159.3, 141.0, 140.2, 138.2, 131.6, 131.5, 127.8, 127.1, 126.7, 125.3, 123.0, 122.1, 121.7, 121.4, 114.9, 114.8, 113.1, 110.1, 55.4, 52.1, 31.6, 22.3; **ATR-IR** *v* 2955 (w), 2925 (w), 1619 (s), 1590 (s), 1513 (s), 1465 (m), 1287 (m), 1249 (s), 1175 (m), 758 (m), 733 (m), 733 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_2^+$ $[M+H]^+$ 383.1754; found 383.1756.

8-Methoxy-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286o**)



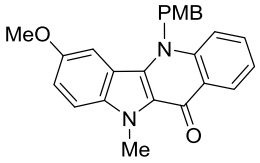

Yield: 19.9 mg (50%), yellow solid; mp: 232 – 234 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.68 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.63 (d, *J* = 9.1 Hz, 1H), 7.57 (ddd, *J* = 8.6, 6.8, 1.7 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.20 – 7.08 (m, 2H), 6.91 – 6.84 (m, 2H), 6.80 (d, *J* = 2.3 Hz, 1H), 6.71 (dd, *J* = 9.0, 2.3 Hz, 1H), 5.83 (s, 2H), 4.41 (s, 3H), 3.91 (s, 3H), 3.77 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.0, 160.4, 159.3, 142.2, 140.1, 132.0, 131.4, 127.6, 127.1, 126.7, 125.4, 123.6, 122.8, 121.4, 114.9, 114.7, 110.8, 109.4, 92.0, 55.7, 55.4, 52.1, 31.7; **ATR-IR** *v* 2933 (w), 2833 (w), 1612 (s), 1588 (s), 1587 (s), 1516 (s), 1459 (s), 1247 (s), 1035 (s), 823 (s), 761 (s); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_3^+$ $[M+H]^+$ 399.1703; found 399.1701.

5-(4-Methoxybenzyl)-7,10-dimethyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286q**)



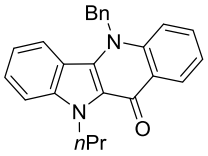

Yield: 30.2 mg (80%), yellow solid; mp: 206 – 208 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.69 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.92 – 6.77 (m, 2H), 5.88 (s, 2H), 4.42 (s, 3H), 3.77 (s, 3H), 2.37 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 170.0, 159.3, 140.4, 139.0, 131.6, 131.0, 129.4, 128.9, 127.9, 127.2, 126.8, 125.1, 123.4, 121.8, 121.3, 115.3, 114.9, 114.8, 110.1, 55.4, 52.1, 31.7, 21.8; **ATR-IR** *v* 2931 (w), 2924 (w), 1622 (s), 1592 (s), 1515 (s), 1468 (m), 1288 (m), 1249 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_2^+$ $[M+H]^+$ 383.1754; found 383.1752.

7-Methoxy-5-(4-methoxybenzyl)-10-methyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286r**)



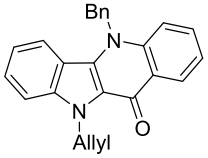

Yield: 25.1 mg (63%), yellow-brown solid; mp: 183 – 185 ºC; Yield: 25.1 mg (63%), yellow-brown solid; mp: 183 – 185 ºC; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.85 – 8.29 (m, 1H), 7.59 (ddd, *J* = 8.5, 6.8, 1.6 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H), 7.40 – 7.30 (m, 2H), 7.23 – 7.12 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.85 (s, 2H), 4.40 (s, 3H), 3.77 (s, 3H), 3.63 (s, 3H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 170.1, 159.3, 153.6, 140.6, 136.1, 131.7, 130.9, 127.9, 127.0, 126.8, 125.0, 123.8, 121.3, 118.3, 114.9 (2C), 114.7, 111.2, 103.9, 55.9, 55.4, 52.1, 31.7; **ATR-IR** *v* 2960 (w), 2934 (w), 1623 (m), 1585 (s), 1518 (s), 1245 (s), 1236 (s), 1030 (s), 806 (m), 756 (s); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O_3^+$ $[M+H]^+$ 399.1703; found 399.1696.

5-Benzyl-10-propyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286u**)




Yield: 14.3 mg (39%), yellow solid; mp: 136 – 138 ºC; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.70 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.39 – 7.24 (m, 6H), 7.04 (t, *J* = 7.7 Hz, 1H), 5.96 (s, 2H), 4.92 (t, *J* = 7.5 Hz, 2H), 1.98 (h, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 169.7, 140.5, 139.7, 136.0, 131.7, 131.5, 129.5, 128.0, 127.4, 126.9, 125.9, 125.3, 122.9, 122.5, 121.5, 119.5, 115.3, 114.9, 110.8, 52.8, 46.4, 24.3, 11.5; **ATR-IR** *v* 2960 (w), 2928 (w), 1619 (m), 1590 (s), 1514 (m), 1460 (m), 1287 (m), 732 (s), 705 (m), 699 (m); **HRMS (ESI)** calcd for $C_{25}H_{23}N_2O^+$ $[M+H]^+$ 367.1805; found 367.1803.

10-Allyl-5-benzyl-5,10-dihydro-11H-indolo[3,2-b]quinolin-11-one (**1.286v**)



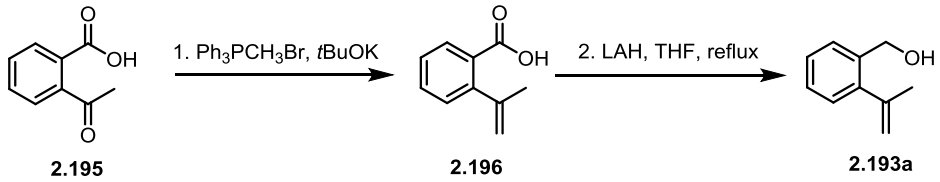

Yield: 14.9 mg (41%), yellow solid; mp: 144 – 146 ºC; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 8.79 – 8.47 (m, 1H), 7.84 – 7.73 (m, 1H), 7.65 – 7.55 (m, 1H), 7.53 – 7.42 (m, 3H), 7.40 – 7.27 (m, 6H), 7.10 – 7.00 (m, 1H), 6.21 – 6.07 (m, 1H), 5.97 (s, 2H), 5.78 – 5.54 (m, 2H), 5.14 (ddt, *J* = 10.1, 3.6, 1.4 Hz, 1H),

5.03 (ddt, *J* = 17.2, 3.6, 1.5 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.8, 140.5, 139.8, 135.9, 134.3, 131.8, 131.7, 129.5, 128.1, 127.6, 126.9, 125.9, 125.3, 122.6, 122.5, 121.6, 119.9, 116.3, 115.6, 114.9, 111.0, 52.8, 47.0; **ATR-IR** *v* 2925 (w), 1620 (s), 1591 (s), 1514 (m), 1459 (m), 1387 (m), 1288 (m), 735 (s); **HRMS (ESI)** calcd for $C_{25}H_{21}N_2O^+$ $[M+H]^+$ 365.1648; found 365.1648.

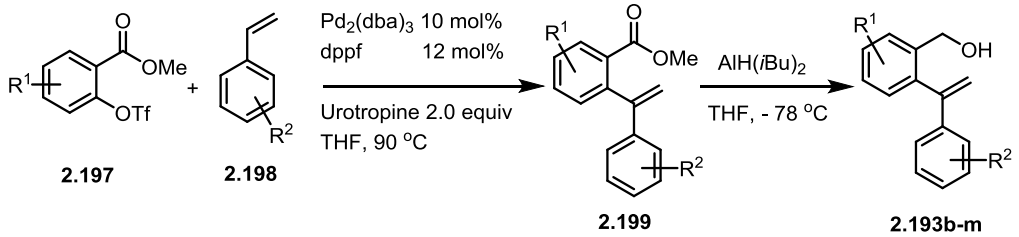
## 3.4. Copper-Catalyzed Cyanoalkylative Cycloetherification of Alkenes to 1,3-Dihydroisobenzofurans

### 3.4.1. Preparation of starting materials 2.193

Compound **2.193a** was prepared according to the reported procedure:[156]



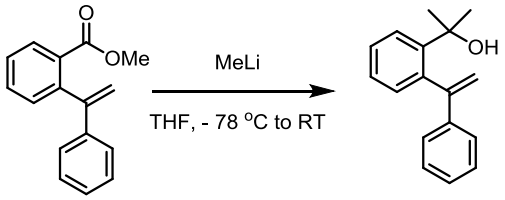

Compounds **2.193b-m** were prepared in 2 steps according to the following general procedure:[161]




**Step 1:** In the glovebox, $Pd_2(dba)_3$ and dppf were dissolved in THF (0.2 M) in a sealed tube. After stirring for 10 min at room temperature, phenol triflate **2.197** (1.0 equiv), styrene **2.198** (2.0 equiv) and urotropine (2.0 equiv) were successively added. The reaction mixture was heated to 90 °C and stirred overnight. After quenching with water, the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/30) to give the corresponding 2-vinylbenzoate **2.199**.

**Step 2:** To a solution of 2-vinylbenzoate **2.199** (1.0 equiv) in THF (0.1 M) was added dropwise at – 78 °C a solution of Al*H*i*Bu*$_2$ in toluene (1.4 M, 2.5 equiv). The reaction mixture was stirred at this temperature for 1 h and then warmed up to 0 °C. After stirring for 3 h, the reaction mixture was quenched by methanol at – 78 °C, then warmed up to room temperature and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/10) to give the corresponding compound **2.193b-m**.

Compound **2.193r** was prepared from 2-(1-phenylvinyl)benzoate according to the following procedure:

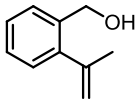



**2.200** **2.193r**

To a solution of methyl 2-(1-phenylvinyl)benzoate (**2.200**) (170 mg, 0.71 mmol) in THF (0.1 M) was added dropwise at – 78 °C a solution of MeLi in THF (1.5 M, 1.2 mL). The reaction mixture was stirred at this temperature for 1 h and then slowly warmed up to room temperature. After stirring overnight, the reaction mixture was quenched with an aqueous $NH_4Cl$ solution, extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/50) to give compound **2.193r** as a colorless oil (121 mg, 71% yield).

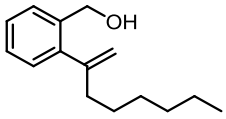
**Characterization Data of Compounds 2.193**

(2-(prop-1-en-2-yl)phenyl)methanol (**2.193a**)



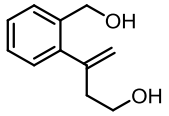

Colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.49 – 7.40 (m, 1H), 7.30 – 7.23 (m, 2H), 7.19 – 7.10 (m, 1H), 5.26 (p, *J* = 1.7 Hz, 1H), 4.90 (d, *J* = 1.7 Hz, 1H), 4.70 (s, 2H), 2.08 (s, 3H), 1.70 (s, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.9, 143.2, 137.5, 128.3, 128.2, 127.7, 127.4, 115.6, 63.4, 25.2; **ATR-IR** *v* 3334 (w), 3316 (w), 3304 (w), 1436 (w), 1195 (w), 1006 (m), 901 (m), 762 (s); **HRMS (ESI)** calcd for $C_{10}H_{12}O$ [M+] 148.0883; found 148.0882.

(2-(oct-1-en-2-yl)phenyl)methanol (**2.193b**)



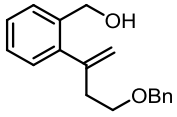

Colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.46 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.33 – 7.23 (m, 2H), 7.12 (dd, *J* = 7.2, 1.8 Hz, 1H), 5.21 (q, *J* = 1.7 Hz, 1H), 4.91 (d, *J* = 2.1 Hz, 1H), 4.68 (s, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.43 – 1.19 (m, 8H), 0.87 (t, *J* = 6.7 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 149.4, 142.6, 137.8, 128.6, 128.3, 127.5, 127.3, 114.4, 63.3, 38.5, 31.8, 29.2, 27.9, 22.8, 14.2; **ATR-IR** *v* 3310 (w), 2956 (w), 2927 (m), 2856 (w), 2855 (w), 1458 (w), 1034 (m), 1008 (m), 902 (m), 762 (s), 727 (m); **HRMS (ESI)** calcd for $C_{15}H_{22}O$ [M+] 218.1665; found 218.1668.

3-(2-(hydroxymethyl)phenyl)but-3-en-1-ol (**2.193c**)



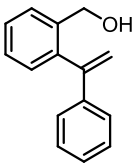

Colorless oil; **$^1$H NMR (400 MHz, $CD_3OD$)** δ 7.50 – 7.41 (m, 1H), 7.29 – 7.21 (m, 2H), 7.16 – 7.10 (m, 1H), 5.29 (q, *J* = 1.4 Hz, 1H), 4.96 (d, *J* = 1.9 Hz, 1H), 4.63 (s, 2H), 3.55 (t, *J* = 6.7 Hz, 2H), 2.62 (td, *J* = 6.8, 1.4 Hz, 2H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 146.9, 142.8, 139.3, 129.6, 129.2, 128.2, 128.2, 116.8, 62.8, 60.8, 42.5; **ATR-IR** *v* 3319 (w), 2933 (w), 2884 (w), 1446 (w), 1427 (w), 1197 (w), 1042 (m), 1016 (s), 761 (s); **HRMS (ESI)** calcd for $C_{11}H_{14}NaO_2^+$ $[M+Na]^+$ 201.0886; found 201.0886.

(2-(4-(benzyloxy)but-1-en-2-yl)phenyl)methanol (**2.193d**)



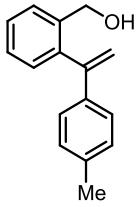

Colorless oil; **$^1$H NMR (400 MHz, $CD_3OD$)** δ 7.45 – 7.39 (m, 1H), 7.36 – 7.21 (m, 7H), 7.16 – 7.10 (m, 1H), 5.33 (q, *J* = 1.5 Hz, 1H), 5.04 (d, *J* = 1.8 Hz, 1H), 4.68 (s, 2H), 4.43 (s, 2H), 3.50 (t, *J* = 6.1 Hz, 2H), 2.73 (t, *J* = 6.1 Hz, 2H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 145.4, 141.5, 138.5, 138.0, 129.4, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 116.8, 72.8, 67.9, 63.3, 38.6; **ATR-IR** *v* 3382 (w), 2914 (w), 2864 (w), 1454 (m), 1362 (w), 1096 (m), 1095 (m), 1078 (m), 1029 (m), 1007 (m), 736 (s), 698 (s); **HRMS (ESI)** calcd for $C_{18}H_{20}NaO_2^+$ $[M+Na]^+$ 291.1355; found 291.1355.

(2-(1-phenylvinyl)phenyl)methanol (**2.193e**)



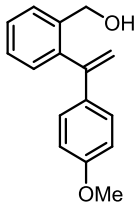

Colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.49 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.40 – 7.24 (m, 8H), 5.80 (d, *J* = 1.3 Hz, 1H), 5.25 (d, *J* = 1.4 Hz, 1H), 4.43 (s, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 148.5, 140.8, 140.6, 138.8, 130.4, 128.7, 128.24, 128.20, 128.1, 127.8, 126.7, 115.8, 63.4; **ATR-IR** *v* 3422 (w), 3416 (w), 3058 (w), 3026 (w), 2924 (w), 1493 (w), 1446 (w), 1026 (m), 757 (s), 700 (s); **HRMS (ESI)** calcd for $C_{15}H_{14}O$ [M+] 210.1039; found 210.1042.

(2-(1-(p-tolyl)vinyl)phenyl)methanol (**2.193f**)



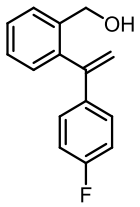

Colorless oil; **$^1$H NMR (400 MHz, $CD_3OD$)** δ 7.54 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 7.28 (td, *J* = 7.5, 1.5 Hz, 1H), 7.17 – 7.08 (m, 5H), 5.76 (d, *J* = 1.4 Hz, 1H), 5.12 (d, *J* = 1.4 Hz, 1H), 4.37 (s, 2H), 2.31 (s, 3H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 149.8, 141.6, 140.4, 139.1, 138.8, 130.8, 130.1, 128.7, 128.0, 127.9, 127.5, 114.7, 62.6, 21.1; **ATR-IR** *v* 3325 (w), 2921 (w), 2886 (w), 2864 (w), 1510 (m), 1035 (m), 1019 (m), 826 (s), 770 (s), 735 (m); **HRMS (ESI)** calcd for $C_{16}H_{16}O$ [M+] 224.1196; found 224.1200.

(2-(1-(4-methoxyphenyl)vinyl)phenyl)methanol (**2.193g**)




Colorless oil; **$^1$H NMR (400 MHz, $CD_3OD$)** δ 7.55 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.36 (td, *J* = 7.5, 1.5 Hz, 1H), 7.28 (td, *J* = 7.5, 1.4 Hz, 1H), 7.19 – 7.15 (m, 3H), 6.83 (d, *J* = 8.9 Hz, 2H), 5.70 (d, *J* = 1.4 Hz, 1H), 5.06 (d, *J* = 1.5 Hz, 1H), 4.38 (s, 2H), 3.77 (s, 3H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 161.0, 149.3, 141.7, 140.4, 134.4, 130.8, 128.74, 128.69, 127.98, 127.96, 114.8, 113.6, 62.6, 55.7; **ATR-IR** *v* 3364 (w), 2934 (w), 2836 (w), 1509 (s), 1249 (s), 1180 (m), 1033 (s), 837 (s), 773 (m); **HRMS (ESI)** calcd for $C_{16}H_{16}NaO_2^+$ $[M+Na]^+$ 263.1042; found 263.1043.

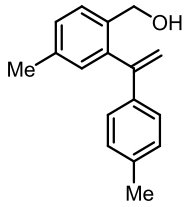
(2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (**2.193h**)




Colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.38 (td, *J* = 7.5, 1.6 Hz, 1H), 7.32 (td, *J* = 7.4, 1.5 Hz, 1H), 7.25 – 7.21 (m, 3H), 6.97 (t, *J* = 8.7 Hz, 2H), 5.73 (d, *J* = 1.1 Hz,

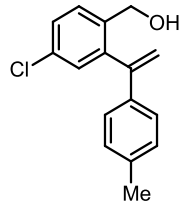
1H), 5.22 (d, *J* = 1.1 Hz, 1H), 4.43 (s, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.7 (d, *J* = 247.7 Hz), 147.4, 140.3, 138.7, 136.8 (d, *J* = 3.3 Hz), 130.3, 128.4 (d, *J* = 8.1 Hz), 128.3, 128.1, 127.8, 115.5 (d, *J* = 21.4 Hz), 115.5, 63.3; **ATR-IR** *v* 3335 (w), 2953 (w), 2926 (w), 2898 (w), 2889 (w), 1508 (s), 1225 (m), 1161 (m), 842 (s), 773 (m); **HRMS (ESI)** calcd for $C_{15}H_{13}FO$ [M+] 228.0945; found 228.0949.

(4-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (**2.193i**)




Colorless oil; **$^{1}$H NMR (400 MHz, $CD_3OD$)** δ 7.41 (d, *J* = 7.8 Hz, 1H), 7.18 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.14 – 7.07 (m, 4H), 6.98 (d, *J* = 1.8 Hz, 1H), 5.73 (d, *J* = 1.5 Hz, 1H), 5.10 (d, *J* = 1.5 Hz, 1H), 4.33 (s, 2H), 2.33 (s, 3H), 2.31 (s, 3H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 149.8, 141.6, 139.2, 138.7, 137.7, 137.3, 131.5, 130.0, 129.3, 128.3, 127.5, 114.5, 62.6, 21.13, 21.10; **ATR-IR** *v* 3383 (w), 2920 (w), 2864 (w), 1510 (w), 1206 (w), 1185 (w), 1035 (m), 1018 (s), 815 (s); **HRMS (ESI)** calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1353.

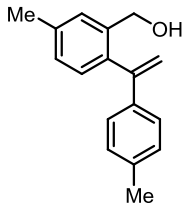
(4-chloro-2-(1-(p-tolyl)vinyl)phenyl)methanol (**2.193j**)




Colorless oil; **$^{1}$H NMR (400 MHz, $CD_3OD$)** δ 7.53 (d, *J* = 8.3 Hz, 1H), 7.37 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.18 – 7.08 (m, 5H), 5.79 (d, *J* = 1.1 Hz, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 4.33 (s, 2H), 2.32 (s, 3H);

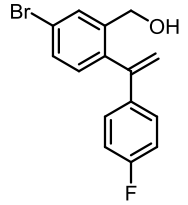
**$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 148.5, 143.3, 139.4, 139.2, 138.3, 133.6, 130.5, 130.2, 129.6, 128.7, 127.39, 115.5, 62.0, 21.2; **ATR-IR** *v* 3312 (w), 3312 (w), 2921 (w), 2864 (w), 1511 (w), 1039 (m), 879 (m), 825 (s); **HRMS (ESI)** calcd for $C_{16}H_{15}ClO$ [M+] 258.0806; found 258.0807.

(5-methyl-2-(1-(p-tolyl)vinyl)phenyl)methanol (**2.193k**)



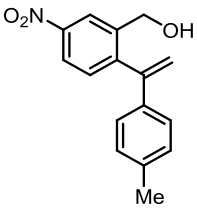

Colorless oil; **$^{1}$H NMR (400 MHz, $CD_3OD$)** δ 7.36 (d, *J* = 1.8 Hz, 1H), 7.17 – 7.00 (m, 6H), 5.72 (d, *J* = 1.4 Hz, 1H), 5.10 (d, *J* = 1.4 Hz, 1H), 4.33 (s, 2H), 2.38 (s, 3H), 2.30 (s, 3H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 149.7, 140.1, 139.3, 138.74, 138.70, 138.4, 130.9, 130.0, 128.7, 128.6, 127.5, 114.6, 62.7, 21.4, 21.1; **ATR-IR** *v* 3391 (w), 2920 (w), 2863 (w), 2862 (w), 1511 (w), 1033 (m), 1032 (m), 1018 (s), 818 (s); **HRMS (ESI)** calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1354.

(5-bromo-2-(1-(4-fluorophenyl)vinyl)phenyl)methanol (**2.193l**)




Colorless oil; **$^{1}$H NMR (400 MHz, $CD_3OD$)** δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.26 (dd, *J* = 8.9, 5.4 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 1H), 7.03 (t, *J* = 8.8 Hz, 2H), 5.79 (d, *J* = 1.0 Hz, 1H), 5.19 (d, *J* = 1.0 Hz, 1H), 4.33 (s, 2H); **$^{13}$C NMR (101 MHz, $CD_3OD$)** δ 164.0 (d, *J* = 246.4 Hz), 147.7, 143.2, 140.0, 137.7 (d, *J* = 3.3 Hz), 132.6, 131.0, 130.9, 129.5 (d, *J* = 8.2 Hz), 122.9, 116.3 (d, *J* = 22.1 Hz), 116.3, 62.0; **ATR-IR** *v* 3309 (w), 2926 (w), 2855 (w), 1507 (s), 1225 (m), 1160 (m), 1037 (m), 1014 (m), 842 (s), 825 (s); **HRMS (ESI)** calcd for $C_{15}H_{12}BrFO$ [M+] 306.0050; found 306.0054.

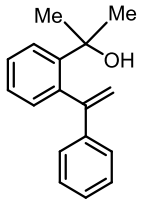
(5-nitro-2-(1-(p-tolyl)vinyl)phenyl)methanol (**2.193m**)




Yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.44 (d, *J* = 2.4 Hz, 1H), 8.16 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.15 – 7.08 (m, 4H), 5.84 (d, *J* = 0.8 Hz, 1H), 5.22 (d, *J* = 0.8 Hz, 1H), 4.50 (s, 2H), 2.35 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 147.9, 147.0, 146.6, 141.0, 138.8, 136.4, 131.1, 129.6, 126.4, 122.6, 122.5, 116.0, 62.2, 21.3; **ATR-IR** *v* 3324 (w), 2951 (w), 2924 (w), 2856 (w),

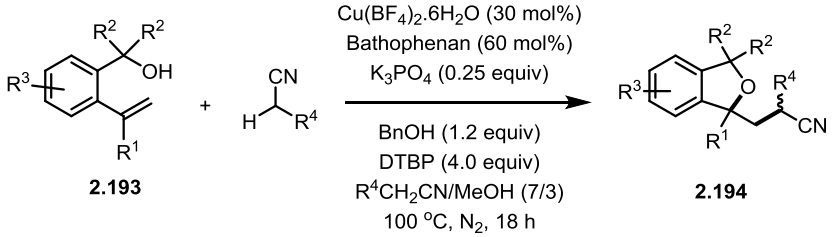
1519 (s), 1344 (s), 1039 (w), 905 (w), 827 (m); **HRMS (ESI)** calcd for $C_{16}H_{15}NO_3$ [M+] 269.1046; found 269.1049.

2-(2-(1-phenylvinyl)phenyl)propan-2-ol (**2.193r**)




Colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.34 – 7.24 (m, 7H), 7.11 (dd, *J* = 7.5, 1.5 Hz, 1H), 5.87 (d, *J* = 1.3 Hz, 1H), 5.23 (d, *J* = 1.3 Hz, 1H), 1.49 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 151.6, 146.7, 141.1, 138.5, 132.6, 128.5, 127.9, 127.6, 126.7, 126.6, 126.5, 114.4, 74.4, 32.5; **ATR-IR** *v* 3432 (w), 2972 (w), 2929 (w), 1494 (w), 1363 (w), 1166 (w), 902 (m), 783 (m), 761 (s), 712 (s); **HRMS (ESI)** calcd for $C_{17}H_{18}O$ [M+] 238.1352; found 238.1354.

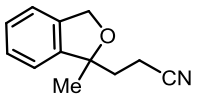
### 3.4.2. Substrate scope for copper-catalyzed cyanoalkylative cycloetherification




In the glovebox, alkene **2.193** (0.1 mmol, 1 equiv), $Cu(BF_4)_2.6H_2O$ (30 mol%), bathophenanthroline (60 mol%), BnOH (120 mol%), and $K_3PO_4$ (25 mol%) were dissolved in degassed $R^4CH_2CN$/MeOH (v/v 7/3, 0.067 M) in a sealed tube. DTBP (4 equiv) was then added and the tube was sealed and heated to 100 °C. After 18 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.194**.

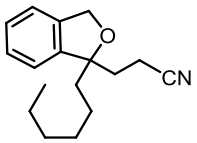
**Characterization Data of Compounds 2.194**

3-(1-Methyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194a**)



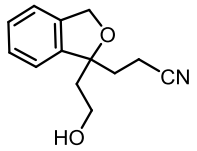

Yield: 12.2 mg (65%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.28 (m, 2H), 7.25 – 7.20 (m, 1H), 7.10 – 7.06 (m, 1H), 5.11 (d, *J* = 12.5 Hz, 1H), 5.05 (d, *J* = 12.5 Hz, 1H), 2.34 (ddd, *J* = 16.1, 10.0, 5.7 Hz, 1H), 2.24 (ddd, *J* = 13.6, 9.9, 5.7 Hz, 1H), 2.14 (ddd, *J* = 13.7, 9.9, 5.1 Hz, 1H), 2.10 – 1.99 (m, 1H), 1.49 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.1, 139.1, 128.3, 128.0, 121.5, 120.9, 120.1, 87.1, 72.0, 37.1, 27.5, 12.4; **ATR-IR** *v* 2970 (w), 2928 (w), 2856 (w), 2247 (w), 1454 (w), 1359 (w), 1031 (s), 1019 (s), 763 (s), 726 (s); **HRMS (ESI)** calcd for $C_{12}H_{12}NO$ [M+] 186.0913; found 186.0916.

3-(1-Hexyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194b**)



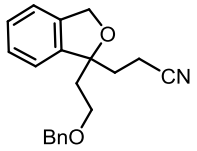

Yield: 16.1 mg (63%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.23 – 7.18 (m, 2H), 7.13 – 7.07 (m, 1H), 6.99 – 6.91 (m, 1H), 4.99 (s, 2H), 2.26 – 2.09 (m, 2H), 2.07 – 1.96 (m, 1H), 1.86 (ddd, *J* = 17.0, 10.6, 5.1 Hz, 1H), 1.75 – 1.58 (m, 2H), 1.20 – 1.05 (m, 7H), 0.90 – 0.82 (m, 1H), 0.73 (t, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.5, 139.9, 128.2, 128.0, 121.3, 121.2, 120.2, 90.1, 73.2, 41.3, 36.5, 31.8, 29.6, 23.6, 22.7, 14.2, 12.2; **ATR-IR** *v* 2929 (m), 2929 (m), 2929 (m), 2856 (w), 2248 (w), 1463 (m), 999 (s), 756 (s), 701 (m); **HRMS (ESI)** calcd for $C_{17}H_{23}NNaO^{+}$ $[M+Na]^{+}$ 280.1672; found 280.1670.

3-(1-(2-Hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194c**)



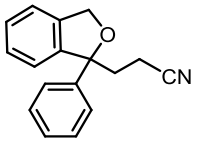

Yield: 10.6 mg (52%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.31 (m, 2H), 7.27 – 7.25 (m, 1H), 7.09 – 7.04 (m, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 3.67 (ddd, *J* = 11.4, 6.8, 4.8 Hz, 1H), 3.58 (ddd, *J* = 11.4, 6.8, 4.8 Hz, 1H), 2.43 – 2.23 (m, 1H), 2.18 – 1.95 (m, 4H), 1.64 (broad, s, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.9, 139.3, 128.8, 128.4, 121.7, 121.1, 119.8, 90.6, 73.0, 59.3, 42.2, 36.2, 12.1; **ATR-IR** *v* 3423 (w), 2952 (w), 2923 (w), 2912 (w), 1028 (s), 1018 (s), 761 (s), 726 (m); **HRMS (ESI)** calcd for $C_{13}H_{15}NNaO_2^{+}$ $[M+Na]^{+}$ 240.0995; found 240.0994.

3-(1-(2-Hydroxyethyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194d**)



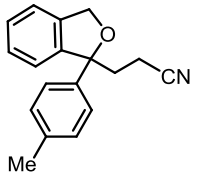

Yield: 15.3 mg (49%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.23 (m, 5H), 7.23 – 7.17 (m, 3H), 7.12 – 7.03 (m, 1H), 5.08 (d, *J* = 12.5 Hz, 1H), 5.04 (d, *J* = 12.5 Hz, 1H), 4.39 (d, *J* = 11.8 Hz, 1H), 4.35 (d, *J* = 11.8 Hz, 1H), 3.53 (ddd, *J* = 9.4, 7.3, 6.1 Hz, 1H), 3.33 (ddd, *J* = 9.4, 7.3, 6.3 Hz, 1H), 2.38 – 2.22 (m, 2H), 2.22 – 2.07 (m, 3H), 1.98 (ddd, *J* = 14.6, 11.0, 4.8 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.0, 139.5, 138.2, 128.5, 128.4, 128.1, 127.8, 127.7, 121.5, 121.4, 120.0, 88.8, 73.2, 72.9, 66.2, 40.6, 36.6, 12.1; **ATR-IR** *v* 2925 (w), 2856 (w), 2246 (w), 1456 (m), 1367 (m), 1366 (m), 1102 (s), 1027 (s), 730 (s), 699 (s); **HRMS (ESI)** calcd for $C_{20}H_{21}NNaO_2^+$ $[M+Na]^+$ 330.1464; found 330.1464.

3-(1-Phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194e**)




Yield: 14.6 mg (58%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.53 – 7.44 (m, 2H), 7.39 – 7.15 (m, 7H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 12.5 Hz, 1H), 2.59 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.47 (ddd, *J* = 14.0, 9.6, 5.7 Hz, 1H), 2.37 – 2.13 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.5, 142.4, 139.2, 128.7, 128.4, 128.0, 127.7, 125.0, 121.9, 121.6, 120.0, 89.9, 72.2, 37.3, 12.7; **ATR-IR** *v* 2929 (w), 2928 (w), 2853 (w), 2853 (w), 2247 (w), 1459 (w), 1446 (w), 1018 (m), 753 (s), 753 (s), 725 (s), 700 (s); **HRMS (ESI)** calcd for $C_{17}H_{15}NNaO^+$ $[M+Na]^+$ 272.1046; found 272.1048.

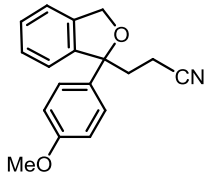
3-(1-(*p*-Tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194f**)




Yield: 20.0 mg (76%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.24 – 7.19 (m, 1H), 7.15 (d, *J* = 8.2 Hz, 2H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* =

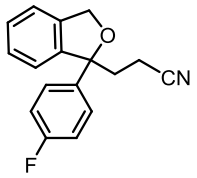
12.5 Hz, 1H), 2.58 (ddd, *J* = 13.9, 10.4, 5.7 Hz, 1H), 2.46 (ddd, *J* = 13.9, 9.8, 5.6 Hz, 1H), 2.37 – 2.17 (m, 2H), 2.32 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 142.6, 140.6, 139.1, 137.4, 129.4, 128.3, 128.0, 124.9, 121.8, 121.6, 120.0, 89.9, 72.2, 37.2, 21.1, 12.7; **ATR-IR** *v* 2953 (w), 2945 (w), 2923 (w), 2858 (w), 2247 (w), 1509 (w), 1459 (w), 1017 (s), 817 (s), 758 (s), 732 (s); **HRMS (ESI)** calcd for $C_{18}H_{17}NNaO^+$ $[M+Na]^+$ 286.1202; found 286.1205.

3-(1-(4-Methoxyphenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194g**)



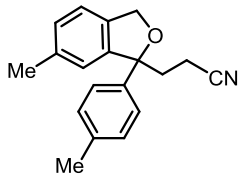

Yield: 22.9 mg (82%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 8.8 Hz, 2H), 7.32 – 7.27 (m, 3H), 7.23 – 7.19 (m, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 3.78 (s, 3H), 2.58 (ddd, *J* = 13.8, 10.4, 5.6 Hz, 1H), 2.45 (ddd, *J* = 13.8, 9.9, 5.4 Hz, 1H), 2.37 – 2.14 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 159.1, 142.6, 139.2, 135.6, 128.3, 128.0, 126.3, 121.8, 121.6, 120.0, 114.1, 89.7, 72.1, 55.4, 37.2, 12.7; **ATR-IR** *v* 2952 (w), 2932 (w), 2839 (w), 2246 (w), 1509 (s), 1248 (s), 1029 (s), 830 (s), 760 (s), 735 (s); **HRMS (ESI)** calcd for $C_{18}H_{17}NNaO_2^+$ $[M+Na]^+$ 302.1151; found 302.1163.

3-(1-(4-Fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194h**)




Yield: 13.9 mg (52%), white solid, mp: 123 – 124 °C; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.49 – 7.40 (m, 2H), 7.36 – 7.28 (m, 3H), 7.25 – 7.22 (m, 1H), 7.09 – 6.92 (m, 2H), 5.19 (d, *J* = 12.5 Hz, 1H), 5.14 (d, *J* = 12.5 Hz, 1H), 2.56 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.46 (ddd, *J* = 14.0, 9.6, 5.6 Hz, 1H), 2.38 – 2.12 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.3 (d, *J* = 246.5 Hz), 142.0, 139.4 (d, *J* = 3.1 Hz), 139.2, 128.5, 128.1, 126.8 (d, *J* = 8.0 Hz), 121.8, 121.7, 119.8, 115.6 (d, *J* = 21.4 Hz), 89.6, 72.2, 37.3, 12.7; **ATR-IR** *v* 2934 (w), 2933 (w), 2932 (w), 2916 (w), 2863 (w), 2241 (w), 1506 (s), 1219 (m), 1158 (m), 1009 (s), 832 (s), 767 (s), 738 (s); **HRMS (ESI)** calcd for $C_{17}H_{14}FNNaO^+$ $[M+Na]^+$ 290.0952; found 290.0957.

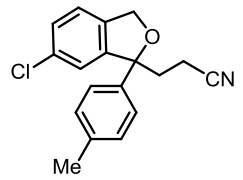
3-(6-Methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194i**)




Yield: 21.0 mg (76%), white solid, mp: 61 – 63 $^{o}$C; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 7.36 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.10 – 7.08 (m, 3H), 5.16 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 2.57 (ddd, *J* = 13.8, 10.6, 5.6 Hz, 1H), 2.45 (ddd, *J* = 13.8, 10.1, 5.3 Hz, 1H), 2.38 (s, 3H), 2.37 – 2.18 (m, 2H), 2.32 (s, 3H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 142.8, 140.8, 137.8, 137.3, 136.2, 129.4, 129.2, 124.9, 122.3, 121.2, 120.1, 89.8, 72.1, 37.1, 21.6, 21.1, 12.7; **ATR-IR** *v* 2955 (w), 2954 (w), 2920 (w), 2920 (w), 2853 (w), 2251 (w), 1437 (w), 1356 (w), 1270 (w), 1022 (s), 1011 (s), 821 (s);

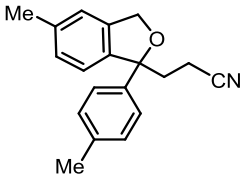
**HRMS (ESI)** calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; found 300.1365.

3-(6-Chloro-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194j**)




Yield: 24.0 mg (81%), colorless oil; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.14 (dd, *J* = 7.8, 0.9 Hz, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.13 (d, *J* = 12.6 Hz, 1H), 2.56 (ddd, *J* = 13.9, 9.4, 6.6 Hz, 1H), 2.42 (ddd, *J* = 13.9, 8.4, 6.9 Hz, 1H), 2.33 – 2.23 (m, 2H), 2.30 (s, 3H); **$^{13}$C NMR (101 MHz, CDCl$_3$)** δ 144.9, 139.8, 137.8, 137.5, 133.9, 129.6, 128.6, 124.8, 122.8, 122.1, 119.8, 89.8, 71.8, 37.0, 21.1, 12.7; **ATR-IR** *v* 2955 (w), 2926 (w), 2925 (w), 2870 (w), 2245 (w), 1510 (w), 1476 (w), 1030 (s), 817 (s); **HRMS (ESI)** calcd for $C_{18}H_{16}ClNNaO^+$ $[M+Na]^+$ 320.0813; found 320.0817.

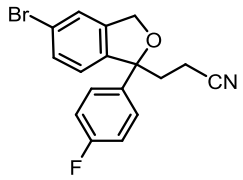
3-(5-Methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194k**)




Yield: 22.1 mg (80%), colorless oil; **$^{1}$H NMR (400 MHz, CDCl$_3$)** δ 7.35 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H), 7.13 – 7.10 (m, 1H), 7.02 (s, 1H), 5.16 (d, *J* = 12.5 Hz, 1H),

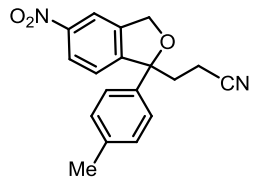
5.11 (d, *J* = 12.5 Hz, 1H), 2.56 (ddd, *J* = 13.8, 10.4, 5.7 Hz, 1H), 2.44 (ddd, *J* = 13.8, 9.9, 5.4 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.33 – 2.19 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.9, 139.7, 139.5, 138.3, 137.3, 129.4, 128.8, 124.9, 122.0, 121.5, 120.1, 89.7, 72.0, 37.2, 21.4, 21.1, 12.7; **ATR-IR** *v* 2946 (w), 2945 (w), 2924 (w), 2859 (w), 2247 (w), 1511 (w), 1441 (w), 1028 (s), 1027 (s), 1017 (s), 815 (s); **HRMS (ESI)** calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; found 300.1363.

3-(5-Bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194l**)



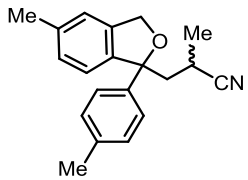

Yield: 24.4 mg (71%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.49 – 7.44 (m, 1H), 7.43 – 7.37 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.06 – 6.99 (m, 2H), 5.16 (d, *J* = 12.9 Hz, 1H), 5.09 (d, *J* = 12.9 Hz, 1H), 2.54 (ddd, *J* = 13.9, 9.9, 6.0 Hz, 1H), 2.42 (ddd, *J* = 13.9, 9.1, 5.9 Hz, 1H), 2.35 – 2.20 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.4 (d, *J* = 247.0 Hz), 141.5, 141.3, 138.7 (d, *J* = 3.2 Hz), 131.3, 126.7 (d, *J* = 8.1 Hz), 125.1, 123.3, 122.6, 119.6, 115.7 (d, *J* = 21.4 Hz), 89.5, 71.5, 37.1, 12.6; **ATR-IR** *v* 2955 (w), 2925 (w), 2862 (w), 2861 (w), 2243 (w), 1506 (s), 1222 (s), 1024 (s), 845 (s), 817 (s), 742 (m); **HRMS (ESI)** calcd for $C_{17}H_{13}BrFNNaO^+$ $[M+Na]^+$ 368.0057; found 368.0058.

3-(5-Nitro-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194m**)



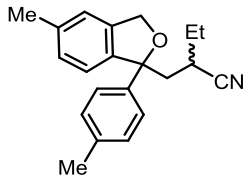

Yield: 24.3 mg (79%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.09 (d, *J* = 1.8 Hz, 1H), 7.49 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.28 (d, *J* = 13.1 Hz, 1H), 5.21(d, *J* = 13.1 Hz, 1H), 2.62 (ddd, *J* = 13.9, 8.6, 7.1 Hz, 1H), 2.47 (ddd, *J* = 14.0, 9.1, 6.3 Hz, 1H), 2.32 (s, 3H), 2.34 – 2.30 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 149.8, 148.6, 140.9, 138.7, 138.2, 129.8, 124.8, 124.0, 122.6, 119.5, 117.4, 89.8, 71.4, 36.8, 21.1, 12.6; **ATR-IR** *v* 2954 (w), 2953 (w), 2925 (w), 2869 (w), 2859 (w), 2858 (w), 2247 (w), 1521 (s), 1345 (s), 1032 (m), 1018 (m), 816 (s), 729 (m); **HRMS (ESI)** calcd for $C_{18}H_{16}N_2NaO_3^+$ $[M+Na]^+$ 331.1053; found 331.1051.

2-Methyl-3-(5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194n**)



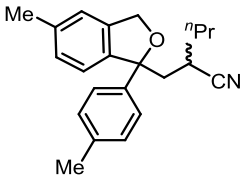

Yield: 21.5 mg (74%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.38 (d, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 0.5H), 7.17 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.02 (s, 0.5H), 7.01 (s, 0.5H), 5.25 – 5.05 (m, 2H), 2.72 – 2.42 (m, 2H), 2.34 (s, 3H), 2.30 (s, 3H), 2.31 – 2.19 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 1.5H), 1.28 (d, *J* = 7.1 Hz, 1.5H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.6, 141.4, 140.1, 140.0, 139.8, 139.3, 138.2, 138.1, 137.14, 137.09, 129.32, 129.27, 128.63, 128.61, 124.9, 124.8, 123.5, 123.4, 122.2, 122.1, 121.9, 121.5, 90.1, 89.9, 71.9 (2C), 45.6, 45.5, 21.7, 21.4, 21.4, 21.3, 21.1, 21.0, 19.8, 19.5; **ATR-IR** *v* 2939 (w), 2938 (w), 2921 (w), 2858 (w), 2857 (w), 2852 (w), 2238 (w), 1510 (w), 1454 (w), 1031 (s), 1018 (s), 819 (s), 813 (s); **HRMS (ESI)** calcd for $C_{20}H_{21}NNaO^+$ $[M+Na]^+$ 314.1515; found 314.1514.

2-((5-Methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)butanenitrile (**2.194o**)



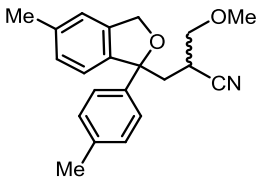

Yield: 20.4 mg (67%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.35 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 0.5H), 7.19 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.5H), 7.02 (s, 0.5H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.40 – 2.22 (m, 1.5H), 1.68 – 1.58 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 1.5H), 1.01 (t, *J* = 7.4 Hz, 1.5H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.63, 128.59, 124.9, 124.8, 122.6, 122.5, 122.2, 122.1, 121.9, 121.4, 90.2, 89.9, 72.0, 71.9, 43.7 (2C), 29.0, 28.6, 27.1, 26.6, 21.4, 21.3, 21.1, 21.0, 11.5, 11.4; **ATR-IR** *v* 2967 (w), 2926 (w), 2861 (w), 2237 (w), 1510 (w), 1459 (w), 1033 (s), 811 (s); **HRMS (ESI)** calcd for $C_{21}H_{23}NNaO^+$ $[M+Na]^+$ 328.1672; found 328.1673.

2-((5-Methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)pentanenitrile (**2.194p**)



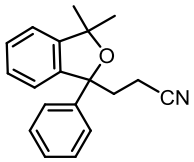

Yield: 21.1 mg (66%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.35 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 0.5H), 7.18 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.04 (s, 0.5H), 7.02 (s, 0.5H), 5.25 – 5.09 (m, 2H), 2.64 – 2.52 (m, 1.5H), 2.45 – 2.38 (m, 0.5H), 2.36 (s, 1.5H), 2.35 (s, 1.5H), 2.31 (s, 3H), 2.33 – 2.22 (m, 1H), 1.62 – 1.50 (m, 3H), 1.44 – 1.35 (m, 1H), 0.88 (t, *J* = 7.3 Hz, 1.5H), 0.87 (t, *J* = 7.3 Hz, 1.5H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.6, 141.5, 140.1, 140.0, 139.9, 139.3, 138.2, 138.1, 137.1, 137.0, 129.3, 129.2, 128.62, 128.6, 125.0, 124.8, 122.8, 122.7, 122.2, 122.1, 121.9, 121.4, 90.2, 90.0, 72.0, 71.9, 44.0 (2C), 35.8, 35.4, 27.2, 26.8, 21.4, 21.3, 21.1, 21.0, 20.2, 20.1, 13.66, 13.64; **ATR-IR** *v* 2959 (w), 2925 (w), 2865 (w), 2237 (w), 1510 (w), 1465 (w), 1458 (w), 1032 (s), 1018 (s), 820 (s), 813 (s); **HRMS (ESI)** calcd for $C_{22}H_{25}NNaO^+$ $[M+Na]^+$ 342.1828; found 342.1830.

3-Methoxy-2-((5-methyl-1-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)methyl)propanenitrile (**2.194q**)




Yield: 21.5 mg (67%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.38 (m, 2H), 7.27 (d, *J* = 7.8 Hz, 0.5H), 7.20 (d, *J* = 7.8 Hz, 0.5H), 7.15 – 7.07 (m, 3H), 7.03 (s, 0.5H), 7.02 (s, 0.5H), 5.24 – 5.09 (m, 2H), 3.54 – 3.39 (m, 2H), 3.32 (s, 1.5H), 3.31 (s, 1.5H), 2.83 (dtd, *J* = 7.3, 6.1, 4.6 Hz, 0.5H), 2.69 (dtd, *J* = 8.4, 6.1, 4.5 Hz, 0.5H), 2.62 – 2.40 (m, 2H), 2.35 (s, 3H), 2.31 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.32, 141.29, 140.0, 139.9, 139.8, 139.3, 138.3, 138.2, 137.2, 137.1, 129.3 129.30, 128.69, 128.68, 124.92, 124.88, 122.2, 122.1, 121.9, 121.6, 121.3, 121.1, 90.0, 89.8, 72.7, 72.4, 72.0, 71.9, 59.1 (2C), 40.5, 40.4, 28.3, 28.0, 21.4, 21.3, 21.11, 21.09; **ATR-IR** *v* 2924 (w), 2923 (w), 2880 (w), 2865 (w), 2864 (w), 2860 (w), 2242 (w), 1448 (s), 1380 (m), 1379 (m), 1348 (s), 1121 (s), 1030 (s), 1018 (s), 813 (s), 711 (s); **HRMS (ESI)** calcd for $C_{21}H_{23}NNaO_2^+$ $[M+Na]^+$ 344.1621; found 344.1628.

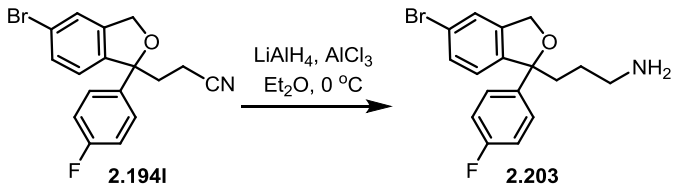
3-(3,3-Dimethyl-1-phenyl-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.194r**)




Yield: 8.3 mg (30%), white solid, mp: 63 – 64 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.59 – 7.53 (m, 2H), 7.40 – 7.30 (m, 5H), 7.26 – 7.22 (m, 1H), 7.15 – 7.09 (m, 1H), 2.62 – 2.48 (m, 1H), 2.38 – 2.19 (m, 3H), 1.61 (s, 3H), 1.42 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 147.1, 144.7, 141.2, 128.7, 128.6, 128.0, 127.5, 125.3, 122.3, 121.2, 120.1, 88.3, 85.7, 39.1, 30.0, 29.9, 12.9; **ATR-IR** *v* 974 (w), 2924 (w), 2867 (w), 2853 (w), 2243 (w), 1440 (w), 1052 (m), 975 (m), 765 (s), 704 (s); **HRMS (ESI)** calcd for $C_{19}H_{19}NNaO^+$ $[M+Na]^+$ 300.1359; found 300.1365.

### 3.4.3. Synthesis of Cetalopram

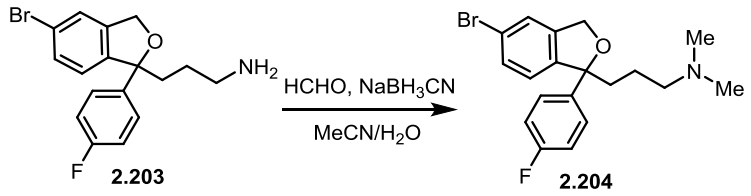
**Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)propan-1-amine (2.203)**




To a suspension of $LiAlH_4$ (14 mg, 1 equiv), and $AlCl_3$ (40 mg, 1 equiv) in diethyl ether (*c* = 0.1 M) was added dropwise a solution of **2.194l** (102 mg, 1 equiv) in diethyl ether at 0 °C. The stirring was continued at the same temperature until the starting material was consumed. The reaction mixture was then treated by successive dropwise addition of ice-cold water (14 µL), an aqueous 15% NaOH (14 µL), and ice-cold water (42 µL). After stirring for 30 min, the mixture was filtered through a sintered glass frit. The filtrate was then concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (DCM/methanol/$Et_3N$ 20/1/0.02) to give compound **2.203** as a colourless oil (73.9 mg, 70% yield).

**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.34 (m, 3H), 7.31 (s, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 8.5 Hz, 2H), 5.17 (d, *J* = 12.7 Hz, 1H), 5.03 (d, *J* = 12.7 Hz, 1H), 2.89 (broad, s, 2H), 2.39 – 2.27 (m, 1H), 2.22 – 2.15 (m, 1H), 1.75 – 1.71 (m, 1H), 1.62 – 1.56 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.1 (d, *J* = 246.3 Hz), 142.7, 141.2, 139.7 (d, *J* = 3.0 Hz), 131.0, 126.9 (d, *J* = 8.1 Hz), 124.8, 123.5, 122.0, 115.5 (d, *J* = 21.4 Hz), 90.7, 71.6, 39.9, 37.8, 22.6; **ATR-IR** ν 3355 (w), 2930 (w), 2856 (w), 2253 (w), 1507 (s), 1224 (s), 1031 (s), 1013 (s), 836 (s), 821 (s), 739 (m), 699 (m); **HRMS (ESI)** calcd for $C_{17}H_{18}BrFNO^+$ $[M+H]^+$ 350.0550; found 350.0551.

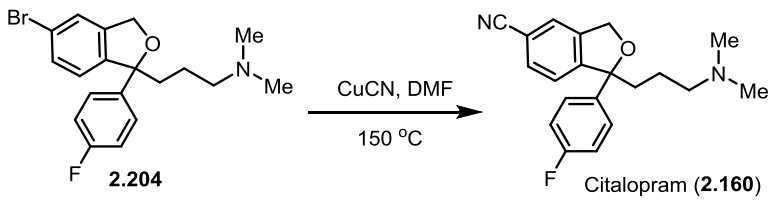
**Synthesis of 3-(5-bromo-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-1-yl)-N,N-dimethyl-propan-1-amine (2.204)**




To a solution of **2.203** (53 mg, 1 equiv) in MeCN ($c$ = 0.1 M) at 0 $^{o}$C was added aqueous formalin (35%, 0.4 mL) and $NaBH_3CN$ (45mg, 5 equiv). The resulting reaction mixture was warmed up to room temperature, occasionally treated with a drop of acetic acid to keep the pH slightly below 7. After stirring for 4 h, the reaction mixture was diluted with ethyl acetate, washed with 1 M NaOH solution, then brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (chloroform/methanol 30/1 to 20/1) to give compound **2.204** as a colorless oil (47.0 mg, 83% yield).

**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.36 (m, 3H), 7.34 (s, 1H), 7.16 (d, $J$ = 8.0 Hz, 1H), 7.09 – 6.96 (m, 2H), 5.13 (d, $J$ = 12.7 Hz, 1H), 5.08 (d, $J$ = 12.7 Hz, 1H), 2.37 (t, $J$ = 7.4 Hz, 2H), 2.24 (s, 6H), 2.28 – 2.03 (m, 2H), 1.61 – 1.47 (m, 1H), 1.45 – 1.33 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.0 (d, $J$ = 245.8 Hz), 143.3, 141.5, 140.4 (d, $J$ = 3.2 Hz), 130.8, 126.9 (d, $J$ = 7.9 Hz), 124.7, 123.5, 121.7, 115.3 (d, $J$ = 21.3 Hz), 90.8, 71.4, 59.4, 45.0, 39.1, 21.8; **ATR-IR** ν 2944 (w), 2926 (w), 2854 (w), 2781 (w), 1507 (s), 1468 (m), 1225 (s), 1160 (m), 1033 (s), 834 (s), 820 (s); **HRMS (ESI)** calcd for $C_{19}H_{22}BrFNO^{+}$ $[M+H]^{+}$ 378.0863; found 378.0865.

**Synthesis of 1-(3-(dimethylamino)propyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile - Citalopram (2.160)**



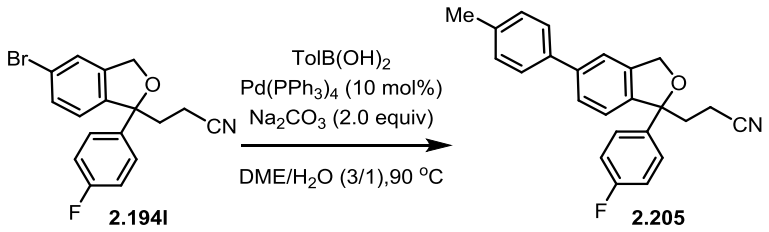

In a sealed tube, compound **2.204** (38 mg, 1 equiv) and CuCN (36 mg, 4 equiv) was dissolved in DMF (1 mL). The reaction mixture was evacuated and filled back with $N_2$ three times. The resultant mixture was then heated to 150 °C for 24 hours. After cooling to room temperature, this solution was partitioned between toluene (5 mL) and aqueous $NH_3$ 25% (5 mL) and stirred vigorously for 10 minutes. The aqueous layer was removed and the organic layer was washed 3 times with aqueous solution of $NH_3$ 25% (3 x 5 mL). The organic phase was then washed with brine (10 mL) and dried

over anhydrous $Na_2SO_4$, filtered and concentrated in *vacuo*. The crude product was purified by preparative thin layer chromatography (chloroform/methanol 20/1) to give compound **2.160** as a colorless oil (23.6 mg, 74% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.60 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.50 (s, 1H), 7.45 – 7.40 (m, 3H), 7.03 – 6.99 (m, 2H), 5.20 (d, *J* = 12.9 Hz, 1H), 5.15 (d, *J* = 12.9 Hz, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.30 – 2.11 (m, 2H), 2.22 (s, 6H), 1.57 – 1.45 (m, 1H), 1.42 – 1.35 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.2 (d, *J* = 246.3 Hz), 149.5, 140.4, 139.5 (d, *J* = 3.2 Hz), 132.1, 126.9 (d, *J* = 8.1 Hz), 125.4, 122.9, 118.8, 115.5 (d, *J* = 21.4 Hz), 111.9, 91.2, 71.5, 59.3, 45.1 (2C), 38.9, 21.9; **ATR-IR** ν 2948 (w), 2858 (w), 2782 (w), 2230 (w), 1508 (s), 1226 (s), 1226 (s), 1035 (s), 835 (s); **HRMS (ESI)** calcd for $C_{20}H_{22}FN_2O^+$ $[M+H]^+$ 325.1711; found 325.1714.

### 3.4.4. Post-transformations of dihydroisobenzofuran 2.193l

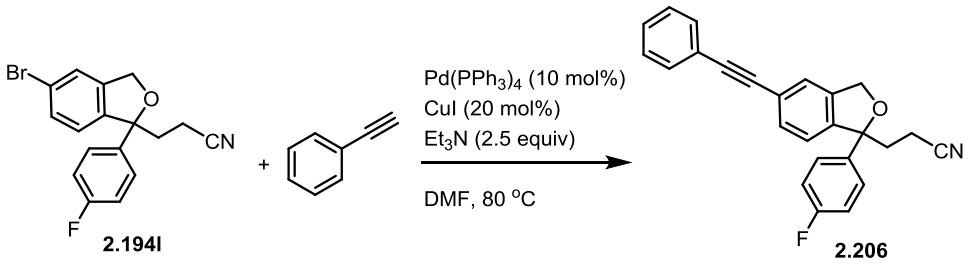
**Synthesis of 3-(1-(4-fluorophenyl)-5-(p-tolyl)-1,3-dihydroisobenzofuran-1-yl)propanenitrile (2.205)**




To a suspension of 4-tolylboronic acid (10.2 mg, 0.075 mmol, 1.5 equiv), **2.194l** (17.3 mg, 0.05 mmol, 1.0 equiv) and $Na_2CO_3$ (10.6 mg, 0.1 mmol, 2.0 equiv) in a mixture of DME/$H_2O$ (3/1, *c* = 0.1 M) was added $Pd(PPh_3)_4$ (5.7 mg, 10 mol%) under $N_2$. The resulting mixture was heated to 90 °C and stirred for 24 h. The solvent was then removed under reduced pressure, and the residue was diluted with water, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound **2.205** as a colourless oil (14.5 mg, 82% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.55 – 7.38 (m, 6H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.26 – 7.24 (m, 2H), 7.07 – 7.01 (m, 2H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.17 (d, *J* = 12.4 Hz, 1H), 2.59 (ddd, *J* = 13.9, 10.2, 5.9 Hz, 1H), 2.49 (ddd, *J* = 14.0, 9.6, 5.6 Hz, 1H), 2.40 (s, 3H), 2.38 – 2.19 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.3 (d, *J* = 246.4 Hz), 142.0, 140.8, 139.9, 139.4 (d, *J* = 3.2 Hz), 137.68, 137.65, 129.7, 127.2, 126.8 (d, *J* = 8.1 Hz), 122.0, 120.2, 119.9, 115.6 (d, *J* = 21.3 Hz), 89.5, 72.2, 37.3, 21.3, 12.7; **ATR-IR** ν 2925 (w), 2856 (w), 2249 (w), 1507 (m), 1225 (m), 908 (m), 835 (m), 813 (s), 730 (s); **HRMS (ESI)** calcd for $C_{24}H_{20}FNNaO^+$ $[M+Na]^+$ 380.1421; found 380.1421.

**Synthesis of 3-(1-(4-fluorophenyl)-5-(phenylethynyl)-1,3-dihydroisobenzofuran-1-yl)-propanenitrile (2.206)**

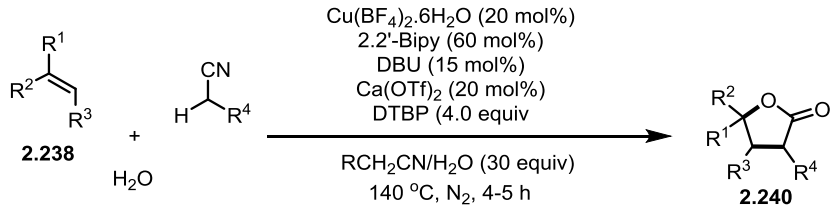



To a solution of **2.194l** (17.3 mg, 0.05 mmol, 1.0 equiv), phenylacetylene (20.4 mg, 0.2 mmol, 4.0 equiv), CuI (1.9 mg, 20 mol%), and $Et_3N$ (18 µL, 0.125 mmol, 2.5 equiv) in DMF (*c* = 0.05 M) was added $Pd(PPh_3)_4$ (5.7 mg, 10 mol%) at room temperature. The resulting mixture was evacuated and filled back with $N_2$ three times, then warmed up to 80 °C. After stirring for 24 h, the reaction mixture was diluted with water, extracted with diethyl ether. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/9 to 2/8) to give compound **2.206** as a yellow oil (11.5 mg, 62% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.53 – 7.50 (m, 3H), 7.45 – 7.42 (m, 3H), 7.37 – 7.34 (m, 3H), 7.29 (d, *J* = 7.9 Hz, 1H), 7.07 – 7.01 (m, 2H), 5.18 (d, *J* = 12.6 Hz, 1H), 5.12 (d, *J* = 12.6 Hz, 1H), 2.57 (ddd, *J* = 13.9, 10.1, 5.9 Hz, 1H), 2.52 – 2.39 (m, 1H), 2.38 – 2.14 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.4 (d, *J* = 246.6 Hz), 142.2, 139.6, 138.9 (d, *J* = 3.4 Hz), 131.8, 131.7, 128.7, 128.6, 126.8 (d, *J* = 8.1 Hz), 124.8, 123.9, 123.0, 121.8, 119.7, 115.7 (d, *J* = 21.4 Hz), 90.2, 89.6, 88.7, 71.9, 37.1, 12.7; **ATR-IR** ν 2955 (w), 2925 (w), 2903 (w), 2855 (w), 2248 (w), 1507 (m), 1225 (m), 836 (s), 835 (s), 757 (s), 691 (s); **HRMS (ESI)** calcd for $C_{25}H_{18}FNNaO^+$ $[M+Na]^+$ 390.1265; found 390.1266.

## 3.5. Copper-Catalyzed Formal [2+2+1] Heteroannulation of Alkenes, Alkylnitriles, and Water in Synthesis of γ-Lactones

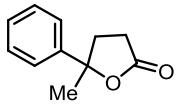
### 3.5.1. Substrate scope




In the glovebox, alkene **2.238** (0.1 mmol, 1 equiv), $Cu(BF_4)_2.6H_2O$ (20 mol%), 2,2'-bipyridine (60 mol%), $Ca(OTf)_2$ (20 mol%), and DBU (15 mol%) were dissolved in degassed $R^4CH_2CN$ (0.025 M) in a sealed tube. DTBP (4 equiv) and $H_2O$ (30 equiv) were then added and the tube was sealed and heated to 140 $^oC$. After 3.5 h, the reaction mixture was cooled down to room temperature, and an aqueous HCl solution (1N, 1 mL) was added. After heating at 80 $^oC$ for 45 minutes, the resulting mixture was cooled down, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.240**.

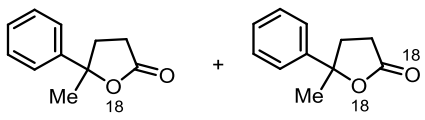
**Characterization data of 2.240**

5-Methyl-5-phenyldihydrofuran-2(3H)-one (**2.240a**)



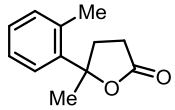

Yield: 12.9 mg (73%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.35 (m, 4H), 7.33 – 7.26 (m, 1H), 2.66 – 2.59 (m, 1H), 2.55 – 2.39 (m, 3H), 1.72 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.7, 144.4, 128.8, 127.8, 124.2, 87.1, 36.3, 29.6, 29.1; **ATR-IR** *ν* 2979 (w), 2937 (w), 1765 (s), 1447 (w), 1242 (m), 1133 (s), 1068 (m), 943 (m), 767 (s), 701 (s); **HRMS (ESI)** calcd for $C_{11}H_{13}O_2^+$ $[M+H]^+$ 177.0910; found 177.0913

5-Methyl-5-phenyldihydrofuran-2(3H)-one-$^{18}O_1$/$^{18}O_2$ (**2.240a**-$^{18}O_1$ + 3a-$^{18}O_2$)



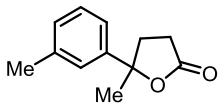
**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.35 (m, 4H), 7.33 – 7.26 (m, 1H), 2.66 – 2.59 (m, 1H), 2.55 – 2.39 (m, 3H), 1.72 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.6, 144.4, 128.7, 127.8, 124.2, 87.1, 36.3, 29.6, 29.1; **HRMS (ESI)** calcd for $C_{11}H_{13}O^{18}O^{+}$ $[M-^{18}O_1+H]^{+}$ 179.0953; found 179.0958; calcd for $C_{11}H_{13}{}^{18}O_2{}^{+}$ $[M-^{18}O_2+H]^{+}$ 181.0995; found 181.1000.

5-Methyl-5-(o-tolyl)dihydrofuran-2(3H)-one (**2.240b**)



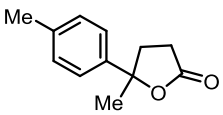

Yield: 12.5 mg (66%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.48 – 7.45 (m, 1H), 7.22 – 7.18 (m, 3H), 2.73 – 2.49 (m, 4H), 2.46 (s, 3H), 1.75 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.3, 142.1, 133.8, 132.6, 127.9, 126.2, 124.9, 88.0, 35.2, 28.9, 28.0, 21.7; **ATR-IR** *ν* 2973 (w), 2928 (w), 1767 (s), 1211 (m), 1134 (m), 1062 (m), 939 (m), 763 (s), 728 (m); **HRMS (ESI)** calcd for $C_{12}H_{15}O_2{}^{+}$ $[M+H]^{+}$ 191.1067; found 191.1070.

5-Methyl-5-(m-tolyl)dihydrofuran-2(3H)-one (**2.240c**)




Yield: 12.0 mg (63%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.28 – 7.24 (m, 1H), 7.20 – 7.10 (m, 3H), 2.66 – 2.58 (m, 1H), 2.53 – 2.38 (m, 3H), 2.37 (s, 3H), 1.71 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.7, 144.4, 138.5, 128.6, 128.5, 124.9, 121.3, 87.2, 36.4, 29.6, 29.1, 21.7; **ATR-IR** ν 2923 (w), 2851 (w), 1771 (s), 1244 (m), 1202 (m), 1131 (m), 943 (m), 789 (m), 707 (m); **HRMS (ESI)** calcd for $C_{12}H_{15}O_2{}^{+}$ $[M+H]^{+}$ 191.1067; found 191.1069.

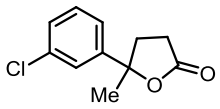
5-Methyl-5-(p-tolyl)dihydrofuran-2(3H)-one (**2.240d**)




Yield: 10.0 mg (54%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.66 – 2.60 (m, 1H), 2.58 – 2.36 (m, 3H), 2.35 (s, 3H), 1.71 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.8, 141.5, 137.5, 129.4, 124.2, 87.2, 36.4, 29.6, 29.2, 21.1; **ATR-IR** ν 2926 (w),

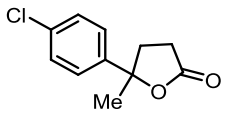
1773 (s), 1242 (m), 1133 (m), 1077 (m), 941 (m), 820 (m); **HRMS (ESI)** calcd for $C_{12}H_{15}O_2^+$ $[M+H]^+$ 191.1067; found 191.1070.

5-(3-Chlorophenyl)-5-methyldihydrofuran-2(3H)-one (**2.240e**)



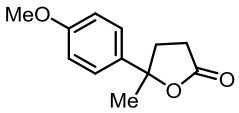

Yield: 8.8 mg (42%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.37 (d, *J* = 1.8 Hz, 1H), 7.33 – 7.24 (m, 3H), 2.69 – 2.62 (m, 1H), 2.56 – 2.39 (m, 3H), 1.71 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.2, 146.5, 134.8, 130.1, 128.0, 124.7, 122.5, 86.4, 36.2, 29.5, 29.0; **ATR-IR** ν 2980 (w), 2927 (w), 1771 (s), 1770 (s), 1244 (m), 1135 (s), 1077 (s), 945 (s), 831 (m), 822 (m); **HRMS (ESI)** calcd for $C_{11}H_{12}ClO_2^+$ $[M+H]^+$ 211.0520; found 211.0526.

5-(4-Chlorophenyl)-5-methyldihydrofuran-2(3H)-one (**2.240f**)



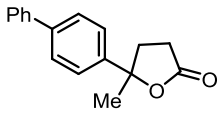

Yield: 11.3 mg (54%), white solid, mp: 48 – 49 °C; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.36 – 7.30 (m, 4H), 2.69 – 2.61 (m, 1H), 2.54 – 2.37 (m, 3H), 1.70 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.3, 143.0, 133.7, 128.9, 125.8, 86.6, 36.2, 29.5, 29.0; **ATR-IR** ν 2980 (w), 2927 (w), 1775 (s), 1491 (w), 1244 (s), 1136 (s), 1077 (s), 944 (s), 831 (s), 821 (s); **HRMS (ESI)** calcd for $C_{11}H_{12}ClO_2^+$ $[M+H]^+$ 211.0520; found 211.0528.

5-(4-Methoxyphenyl)-5-methyldihydrofuran-2(3H)-one (**2.240g**)



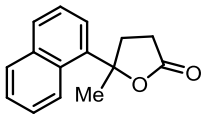

Yield: 9.7 mg (48%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.81 (s, 3H), 2.66 – 2.58 (m, 1H), 2.55 – 2.34 (m, 3H), 1.70 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.7, 159.1, 136.5, 125.5, 114.0, 87.1, 55.5, 36.3, 29.6, 29.2; **ATR-IR** ν 2934 (w), 2934 (w), 2838 (w), 1768 (s), 1515 (s), 1249 (s), 1133 (s), 1030 (s), 833 (s); **HRMS (ESI)** calcd for $C_{12}H_{15}O_3^+$ $[M+H]^+$ 207.1016; found 207.1022.

5-([1,1'-Biphenyl]-4-yl)-5-methyldihydrofuran-2(3H)-one (**2.240h**)



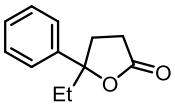

Yield: 18.1 mg (72%), yellow solid, mp: 122 – 124 °C; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.61 – 7.58 (m, 4H), 7.47 – 7.43 (m, 4H), 7.38 – 7.34 (m, 1H), 2.70 – 2.63 (m, 1H), 2.62 – 2.41 (m, 3H), 1.77 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.6, 143.4, 140.7, 140.5, 129.0, 127.6, 127.4, 127.2, 124.7, 87.0, 36.3, 29.5, 29.1; **ATR-IR** ν 2975 (w), 2921 (w), 1760 (s), 1489 (w), 1249 (m), 1140 (m), 1076 (s), 837 (m), 765 (s), 728 (s), 691 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$ 253.1223; found 253.1227.

5-Methyl-5-(naphthalen-1-yl)dihydrofuran-2(3H)-one (**2.240i**)



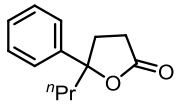

Yield: 15.6 mg (69%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 8.7 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.71 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.55 – 7.43 (m, 3H), 2.95 – 2.87 (m, 1H), 2.76 – 2.68 (m, 2H), 2.58 – 2.50 (m, 1H), 2.01 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.3, 139.5, 134.8, 129.7, 129.2, 129.1, 126.1, 125.6, 125.3, 125.0, 122.6, 88.0, 35.6, 29.3, 29.0; **ATR-IR** ν 2979 (w), 2973 (w), 2934 (w), 1769 (s), 1510 (w), 1209 (m), 1198 (m), 1089 (m), 943 (m), 805 (m), 777 (s); **HRMS (ESI)** calcd for $C_{15}H_{15}O_2^+$ $[M+H]^+$ 227.1067; found 227.1066.

5-Ethyl-5-phenyldihydrofuran-2(3H)-one (**2.240j**)



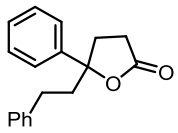

Yield: 12.4 mg (66%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.27 (m, 5H), 2.63 – 2.54 (m, 1H), 2.51 – 2.41 (m, 3H), 2.00 (q, *J* = 7.4 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.8, 142.8, 128.6, 127.6, 124.9, 90.0, 35.4, 34.7, 28.9, 8.4; **ATR-IR** ν 2927 (w), 2886 (w), 1770 (s), 1242 (m), 1196 (m), 1183 (m), 1135 (m), 780 (m), 764 (m), 703 (m); **HRMS (ESI)** $C_{12}H_{15}O_2^+$ $[M+H]^+$ 191.1067; found 191.1072.

5-Phenyl-5-propyldihydrofuran-2(3H)-one (**2.240k**)



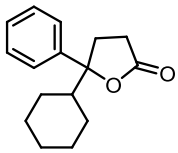

Yield: 13.0 mg (64%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.27 (m, 5H), 2.62 – 2.58 (m, 1H), 2.50 – 2.40 (m, 3H), 2.01 – 1.79 (m, 2H), 1.41 – 1.31 (m, 1H), 1.14 – 1.05 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.8, 143.1, 128.6, 127.6, 124.8, 89.7, 44.8, 35.2, 28.8, 17.4, 14.2; **ATR-IR** ν 2960 (w), 2913 (w), 1772 (s), 1448 (w), 1193 (m), 1181 (m), 765 (m), 702 (s); **HRMS (ESI)** calcd for $C_{13}H_{16}NaO_2^+$ $[M+Na]^+$ 227.1042; found 227.1041.

5-Phenethyl-5-phenyldihydrofuran-2(3H)-one (**2.240l**)



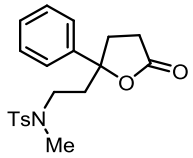

Yield: 18.8 mg (71%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.39 (m, 4H), 7.35 – 7.31 (m, 1H), 7.26 – 7.23 (m, 2H), 7.18 – 7.16 (m, 1H), 7.10 – 7.07 (m, 2H), 2.74 – 2.67 (m, 1H), 2.65 – 2.44 (m, 4H), 2.38 – 2.24 (m, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.7, 142.6, 141.4, 128.9, 128.8, 128.6, 128.3, 127.8, 126.1, 124.7, 89.2, 44.6, 35.6, 30.4, 28.7; **ATR-IR** ν 2934 (w), 2927 (w), 2868 (w), 1773 (s), 1497 (w), 1456 (w), 1449 (w), 1193 (m), 1166 (m), 936 (m), 767 (m), 752 (m), 700 (s); **HRMS (ESI)** calcd for $C_{18}H_{18}NaO_2^+$ $[M+Na]^+$ 289.1199; found 289.1202.

5-Cyclohexyl-5-phenyldihydrofuran-2(3H)-one (**2.240m**)



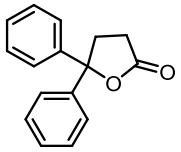

Yield: 17.3 mg (71%), light yellow solid, mp: 67 – 69 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.37 – 7.26 (m, 5H), 2.56 – 2.35 (m, 4H), 1.88 – 1.83 (m, 1H), 1.78 – 1.70 (m, 3H), 1.62 – 1.56 (m, 2H), 1.25 – 0.83 (m, 5H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.9, 142.0, 128.2, 127.6, 125.7, 92.1, 48.5, 32.2, 29.1, 27.5, 27.2, 26.5, 26.2, 26.1; **ATR-IR** ν 2940 (w), 2928 (w), 2928 (w), 2853 (w), 1754 (s), 1446 (w), 1238 (m), 1195 (m), 1176 (m), 986 (m), 923 (m), 740 (m), 713 (s); **HRMS (ESI)** calcd for $C_{16}H_{20}NaO_2^+$ $[M+Na]^+$ 267.1355; found 267.1355.

N,4-dimethyl-N-(2-(5-oxo-2-phenyltetrahydrofuran-2-yl)ethyl)benzenesulfonamide (**2.240n**)



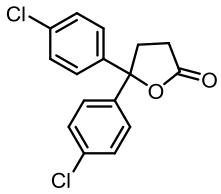

Yield: 20.6 mg (56%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.42 – 7.37 (m, 2H), 7.35 – 7.31 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 2H), 2.98 (ddd, *J* = 13.9, 10.9, 5.2 Hz, 1H), 2.78 – 2.69 (m, 1H), 2.64 (s, 3H), 2.59 – 2.36 (m, 5H), 2.40 (s, 3H), 2.27 (ddd, *J* = 14.0, 10.8, 5.2 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.4, 143.5, 141.8, 134.1, 129.8, 129.0, 128.1, 127.4, 124.5, 87.8, 46.2, 40.5, 35.9, 35.8, 28.3, 21.6; **ATR-IR** ν 2925 (w), 2924 (w), 1775 (s), 1449 (w), 1337 (m), 1336 (m), 1191 (m), 1158 (s), 1089 (m), 934 (m), 735 (m), 702 (s); **HRMS (ESI)** calcd for $C_{20}H_{24}NO_4S^+$ $[M+H]^+$ 374.1421; found 374.1416.

5,5-Diphenyldihydrofuran-2(3H)-one (**2.240o**)



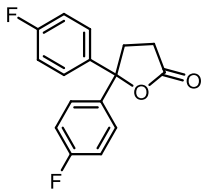

Yield: 11.8 mg (50%), yellow solid. 83 – 85 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.41 (m, 4H), 7.37 – 7.33 (m, 4H), 7.29 – 7.26 (m, 2H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.2, 143.2, 128.7, 128.0, 125.5, 89.9, 35.8, 29.2; **ATR-IR** ν 2926 (w), 1766 (s), 1449 (w), 1220 (m), 1154 (s), 973 (m), 901 (m), 755 (s), 700 (s);

5,5-Bis(4-chlorophenyl)dihydrofuran-2(3H)-one (**2.240p**)



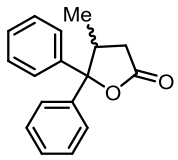

Yield: 17.2 mg (56%), yellow solid, mp: 86 – 87 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.32 (s, 8H), 2.86 (t, *J* = 7.8 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.5, 141.3, 134.3, 129.1, 126.9, 88.7, 35.7, 29.0; **ATR-IR** ν 2924 (w), 2853 (w), 1774 (s), 1489 (m), 1215 (m), 1160 (s), 1092 (s), 1053 (m), 1013 (m), 986 (s), 908 (m), 830 (m), 824 (m), 813 (s); **HRMS (ESI)**calcd for $C_{16}H_{12}Cl_2NaO_2^+$ $[M+Na]^+$ 329.0107; found 329.0107.

5,5-Bis(4-fluorophenyl)dihydrofuran-2(3H)-one (**2.240q**)




Yield: 13.7 mg (50%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.34 (m, 4H), 7.06 – 7.02 (m, 4H), 2.87 (t, *J* = 7.7 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.8, 162.4 (d, *J* = 247.9 Hz), 138.8 (d, *J* = 3.3 Hz), 127.4 (d, *J* = 8.3 Hz), 115.8 (d, *J* = 21.6 Hz), 89.0, 36.0, 29.2; **ATR-IR** ν 2953 (w), 2952 (w), 2929 (w), 2924 (w), 1775 (s), 1601 (w), 1508 (s), 1220 (s), 1157 (s), 985 (m), 906 (m), 832 (s); **HRMS (ESI)** calcd for $C_{16}H_{12}F_2NaO_2^+$ $[M+Na]^+$ 297.0698; found 297.0695.

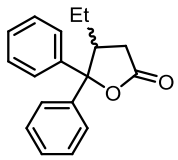
4-Methyl-5,5-diphenyldihydrofuran-2(3H)-one (**2.240r**)




Yield: 20.0 mg (79%), yellow solid, mp: 101 – 103 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.53 – 7.47 (m, 2H), 7.39 – 7.17 (m, 8H), 3.45 – 3.38 (m, 1H), 2.71 (dd, *J* = 17.1, 7.4 Hz, 1H), 2.32 (dd, *J* = 17.1, 4.9 Hz, 1H), 0.91 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.9, 142.9, 140.6, 128.7, 128.3, 128.2, 127.6, 126.3, 125.8, 92.4, 38.2, 37.7, 17.3; **ATR-IR** ν 2958 (w), 2922 (w), 2922 (w), 1777 (s), 1765 (m), 1451 (w), 1223 (m), 1162 (s), 1162 (s), 970 (m), 927 (s), 754 (m), 747 (s), 697 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$ 253.1223;

found 253.1222.

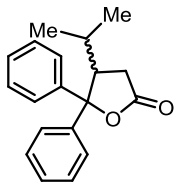
4-Ethyl-5,5-diphenyldihydrofuran-2(3H)-one (**2.240s**)




Yield: 18.6 mg (70%), yellow solid, mp: 95 – 97 °C; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.50 – 7.47 (m, 2H), 7.39 – 7.18 (m, 8H), 3.17 – 3.12 (m, 1H), 2.70 (dd, *J* = 17.3, 7.6 Hz, 1H), 2.43 (dd, *J* = 17.3, 6.3 Hz, 1H), 1.55 – 1.42 (m, 1H), 0.93 – 0.78 (m, 4H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.0, 143.0, 140.8, 128.7, 128.3, 127.6, 126.5, 126.0, 92.4, 45.5, 34.6, 24.6, 12.3; **ATR-IR** ν 2933 (w), 2932 (w),

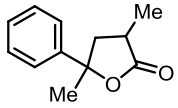
1773 (s), 1446 (w), 1231 (m), 1230 (m), 1215 (m), 1157 (m), 990 (m), 973 (m), 768 (m), 767 (m), 701 (s); **HRMS (ESI)** calcd for $C_{18}H_{19}O_2^+$ $[M+H]^+$ 267.1380; found 267.1380.

4-Isopropyl-5,5-diphenyldihydrofuran-2(3H)-one (**2.240t**)



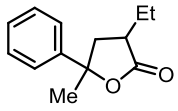

Yield: 14.0 mg (50%), yellow solid, mp: 146 – 148 °C; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.54 – 7.51 (m, 2H), 7.39 – 7.21 (m, 8H), 3.27 – 3.24 (m, 1H), 2.51 (d, *J* = 5.7 Hz, 2H), 1.94 – 1.90 (m, 1H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.58 (d, *J* = 6.7 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.4, 144.1, 140.6, 128.7, 128.4, 128.0, 127.4, 125.9, 125.7, 92.5, 48.6, 30.9, 27.3, 22.4, 16.4; **ATR-IR** ν 2963 (w), 2933 (w), 2929 (w), 2928 (w), 2927 (w), 2923 (w), 2922 (w), 1764 (s), 1448 (w), 1191 (m), 1155 (m), 979 (m), 972 (m), 706 (s), 696 (s); **HRMS (ESI)** calcd for $C_{19}H_{20}NaO_2^+$ $[M+Na]^+$ 303.1355; found 303.1353.

3,5-Dimethyl-5-phenyldihydrofuran-2(3H)-one (**2.240u**)




Yield: 12.9 mg (67%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.27 (m, 5H), 2.94 (ddq, *J* = 10.8, 8.8, 7.1 Hz, 0.54H), 2.80 – 2.68 (m, 1H), 2.51 (ddq, *J* = 14.1, 8.2, 7.1 Hz, 0.46H), 2.15 – 1.98 (m, 1H), 1.73 (s, 1.4H), 1.68 (s, 1.6H), 1.26 – 1.24 (m, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 179.4, 179.0, 145.5, 144.0, 128.7, 128.7, 127.7, 127.6, 124.4, 124.0, 84.7, 84.6, 45.2, 44.1, 35.4, 35.1, 30.5, 29.0, 15.6, 14.8; **ATR-IR** ν 2976 (w), 2934 (w), 1767 (s), 1457 (w), 1448 (w), 1222 (m), 952 (m), 766 (m), 700 (s); **HRMS (ESI)** calcd for $C_{12}H_{14}NaO_2^+$ $[M+Na]^+$ 213.0886; found 213.0883.

3-Ethyl-5-methyl-5-phenyldihydrofuran-2(3H)-one (**2.240v**)




Yield: 13.3 mg (65%), colorless oil;

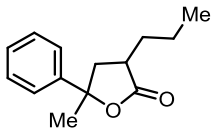
**Isomer 1:**

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.27 (m, 5H), 2.81 (dtd, *J* = 10.6, 8.9, 4.8 Hz, 1H), 2.65 (dd, *J* = 12.5, 8.8 Hz, 1H), 2.11 (dd, *J* = 12.5, 10.7 Hz, 1H), 1.91 (dqd, *J* = 13.8, 7.6, 4.8 Hz, 1H), 1.68 (s, 3H), 1.45 (dtd, *J* = 14.0, 7.3, 1.5 Hz, 1H), 0.97 (t, *J* = 7.5 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.2, 145.6, 128.7, 127.6, 124.1, 84.8, 42.0, 41.7, 29.1, 23.8, 11.9; **ATR-IR** ν 2966 (w), 2933 (w), 2900 (w), 1770 (s), 1447 (w), 1223 (m), 1140 (w), 1062 (w), 951 (w), 768 (w), 705 (m); **HRMS (ESI)** calcd for $C_{13}H_{17}O_2^+$ $[M+H]^+$ 205.1223; found 205.1224.

**Isomer 2:**

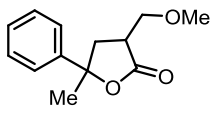
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.27 (m, 5H), 2.72 (dd, *J* = 12.4, 8.2 Hz, 1H), 2.46 – 2.30 (m, 1H), 2.11 – 2.00 (m, 1H), 1.97 – 1.84 (m, 1H), 1.73 (s, 3H), 1.56 – 1.45 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.7, 144.2, 128.7, 127.7, 124.4, 84.8, 42.7, 41.6, 30.5, 23.2, 11.8; **ATR-IR** ν 2964 (w), 2929 (w), 2877 (w), 2860 (w), 2859 (w), 1767 (s), 1447 (m), 1222 (s), 1222 (s), 1139 (s), 1062 (s), 950 (s), 767 (s); **HRMS (ESI)** calcd for $C_{13}H_{17}O_2^+$ $[M+H]^+$ 205.1223; found 205.1228.

5-Methyl-5-phenyl-3-propyldihydrofuran-2(3H)-one (**2.240w**)




Yield: 14.2 mg (65%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.27 (m, 5H), 2.93 – 2.79 (m, 0.47H), 2.79 – 2.61 (m, 1H), 2.53 – 2.34 (m, 0.53H), 1.94 – 1.90 (m, 1H), 1.93 – 1.82 (m, 1H), 1.73 (s, 1.6H), 1.68 (s, 1.4H), 1.50 – 1.30 (m, 3H), 0.94 – 0.89 (m, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.9, 178.5, 145.6, 144.2, 128.7, 128.7, 127.7, 127.6, 124.4, 124.0, 84.8, 84.7, 43.2, 42.2, 40.4, 40.0, 32.8, 32.3, 30.6, 29.1, 20.7 (2C), 14.0, 13.9; **ATR-IR** ν 2960 (w), 2959 (w), 2930 (w), 2930 (w), 2872 (w), 1767 (s), 1447 (w), 1230 (m), 1215 (m), 956 (m), 767 (m), 701 (s); **HRMS (ESI)** calcd for $C_{14}H_{19}O_2^+$ $[M+H]^+$ 219.1380; found 219.1386.

3-(Methoxymethyl)-5-methyl-5-phenyldihydrofuran-2(3H)-one (**2.240x**)

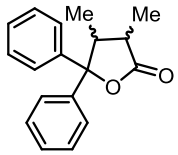



Yield: 15.1 mg (68%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.27 (m, 5H), 3.71 – 3.52 (m, 2H), 3.37 (s, 1.6H), 3.31 (s, 1.4H), 3.21 – 3.05 (m, 0.53H), 2.77 – 2.58 (m, 1.47H), 2.51 – 2.30 (m,

1H), 1.75 (s, 1.6H), 1.69 (s, 1.4H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 176.7, 176.1, 145.2, 144.3, 128.8, 128.7, 127.8, 127.7, 124.4, 124.2, 85.3, 85.2, 70.9, 70.4, 59.3, 59.2, 41.8, 41.6, 40.1, 39.4, 30.3, 29.2;

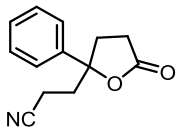
**ATR-IR** ν 2930 (w), 2929 (w), 2928 (w), 2927 (w), 2926 (w), 2894 (w), 2893 (w), 2885 (w), 1771 (s), 1225 (w), 1128 (m), 1037 (w), 1037 (w), 953 (w), 770 (w), 704 (m); **HRMS (ESI)** calcd for $C_{13}H_{16}NaO_3^+$ $[M+Na]^+$ 243.0992; found 243.0993.

3,4-Dimethyl-5,5-diphenyldihydrofuran-2(3H)-one (**2.240y**)



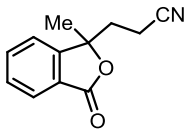

Yield: 12.6 mg (47%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.59 – 7.54 (m, 0.3H), 7.48 – 7.43 (m, 1.7H), 7.41 – 7.27 (m, 6.3H), 7.14 – 7.01 (m, 1.7H), 3.38 (p, *J* = 7.0 Hz, 0.15H), 2.93 (dq, *J* = 11.8, 6.8 Hz, 0.85H), 2.81 (p, *J* = 7.2 Hz, 0.15H), 2.37 (dq, *J* = 11.9, 7.0 Hz, 0.85H), 1.27 (d, *J* = 7.0 Hz, 2.55H), 1.17 (d, *J* = 7.2 Hz, 0.45H), 1.06 (d, *J* = 6.8 Hz, 2.55H), 0.72 (d, *J* = 7.1 Hz, 0.45H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.7, 178.3, 143.2, 142.9, 141.3, 140.2, 128.8, 128.6, 128.5, 128.4, 128.1, 128.0, 127.8, 127.3, 127.0, 126.8, 125.8, 125.3, 90.6, 90.5, 46.2, 42.5, 41.1, 40.3, 16.2, 13.2, 11.8, 10.4; **ATR-IR** ν 2971 (w), 2933 (w), 1772 (s), 1448 (w), 1230 (m), 1194 (m), 1181 (m), 978 (m), 765 (m), 742 (m), 699 (s); **HRMS (ESI)** calcd for $C_{18}H_{19}O_2^+$ $[M+H]^+$ 267.1380; found 267.1378.

3-(5-Oxo-2-phenyltetrahydrofuran-2-yl)propanenitrile (**2.249**)



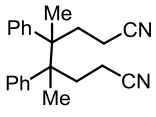

Yield: 12.0 mg (55%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.44– 7.30 (m, 5H), 2.67 – 2.55 (m, 1H), 2.55 – 2.28 (m, 6H), 2.10 – 1.95 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.6, 140.4, 129.3, 128.7, 124.6, 118.9, 87.3, 38.1, 35.8, 28.3, 12.6; **ATR-IR** ν 2927 (w), 2878 (w), 1777 (s), 1448 (w), 1194 (m), 1176 (m), 1088 (m), 1055 (m), 942 (m), 767 (w), 704 (m); **HRMS (ESI)** calcd for $C_{13}H_{13}NNaO_2^+$ $[M+Na]^+$ 238.0838; found 238.0844.

3-(1-Methyl-3-oxo-1,3-dihydroisobenzofuran-1-yl)propanenitrile (**2.251**)



Yield: 15.9 mg (79%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.90 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.73 (td, *J* = 7.5, 1.1 Hz, 1H), 7.58 (td, *J* = 7.5, 0.9 Hz, 1H), 7.42 (dt, *J* = 7.7, 0.9 Hz, 1H), 2.49 (ddd, *J* = 14.0, 9.9, 5.3 Hz, 1H), 2.37 (ddd, *J* = 16.3, 9.7, 5.3 Hz, 1H), 2.25 (ddd, *J* = 13.9, 9.7, 5.3 Hz, 1H), 2.04 (ddd, *J* = 16.3, 9.9, 5.3 Hz, 1H), 1.70 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 169.2, 151.7, 135.0, 130.0, 126.4, 125.8, 121.1, 118.6, 85.5, 35.4, 26.1, 12.2; **ATR-IR** ν 2975 (w), 2922 (w), 2852 (w), 1759 (s), 1249 (m), 1140 (m), 1076 (s), 765 (s), 728 (s), 692 (s); **HRMS (ESI)** calcd for $C_{12}H_{12}NO_2^+$ $[M+H]^+$ 202.0863; found 202.0871.

4,5-Dimethyl-4,5-diphenyloctanedinitrile (**2.246**)

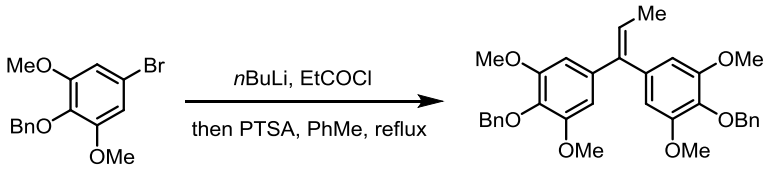


dr ~ 1/1

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.20 (m, 6H), 6.95 – 6.92 (m, 4H), 2.66 – 2.52 (m, 1H), 2.43 – 2.27 (m, 1H), 2.08 – 1.77 (m, 6H), 1.31 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.5, 140.3, 129.2 (2C), 127.9 (2C), 127.1, 127.0, 120.4 (2C), 47.9, 47.7, 32.2, 32.0, 21.6, 21.1, 13.2, 13.1; **ATR-IR** ν 2980 (w), 2957 (w), 2924 (w), 2851 (w), 2245 (w), 1444 (w), 1383 (w), 1068 (w), 1031 (w), 790 (m), 766 (w), 706 (s); **HRMS (ESI)** calcd for $C_{22}H_{24}N_2Na^+$ $[M+Na]^+$ 339.1832; found 339.1830.

### 3.5.2. Total synthesis of (±)-Sacidumlignan D (2.253)

**Synthesis of 5,5'-(prop-1-ene-1,1-diyl)bis(2-(benzyloxy)-1,3-dimethoxybenzene) (2.255)**



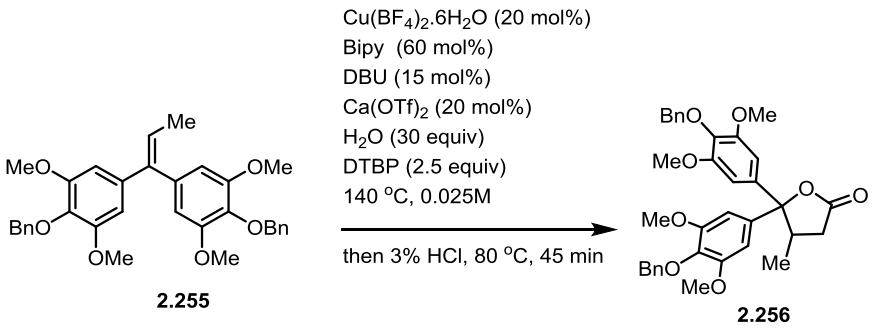

**2.254** **2.255**

To a solution of **2.254**[177d] (0.5 mmol, 162 mg) in THF (10 mL) was added dropwise a solution of *n*-BuLi in hexane (0.5 mmol, 0.22 mL, 2.3 M) at – 78 °C. The reaction mixture was stirred at this temperature for another 1 h followed by the addition of propionyl chloride (0.2 mmol, 18.5 mg). The resulting mixture was stirred at – 78 °C for additional 30 min, warmed up to room temperature and heated to 60 °C for 2 h. After quenching with aqueous saturated $NH_4Cl$, the reaction mixture was extracted with ethyl acetate, the combined organic phases were dried over $MgSO_4$, filtered and

concentrated in *vacuo*. The crude tertiary alcohol product was dissolved in toluene (5 mL) followed by addition of PTSA (0.02 mmol, 38 mg). The mixture was heated to reflux for 4 h, then cooled down to room temperature, evaporated. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/10 to 1/8) afforded desired product **2.255** as yellow oil (60 mg, 56% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.48 (m, 4H), 7.38 – 7.28 (m, 6H), 6.45 (s, 2H), 6.39 (s, 2H), 6.13 (q, *J* = 7.0 Hz, 1H), 5.10 (s, 2H), 5.02 (s, 2H), 3.78 (s, 6H), 3.75 (s, 6H), 1.79 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 153.4, 153.2, 142.5, 138.5, 138.0, 138.0, 135.5, 128.6, 128.5, 128.2, 128.1, 127.9, 127.8, 123.6, 107.3, 104.7, 75.2, 75.0, 56.3, 56.2, 16.0; **ATR-IR** ν 2935 (w), 2858 (w), 2837 (w), 1579 (m), 1502 (m), 1454 (m), 1410 (m), 1235 (m), 1123 (s), 735 (m), 697 (m); **HRMS (ESI)** calcd for $C_{33}H_{34}NaO_6^+$ $[M+Na]^+$ 549.2248; found 549.2241.

**Synthesis of 5,5-bis(4-(benzyloxy)-3,5-dimethoxyphenyl)-4-methyldihydrofuran-2(3H)-one (2.256)**

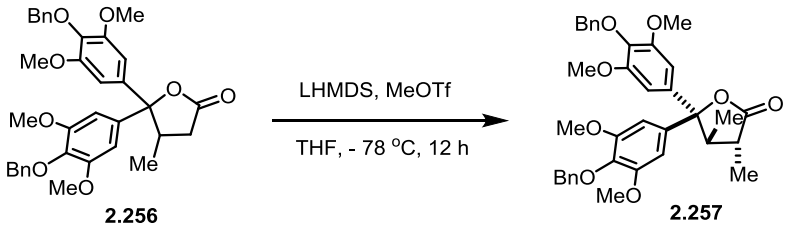



In the glovebox, alkene **2.255** (0.1 mmol, 52.6 mg), $Cu(BF_4)_2.6H_2O$ (0.02 mmol, 7.0 mg), 2,2'-bipyridine (0.06 mmol, 9.6 mg), $Ca(OTf)_2$ (0.02 mmol, 6.8 mg), and DBU (0.015 mmol, 2.3 mg) were dissolved in degassed MeCN (4.0 mL, 0.025 M) in a sealed tube. DTBP (2.5 equiv) and $H_2O$ (30 equiv) were then added and the tube was sealed and heated to 140 °C. After 4 h, the reaction mixture was cooled down to room temperature, and an aqueous HCl solution (1N, 1 mL) was added. After heating at 80 °C for 45 minutes, the reaction mixture was cooled down, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 2/8 to 3/7) to give compound **2.256** as yellow solid (35.0 mg, 60% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.52 – 7.43 (m, 4H), 7.38 – 7.28 (m, 6H), 6.70 (s, 2H), 6.45 (s, 2H), 5.02 (s, 2H), 5.00 (s, 2H), 3.82 (s, 6H), 3.75 (s, 6H), 3.30 (pd, *J* = 6.9, 4.1 Hz, 1H), 2.74 (dd, *J* = 17.1, 7.3 Hz, 1H), 2.33 (dd, *J* = 17.2, 4.2 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 175.9, 153.6, 153.4, 138.4, 137.8, 137.7, 137.1, 136.3, 136.2, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9,

104.1, 103.2, 92.4, 75.1, 75.0, 56.6, 56.5, 38.6, 37.8, 17.3; **ATR-IR** ν 2932 (w), 2872 (w), 2866 (w), 1784 (w), 1776 (w), 1589 (m), 1455 (m), 1414 (m), 1124 (s), 977 (m), 732 (m), 698 (m); **HRMS (ESI)** calcd for $C_{35}H_{37}O_8^+$ $[M+H]^+$ 585.2483; found 585.2473. **Mp**: 42 – 44 °C;

**Synthesis of trans-5,5-bis(4-(benzyloxy)-3,5-dimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3H)-one (2.257)**

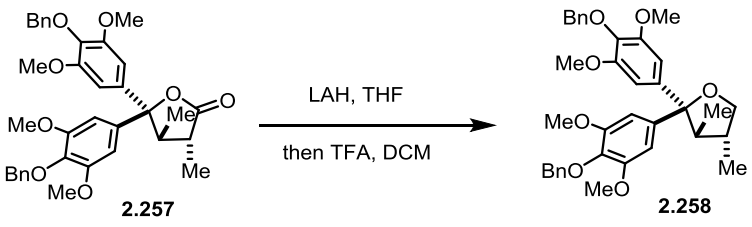


**2.256** **2.257**

To a solution of LHMDS (0.88 mmol, 0.88 mL, 1 M in THF) in THF (1 mL) at – 78 °C was added a solution of **2.256** (0.22 mmol, 130 mg) in THF (3 mL) dropwise *via* syringe and stirring was continued for 1.0 h at this temperature. The resulting enolate was treated with MeOTf (0.66 mmol, 108 mg) at – 78 °C, and the reaction mixture was stirred for 1.0 h at the same temperature. The reaction was quenched with an aqueous $NH_4Cl$ solution. The reaction mixture was allowed to warm to room temperature, extracted with ethyl acetate. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 2/8) to give compound **2.257** as yellow solid (118 mg, 89% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.48 – 7.43 (m, 4H), 7.36 – 7.28 (m, 6H), 6.65 (s, 2H), 6.24 (s, 2H), 5.04 (s, 2H), 5.01 (s, 2H), 3.80 (s, 6H), 3.70 (s, 6H), 2.85 (dq, *J* = 11.4, 6.7 Hz, 1H), 2.40 (dq, *J* = 11.7, 7.0 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 178.6, 153.5, 153.2, 138.6, 137.7, 137.1, 136.5, 135.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 104.8, 104.3, 90.7, 75.1, 74.9, 56.6, 56.3, 46.5, 41.3, 16.4, 13.4; **ATR-IR** ν 2935 (w), 2872 (w), 2865 (w), 2837 (w), 1763 (w), 1753 (w), 1590 (m), 1502 (m), 1455 (m), 1415 (m), 1239 (m), 1121 (s), 735 (m), 728 (m), 698 (s); **HRMS (ESI)** calcd for $C_{36}H_{39}O_8^+$ $[M+H]^+$ 599.2639; found 599.2641.

**Synthesis of trans-2,2-bis(4-(benzyloxy)-3,5-dimethoxyphenyl)-3,4-dimethyltetrahydrofuran (2.258)**

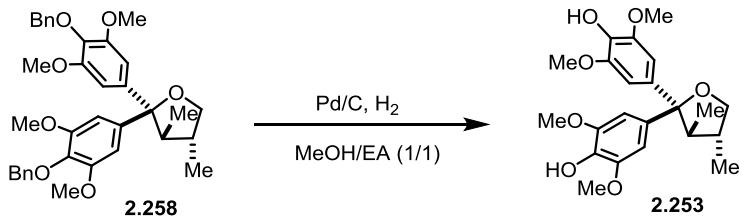


**2.257** **2.258**

To a stirred solution of **2.257** (0.136 mmol, 82 mg) in THF (8.0 mL) at 0 °C was added $LiAlH_4$ (0.41 mmol, 15.6 mg). The reaction mixture was stirred at room temperature for 1.0 h and quenched with a saturated aqueous $NH_4Cl$ solution (15 mL). The resulting precipitate was then filtered through a short plug of Celite and the filtrate was extracted with DCM. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. The resulting diol crude product could be used directly without further purification. To a solution of the above crude diol in DCM (4.0 mL) was added TFA (0.272 mmol, 20 µL) in one portion. After stirring for 20 minutes, the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL) and extracted with DCM. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether 2/8) to give compound **2.258** as colorless oil (72 mg, 91% yield).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.50 – 7.43 (m, 4H), 7.35 – 7.26 (m, 6H), 6.67 (s, 2H), 6.37 (s, 2H), 5.03 (s, 2H), 4.99 (s, 2H), 4.31 (t, *J* = 7.8 Hz, 1H), 3.81 (s, 6H), 3.71 (s, 6H), 3.48 (dd, *J* = 10.5, 8.3 Hz, 1H), 2.48 – 2.29 (m, 1H), 2.09 – 1.93 (m, 1H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 153.1, 152.6, 142.7, 140.6, 138.0, 136.2, 135.6, 128.6, 128.2, 128.1, 127.9, 127.8, 105.1, 104.8, 90.9, 75.1, 75.0, 74.0, 56.5, 56.2, 50.0, 40.9, 15.8, 14.6; **ATR-IR** ν 2958 (w), 2932 (w), 2932 (w), 2835 (w), 1587 (m), 1500 (m), 1454 (m), 1410 (m), 1328 (m), 1236 (m), 1124 (s), 1012 (m), 994 (m), 731 (m), 731 (m), 697 (m); **HRMS (ESI)** calcd for $C_{36}H_{41}O_7^+$ $[M+H]^+$ 585.2847; found 585.2841.

**Synthesis of (±)-Scidumlignan D (2.253)**



**2.258** **2.253**

To a solution of **2.258** (0.072mmol, 42 mg) in a mixture of MeOH and EtOAc (1:1, 0.1 M) was added 10 wt% Pd/C (0.072 mmol, 77 mg) at room temperature. The flask was carefully evacuated and filled back with $H_2$ atmosphere 3 times. The heterogeneous mixture was allowed to stir at room temperature for 24 h. The reaction mixture was filtered directly through a short plug of Celite, washed with EtOAc, and concentrated to afford the crude product. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether 1/2 to 1/1) gave desired product **2.253** as yellow oil (27 mg, 93% yield).

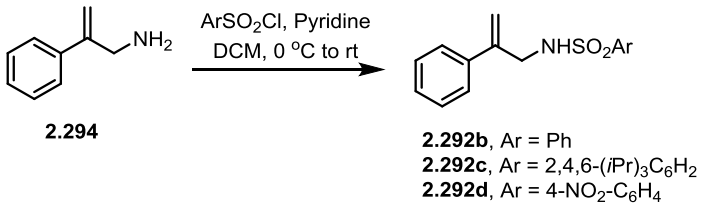
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 6.68 (s, 2H), 6.39 (s, 2H), 5.52 (s, 1H), 5.44 (s, 1H), 4.29 (t, *J* = 7.8 Hz, 1H), 3.86 (s, 6H), 3.79 (s, 6H), 3.45 (dd, *J* = 10.5, 8.2 Hz, 1H), 2.37 (dq, *J* = 10.4, 6.9 Hz, 1H),

2.05 – 1.89 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 146.6, 146.2, 138.3, 136.3, 134.0, 133.5, 104.6, 104.3, 90.9, 73.9, 56.6, 56.4, 49.8, 40.8, 15.9, 14.6; **ATR-IR** ν 3415 (w), 2960 (w), 2960 (w), 2933 (w), 2873 (w), 2838 (w), 1612 (w), 1513 (m), 1453 (m), 1418 (m), 1326 (m), 1211 (s), 1110 (s), 910 (m), 727 (s); **HRMS (ESI)** calcd for $C_{22}H_{29}O_7^+$ $[M+H]^+$ 405.1908; found 405.1905.

## 3.6. Copper-Catalyzed Cyanoalkylative Aziridination of Alkenes

### 3.6.1. Synthesis of starting materials

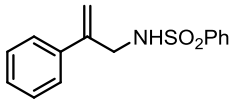
**Synthesis of of 2.292b-d**




To a solution of **2.294**[192] (1.0 mmol) and pyridine (1.5 mmol, 120 mg) in DCM (5.0 mL) was added dropwise a solution of arylsulfonyl chloride (1.3 mmol) in DCM (5.0 mL) at 0ºC. The reaction mixture was warmed up to room temperature and stirred overnight. After quenching with water, the reaction mixture was extracted with DCM. The combined organic layers were washed with 1M HCl, aqueous $NaHCO_3$ and brine, dried over $Na_2SO_4$, filtered and concentrated in *vacuo*. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether) gave desired product **2.292b-d**.

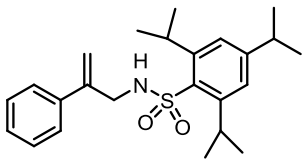
**Characterization data of 2.292b-d**

*N*-(2-phenylallyl)benzenesulfonamide (**2.292b**)[209]




**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.84 – 7.81 (m, 2H), 7.60 – 7.55 (m, 1H), 7.51 – 7.47 (m, 2H), 7.30 – 7.20 (m, 5H), 5.35 (s, 1H), 5.19 (s, 1H), 4.64 (t, *J* = 6.8 Hz, 1H), 4.02 (dd, *J* = 6.1, 1.2 Hz, 1H).

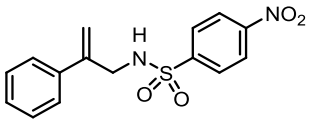
2,4,6-triisopropyl-*N*-(2-phenylallyl)benzenesulfonamide (**2.292c**)




**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.29 – 8.25 (m, 5H), 7.16 (s, 2H), 5.42 (s, 1H), 5.26 (s, 1H), 4.41 (t, *J* = 6.2 Hz, 1H), 4.13 (p, *J* = 6.8 Hz, 2H), 4.05 (dd, *J* = 6.2, 1.1 Hz, 2H), 2.92 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.7 Hz, 12H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 153.0, 150.4, 143.2, 138.0, 132.3, 128.7, 128.3, 126.1, 123.9, 115.5, 46.8, 34.3, 29.9, 25.0, 23.8.

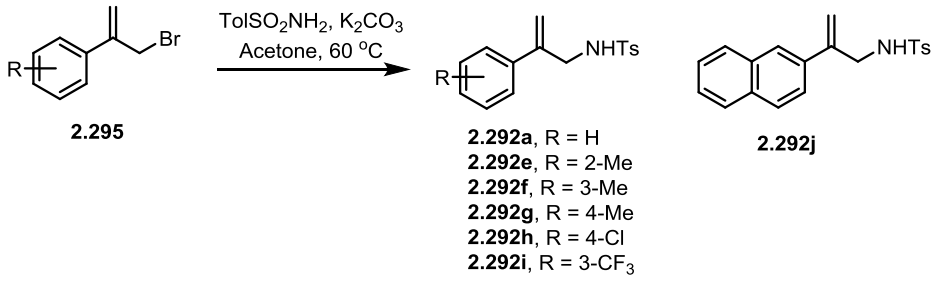
[209] Wei, Y.; Liang, F.; Zhang, X. *Org. Lett.* **2013**, *15*, 5186.

4-nitro-*N*-(2-phenylallyl)benzenesulfonamide (**2.292d**)



**$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.37 – 8.21 (m, 2H), 7.98 – 7.80 (m, 2H), 7.32 – 7.21 (m, 3H), 7.20 – 7.14 (m, 2H), 5.35 (s, 1H), 5.19 (s, 1H), 4.86 (t, *J* = 6.1 Hz, 1H), 4.12 (dd, *J* = 6.0, 1.1 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 150.1, 146.0, 142.6, 137.5, 128.8, 128.6, 128.5, 126.1, 124.4, 116.0, 47.4.

**Synthesis of of 2.292a and 2.292e-j**




**2.295**

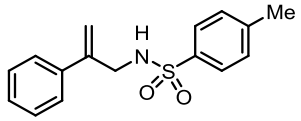
**2.292a**, R = H
**2.292e**, R = 2-Me
**2.292f**, R = 3-Me
**2.292g**, R = 4-Me
**2.292h**, R = 4-Cl
**2.292i**, R = 3-$CF_3$

**2.292j**

To a suspension of $TsNH_2$ (2.0 equiv) and $K_2CO_3$ (2.5 equiv) in acetone (5-10 mL) was added allylbromide **2.295** (0.5-1.0 mmol) at room temperature. The reaction mixture was heated to 60 °C and stirred for 24 h. The reaction mixture was then cooled down to room temperature, filtered through a short plug of silica gel, washed with EtOAc and concentrated to afford the crude product. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether) afforded desired product **2.292a** and **2.292e-j**.

**Characterization data of 2.292a and 2.292e-j**

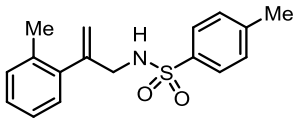
4-methyl-*N*-(2-phenylallyl)benzenesulfonamide (**2.292a**)[210]



**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.83 – 7.62 (m, 2H), 7.34 – 7.07 (m, 7H), 5.36 (s, 1H), 5.19 (s, 1H), 4.62 – 4.57 (m, 1H), 3.98 (d, *J* = 6.2 Hz, 2H), 2.43 (s, 3H).

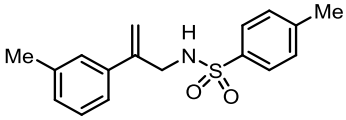
4-methyl-*N*-(2-(*o*-tolyl)allyl)benzenesulfonamide (**2.292e**)

[210] Kiyokawa, K.; Kojima, T.; Hishikawa, Y.; Minakata, S. *Chem. Eur. J.* **2015**, *21*, 15548.



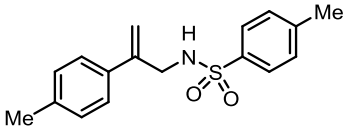
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.55 (m, 2H), 7.23 – 7.20 (m, 2H), 7.14 – 7.03 (m, 3H), 6.91 (dd, *J* = 7.6, 1.4 Hz, 1H), 5.37 (q, *J* = 1.5 Hz, 1H), 5.06 (t, *J* = 6.3 Hz, 1H), 4.95 (q, *J* = 1.2 Hz, 1H), 3.75 (dt, *J* = 6.4, 1.5 Hz, 2H), 2.38 (s, 3H), 2.14 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.5, 143.4, 139.4, 136.9, 135.3, 130.3, 129.7, 128.6, 127.7, 127.2, 127.1, 125.7, 115.9, 48.2, 21.6, 19.7; **ATR-IR** ν 3285 (w), 2987 (m), 2972 (m), 2901 (m), 1408 (m), 1395 (m), 1324 (m), 1156 (s), 1066 (s), 1059 (s); **HRMS (ESI)** calcd for $C_{17}H_{20}NO_2S^+$ $[M+H]^+$ 302.1209; found 302.1217.

4-methyl-*N*-(2-(*m*-tolyl)allyl)benzenesulfonamide (**2.292f**)



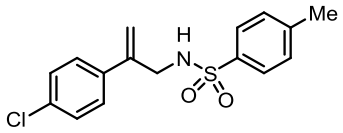
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.84 – 6.69 (m, 3H), 5.07 (s, 1H), 4.93 (s, 1H), 4.70 (t, *J* = 6.2 Hz, 1H), 3.71 (d, *J* = 6.2 Hz, 2H), 2.16 (s, 3H), 2.03 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.4, 143.0, 138.1, 183.0, 136.8, 129.7, 128.9, 128.4, 127.3, 126.8, 123.2, 114.9, 47.0, 21.6, 21.5; **ATR-IR** ν 3269 (w), 2987 (m), 2972 (m), 2909 (m), 2901 (m), 1155 (m), 1090 (m), 1066 (s); **HRMS (ESI)** calcd for $C_{17}H_{20}NO_2S^+$ $[M+H]^+$ 302.1209; found 302.1211.

4-methyl-*N*-(2-(*p*-tolyl)allyl)benzenesulfonamide (**2.292g**)



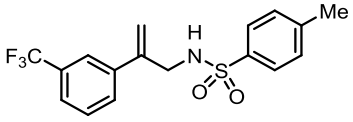
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.77 – 7.67 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.17 – 7.01 (m, 4H), 5.33 (s, 1H), 5.14 (q, *J* = 1.1 Hz, 1H), 4.48 (t, *J* = 6.2 Hz, 1H), 4.00 – 3.95 (m, 2H), 2.44 (s, 3H), 2.33 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.6, 142.7, 138.2, 136.9, 135.0, 129.8, 129.4, 127.4, 126.1, 114.5, 47.2, 21.7, 21.3; **HRMS (ESI)** calcd for $C_{17}H_{20}NO_2S^+$ $[M+H]^+$ 302.1209; found 302.1215.

*N*-(2-(4-chlorophenyl)allyl)-4-methylbenzenesulfonamide (**2.292h**)



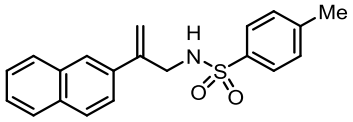
**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.62 (dd, *J* = 8.2, 1.8 Hz, 2H), 7.28 – 6.96 (m, 6H), 5.33 (s, 1H), 5.14 (q, *J* = 1.1 Hz, 1H), 5.29 (d, *J* = 1.8 Hz, 1H), 5.15 (s, 1H), 4.61 (t, *J* = 6.4 Hz, 1H), 3.88 (d, *J* = 6.3 Hz, 2H), 2.37 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.7, 142.0, 136.8, 136.4, 134.1, 129.8, 128.8, 127.5, 127.3, 116.0, 47.1, 21.7; **ATR-IR** ν 3249 (w), 2923 (w), 2853 (w), 1493 (w), 1427 (w), 1332 (m), 1319 (m), 1160 (s), 834 (s), 814 (s); **HRMS (ESI)** calcd for $C_{16}H_{17}ClNO_2S^+$ $[M+H]^+$ 322.0663; found 322.0672.

4-methyl-*N*-(2-(3-(trifluoromethyl)phenyl)allyl)benzenesulfonamide (**2.292i**)



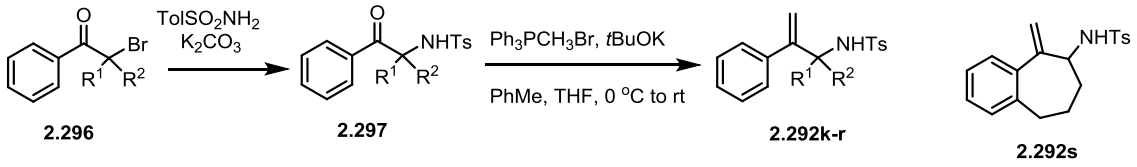
**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.58 (m, 2H), 7.49 – 7.43 (m, 1H), 7.42 – 7.29 (m, 3H), 7.25 – 7.14 (m, 2H), 5.36 (s, 1H), 5.25 (d, *J* = 1.4 Hz, 1H), 4.56 (t, *J* = 6.3 Hz, 1H), 3.95 (d, *J* = 6.4 Hz, 2H), 2.36 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.9, 142.0, 138.9, 136.8, 131.1 (q, *J* = 32.3 Hz), 129.9, 129.5, 129.2, 127.3, 125.0 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.7 Hz), 123.1 (q, *J* = 3.9 Hz), 117.2, 47.1, 21.7.

4-methyl-*N*-(2-(naphthalen-2-yl)allyl)benzenesulfonamide (**2.292j**)



**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.79 (m, 2H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.52 – 7.31 (m, 3H), 7.17 – 7.15 (m, 3H), 5.64 (s, 1H), 5.21 (s, 1H), 5.03 (t, *J* = 6.3 Hz, 1H), 3.98 (d, *J* = 6.4 Hz, 2H), 2.38 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.4, 143.3, 137.6, 136.8, 133.7, 131.2, 129.6, 128.4, 128.1, 127.1, 126.3, 125.9, 125.8, 125.3, 125.1, 117.6, 49.0, 21.6; **ATR-IR** ν 3284 (w), 2922 (w), 1324 (m), 1156 (s), 1092 (m), 804 (s), 779 (s); **HRMS (ESI)** calcd for $C_{20}H_{20}NO_2S^+$ $[M+H]^+$ 338.1209; found 338.1217.

**Synthesis of 2.292k-s**

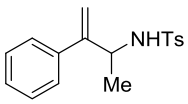



**Step 1:** To a suspension of $TsNH_2$ (2.0 equiv) and $K_2CO_3$ (2.5 equiv) in acetone (5-10 mL) was added α-bromide acetophenone **2.296** (0.5-1.0 mmol) at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 24 h. The reaction mixture was then filtered through a short plug of silica gel, washed with EtOAc and concentrated to afford the crude product. Purification by flash column chromatography on silica gel (ethyl acetate/petroleum ether) afforded **2.297**.

**Step 2:** To a suspension of methyltriphenylphosphonium bromide (4.0 equiv) in PhMe (5-10 mL) was added potionwise tBuOK (4.0 equiv) at 0 ºC. The reaction mixture was warmed up to room temperature and stirred for 1 h. To the resulting yellow mixture was added dropwise a solution of **2.297** (0.5-1.0 mmol) in THF (5-10 mL) at 0 ºC. The suspension was stirred at room temperature for 12-24 h then diluted with an aliquot amount of EtOAc and filtered through a short plug of silica gel. The solvent was removed and the crude product was purified by flash chromatography on silica gel to yield **2.292k-s**.

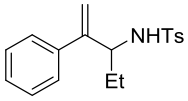
**Characterization data of 2.292k-s**

4-methyl-*N*-(3-phenylbut-3-en-2-yl)benzenesulfonamide (**2.292k**)



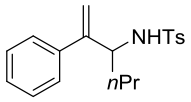

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.75 – 7.66 (m, 2H), 7.28 – 7.20 (m, 5H), 7.17 – 7.12 (m, 2H), 5.23 – 5.18 (m, 1H), 5.15 (s, 1H), 4.93 – 4.85 (m, 1H), 4.45 – 4.33 (m, 2H), 2.41 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 150.0, 143.3, 139.8, 137.8, 129.7, 128.4, 127.8, 127.2, 126.9, 113.8, 52.8, 22.2, 21.6; **ATR-IR** ν 3275 (w), 2979 (w), 1322 (m), 1159 (s), 1088 (m), 666 (s).

4-methyl-*N*-(2-phenylpent-1-en-3-yl)benzenesulfonamide (**2.292l**)



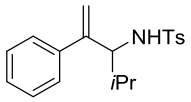

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.78 (m, 2H), 7.34 – 7.15 (m, 7H), 5.64 (d, *J* = 8.4 Hz, 1H), 5.19 (s, 1H), 5.17 (s, 1H), 4.35 – 4.22 (m, 1H), 2.41 (s, 3H), 1.71 – 1.59 (m, 1H), 1.60 – 1.50 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 148.6, 143.1, 140.2, 138.1, 129.5, 128.3, 127.6, 127.2, 126.8 114.3, 58.8, 28.4, 21.5, 10.0; **ATR-IR** ν 3281 (w), 2969 (w), 1160 (s), 907 (s), 730 (s), 667 (s).

4-methyl-*N*-(2-phenylhex-1-en-3-yl)benzenesulfonamide (**2.292m**)



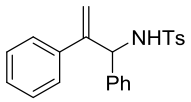

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.70 – 7.54 (m, 2H), 7.22 – 7.11 (m, 5H), 7.09 – 6.96 (m, 2H), 5.02 (s, 1H), 4.99 (s, 1H), 4.69 (d, *J* = 8.3 Hz, 1H), 4.20 (q, *J* = 7.8 Hz, 1H), 2.32 (s, 3H), 1.57 – 1.09 (m, 4H), 0.72 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 149.1, 143.3, 140.0, 138.1, 129.6, 128.5, 127.8, 127.3, 127.0, 114.3, 57.5, 38.0, 21.6, 19.0, 13.7; **ATR-IR** ν 3287 (w), 2959 (w), 2930 (w), 2873 (w), 1322 (m), 1161 (s), 667 (s).

4-methyl-*N*-(4-methyl-2-phenylpent-1-en-3-yl)benzenesulfonamide (**2.292n**)



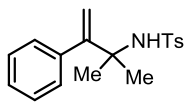

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.79 (dd, *J* = 8.1, 1.7 Hz, 2H), 7.37 – 7.02 (m, 7H), 5.12 (s, 1H), 5.12 – 5.02 (m, 1H), 5.02 (s, 1H), 4.21 (dd, *J* = 9.3, 5.3 Hz, 1H), 2.41 (s, 3H), 1.77 (h, *J* = 6.6 Hz, 1H), 0.91 (dd, *J* = 6.7, 1.6 Hz, 3H), 0.82 (dd, *J* = 6.8, 1.6 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 148.1, 143.2, 140.6, 138.2, 129.5, 128.5, 127.8, 127.3, 127.0, 126.9, 114.6, 62.8, 31.0, 21.6, 20.1, 16.7.

*N*-(1,2-diphenylallyl)-4-methylbenzenesulfonamide (**2.292o**)



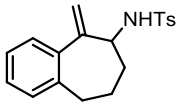

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.51 (m, 2H), 7.31 – 6.95 (m, 12H), 5.49 (d, *J* = 7.9 Hz, 1H), 5.39 (s, 1H), 5.22 – 5.07 (m, 2H), 2.40 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 147.2, 143.2, 139.1, 138.8, 137.5, 129.4, 128.6, 128.4, 127.9, 127.7, 127.4, 127.3, 126.9, 116.5, 60.9, 21.5.

4-methyl-*N*-(2-methyl-3-phenylbut-3-en-2-yl)benzenesulfonamide (**2.292p**)



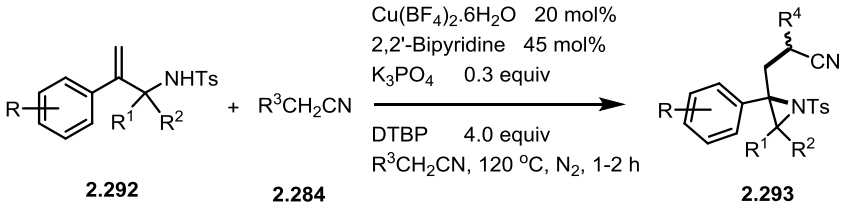

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.73 – 7.55 (m, 2H), 7.33 – 6.94 (m, 7H), 5.33 (d, *J* = 0.9 Hz, 1H), 4.92 (d, *J* = 0.8 Hz, 1H), 4.75 (s, 1H), 2.32 (s, 3H), 1.29 (s, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 154.5, 142.8, 140.8, 140.4, 129.4, 129.2, 127.8, 127.2, 127.0, 114.9, 59.3, 27.9, 21.5.

4-methyl-N-(5-methylene-6,7,8,9-tetrahydro-5H-benzo[7]annulen-6-yl)benzenesulfonamide (**2.292q**)




**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.73 – 7.62 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.17 (td, *J* = 7.7, 7.3, 1.4 Hz, 1H), 7.08 – 7.04 (m, 2H), 6.62 – 6.47 (m, 1H), 5.03 (s, 1H), 4.80 (d, *J* = 1.4 Hz, 1H), 4.42 (d, *J* = 8.9 Hz, 1H), 4.28 – 4.25 (m, 1H), 2.75 – 2.58 (m, 2H), 2.46 (s, 3H), 2.17 – 2.06 (m, 1H), 1.96 – 1.60 (m, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 150.6, 143.4, 140.2, 139.0, 138.0, 130.1, 129.6, 129.2, 128.3, 127.4, 126.6, 115.2, 57.3, 38.5, 36.1, 22.4, 21.7; **ATR-IR** ν 3280 (w), 2927 (w), 2854 (w), 1329 (m), 1329 (m), 1159 (s), 1093 (m); **HRMS (ESI)** calcd for $C_{19}H_{22}NO_2S^+$ $[M+H]^+$ 328.1366; found 328.1374.

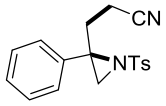
### 3.6.2. Substrate scope




In the glovebox, alkene **2.292** (0.1 mmol, 1 equiv), $Cu(BF_4)_2.6H_2O$ (20 mol%), 2,2'-bipyridine (45 mol%), and $K_3PO_4$ (30 mol%) were dissolved in degassed $R^4CH_2CN$ (v/v 7/3, 0.067 M) in a sealed tube. DTBP (4 equiv) was then added and the tube was sealed and heated to 120 °C. After 1-2 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.293**.

#### Characterization data of 2.293

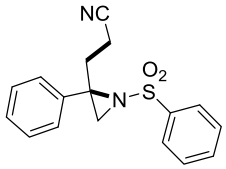
3-(2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293a**)




Yield: 27.4 mg (84%), colourless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.87 – 7.67 (m, 2H), 7.46 – 7.29 (m, 7H), 3.00 (s, 1H), 2.81 – 2.70 (m, 2H), 2.68 – 2.54 (m, 2H), 2.43 (s, 3H), 2.27 – 2.14 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.6, 137.0, 136.6, 129.8, 129.0, 128.9, 128.0, 127.7, 118.8, 54.2, 40.4,

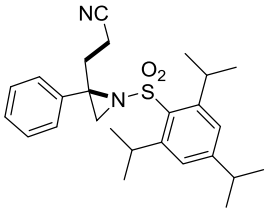
31.4, 21.8, 14.9; **ATR-IR** ν 2927 (w), 2249 (w), 1449 (w), 1321 (m), 1159 (s), 700 (s); **HRMS (ESI)** calcd for $C_{18}H_{19}N_2O_2S^+$ $[M+H]^+$ 327.1162; found 327.1162.

3-(2-phenyl-1-(phenylsulfonyl)aziridin-2-yl)propanenitrile (**2.293b**)



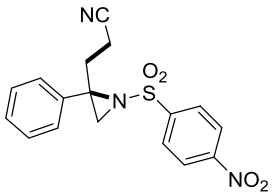

Yield: 22.4 mg (72%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.00 – 7.89 (m, 2H), 7.67 – 7.59 (m, 1H), 7.53 (td, *J* = 7.6, 1.5 Hz, 2H), 7.47 – 7.30 (m, 5H), 3.03 (s, *1*H), 2.79 – 2.74 (m, 2H), 2.68 – 2.59 (m, 2H), 2.25 – 2.20 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.9, 136.4, 133.6, 129.2, 129.0 (2C), 128.0, 127.7, 118.8, 54.4, 40.5, 31.5, 14.9; **ATR-IR** ν 2987 (w), 2969 (w), 2249 (w), 1448 (m), 1322 (m), 1322 (m), 1311 (m), 1161 (s), 740 (s), 688 (s); **HRMS (ESI)** calcd for $C_{17}H_{16}N_2NaO_2S^+$ $[M+Na]^+$ 335.0825; found 335.0831.

3-(2-phenyl-1-((2,4,6-triisopropylphenyl)sulfonyl)aziridin-2-yl)propanenitrile (**2.293c**)



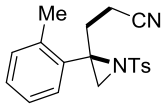

Yield: 28.0 mg (64%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.46 – 7.43 (m, 2H), 7.42 – 7.31 (m, 3H), 7.17 (s, 2H), 4.36 (p, *J* = 6.8 Hz, 2H), 3.09 (s, 1H), 2.95 – 2.75 (m, 3H), 2.72 – 2.54 (m, 2H), 2.35 – 2.06 (m, 1H), 1.28 (d, *J* = 6.7 Hz, 6H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.7 Hz, 6H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 153.6, 150.9, 137.0, 133.4, 128.9, 128.8, 127.9, 123.9, 118.9, 54.3, 40.6, 34.4, 31.2, 29.9, 25.0, 24.9, 23.7, 15.1; **ATR-IR** ν 2960 (w), 2925 (w), 2867 (w), 2246 (w), 1602 (w), 1313 (m), 1164 (m), 1155 (m), 776 (s), 702 (s); **HRMS (ESI)** calcd for $C_{26}H_{34}N_2NaO_2S^+$ $[M+Na]^+$ 461.2233; found 461.2231.

3-(1-((4-nitrophenyl)sulfonyl)-2-phenylaziridin-2-yl)propanenitrile (**2.293d**)



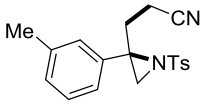

Yield: 22.4 mg (45%), colourless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.42 – 8.34 (m, 2H), 8.21 – 7.87 (m, 2H), 7.49 – 7.37 (m, 5H), 3.10 (s, 1H), 2.87 (s, 1H), 2.82 – 2.71 (m, 1H), 2.66 – 2.56 (m, 2H), 2.26 – 2.20 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 150.6, 145.3, 135.7, 129.4, 129.2, 129.1, 128.0, 124.4, 118.5, 55.3, 41.1, 31.9, 14.9; **ATR-IR** ν 2971 (w), 2250 (w), 1529 (s), 1349 (s), 1308 (m), 1164 (s), 1090 (m), 744 (s), 688 (s); **HRMS (ESI)** calcd for $C_{17}H_{15}N_3NaO_4S^+$ $[M+Na]^+$ 380.0675; found 380.0673.

3-(2-(*o*-tolyl)-1-tosylaziridin-2-yl)propanenitrile (**2.293e**)



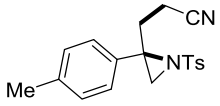

Yield: 22.1 mg (65%), colourless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.80 – 7.74 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.18 (m, 1H), 7.17 – 7.15 (m, 2H), 7.12 – 7.06 (m, 1H), 2.94 (s, 1H), 2.72 – 2.66 (m, 2H), 2.61 – 2.52 (m, 2H), 2.39 (s, 3H), 2.31 (s, 3H), 2.20 – 2.11 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.5, 138.8, 136.9, 136.4, 129.7, 129.7, 128.8, 128.6, 127.7, 125.1, 118.9, 54.2, 40.3, 31.3, 21.8, 21.6, 14.9; **ATR-IR** ν 2923 (w), 2770 (w), 2249 (w), 1322 (m), 1158 (s), 1092 (m), 702 (s); **HRMS (ESI)** calcd for $C_{19}H_{21}N_2O_2S^+$ $[M+H]^+$ 341.1318; found 341.1329.

3-(2-(*m*-tolyl)-1-tosylaziridin-2-yl)propanenitrile (**2.293f**)



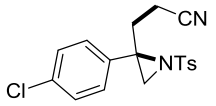

Yield: 26.9 mg (79%), colourless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.27 – 7.14 (m, 4H), 3.13 (s, 1H), 2.83 – 2.61 (m, 3H), 2.58 (s, 1H), 2.50 (s, 3H), 2.42 (s, 3H), 2.32 – 2.12 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.6, 137.2, 135.0, 131.4, 129.8, 129.6, 128.9, 127.6, 126.1, 118.9, 54.6, 41.3, 29.8, 21.7, 19.1, 15.2; **HRMS (ESI)** calcd for $C_{19}H_{21}N_2O_2S^+$ $[M+H]^+$ 341.1318; found 341.1320.

3-(2-(*p*-tolyl)-1-tosylaziridin-2-yl)propanenitrile (**2.293f**)



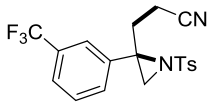

Yield: 14.6 mg (43%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.79 (m, 2H), 7.33 – 7.28 (m, 4H), 7.19 – 7.17 (m, 2H), 2.96 (s, 1H), 2.81 – 2.66 (m, 2H), 2.65 – 2.50 (m, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 2.27 – 2.08 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.5, 138.9, 137.1, 133.4, 129.7, 129.6, 128.0, 127.8, 118.8, 54.1, 40.3, 31.6, 21.8, 21.3, 14.8; **HRMS (ESI)** calcd for $C_{19}H_{21}N_2O_2S^+$ $[M+H]^+$ 341.1318; found 341.1324.

3-(2-(4-chlorophenyl)-1-tosylaziridin-2-yl)propanenitrile (**2.293g**)



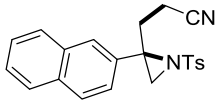

Yield: 25.9 mg (72%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.86 – 7.69 (m, 2H), 7.42 – 7.28 (m, 6H), 2.98 (s, 1H), 2.77 – 2.68 (m, 2H), 2.68 – 2.53 (m, 2H), 2.44 (s, 3H), 2.24 – 2.17 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.8, 136.8, 135.0 (2C), 129.8, 129.5, 129.2, 127.8, 118.6, 53.4, 40.3, 31.3, 21.8, 14.8; **ATR-IR** ν 2924 (w), 2248 (w), 1494 (w), 1322 (m), 1159 (s), 1089 (m), 816 (s), 711 (s); **HRMS (ESI)** calcd for $C_{18}H_{18}ClN_2O_2S^+$ $[M+H]^+$ 361.0772; found 361.0769.

3-(1-tosyl-2-(3-(trifluoromethyl)phenyl)aziridin-2-yl)propanenitrile (**2.293h**)



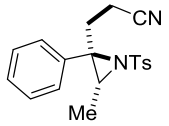

Yield: 31.1 mg (79%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.86 – 7.79 (m, 2H), 7.69 – 7.58 (m, 3H), 7.53 – 7.51 (m, 1H), 7.39 – 7.30 (m, 2H), 3.04 (s, 1H), 2.80 – 2.59 (m, 4H), 2.44 (s, 3H), 2.29 – 2.09 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.9, 137.8, 136.6, 131.54, 131.5 (q, $J$ = 32.5 Hz), 129.9, 129.6, 127.8, 125.9 (q, $J$ = 3.7 Hz), 124.8 (q, $J$ = 3.8 Hz), 123.8 (q, $J$ = 272.4 Hz), 118.4, 53.4, 40.2, 31.0, 21.8, 14.8; **ATR-IR** ν 2926 (w), 1324 (s), 1160 (s), 1124 (s), 1096 (s), 1072 (s), 703 (s); **HRMS (ESI)** calcd for $C_{19}H_{18}F_3N_2O_2S^+$ $[M+H]^+$ 395.1036; found 395.1040.

3-(2-(naphthalen-2-yl)-1-tosylaziridin-2-yl)propanenitrile (**2.293i**)



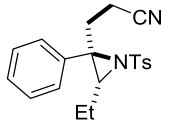
Yield: 29.7 mg (79%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.94 – 7.83 (m, 5H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 3.33 (s, 1H), 3.10 – 2.96 (m, 1H), 2.90 – 2.57 (m, 3H), 2.41 (s, 3H), 2.17 – 2.00 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.6, 137.2, 134.1, 132.8, 129.9, 129.8, 129.2, 127.7, 127.2, 126.4, 125.0, 118.8, 54.2, 41.2, 30.2, 21.7, 15.7; **HRMS (ESI)** calcd for $C_{22}H_{21}N_2O_2S^+$ $[M+H]^+$ 377.1318; found 377.1325.

3-(3-methyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293k**)



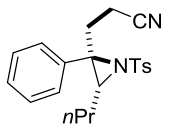

Yield: 30.4 mg (84%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.79 – 7.56 (m, 2H), 7.53 – 7.45 (m, 2H), 7.42 – 7.35 (m, 3H), 7.33 – 7.19 (m, 2H), 3.48 (q, *J* = 5.9 Hz, 1H), 2.58 – 2.48 (m, 1H), 2.43 (s, 3H), 2.35 – 2.26 (m, 1H), 2.14 – 1.98 (m, 2H), 1.39 (d, *J* = 6.0 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.1, 137.0, 134.4, 129.6, 129.5, 129.3, 128.8, 127.6, 118.7, 57.8, 45.6, 30.7, 21.7, 13.8, 13.0; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s), 1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{19}H_{20}N_2NaO_2S^+$ $[M+Na]^+$ 363.1138; found 363.1136.

3-(3-ethyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293l**)




Yield: 27.6 mg (78%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.54 (m, 2H), 7.41 – 7.37 (m, 2H), 7.33 – 7.26 (m, 3H), 7.23 – 7.11 (m, 2H), 3.20 (dd, *J* = 8.8, 4.7 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.34 (s, 3H), 2.25 – 2.15 (m, 1H), 2.09 – 1.92 (m, 2H), 1.88 – 1.72 (m, 1H), 0.76 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.2, 136.5, 134.5, 129.6, 129.5, 129.3, 128.7, 128.2, 118.7, 58.1, 51.9, 31.4, 21.7, 21.1, 13.9, 11.9; **ATR-IR** ν 2968 (w), 2248 (w), 1461 (w), 1321 (s), 1154 (s), 996 (m), 926 (s); **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O_2S^+$ $[M+H]^+$ 355.1475; found 355.1483.

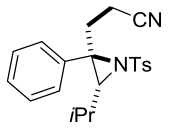
3-(2-phenyl-3-propyl-1-tosylaziridin-2-yl)propanenitrile (**2.293m**)



Yield: 29.8 mg (81%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.70 – 7.58 (m, 2H), 7.46 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.43 – 7.34 (m, 3H), 7.29 – 7.17 (m, 2H), 3.33 (dd, *J* = 8.6, 4.7 Hz, 1H), 2.57 – 2.48 (m, 1H), 2.42 (s, 3H), 2.34 – 2.24 (m, 1H), 2.19 – 2.02 (m, 2H), 1.82 – 1.77 (m, 1H), 1.47 – 1.39 (m, 1H), 1.31 – 1.15 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.2, 136.4, 134.4, 129.6, 129.4, 129.3, 128.7, 128.1, 118.7, 57.9, 50.2, 31.4, 29.7, 21.7, 20.9, 14.0, 13.9; **ATR-IR** ν 2960 (w), 2245 (w), 2244 (w), 1450 (w), 1321 (m), 1154 (s), 1090 (s), 983 (m), 916 (m), 767 (s), 701 (s); **HRMS (ESI)** calcd for C

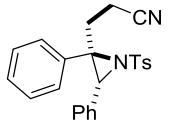
$_{21}H_{25}N_2O_2S^+$ $[M+H]^+$ 369.1631; found 369.1640.

3-(3-isopropyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293n**)



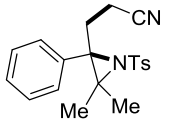

Yield: 22.8 mg (62%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.01 – 7.60 (m, 2H), 7.53 – 7.43 (m, 2H), 7.41 – 7.34 (m, 3H), 7.29 – 7.19 (m, 2H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.41 (s, 3H), 2.50 – 2.25 (m, 3H), 2.14 – 1.94 (m, 1H), 1.64 – 1.55 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.4, 136.4, 135.0, 129.6, 129.4, 129.2, 128.7, 128.4, 118.9, 58.5, 57.4, 31.8, 26.9, 21.8, 20.8, 20.4, 14.2; **ATR-IR** ν 2964 (w), 2245 (w), 1454 (w), 1322 (m), 1154 (s), 1090 (s), 983 (m), 916 (m); **HRMS (ESI)** calcd for $C_{21}H_{25}N_2O_2S^+$ $[M+H]^+$ 369.1631; found 369.1645.

3-(2,3-diphenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293o**)



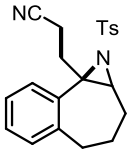

Yield: 30.1 mg (75%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.78 – 7.72 (m, 2H), 7.71 – 7.64 (m, 2H), 7.51 – 7.48 (m, 3H), 7.37 – 7.33 (m, 3H), 7.30 – 7.20 (m, 4H), 4.58 (s, 1H), 2.44 (s, 3H), 2.30 (ddd, *J* = 13.7, 10.2, 5.0 Hz, 1H), 2.12 (ddd, *J* = 16.7, 10.1, 5.0 Hz, 1H), 2.05 – 1.94 (m, 1H), 1.83 (ddd, *J* = 13.8, 10.1, 6.3 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.5, 136.4, 133.9, 132.1, 129.8, 129.7, 129.6, 128.9, 128.9, 128.6, 127.9, 127.3, 118.5, 59.7, 51.2, 31.2, 21.7, 13.3; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s), 1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{24}H_{23}N_2O_2S^+$ $[M+H]^+$ 403.1475; found 403.1486.

3-(2,3-diphenyl-1-tosylaziridin-2-yl)propanenitrile (**2.293p**)



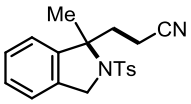

Yield: 29.7 mg (86%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.02 – 7.80 (m, 2H), 7.40 – 7.24 (m, 5H), 7.22 – 7.09 (m, 2H), 2.96 – 2.83 (m, 1H), 2.75 – 2.57 (m, 2H), 2.46 (s, 3H), 2.18 – 1.99 (m, 1H), 1.81 (s, 3H), 0.88 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.2, 138.6, 137.3, 129.8, 128.8, 128.2, 127.5, 127.4, 119.3, 60.6, 54.0, 28.3, 24.4, 21.8, 17.1, 15.0; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s), 1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O_2S^+$ $[M+H]^+$ 355.1475; found 355.1482.

3-(1-tosyl-1a,2,3,4-tetrahydrobenzo[3,4]cyclohepta[1,2-b]azirin-8b(1H)-yl)propanenitrile (**2.293q**)




Yield: 30.7 mg (84%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.88 – 7.74 (m, 2H), 7.42 – 7.20 (m, 5H), 7.16 – 6.87 (m, 1H), 3.15 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.09 – 2.88 (m, 2H), 2.80 (ddd, *J* = 14.4, 10.7, 5.0 Hz, 1H), 2.72 – 2.47 (m, 3H), 2.42 (s, 3H), 2.02 – 1.79 (m, 2H), 1.64 – 1.49 (m, 1H), 0.80 – 0.65 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.3, 137.7, 136.3, 134.8, 130.1, 129.7, 129.5, 129.1, 127.4, 127.4, 119.4, 56.0, 48.0, 30.5, 29.9, 25.6, 21.7, 21.3, 14.5; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s), 1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{21}H_{23}N_2O_2S^+$ $[M+H]^+$ 367.1475; found 367.1474.

3-(1-methyl-2-tosylisoindolin-1-yl)propanenitrile (**2.293v**)

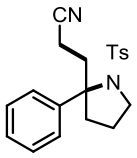



Yield: 28.7 mg (85%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.82 (dd, *J* = 8.3, 1.9 Hz, 2H), 7.38 – 7.25 (m, 4H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.10 – 6.98 (m, 1H), 4.66 (d, *J* = 13.1 Hz, 1H), 4.54 (d, *J* = 12.9 Hz, 1H), 3.03 – 2.95

(m, 1H), 2.42 (s, 3H), 2.42 – 2.29 (m, 1H), 2.19 – 2.14 (m, 1H), 1.85 – 1.76 (m, 1H), 1.69 (d, *J* = 1.9 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.8, 142.4, 137.2, 134.4, 129.9, 128.8, 128.7 (2C), 127.5, 122.8, 121.5, 119.4, 53.7, 37.8, 28.0, 21.6, 12.8; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s),

1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{19}H_{21}N_2O_2S^+$ $[M+H]^+$ 341.1318; found 341.1319.

3-(2-phenyl-1-tosylpyrrolidin-2-yl)propanenitrile (**2.293w**)

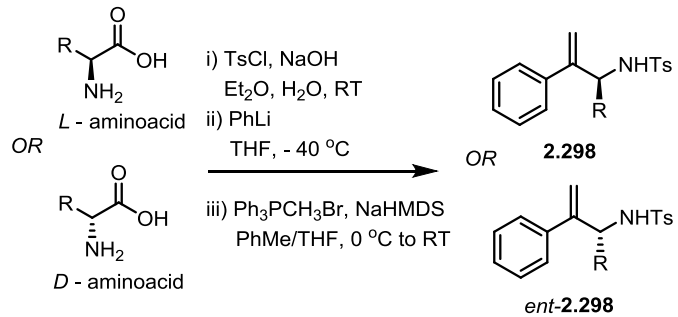



Yield: 31.8 mg (90%), colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.32 (d, *J* = 8.2 Hz, 2H), 7.24 – 7.19 (m, 5H), 7.15 (d, *J* = 8.1 Hz, 2H), 3.69 (dt, *J* = 9.5, 7.2 Hz, 1H), 3.59 (dt, *J* = 9.5, 6.7 Hz, 1H), 2.97 (ddd, *J* = 13.8, 9.2, 6.5 Hz, 1H), 2.69 (ddd, *J* = 13.9, 8.5, 6.9 Hz, 1H), 2.55 – 2.48 (m, 2H), 2.39 (s, 3H), 2.29 – 2.14 (m, 2H), 1.92 (p, *J* = 7.1 Hz, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.5, 143.1, 137.2, 129.4, 128.5, 127.5, 127.1, 126.3, 120.0, 71.6, 50.4, 41.9, 34.6, 22.8, 21.6, 13.6; **ATR-IR** ν 2987 (w), 2973 (w), 2249 (w), 1322 (s), 1152 (s), 974 (s), 768 (s), 700 (s); **HRMS (ESI)** calcd for $C_{20}H_{23}N_2O_2S^+$ $[M+H]^+$ 355.1475; found 355.1474.

### 3.6.3. Synthesis of chiral trisubstituted aziridine by chiral pool approach

**Synthesis of chiral starting materials**

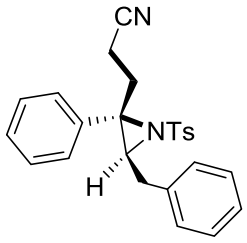
Synthesis of chiral starting material for copper-catalyzed cyanoalkylative aziridination was done by the procedure developed by Burgess and co-workers.[211] Enantiorich 1-monosubstituted 2-phenylprop-2-en-1-amines **2.298**, ***ent*-2.298** were accessed from the corresponding commercially available L/D-amino acids through three-step sequence including: (i) protection of amino group by tosyl chloride; (ii) reaction with organoaryl lithium to form enantiorich *N*-tosylated α-aminoketones; (iii) subsequent Wittig reaction of these intermediates to afford chiral 1-monosubstituted 2-phenylprop-2-en-1-amines **2.298**, ***ent*-2.298**.




[211] Burgess, K.; Liu, L. T.; Biman, P. *J. Org. Chem.* **1993**, *2*, 4758.

## Synthesis of chiral trisubstituted aziridines

3-((2S,3S)-3-benzyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.299a**)

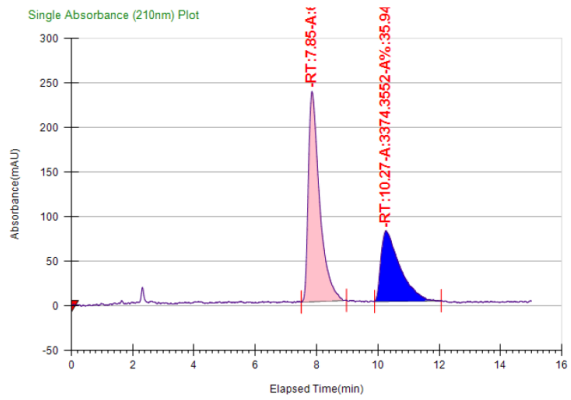



**2.299a**, 77% (dr = 5 : 1)

Yield 77%, white solid; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.48 – 7.32 (m, 5H), 7.16 – 7.08 (m, 3H), 7.03 – 6.97 (m, 2H), 6.76 (d, *J* = 7.5 Hz, 2H), 3.45 (dd, *J* = 8.9, 4.2 Hz, 1H), 2.99 – 2.76 (m, 3H), 2.70 (dd, *J* = 14.5, 4.2 Hz, 1H), 2.42 (s, 3H), 2.31 – 2.21 (m, 1H), 1.94 (dd, *J* = 14.5, 8.8 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.0, 137.3, 137.1, 135.5, 129.6, 129.0, 128.7, 128.7, 128.5, 128.2, 128.1, 127.7, 126.4, 119.3, 58.7, 54.0, 35.5, 31.6, 21.8, 14.8; **ATR-IR** ν 3281 (w), 2969 (w), 1160 (s), 907 (s), 730 (s), 667 (s); **HRMS (ESI)** calcd for $C_{25}H_{25}N_2O_2S^+$ $[M+H]^+$ 417.1631; found 417.1635.

| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 12 | 4 | OD-H | MeOH | 150 |

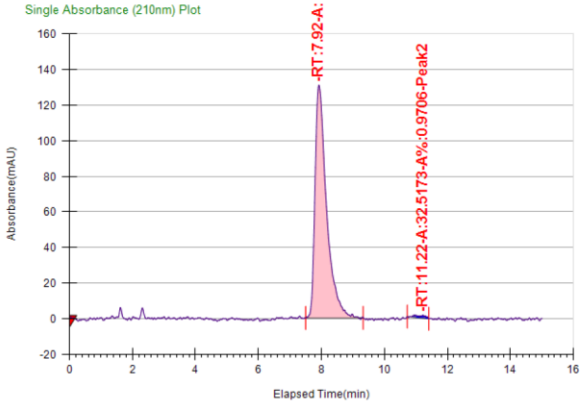
| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 7.85 min | 6013.2737 | 64.0553 |
| 2 | 10.27 min | 3374.3552 | 35.9447 |




Mixture of isomers

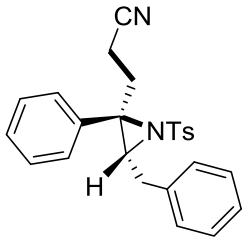
| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 12 | 4 | OD-H | MeOH | 150 |

| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 7.92 min | 3317.6652 | 99.0294 |
| 2 | 11.22 min | 32.5173 | 0.9706 |




**2.299a** (98% ee)

3-((2R,3R)-3-benzyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (ent-**2.299a**)

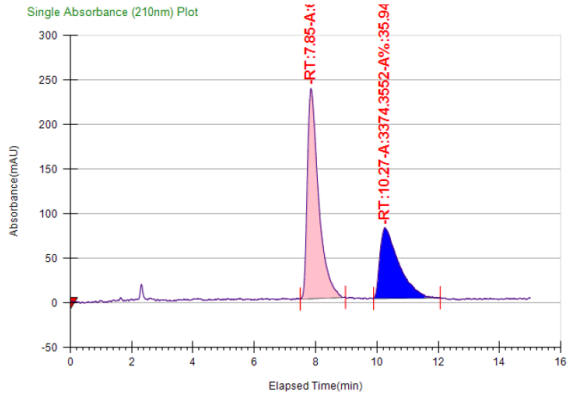



***ent*-2.299a**, 75% (dr = 5 : 1)

Yield 77%, white solid; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.57 (d, *J* = 7.9 Hz, 2H), 7.48 – 7.32 (m, 5H), 7.16 – 7.08 (m, 3H), 7.03 – 6.97 (m, 2H), 6.76 (d, *J* = 7.5 Hz, 2H), 3.45 (dd, *J* = 8.9, 4.2 Hz, 1H), 2.99 – 2.76 (m, 3H), 2.70 (dd, *J* = 14.5, 4.2 Hz, 1H), 2.42 (s, 3H), 2.31 – 2.21 (m, 1H), 1.94 (dd, *J* = 14.5, 8.8 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.0, 137.3, 137.1, 135.5, 129.6, 129.0, 128.7, 128.7, 128.5, 128.2, 128.1, 127.7, 126.4, 119.3, 58.7, 54.0, 35.5, 31.6, 21.8, 14.8; **ATR-IR** ν 3281 (w), 2969 (w), 1160 (s), 907 (s), 730 (s), 667 (s); **HRMS (ESI)** calcd for $C_{25}H_{25}N_2O_2S^+$ $[M+H]^+$ 417.1631; found 417.1642.

| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 12 | 4 | OD-H | MeOH | 150 |

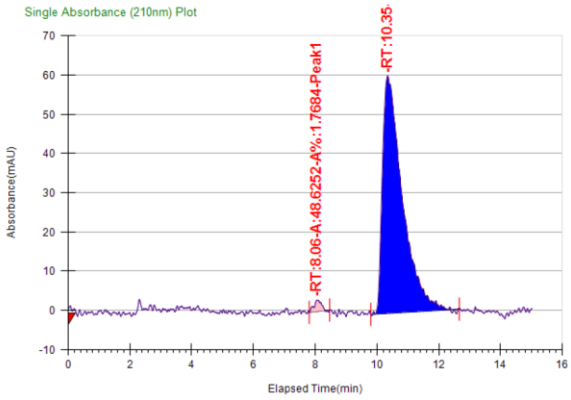
| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 7.85 min | 6013.2737 | 64.0553 |
| 2 | 10.27 min | 3374.3552 | 35.9447 |




Mixture of isomers

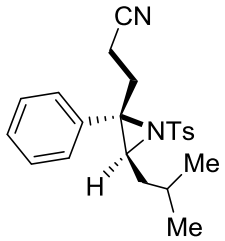
| Co-Solvent % | Total Flow | Column | Co-Solvent | Back Pressure |
|---|---|---|---|---|
| 12 | 4 | OD-H | MeOH | 150 |

| Peak # | Ret. Time | Area | Area % |
|---|---|---|---|
| 1 | 8.06 min | 48.6252 | 1.7684 |
| 2 | 10.35 min | 2701.0635 | 98.2316 |



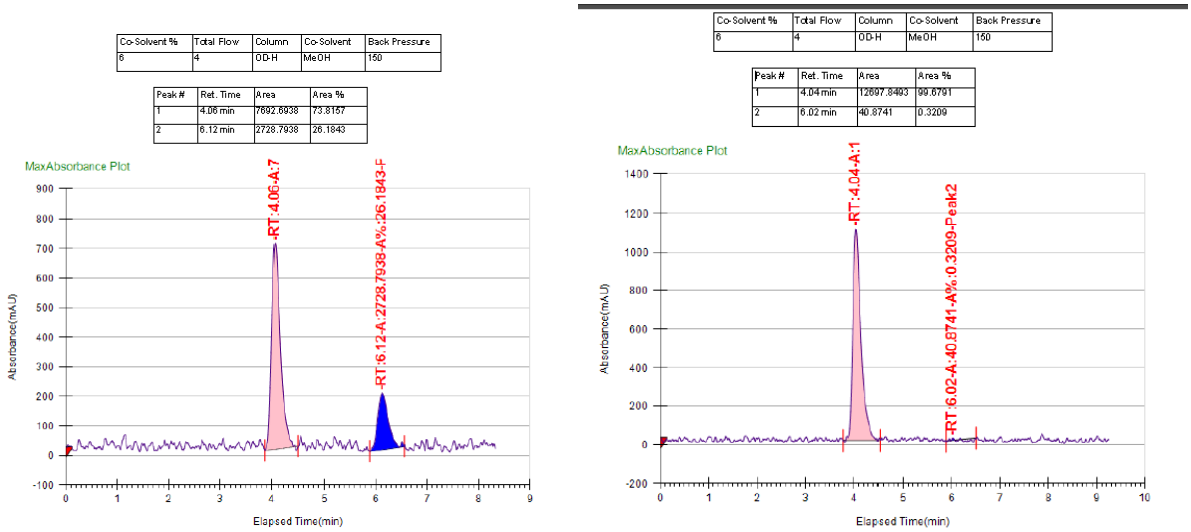

ent-**2.299a (96.5% ee)**

3-((2R,3R)-3-isobutyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.299b**)



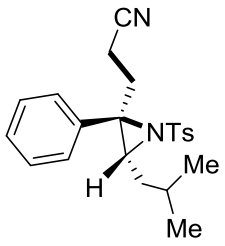

**2.299b**, 85% (dr = 10 : 1)

Yield 85%, white solid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.79 – 7.61 (m, 2H), 7.52 – 7.42 (m, 2H), 7.40 – 7.35 (m, 3H), 7.24 (d, *J* = 8.1 Hz, 2H), 3.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 2.58 – 2.46 (m, 1H), 2.42 (s, 3H), 2.19 – 1.99 (m, 2H), 1.69 – 1.54 (m, 1H), 1.46 – 1.30 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.2, 136.6, 134.5, 129.6, 129.4, 129.3, 128.7, 128.0, 118.7, 57.7, 49.0, 36.4, 31.3, 26.9, 23.3, 22.2, 21.7, 14.0; **ATR-IR** ν 3281 (w), 2969 (w), 1160 (s), 907 (s), 730 (s), 667 (s); **HRMS (ESI)** calcd for $C_{22}H_{27}N_2O_2S^+$ $[M+H]^+$ 383.1788; found 383.1790.



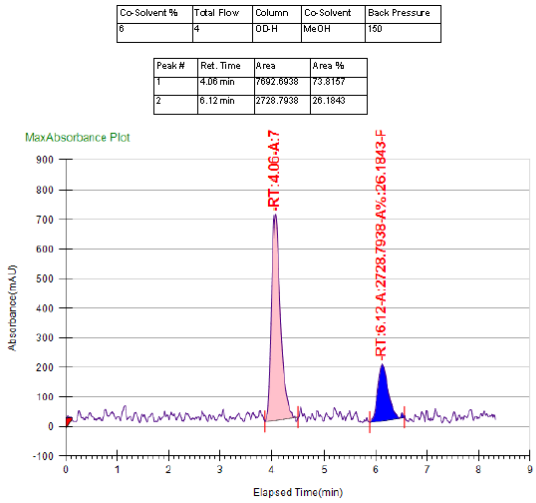

Mixture of isomers **2.299b (99.3% ee)**

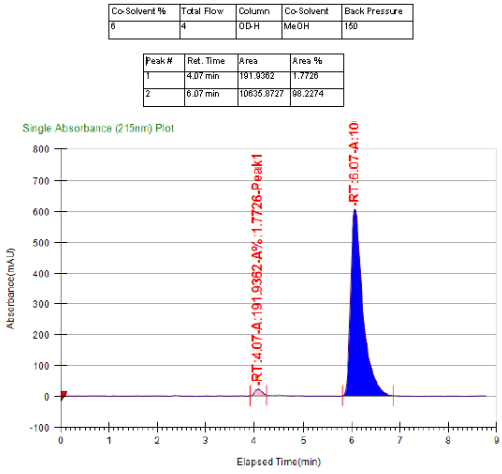
3-((2R,3R)-3-isobutyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (ent-**2.299b**)




***ent*-2.299b**, 83% (dr = 10 : 1)

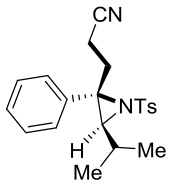
Yield 83%, white solid; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.79 – 7.61 (m, 2H), 7.52 – 7.42 (m, 2H), 7.40 – 7.35 (m, 3H), 7.24 (d, *J* = 8.1 Hz, 2H), 3.38 (dd, *J* = 7.9, 4.8 Hz, 1H), 2.58 – 2.46 (m, 1H), 2.42 (s, 3H), 2.19 – 1.99 (m, 2H), 1.69 – 1.54 (m, 1H), 1.46 – 1.30 (m, 2H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.2, 136.6, 134.5, 129.6, 129.4, 129.3, 128.7, 128.0, 118.7, 57.7, 49.0, 36.4, 31.3, 26.9, 23.3, 22.2, 21.7, 14.0; **ATR-IR** ν 3281 (w), 2969 (w), 1160 (s), 907 (s), 730 (s), 667 (s); **HRMS (ESI)** calcd for $C_{22}H_{27}N_2O_2S^+$ $[M+H]^+$ 383.1788; found 383.1795.



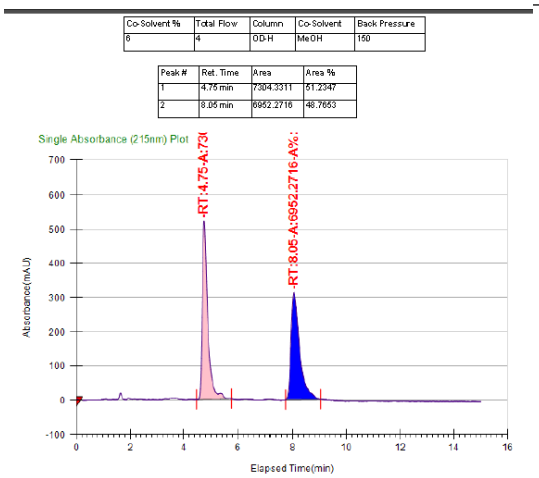

Mixture of isomers ent-**2.299b (96.5% ee)**

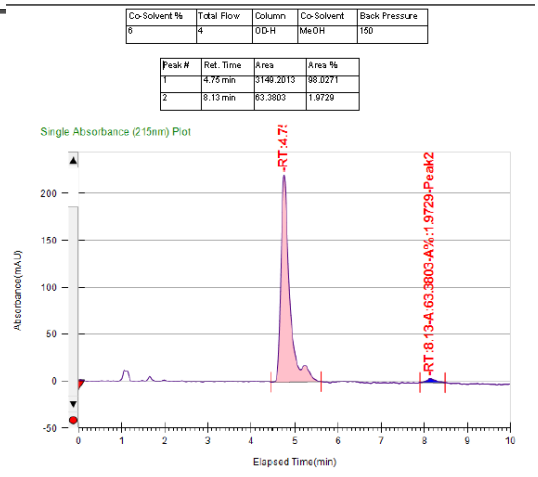
3-((2S,3S)-3-isopropyl-2-phenyl-1-tosylaziridin-2-yl)propanenitrile (**2.299c**)




**2.299c**, 75% (dr = 5 : 1)

Yield 77%, colourless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.01 – 7.60 (m, 2H), 7.53 – 7.43 (m, 2H), 7.41 – 7.34 (m, 3H), 7.29 – 7.19 (m, 2H), 2.97 (d, *J* = 9.9 Hz, 1H), 2.41 (s, 3H), 2.50 – 2.25 (m, 3H), 2.14 – 1.94 (m, 1H), 1.64 – 1.55 (m, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.62 (d, *J* = 6.6 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 144.4, 136.4, 135.0, 129.6, 129.4, 129.2, 128.7, 128.4, 118.9, 58.5, 57.4, 31.8, 26.9, 21.8, 20.8, 20.4, 14.2; **ATR-IR** ν 2964 (w), 2245 (w), 1454 (w), 1322 (m), 1154 (s), 1090 (s), 983 (m), 916 (m); **HRMS (ESI)** calcd for $C_{21}H_{25}N_2O_2S^+$ $[M+H]^+$ 369.1631; found 369.1645.

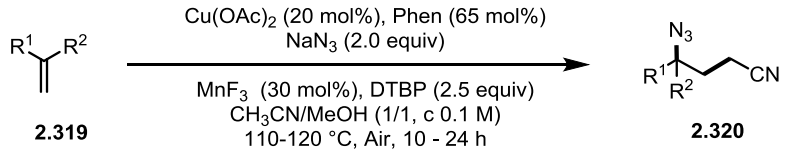



Racemic mixture **2.299c** (96.2% ee)

## 3.7. Copper-Catalyzed Carboazidation of Alkenes with Acetonitrile and Sodium Azide

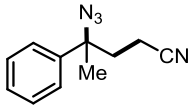
### 3.7.1. Substrate scope




Alkene **2.319** (0.2 mmol, 1 equiv), $Cu(OAc)_2$ (20 mol%), 1,10-phenanthroline (65 mol%), $MnF_3$ (30 mol%), and $NaN_3$ (2 equiv) were dissolved in degassed MeCN/MeOH (v/v 1/1, *c* 0.1 M) in a sealed tube. DTBP (2 equiv) was then added and the tube was sealed and heated to 110-120 $^oC$. After 10-18 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.320**.

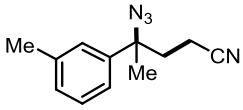
**Characterization Data of Compounds 2.320**

4-azido-4-phenylpentanenitrile (**2.320a**)




Yield: 28.8 mg (72%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.47 – 7.27 (m, 5H), 2.36 – 2.28 (m, 1H), 2.20 – 2.13 (m, 2H), 2.12 – 2.01 (m, 1H), 1.76 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.4, 129.2, 128.2, 125.4, 119.3, 65.8, 38.4, 25.8, 12.7; **ATR-IR** *v* 2934 (w), 2933 (w), 2248 (w), 2094 (s), 1447 (w), 1253 (m), 764 (m), 700 (s); **HRMS (ESI)** calcd for $C_{11}H_{12}N_4Na^+$ $[M+Na]^+$ 223.0954; found 223.0958.

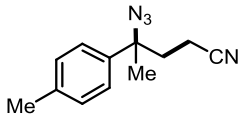
4-azido-4-(m-tolyl)pentanenitrile (**2.320b**)




Yield: 26.4 mg (62%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.29 (td, *J* = 7.4, 1.1 Hz, 1H), 7.16 – 7.12 (m, 3H), 2.39 (s, 3H), 2.36 – 2.27 (m, 1H), 2.19 – 2.12 (m, 2H), 2.11 – 2.00 (m, 1H), 1.75 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.3, 138.9, 129.0, 128.9, 126.1, 122.4, 119.4, 65.7, 38.3,

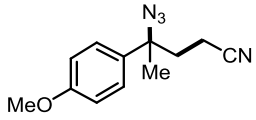
25.8, 21.8, 12.7; **ATR-IR** *v* 2975 (w), 2927 (w), 2248 (w), 2104 (s), 1251 (m), 788 (m), 706 (s); **HRMS (ESI)** calcd for $C_{12}H_{14}N_4Na^+$ $[M+Na]^+$ 237.1111; found 237.1107.

4-azido-4-(p-tolyl)pentanenitrile (**2.320c**)



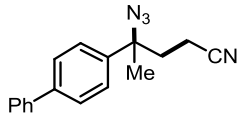

Yield: 31.0 mg (72%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.23 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 2.34 (s, 3H), 2.37 – 2.26 (m, 1H), 2.15 – 2.01 (m, 3H), 1.72 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 138.3, 137.9, 129.7, 125.3, 119.4, 65.6, 38.3, 25.6, 21.1, 12.7; **ATR-IR** *v* 2975 (w), 2930 (w), 2928 (w), 2248 (w), 2095 (s), 1253 (m), 1082 (m), 819 (s); **HRMS (ESI)** calcd for $C_{12}H_{14}N_4Na^+$ $[M+Na]^+$ 237.1111; found 237.1112.

4-azido-4-(4-methoxyphenyl)pentanenitrile (**2.320d**)



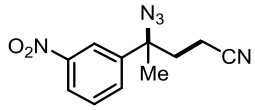

Yield: 33.6 mg (73%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 8.9 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.34 – 2.25 (m, 1H), 2.19 – 2.04 (m, 3H), 1.74 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 159.3, 133.3, 126.7, 119.4, 114.3, 65.4, 55.4, 38.4, 25.6, 12.7; **ATR-IR** *v* 2956 (w), 2931 (w), 2247 (w), 2246 (w), 2097 (s), 1512 (m), 1249 (s), 1182 (m), 1031 (m), 832 (s); **HRMS (ESI)** calcd for $C_{12}H_{14}N_4NaO^+$ $[M+Na]^+$ 253.1060; found 253.1057.

4-([1,1'-biphenyl]-4-yl)-4-azidopentanenitrile (**2.320e**)



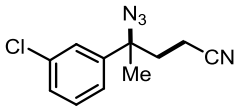

Yield: 40.8 mg (74%), white solid, mp: 46 – 47 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.59 (m, 4H), 7.50 – 7.36 (m, 5H), 2.42 – 2.34 (m, 1H), 2.23 – 2.19 (m, 2H), 2.16 – 2.08 (m, 1H), 1.80 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.0, 140.3, 140.2, 129.0, 127.8 (2C), 127.2, 125.9, 119.4, 65.6, 38.3, 25.7, 12.7; **ATR-IR** *v* 2977 (w), 2952 (w), 2931 (w), 2246 (w), 2113 (s), 1489 (m), 1246 (s), 1086 (m), 839 (m), 766 (s); **HRMS (ESI)** calcd for $C_{17}H_{16}N_4Na^+$ $[M+Na]^+$ 299.1267; found 299.1270.

4-azido-4-(3-nitrophenyl)pentanenitrile (**2.320f**)



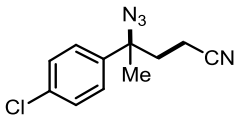

Yield: 26.4 mg (54%), white solid, mp: 72 – 73 ºC;**$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 8.27 (t, *J* = 2.1 Hz, 1H), 8.21 (ddd, *J* = 8.1, 2.2, 1.1 Hz, 1H), 7.75 (ddd, *J* = 7.9, 1.9, 1.1 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 2.38 (ddd, *J* = 16.1, 8.9, 6.0 Hz, 1H), 2.26 – 2.21 (m, 2H), 2.12 (ddd, *J* = 16.1, 9.1, 5.8 Hz, 1H), 1.82 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 148.7, 144.0, 131.6, 130.3, 123.3, 120.8, 118.7, 65.1, 38.0, 25.7, 12.7; **ATR-IR** *v* 2977 (w), 2955 (w), 2933 (w), 2247 (w), 2109 (s), 1524 (s), 1353 (s), 1260 (s), 738 (s), 684 (s), 684 (s); **HRMS (ESI)** calcd for $C_{11}H_{12}N_5O_2^+$ $[M+H]^+$ 246.0986; found 246.0987.

4-azido-4-(3-chlorophenyl)pentanenitrile (**2.320g**)



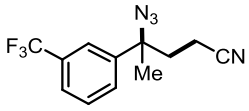

Yield: 26.6 mg (57%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.30 (m, 3H), 7.27 – 7.24 (m, 1H), 2.39 – 2.31 (m, 1H), 2.19 – 2.04 (m, 3H), 1.76 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.6, 135.2, 130.5, 128.4, 125.9, 123.6, 119.1, 65.3, 38.2, 25.7, 12.7; **ATR-IR** *v* 2975 (w), 2952 (w), 2932 (w), 2931 (w), 2249 (w), 2098 (s), 1249 (m), 786 (m), 698 (s); **HRMS (ESI)** calcd for $C_{11}H_{12}ClN_4^+$ $[M+H]^+$ 235.0745; found 235.0746.

4-azido-4-(4-chlorophenyl)pentanenitrile (**2.320h**)



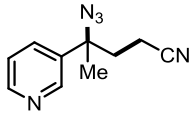

Yield: 23.6 mg (50%), colorless oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.35 (m, 2H), 7.32 – 7.29 (m, 2H), 2.33 (ddd, *J* = 15.6, 9.7, 5.3 Hz, 1H), 2.19 – 2.03 (m, 3H), 1.74 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.0, 134.2, 129.3, 126.9, 119.1, 65.3, 38.2, 25.7, 12.7; **ATR-IR** *v* 2976 (w), 2933 (w), 2249 (w), 2106 (s), 2105 (s), 1490 (m), 1250 (m), 1096 (s), 1012 (s), 829 (s); **HRMS (ESI)** calcd for $C_{11}H_{11}AgClN_4^+$ $[M+Ag]^+$ 340.9718; found 340.9731.

4-azido-4-(3-(trifluoromethyl)phenyl)pentanenitrile (**2.320i**)



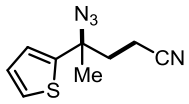
Yield: 27.1 mg (51%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.64 – 7.53 (m, 4H), 2.36 (ddd, *J* = 16.2, 9.4, 5.9 Hz, 1H), 2.23 – 2.18 (m, 2H), 2.08 (ddd, *J* = 16.2, 9.5, 5.7 Hz, 1H), 1.79 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 142.8, 131.6 (q, *J* = 32.4 Hz), 129.8, 128.9, 125.2 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.5 Hz), 122.3 (q, *J* = 3.8 Hz), 119.0, 65.3, 38.2, 25.8, 12.7; **ATR-IR** *v* 2976 (w), 2962 (w), 2932 (w), 2250 (w), 2102 (s), 1330 (s), 1165 (s), 1122 (s), 1072 (s), 704 (s); **HRMS (ESI)** calcd for $C_{12}H_{11}F_3N_4Na^+$ $[M+Na]^+$ 291.0828; found 291.0829.

4-azido-4-(pyridin-3-yl)pentanenitrile (**2.320j**)



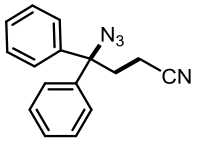
Yield: 20.9 mg (52%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 8.66 (s, 1H), 8.63 – 8.59 (m, 1H), 7.71 (ddd, *J* = 8.1, 2.5, 1.5 Hz, 1H), 7.35 (dd, *J* = 8.1, 4.7 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.22 – 2.07 (m, 3H), 1.79 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 149.6, 147.1, 137.2, 133.4, 123.8, 118.9, 64.2, 38.1, 25.5, 12.6; **ATR-IR** *v* 2976 (w), 2933 (w), 2248 (w), 2102 (s), 1418 (m), 1251 (m), 714 (s); **HRMS (ESI)** calcd for $C_{10}H_{12}N_5^+$ $[M+H]^+$ 202.1087; found 202.1092.

4-azido-4-(thiophen-2-yl)pentanenitrile (**2.320k**)



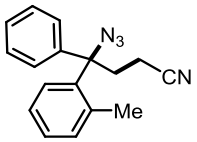
Yield: 19.9 mg (48%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.30 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.02 – 6.98 (m, 3H), 2.44 – 2.36 (m, 1H), 2.30 – 2.15 (m, 3H), 1.80 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 145.7, 127.3, 125.7, 124.6, 119.2, 64.0, 39.0, 26.3, 12.8; **ATR-IR** *v* 2976 (w), 2956 (w), 2933 (w), 2248 (w), 2105 (s), 1242 (s), 856 (w), 836 (w), 704 (s); **HRMS (ESI)** calcd for $C_9H_{11}N_4S^+$ $[M+H]^+$ 207.0699; found 207.0703.

4-azido-4,4-diphenylbutanenitrile (**2.320l**)



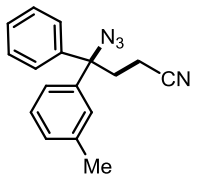

Yield: 40.0 mg (76%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.28 (m, 10H), 2.78 – 2.74 (m, 2H), 2.23 – 2.19 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.0, 128.9, 128.4, 127.0, 119.4, 71.5, 35.4, 12.8; **ATR-IR** *v* 2958 (w), 2929 (w), 2249 (w), 2099 (s), 1447 (w), 1248 (m), 1031 (w), 770 (w), 757 (m); **HRMS (ESI)** calcd for $C_{16}H_{14}N_4Na^+$ $[M+Na]^+$ 285.1111; found 285.1116.

4-azido-4-phenyl-4-(o-tolyl)butanenitrile (**2.320m**)



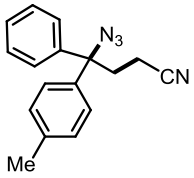

Yield: 33.7 mg (61%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.66 – 7.63 (m, 1H), 7.35 – 7.28 (m, 5H), 7.21 – 7.15 (m, 3H), 2.85 (ddd, *J* = 13.4, 10.7, 5.4 Hz, 1H), 2.69 (ddd, *J* = 13.4, 10.6, 5.2 Hz, 1H), 2.31 (ddd, *J* = 17.0, 10.6, 5.4 Hz, 1H), 2.12 (ddd, *J* = 16.9, 10.7, 5.2 Hz, 1H), 1.87 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.5, 138.4, 137.3, 133.3, 128.9, 128.7, 128.0, 126.7, 126.4, 126.0, 119.5, 71.3, 35.6, 21.2, 12.9; **ATR-IR** *v* 2930 (w), 2249 (w), 2100 (s), 1448 (w), 1250 (m), 756 (s), 730 (m), 701 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}N_4^+$ $[M+H]^+$ 277.1448; found 277.1454.

4-azido-4-phenyl-4-(m-tolyl)butanenitrile (**2.320n**)



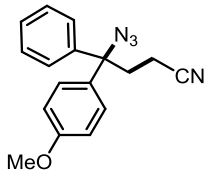

Yield: 40.3 mg (73%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.22 (m, 6H), 7.13 – 7.10 (m, 1H), 7.07 – 7.03 (m, 2H), 2.74 – 2.70 (m, 2H), 2.32 (s, 3H), 2.20 – 2.16 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.2, 141.0, 138.6, 129.1, 128.8, 128.7, 128.3, 127.5, 127.0, 124.1, 119.5, 71.6, 35.5, 21.7, 12.8; **ATR-IR** *v* 2957 (w), 2926 (w), 2248 (w), 2100 (s), 1447 (w), 1249 (m), 765 (m), 717 (m), 700 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}N_4^+$ $[M+H]^+$ 277.1448; found 277.1455.

4-azido-4-phenyl-4-(p-tolyl)butanenitrile (**2.320o**)



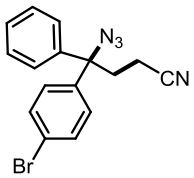

Yield: 40.2 mg (73%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.26 (m, 5H), 7.20 – 7.15 (m, 4H), 2.80 – 2.67 (m, 2H), 2.36 (s, 3H), 2.26 – 2.14 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 141.2, 138.2, 138.1, 129.5, 128.8, 128.3, 126.94, 126.91, 119.5, 71.5, 35.5, 21.1, 12.8; **ATR-IR** *v* 2944 (w), 2925 (w), 2249 (w), 2100 (s), 1250 (m), 1249 (m), 816 (m), 765 (m), 726 (m), 700 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}N_4^+$ $[M+H]^+$ 277.1448; found 277.1454.

4-azido-4-(4-methoxyphenyl)-4-phenylbutanenitrile (**2.320p**)



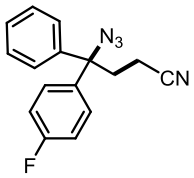

Yield: 20.4 mg (67%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.43 – 7.29 (m, 5H), 7.24 – 7.21 (m, 5H), 6.94 – 6.91 (m, 2H), 3.84 (s, 3H), 2.81 – 2.69 (m, 2H), 2.28 (ddd, *J* = 17.0, 9.8, 6.1 Hz, 1H), 2.18 (ddd, *J* = 17.0, 10.1, 6.0 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 159.4, 141.3, 133.2, 128.8, 128.34, 128.27, 126.9, 119.5, 114.1, 71.4, 55.4, 35.7, 12.8; **ATR-IR** *v* 2957 (w), 2934 (w), 2248 (w), 2100 (s), 1511 (s), 1250 (s), 1181 (m), 1031 (s), 830 (s), 699 (s); **HRMS (ESI)** calcd for $C_{17}H_{17}N_4O^+$ $[M+H]^+$ 293.1397; found 293.1393.

4-azido-4-(4-bromophenyl)-4-phenylbutanenitrile (**2.320q**)



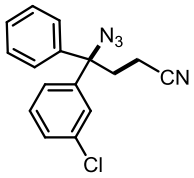

Yield: 47.1 mg (69%), yellow oil; **$^{1}$H NMR (400 MHz, $CDCl_3$)** δ 7.55 – 7.52 (m, 3H), 7.44 – 7.37 (m, 3H), 7.30 – 7.28 (m, 2H), 7.21 – 7.18 (m, 2H), 2.78 – 2.74 (m, 2H), 2.26 – 2.22 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.5, 140.3, 132.1, 129.1, 128.8, 128.7, 126.9, 122.7, 119.2, 71.1, 35.3, 12.8; **ATR-IR** *v* 2987 (w), 2958 (w), 2248 (w), 2100 (s), 1249 (m), 1009 (m), 821 (m), 767 (m), 700 (s); **HRMS (ESI)** calcd for $C_{16}H_{14}BrN_4^+$ $[M+H]^+$ 341.0396; found 341.0397.

4-azido-4-(4-fluorophenyl)-4-phenylbutanenitrile (**2.320r**)



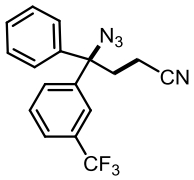

Yield: 40.8 mg (73%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.35 (m, 3H), 7.32 – 7.28 (m, 4H), 7.12 – 7.08 (m, 2H), 2.77 (dd, *J* = 8.4, 7.6 Hz, 2H), 2.31 – 2.17 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.4 (d, *J* = 248.6 Hz), 140.8, 137.1 (d, *J* = 3.3 Hz), 129.0, 128.9 (d, *J* = 8.3 Hz), 128.5, 126.9, 119.2, 115.8 (d, *J* = 21.6 Hz), 71.1, 35.5, 12.8; **ATR-IR** *v* 2960 (w), 2249 (w), 2101 (s), 1509 (s), 1229 (s), 834 (s), 699 (s); **HRMS (ESI)** calcd for $C_{16}H_{13}FN_4Na^+$ $[M+Na]^+$ 303.1016; found 303.1018.

4-azido-4-(3-chlorophenyl)-4-phenylbutanenitrile (**2.320s**)




Yield: 34.8 mg (59%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.45 – 7.28 (m, 8H), 7.21 – 7.17 (m, 1H), 2.84 – 2.71 (m, 2H), 2.32 – 2.18 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 143.3, 140.4, 135.0, 130.2, 129.1, 128.7, 128.7, 127.2, 126.9, 125.2, 119.1, 71.1, 35.3, 12.8; **ATR-IR** *v* 2969 (w), 2947 (w), 2929 (w), 2249 (w), 2101 (s), 1248 (m), 791 (m), 768 (m), 697 (s); **HRMS (ESI)** calcd for $C_{16}H_{14}ClN_4^+$ $[M+H]^+$ 297.0901; found 297.0914.

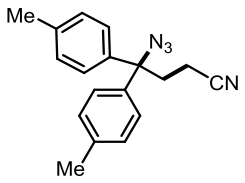
4-azido-4-phenyl-4-(3-(trifluoromethyl)phenyl)butanenitrile (**2.320t**)




Yield: 46.9 mg (71%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.63 (m, 2H), 7.54 (td, *J* = 8.0, 0.8 Hz, 1H), 7.48 – 7.39 (m, 4H), 7.32 – 7.29 (m, 2H), 2.88 – 2.77 (m, 2H), 2.34 – 2.17 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 142.5, 140.3, 131.3 (q, *J* = 32.5 Hz), 130.5, 129.6, 129.2, 128.9, 126.9, 125.4 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.4 Hz), 123.5 (q, *J* = 3.9 Hz), 119.0, 71.1, 35.2, 12.7;

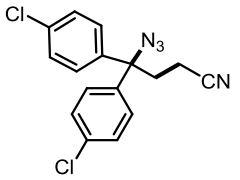
**ATR-IR** *v* 2969 (w), 2935 (w), 2250 (w), 2103 (s), 1329 (s), 1165 (s), 1123 (s), 1077 (s), 700 (s); **HRMS (ESI)** calcd for $C_{17}H_{13}F_3N_4Na^+$ $[M+Na]^+$ 353.0984; found 353.0988.

4-azido-4,4-di-p-tolylbutanenitrile (**2.320u**)



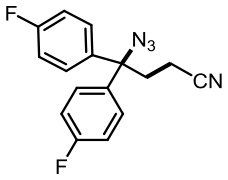

Yield: 43.6 mg (75%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.19 – 7.14 (m, 8H), 2.73 – 2.69 (m, 2H), 2.35 (s, 6H), 2.22 – 2.18 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 138.3, 138.2, 129.5, 126.9, 119.6, 71.4, 35.6, 21.2, 12.8; **ATR-IR** *v* 3025 (w), 2924 (w), 2248 (w), 2101 (s), 1510 (w), 1252 (m), 1046 (w), 1019 (w), 811 (s), 790 (m), 739 (w); **HRMS (ESI)** calcd for $C_{18}H_{18}N_4Na^+$ $[M+Na]^+$ 313.1424; found 313.1422.

4-azido-4,4-bis(4-chlorophenyl)butanenitrile (**2.320v**)




Yield: 45.6 mg (69%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.34 (m, 4H), 7.22 – 7.19 (m, 4H), 2.73 – 2.69 (m, 2H), 2.22 – 2.19 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.3, 134.7, 129.2, 128.3, 118.9, 70.6, 35.2, 12.7; **ATR-IR** *v* 2969 (w), 2956 (w), 2249 (w), 2102 (s), 1490 (m), 1247 (m), 1094 (s), 1012 (s), 818 (s); **HRMS (ESI)** calcd for $C_{16}H_{13}Cl_2N_4^+$ $[M+H]^+$ 331.0512; found 331.0521.

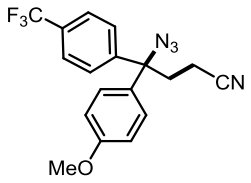
4-azido-4,4-bis(4-fluorophenyl)butanenitrile (**2.320w**)




Yield: 42.8 mg (72%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.31 – 7.26 (m, 4H), 7.13 – 7.07 (m, 4H), 2.77 – 2.73 (m, 2H), 2.26 – 2.22 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 162.5 (d, *J* = 248.9 Hz), 136.8 (d, *J* = 3.3 Hz), 128.8 (d, *J* = 8.3 Hz), 119.0, 116.0 (d, *J* = 21.6 Hz), 70.6, 35.6, 12.8; **ATR-**

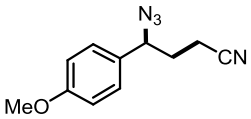
**IR** *v* 2958 (w), 2933 (w), 2250 (w), 2249 (w), 2103 (s), 1507 (s), 1229 (s), 1162 (m), 832 (s); **HRMS (ESI)** calcd for $C_{16}H_{13}F_2N_4^+$ $[M+H]^+$ 299.1103; found 299.1097.

4-azido-4-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)butanenitrile (**2.320x**)



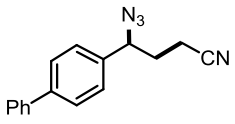

Yield: 48.3 mg (67%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.65 – 7.62 (m, 2H), 7.44 – 7.41 (m, 2H), 7.20 – 7.16 (m, 2H), 6.93 – 6.89 (m, 2H), 3.82 (s, 3H), 2.83 – 2.67 (m, 2H), 2.29 (ddd, *J* = 17.0, 10.2, 5.5 Hz, 1H), 2.12 (ddd, *J* = 17.0, 10.5, 5.5 Hz, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 159.7, 145.5, 132.4, 130.5 (q, *J* = 32.7 Hz), 128.3, 127.4, 125.9 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 273.3 Hz), 119.1, 114.4, 71.0, 55.4, 35.4, 12.8; **ATR-IR** *v* 2958 (w), 2935 (w), 2250 (w), 2104 (s), 1513 (m), 1325 (s), 1253 (s), 1070 (s), 1032 (m), 1016 (m), 829 (s); **HRMS (ESI)** calcd for $C_{18}H_{15}F_3N_4NaO^+$ $[M+Na]^+$ 383.1090; found 383.1093.

(S)-4-azido-4-(4-methoxyphenyl)butanenitrile (**2.320y**)




Yield: 20.0 mg (46%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.22 – 7.10 (m, 2H), 6.89 – 6.84 (m, 2H), 4.51 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.75 (s, 3H), 2.43 – 2.35 (m, 1H), 2.32 – 2.24 (m, 1H), 2.05 – 1.90 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 160.1, 129.7, 128.3, 118.9, 114.6, 64.1, 55.5, 32.0, 14.5; **ATR-IR** *v* 2958 (w), 2932 (w), 2247 (w), 2097 (s), 2096 (s), 1514 (s), 1248 (s), 1177 (m), 1031 (s), 831 (s); **HRMS (ESI)** calcd for $C_{11}H_{12}N_4NaO^+$ $[M+Na]^+$ 239.0903; found 239.0907.

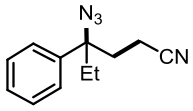
4-([1,1'-biphenyl]-4-yl)-4-azidobutanenitrile (**2.320z**)




Yield: 30.5 mg (46%), white solid, mp: 42 – 43 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.68 – 7.63 (m, 2H), 7.62 – 7.59 (m, 2H), 7.49 – 7.36 (m, 5H), 4.69 (dd, *J* = 8.7, 5.8 Hz, 1H), 2.56 – 2.48 (m, 1H), 2.45 – 2.37 (m, 1H), 2.19 – 2.04 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 142.1, 140.3, 136.8, 129.0,

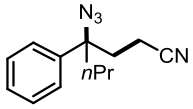
128.0, 127.8, 127.4, 127.2, 118.8, 64.2, 32.1, 14.5; **ATR-IR** *v* 2936 (w), 2247 (w), 2099 (s), 1486 (m), 1247 (m), 847 (m), 838 (m), 768 (s), 735 (s), 698 (s); **HRMS (ESI)** calcd for $C_{16}H_{14}N_4Na^+$ $[M+Na]^+$ 285.1111; found 285.1110.

4-azido-4-phenylhexanenitrile (**2.320aa**)



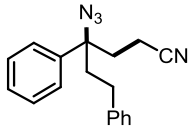

Yield: 27.7 mg (65%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.37 (m, 2H), 7.33 – 7.29 (m, 3H), 2.34 – 2.18 (m, 3H), 2.13 – 1.94 (m, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.2, 129.0, 128.0, 125.9, 119.4, 69.5, 36.1, 32.7, 12.5, 8.3; **ATR-IR** *v* 2973 (w), 2937 (w), 2249 (w), 2099 (s), 1256 (m), 761 (m), 701 (s); **HRMS (ESI)** calcd for $C_{12}H_{14}N_4Na^+$ $[M+Na]^+$ 237.1111; found 237.1116.

4-azido-4-phenylheptanenitrile (**2.320ab**)




Yield: 28.7 mg (63%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.35 (m, 2H), 7.34 – 7.28 (m, 3H), 2.34 – 2.19 (m, 3H), 2.04 – 1.89 (m, 3H), 1.40 – 1.26 (m, 1H), 1.14 – 1.05 (m, 1H), 0.89 (t, *J* = 7.3 Hz, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.5, 129.0, 127.9, 125.8, 119.3, 69.1, 42.1, 36.4, 17.2, 14.2, 12.5; **ATR-IR** *v* 2961 (w), 2934 (w), 2248 (w), 2105 (s), 1448 (w), 1257 (m), 765 (m), 701 (s); **HRMS (ESI)** calcd for $C_{13}H_{17}N_4^+$ $[M+H]^+$ 229.1448; found 229.1443.

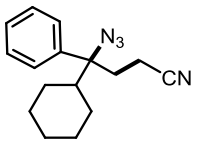
4-azido-4,6-diphenylhexanenitrile (**2.320ac**)




Yield: 35.4 mg (61%), yellow solid, mp: 69 – 70 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.33 (m, 5H), 7.27 – 7.23 (m, 2H), 7.20 – 7.16 (m, 1H), 7.10 – 7.08 (m, 2H), 2.65 – 2.56 (m, 1H), 2.36 – 2.21 (m, 6H), 2.03 – 1.95 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.9, 139.0, 129.2, 128.7, 128.3, 128.2, 126.3, 125.8, 119.2, 68.9, 42.1, 36.5, 30.4, 12.5; **ATR-IR** *v* 2952 (w), 2937 (w), 2932 (w), 2121

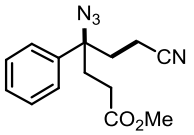
(m), 2097 (s), 1252 (s), 763 (m), 705 (s); **HRMS (ESI)** calcd for $C_{18}H_{18}N_4Na^+$ $[M+Na]^+$ 313.1424; found 313.1424.

4-azido-4-cyclohexyl-4-phenylbutanenitrile (**2.320ad**)



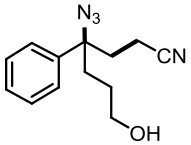

Yield: 31.1 mg (58%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.39 – 7.34 (m, 2H), 7.32 – 7.25 (m, 3H)), 2.46 (dd, *J* = 8.8, 6.9 Hz, 2H), 2.29 (ddd, *J* = 16.5, 8.8, 7.6 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.95 – 1.89 (m, 1H), 1.82 – 1.68 (m, 3H), 1.66 – 1.59 (m, 1H), 1.57 – 1.51 (m, 1H), 1.28 – 1.12 (m, 2H), 1.08 – 0.86 (m, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 138.3, 128.6, 127.8, 126.6, 119.4, 72.0, 48.6, 32.7, 28.0, 27.7, 26.6, 26.5, 26.2, 12.8; **ATR-IR** *v* 2932 (m), 2854 (w), 2247 (w), 2094 (s), 1447 (m), 1254 (m), 763 (m), 704 (s); **HRMS (ESI)** calcd for $C_{16}H_{21}N_4^+$ $[M+H]^+$ 269.1761; found 269.1759.

methyl 4-azido-6-cyano-4-phenylhexanoate (**2.320ae**)




Yield: 33.4 mg (61%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.37 (m, 2H), 7.34 – 7.29 (m, 3H), 3.61 (s, 3H), 2.40 – 2.23 (m, 6H), 2.11 – 1.94 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 172.9, 138.1, 129.3, 128.3, 125.8, 119.0, 68.4, 52.0, 36.2, 34.7, 28.8, 12.5; **ATR-IR** *v* 2953 (w), 2924 (w), 2853 (w), 2248 (w), 2101 (s), 1734 (s), 1253 (s), 1199 (m), 1168 (m), 764 (m), 702 (s); **HRMS (ESI)** calcd for $C_{14}H_{16}N_4NaO_2^+$ $[M+Na]^+$ 295.1165; found 295.1167.

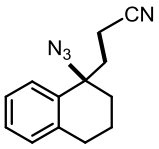
4-azido-7-hydroxy-4-phenylheptanenitrile (**2.320af**)




Yield: 24.3 mg (50%), yellow oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.42 – 7.35 (m, 2H), 7.32 – 7.28 (m, 3H), 3.58 (t, *J* = 6.2 Hz, 2H), 2.34 – 2.20 (m, 3H), 2.16 – 2.08 (m, 2H), 2.04 – 1.93 (m, 1H), 1.59 (broand, s, 1H), 1.64 – 1.53 (m, 1H), 1.37 – 1.25 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 139.2,

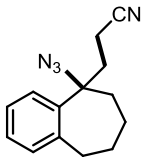
129.1, 128.1, 125.8, 119.3, 68.9, 62.3, 36.4, 36.1, 27.1, 12.5; **ATR-IR** *v* 3389 (w), 2949 (w), 2930 (w), 2249 (w), 2100 (s), 1255 (m), 763 (m), 702 (s); **HRMS (ESI)** calcd for $C_{13}H_{16}N_4NaO^+$ $[M+Na]^+$ 267.1216; found 267.1219.

3-(1-azido-1,2,3,4-tetrahydronaphthalen-1-yl)propanenitrile (**2.320ag**)



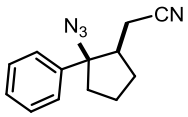

Yield: 21.9 mg (48%), yellow solid, mp: 41 – 42 ºC; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.36 (m, 1H), 7.28 – 7.25 (m, 2H), 7.18 – 7.14 (m, 1H), 2.92 – 2.76 (m, 2H), 2.50 – 2.35 (m, 2H), 2.28 – 2.14 (m, 2H), 2.09 – 1.84 (m, 4H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 137.5, 135.7, 130.0, 128.5, 126.8, 126.5, 119.5, 64.6, 36.5, 33.1, 29.3, 19.5, 12.6; **ATR-IR** *v* 2942 (w), 2871 (w), 2863 (w), 2245 (w), 2105 (s), 1440 (m), 1246 (s), 763 (s), 735 (s); **HRMS (ESI)** calcd for $C_{13}H_{15}N_4^+$ $[M+H]^+$ 227.1291; found 227.1292.

3-(5-azido-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)propanenitrile (**2.320ah**)




Yield: 22.1 mg (46%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.15 (dd, *J* = 7.3, 1.8 Hz, 1H), 2.93 – 2.81 (m, 2H), 2.47 – 2.36 (m, 2H), 2.17 – 1.87 (m, 7H), 1.60 – 1.49 (m, 1H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.0, 139.7, 132.3, 128.4, 127.4, 126.9, 119.6, 70.2, 37.4, 36.7, 33.4, 27.5, 25.4, 12.6; **ATR-IR** *v* 2932 (w), 2857 (w), 2247 (w), 2098 (s), 1445 (w), 1253 (m), 759 (s), 747 (m); **HRMS (ESI)** calcd for $C_{14}H_{16}N_4Na^+$ $[M+Na]^+$ 263.1267; found 263.1268.

2-(2-azido-2-phenylcyclopentyl)acetonitrile (**2.320ai**)

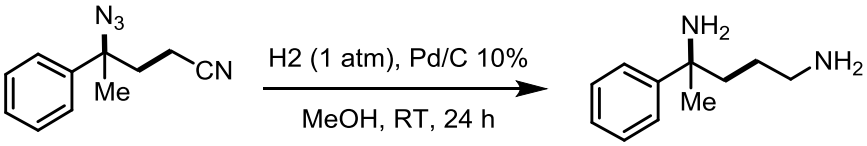



Yield: 21.1 mg (46%), colorless oil; **$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.45 – 7.40 (m, 2H), 7.39 – 7.33 (m, 3H), 2.55 – 2.46 (m, 1H), 2.46 – 2.39 (m, 1H), 2.33 – 2.24 (m, 2H), 2.12 – 1.97 (m, 3H), 1.79 –

1.70 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 138.1, 129.2, 128.8, 127.2, 118.7, 77.3, 45.9, 32.8, 28.9, 21.1, 20.3; **ATR-IR** *v* 2956 (w), 2249 (w), 2096 (s), 2095 (s), 1246 (m), 764 (m), 701 (s); **HRMS (ESI)** calcd for $C_{13}H_{15}N_4^+$ $[M+H]^+$ 227.1291; found 227.1294.

### 3.7.2. Post-transformation of γ-azidonitrile 2.320a

**Synthesis of 4-phenylpentane-1,4-diamine (2.327)**

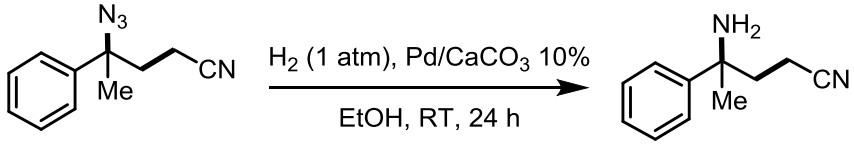



**2.320a** **2.327**

To a solution of **2.320a** (40 mg, 0.2 mmol) in MeOH (2 mL, 0.1 M) was added Pd/C (m/m 10%, 21 mg, 10 mol%). The reaction mixture was evacuated and filled with $H_2$ (from balloom) three times. After stirring at room temperature for 24 hours, the reaction mixture was then filtered through a plug of Celite. The resulting filtrate was concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (dichloro methane/methanol 15/1) to give compound **2.327** (colorless oil, 20.0 mg, 56%).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.50 – 7.47 (m, 2H), 7.34 – 7.30 (m, 2H), 7.23 – 7.19 (m, 1H), 3.18 – 3.12 (m, 1H), 3.05 – 2.99 (m, 1H), 2.30 (s, broad, 2H), 2.15 – 2.08 (m, 1H), 1.94 – 1.88 (m, 2H), 1.80 – 1.74 (m, 1H), 1.46 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 148.6, 128.4, 126.4, 125.6, 65.6, 45.8, 40.0, 30.2, 25.4; **ATR-IR** ν 2960 (w), 2925 (w), 2869 (w), 1665 (w), 1445 (w), 1372 (w), 763 (m), 700 (s); **HRMS (ESI)** calcd for $C_{11}H_{20}N_2^{2+}$ $[M+2H]^{2+}$ 180.1616; found 180.1623.

**Synthesis of 4-amino-4-phenylpentanenitrile (2.328)**



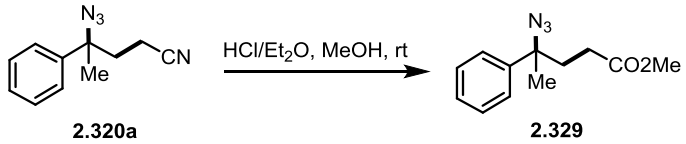

**2.320a** **2.328**

To a solution of **2.320a** (110 mg, 0.55 mmol) in EtOH (5.5 mL, 0.1 M) was added Pd/$CaCO_3$ (m/m 10%, 60 mg, 5 mol%). The reaction mixture was evacuated and filled with $H_2$ (from balloom) three times. After stirring at room temperature for 24 hours, the reaction mixture was then filtered through a plug of Celite. The resulting filtrate was concentrated in *vacuo*. The crude product was purified by

flash column chromatography on silica gel (dichloro methane/methanol 50/1) to give compound **2.328** (colorless oil, 69.0 mg, 72%).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.44 – 7.40 (m, 2H), 7.38 – 7.34 (m, 2H), 7.28 – 7.24 (m, 1H), 2.37 – 2.30 (m, 1H), 2.14 – 2.02 (m, 3H), 1.60 (s, broad, 2H), 1.53 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 146.3, 146.3, 128.8, 127.1, 125.1, 120.4, 54.7, 40.4, 32.0, 12.7; **ATR-IR** ν 2963 (w), 2927 (w), 2245 (w), 1650 (w), 1602 (w), 1445 (w), 765 (m), 700 (s); **HRMS (ESI)** calcd for $C_{11}H_{15}N_2^+$ $[M+H]^+$ 175.1230; found 175.1239.

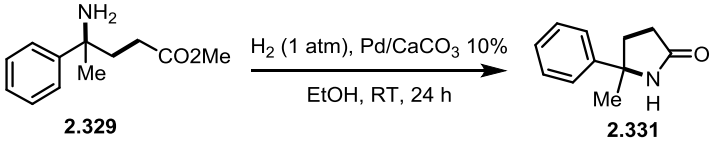
**Synthesis of 5-methyl-5-phenylpyrrolidin-2-one (2.331)**




**2.320a** **2.329**

**Step 1:** To a solution of **2.320a** (100 mg, 0.5 mmol) in MeOH (1.0 mL, 0.5 M) was added a solution of HCl in $Et_2O$ (1M, 2.0 mL). After stirring at room temperature for 24 hours, the reaction mixture was quenched with $NaHCO_3$, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo.* The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 9/1) to give compound **2.329** (colorless oil, 52.4 mg, 45%), and recover **2.320a** (51.0 mg).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.41 – 7.27 (m, 5H), 3.61 (d, *J* = 1.6 Hz, 3H), 2.43 – 2.25 (m, 1H), 2.23 – 1.99 (m, 3H), 1.71 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 173.6, 142.6, 128.8, 127.7, 125.6, 66.3, 51.8, 37.3, 29.5, 26.0; **ATR-IR** ν 2930 (w), 2246 (w), 2102 (w), 1450 (w), 1426 (w), 761 (s), 739 (s); **HRMS (ESI)** calcd for $C_{12}H_{16}N_3O_2^+$ $[M+H]^+$ 234.1237; found 234.1239.




**2.329** **2.331**

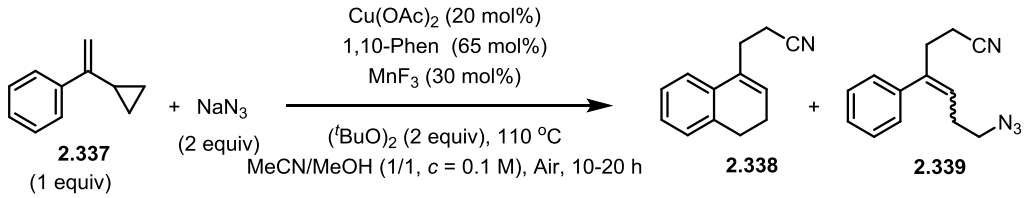
**Step 2:** To a solution of **2.329** (41.4 mg, 0.2 mmol) in EtOH (2.0 mL, 0.1 M) was added $Pd/CaCO_3$ (m/m 10%, 22 mg, 5 mol%). The reaction mixture was evacuated and filled with $H_2$ (from balloom) three times. After stirring at room temperature for 24 hours, the reaction mixture was then filtered through a short plug of Celite. The resulting filtrate was added $K_2CO_3$ (110 mg, 0.8 mmol), stirred at room temperature overnight.The reaction mixture was then extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo.* The

crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 1/2) to give compound **2.331** (colorless oil, 30.8 mg, 88%).

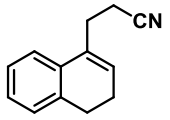
**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.23 (m, 5H), 6.84 (s, 1H), 2.53 – 2.23 (m, 4H), 1.66 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 177.8, 146.6, 128.8, 127.2, 124.6, 62.1, 37.8, 30.7, 29.6.; **ATR-IR** ν 2930 (w), 2246 (w), 2102 (w), 1450 (w), 1426 (w), 761 (s), 739 (s); **HRMS (ESI)** calcd for $C_{11}H_{14}NO^+$ $[M+H]^+$ 176.1070; found 176.1082.

### 3.7.3. Radical clock experiments

**Carboazidation reaction of (1-cyclopropylvinyl)benzene 2.337**

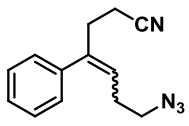



Alkene **2.337** (0.2 mmol, 1 equiv), $Cu(OAc)_2$ (20 mol%), 1,10-phenanthroline (65 mol%), $MnF_3$ (30 mol%), and $NaN_3$ (2 equiv) were dissolved in degassed MeCN/MeOH (v/v 1/1, 0.1 M) in a sealed tube. DTBP (2 equiv) was then added and the tube was sealed and heated to 110 °C. After 20 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.338**[129c] (colorless oil, 13.4 mg, 36%), and **2.339** (colorless oil, 9.0 mg, 20%).




**2.338**

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.23 – 7.12 (m, 4H), 6.00 (t, *J* = 4.5 Hz, 1H), 2.85 – 2.73 (m, 4H), 2.57 (t, *J* = 7.4 Hz, 2H), 2.32 – 2.27 (m, 2H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 137.0, 133.3, 133.2, 128.2, 127.6, 127.4, 126.7, 121.9, 119.5, 28.8, 28.2, 23.1, 16.9.

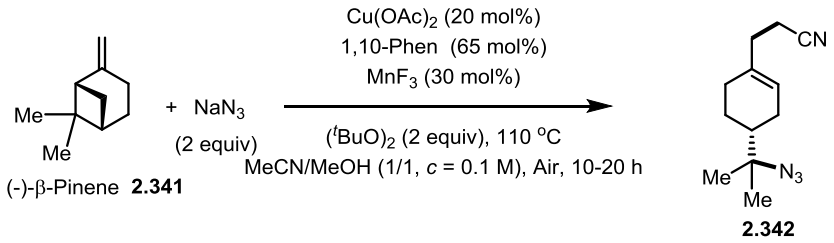



isomer ratio 2.5/1.0

**2.339**

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.20 (m, 15.5H), 7.33 – 7.11 (m, 2H), 5.70 (t, *J* = 7.4 Hz, 2.5H), 5.57 (t, *J* = 7.4 Hz, 1.0H), 3.37 (t, *J* = 6.8 Hz, 5H), 3.19 (t, *J* = 6.9 Hz, 2H), 2.83 (t, *J* = 7.3 Hz, 5H), 2.63 (t, *J* = 7.2, 2H), 2.50 (q, *J* = 7.0 Hz, 5H), 2.32 – 2.11 (m, 9H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 140.6, 140.5, 139.4, 138.3, 128.9 (2C), 128.4, 127.9, 127.8, 127.5, 126.7, 126.0, 119.19, 119.15, 51.17, 51.15, 35.2, 28.9, 28.7, 26.1, 16.6, 16.5; **ATR-IR** ν 2930 (w), 2246 (w), 2102 (w), 1450 (w), 1426 (w), 761 (s), 739 (s); **HRMS (ESI)** calcd for $C_{13}H_{15}N_4^+$ $[M+H]^+$ 227.1291; found 227.1287.

**Carboazidation reaction of (-)-β-pinene 2.341**




Alkene **2.341** (0.2 mmol, 1 equiv), $Cu(OAc)_2$ (20 mol%), 1,10-phenanthroline (65 mol%), $MnF_3$ (30 mol%), and $NaN_3$ (2 equiv) were dissolved in degassed MeCN/MeOH (v/v 1/1, 0.1 M) in a sealed tube. ($^t$BuO)$_2$ (2 equiv) was then added and the tube was sealed and heated to 110 $^o$C. After 20 h, the reaction mixture was cooled down to room temperature, diluted with water, extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give compound **2.342** (colorless oil, 18.3 mg, 42%).

**$^1$H NMR (400 MHz, $CDCl_3$)** δ 5.54 – 5.52 (m, 1H), 2.43 (td, *J* = 7.2, 0.9 Hz, 2H), 2.33 – 2.23 (m, 2H), 2.18 – 1.79 (m, 5H), 1.60 – 1.51 (m, 1H), 1.34 – 1.22 (m, 1H), 1.27 (s, 3H), 1.24 (s, 3H); **$^{13}$C NMR (101 MHz, $CDCl_3$)** δ 134.0, 123.1, 119.7, 64.1, 43.4, 32.8, 28.8, 26.8, 24.0, 24.0, 23.2, 16.2; **ATR-IR** ν 2964 (w), 2924 (w), 2924 (w), 2246 (w), 2098 (s), 1372 (w), 1260 (m), 1223 (w), 1134 w); **HRMS (ESI)** calcd for $C_{12}H_{18}N_4Na^+$ $[M+Na]^+$ 241.1424; found 241.1424.

# Bibliography


1) G. R. Humphrey, J. T. Keuthe, *Chem. Rev.* **2006**, *106*, 2875.

2) Barden, T. In *Heterocyclic Scaffolds II:*; Gribble, G. W., Ed.; Springer Berlin Heidelberg, **2010**; *Vol. 26*; pp 31.

3) Recent review on indole synthesis: (a) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195. (b) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (c) Zhang, M.-Z.; Chen, Q.; Yang, G.-F. *Eur. J. Med. Chem.* **2015**, *89*,421.

4) Review on paladdium-catalyzed indole synthesis: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (b) Song, J. J.; Reeves, J. T.; Fandrick, D. R.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Arkivoc* **2010**, *1*, 390. (c) Shi, Z.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 9220.

5) Review on Pd-catalyzed difunctionalization of alkenes: (a) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *3*, 351. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (c) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem*. **2008**, *6*, 4083. (d) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (e) Wu, W.; Jiang, H. *Acc. Chem. Res*. **2012**, *45*, 1736. (f) Kocovsky, P.; Bäckvall, J.-E. *Chem. Eur. J*. **2015**, *21*, 36. Reviews on Cu-catalyzed difunctionalization of alkenes: (g) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev*. **2007**, *36*, 1153. (h) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed*. **2011**, *50*, 11062. (i) Shimizu,Y.; Kanai, M. *Tetrahedron Lett*. **2014**, *55*, 3727.

6) Review on hypervalent iodane mediated difunctionalization of alkenes: (a) Romero, R. M.; Woste, T. H; Muniz, K. *Chem. Asian. J.* **2014**, *9*, 972. (b) Arnold, A. M.; Ulmer, A.; Gulder, T. *Chem. Eur. J.* **2016**, *22*, 8728.

7) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136

8) (a) A. Arcadi, S. Cacchi, F. Marinelli, *Tetrahedron Lett.* **1992**, *33*, 3915. (b) A. Arcadi, S. Cacchi, A. Cassetta, G. Fabrizi, L. M. Parisi, *Synlett* **2001**, 1605. (c) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synthesis* **2003**, 728. (d) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synthesis* **2004**, 1889.

9) (a) S. Cacchi, G. Fabrizi, A. Goggiamani, A. Perboni, A. Sferrazza, P Stabile, *Org. Lett.* **2010**, *12*, 3279. (b) S. Cacchi, G. Fabrizi, L. M. Parisi, *Synlett* **2000**, 394. (c) A. Arcadi, S. Cacchi, G. Fabrizi, F. Marinelli, L. M. Parisi, *J. Org. Chem.* **2005**, *70*, 6213. (d) X. Han, X. Lu, *Org. Lett.*, **2010**, *12*, 3336. (e) Mizukami, A.; Ise, Y.; Kimachi, T.; Inamoto, K. *Org. Lett.* **2016**, *18*, 748. (f) Xia, G.; Han, X.; Lu, X. *Org. Lett.* **2014**, *16*, 2058.

10) S. Cacchi, G. Fabrizi, L. M. Parisi, *Adv. Synth. Catal.* **2006**, *348*, 1301.

11) B. Z. Lu, W. Zhao, H. –X. Wei, M. Dufour, V. Farina, C. H. Senanayake, *Org. Lett*. **2006**, *8*, 3271.

12) X. Han, X. Lu, *Org. Lett.*, **2010**, *12*, 3336.

13) (a) Larock, R. C.; Kgun Yum, E. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. J. Org. Chem. **1998**, *63*, 7652. (c) Roesch, K. R.; Larock, R. C. Org. Lett. **1999**, *1*, 1551. (d) Roesch, K. R.; Larock, R. C. J. Org. Chem. **2001**, *66*, 412

14) (a) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (b) Leogane, O.; Lebel, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 350.

15) Kumi, S.; Hiroshi, Y.; Toshio, N.; Minoru, I. *Biosci., Biotechnol., Biochem.* **2008**, *72*, 2092.

16) (a) Liu, X.; Deschamp, J. R.; Cook, J. M. *Org. Lett.* **2002**, *4*, 3339. (b) Gathergood, N.; Scammells, P. J. *Org. Lett.* **2003**, *5*, 921. (c) Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Takizawa, S.; Shimamura, H.; Tomishima, M.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, 16036. (d) Shimamura, H.;

Breazzano, S. P.; Garfunkle, J.; Kimball, F. S.; Trzupek, J. D.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 7776.

17) (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Chem. Comm.* **2004**, 2824. (b) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2008**, *64*, 769.

18) (a) Ackermann, L. *Organometallics* **2003**, *22*, 4367e4368. (b) Ackermann, L.; Kaspar, L. T. *J. Org. Chem.* **2007**, *72*, 6149.

19) Ackermann, L.; Althammer, A. *Synlett* **2006**, *3*, 3125.

20) Jiao, N.; Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y. *Angew. Chem. Int. Ed.* **2009**, *48*, 4572.

21) (a) Chen, X.; Li, X.; Wang, N.; Jin, J.; Lu, P.; Wang, Y. *Eur. J. Org. Chem.* **2012**, *23*, 4380.

22) Chen, J.; Pang, Q.; Sun, Y.; Li, X. *J. Org. Chem.* **2011**, *76*, 3523.

23) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474.

24) Zhou, F.; Han, X.; Lu, X. *Tetrahedron Lett.* **2011**, *52*, 4681.

25) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257.

26) Frischmuth, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10084.

27) Shu, C.; Wang, Y.-H.; Zhou, B.; Li, X.-L.; Ping, Y.-F.; Lu, X.; Ye, L.-W. *J. Am. Chem. Soc.* **2015**, *137*, 9567.

28) (a) Michalson, E. T.; Szmuszkovicz, J. Prog. Drug Res. **1989**, *33*, 135. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (c) Saibabu Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101.

29) De Jong, S.; Nosal, D. G.; Wardrop, D. J. *Tetrahedron* **2012**, *68*, 4067.

30) Reviews on vicinal diamines: (a) Cardona, F.; Goti, A. *Nat. Chem.* **2009**, *1*, 269. (b) De Figueiredo, R. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 1190. (c) Muniz, K.; Martinez, C. *J. Org. Chem.* **2013**, *78*, 2168. (d) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665.

31) Ding, H.; Chen, D. Y.-K. *Angew. Chem. Int. Ed*. **2011**, *50*, 676.

32) (a) Fu, R.; Zhao, B.; Shi, Y. J. Org. Chem. **2009**, *74*, 7577. (b) Wen, Y.; Zhao, B.; Shi, Y. Org. Lett. **2009**, *11*, 2365.

33) K. Muniz, *J. Am. Chem. Soc.*, **2007**, *129*, 14542.

34) B. Yao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 5170.

35) Yao, B.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2014**, *20*, 12255.

36) T. Saito, S. Ogawa, N. Takei, N. Kutsumura, and T. Otani, *Org. Lett*. **2011**, *13*, 1098.

37) K. C. Majumdar, Nirupam De, B. Roy, *Synthesis*, **2010**, *24*, 4207.

38) Okano, A.; Tsukamoto, K.; Kosaka, S.; Maeda, H.; Oishi, S.; Tanaka, T.; Fujii, N.; Ohno, H. *Chem. Eur. J*. **2010**, *16*, 8410.

39) Montgomery, T. D.; Rawal, V. H. *Org. Lett.* **2016**, *18*, 740.

40) (a) Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2395. (b) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2012**, *77*, 617.

41) Hu, Z.; Tong, X.; Liu, G. *Org. Lett.* **2016**, *18*, 2058.

42) Ho, H. E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2016**, *18*, 2487.

43) Yu, J.; Zhang-Negrerie, D.; Du, Y. *Org. Lett.* **2016**, *18*, 3322.

44) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820.

45) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727.

46) Zeng, J.; Tan, Y. J.; Leow, M. L.; Liu, X. W. *Org. Lett.* **2012**, *14*, 4386.

47) Li, J.; Neuville, L. *Org. Lett.* **2013**, *15*, 1752.

48) For review on gold catalysis: (a) Garayalde, D.; Nevado, C. *ACS Catal.* **2012**, *2*, 1462. (b) Obradors, C.; Echavarren, A. M. *Acc. Chem. Res.* **2014**, *47*, 902. (c) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, *47*, 953.

49) For review on gold catalysis in heterocycles synthesis and total synthesis: (a) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (b) Debrouwer, W.; Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Adv. Synth. Catal.* **2015**, *357*, 2975. (c) Pflasterer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331.

50) Review on α-carbonyl gold carbenes: Xiao, J.; Li, X. *Angew. Chem. Int. Ed*., **2011**, *50*, 7226.

51) Talbot, E. P. A.; Richardson, M.; McKenna, J. M.; Toste, F. D. *Adv. Synth. Catal.* **2014**, *356*, 687.

52) (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (b) Wetzel, A.; Gagosz, F. *Angew. Chem, Int. Ed.* **2011**, *50*, 7354. (c) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8358.

53) Xiao, Y.; Zhang, L. *Org. Lett.* **2012**, *14*, 4662.

54) Garzón, M; Davies, P. W. *Org. Lett*. **2014**, *16*, 4850.

55) (a) Wang, Z. H.; Bois-Choussy, M.; Jia, Y. X.; Zhu, J. *Angew. Chem. Int. Ed*., **2010**, *49*, 2018; (b) Gerfaud, T.; Xie, C.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed*., **2011**, *50*, 3954; (c) Buyck, T.; Wang, Q.; Zhu, J. *Org. Lett.*, **2012**, *14*, 1338; (d) Xu, Z.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.*, **2013**, *52*, 3272.

56) (a) Crouch, R. C.; Davis, A. O.; Spitzer, T. D.; Martin,G. E.; Sharaf, M. M. H.; Schiff, Jr.,P. L.; Phoebe, Jr., C. H.; Tackie, A. N. *J. Heterocycl. Chem.* **1995**, *32*, 1077. (b) Tackie, A. N.; Boye, G. L.; Sharaf, M. H. M.; Schiff, Jr., P. L.; Crouch, R. C.; Spitzer, T. D.; Johnson, R. L.; Dunn, J.; Minick, D.; Martin, G. E. *J. Nat. Prod.* **1993**, *56*, 653. (c) Sharaf, Jr., M. H. M.; Schiff, Jr., P. L.; Tackie, A. N.; Phoebe, Jr., C. H.; Davis, A. O.; Andrews, C. W.; Crouch, R. C. *J. Heterocycl. Chem.* **1995**, *32*, 1631.

57) Li, L.; Chua, W. S. *Tetrahedron Letters* **2011**, *52*, 1574.

58) (a) Gorlitzer, K.; Kramer, C.; Meyer, H.; Walter, R. D.; Jomaa, H.; Wiesner, J. *Pharmazie*, **2004**, *59*, 243. (b) Arzel, E.; Rocca, P.; Grellier, P.; Labaed, M.; Frappier, F.; Guritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quguiner, G. *J. Med. Chem.* **2001**, *44*, 949.

59) (a) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Letters* **2010**, *51*, 6022. (b) Cirrincione, G.; Almerico, A. M.; Barraja, P.; Diana, P.; Lauria, A.; Passannanti, A.; Pani, C. A.; Murtas, P.; Minnei, C.; Marongiu, M. E.; Colla, P. *J. Med. Chem.* **2009**, *42*, 2561.

60) (a) Solé, D.; Serrano, O. *Angew. Chem. Int. Ed*. **2007**, *46*, 7270. (b) Solé, D.; Vallverdu, L.; Solans, X.; Font-Bardia, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587.

61) (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (b) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem*. **2006**, *71*, 62. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243. (d) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173. (e) Du, H.-A.; Tang, R.-Y.; Deng, C.-L.; Liu, Y.; Li, J.-H.;

Zhang, X.-G. *Adv. Synth. Catal*. **2011**, *353*, 2739. (f) Song, H.; Liu, Y.; Wang, Q. *Org. Lett.* **2013**, *15*, 3274. Friedel-Crafts type cyclization: (g) Moody, C. J.; Swann, E. *Synlett* **1998**, 135.

62) a) Jagtap, P. G. et. al., US 2004/0039009 b) Jagtap, P. G. et. al., WO 2005/082368.

63) Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Salman, A.; Szabó, C. *Org. Lett.*, **2005**, *7*, 1753.

64) Bordwell, F.G. *Acc. Chem.Res.* **1988**, *21*, 456.

65) (a) Shabat, D.; Rader, C.; List, B.; Lerner, R. A.; Barras III, C. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 6925. (b) Chen, J.; Armstrong, R. N. *Chem. Res. Toxicol.* **1995**, *8*, 580.

66) (a) Boncel, S.; Maczka, M.; Walczak, K. Z. *Tetrahedon* **2000**, *66*, 8450. (b) Chen, W.; Yu, W. –G.; Shi, H. –B.; Lu, X. –Z. *Chemical Papers* **2012**, *66*, 308. (c) Sánta-Csutor, A.; Mucsi, Z.; Finta, Z.; Gönczi, C.; Halász, J.; Csikós, É.; Hermecz, I. *Eur. J. Org. Chem.* **2006,** 1769.

67) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 12311.

68) Chen, Y.; Markina, N. A.; Larock, R. C. *Tetrahedron* **2009**, *65*, 8908.

69) Chen, Y.; Cho, C.-H.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173.

70) Ha, T. M.; Yao, B.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1750.

71) (a) Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. Curr. Med. Chem. **2003**, *10*, 925. (b) Shah, S. S. A.; Rivera, G.; Ashfaq, M. *Mini-Reviews in Medicinal Chemistry* **2013**, *13*, 70. (c) Drews, J. Science **2000**, *287*, 1960.

72) Rabasseda, X.; Hopkins, S. J. Drugs Today **1994**, *30*, 557.

73) Wroblewski, T.; Graul, A.; Castaner, J. Drugs Future **1998**, *23*, 365.

74) (a) Brzozowski, F.; Saczewski, F.; Neamati, N. Bioorg. Med. Chem. Lett. **2006**, *16*, 5298. (b) Wells, G. J.; Tao, M.; Josef, K. A.; Rihovsky, R. Med. Chem. Lett. **2001**, *44*, 3488. (c) Bihovsky, R; Tao, M.; Mallamo, J. P.; Wells, G. J. Med. Chem. Lett. **2004**, *14*, 1035. (d) Kim, S. H.; Ramu, R.; Kwon, S. W.; Lee, S. H.; Kim, C. H.; Kang, S. K.; Rhee, S. D.; Bae, M. A.; Ahn, S. H.; Ha, D. C.; Cheon, H. G.; Kim, K. Y.; Ahn, J. H. Bioorg. Med. Chem. Lett. **2010**, *20*, 1065.

75) Barange, D. K.; Nishad, T. C.; Swamy, N. K.; Bandameedi, V.; Kumar, D.; Sreekanth, B. R.; Vyas, K.; Pal, M. *J. Org. Chem.* **2007**, 8547.

76) Debnath, S.; Mondal, S. *J. Org. Chem.* **2015**, *80*, 3940.

77) Nørager, N. G.; Juhl, K. *Synthesis* **2010**, *24*, 4273.

78) Layman, W. J.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem.* **2005**, *70*, 9147.

79) Pham, M. V.; Ye, B.; Cramer, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10610.

80) Planas, O.; Whiteoak, C. J.; Company, A.; Ribas, X. *Adv. Synth. Catal.* **2015**, *357*, 4003.

81) Mi, P.; Liao, P.; Tu, T.; Bi, X. *Chem. Eur. J.* **2015**, *21*, 5332.

82) M. Harmata, K. Rayanil, M. G. Gomes, P. Zheng, N. L. Calkins, S. Kim, Y. Fan, V. Bumbu, D. R. Lee, S. Wacharasindhu, X. Hong, *Org. Lett.* **2005**, *7*, 143.

83) Ha, T. M.; Yao, B.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 5256.

84) Lavrado, J.; Moreira, R.; Paulo, A. *Curr. Med. Chem.* **2010,** 17, 2348

85) (a) Gellbert, E.; Hamet, R.; Schlitter, E. *Helv. Chim. Acta.* **1951**, *34*, 642. (b) Dwuma-Badu, D.; Ayin, J. S. K.; Figabe, N. I. Y.; Schiff, P. L.; Slatkin, D. J. *J. Pharm. Sci.* **1978**, *67*, 433. (c) Tackie, A. N.; Sharaf, M. H. M.; Schiff, P. L.; Boye, G. L.; Crouch, R. C.; Martin, G. E. *J. Heterocyclic Chem.*

**1991**, *28*, 1429. (d) Crouch, R. C.; Davis, A. O.; Spitzer, T. D.; Martin, G. E.; Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N. *J. Heterocyclic Chem.* **1995**, *32*, 1077. (e) Paulo, A.; Gomes, E. T.; Houghton, P. J. *J. Nat. Prod.* **1995**, *58*, 1485.

86) (a) Gorlitzer, K.; Ventzke-Nue, K. *Pharmazie* **1998**, *53*,1. (b) Oliver-Bever, B. E. P. *Medicinal Plants in Tropical West Africa*; Cambridge University Press: Cambridge, **1986**; pp 18, 41, 131. (c) Boakye-Yiadom, K. *Quart. J. Crude Drug Res.* **1979**, *17*,7. (c) Boye, G. L. *Proceedings of the International Symposium on East-West Medicine*, Oct. 10-11, 1989, Seoul, Korea; **1990**, pp 243. (d) Luo, J.; Fort, D. M.; Carlson, T. J.; Noamesi, B.; nii-Amon-Kotei, D.; King, S. R.; Tsai, J.; Quan, J.; Hobensack, C.; Lapresca, P.; Waldeck, N.; Mendez, C. D.; Jolad, S. D.; Bierer, D. E.; Reaven, G. M. *Diabetic Med.* **1998**, *15*, 367.

87) Mardenborough, L. G.; Zhu, X. Y.; Fan, P.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordeppey, S. Y. *Bioorganic Med. Chem.* **2005**, *13*, 3955.

88) Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Y.; Kendrick, H.; Philips, R. M.; Pollet, P. L. *J. Med. Chem*. **2001**, *44*, 3187.

89) Lavrado, J.; Borralho, P. M.; Ohnmacht, S. A.; Castro, R. E.; Rodrigues, C. M. P.; Moreira, R.; Dos Santos, D. J. V. A.; Neidle, S.; Paulo, A. *ChemMedChem* **2013**, *8*, 1648.

90) Kumar, E. V. K. S.; Etukala, J. R.; Ablordeppey, S. Y. *Mini Rev. Med. Chem.* **2008**, *8*, 538.

91) Cooper, M. M.; Lovell, J. M.; Joule, J. A. *Tetrahedron Lett.* **1996**, *37*, 4283.

92) Rádl, S.; Konvička, P.; Váchal, P. A. *J. Heterocyclic Chem.* **2000**, *37*, 855.

93) Bierer, D. E.; Dubenko, L. G.; Zhang, P.; Lu, Q.; Imbach, P. A.; Garofalo, A. W.; Phuan, P. W.; Fort, D. M.; Litvak, J.; Gerber, R. E.; Sloan, B.; Luo, J.; Cooper, R.; Reaven, G. M. *J. Med. Chem.* **1998**, *41*, 2754.

94) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 3683. (b) You, S. L. *Chem. - An Asian J.* **2007**, *2*, 820. (c) Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407. (d) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327. (e) Richter, D.; Mayr, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1958.

95) Cariou, K.; Ronan, B.; Mignani, S.; Fensterbank, L.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1881.

96) (a) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5004. (b) Pintér, Á.; Klussmann, M. *Adv. Synth. Catal.* **2012**, *354*, 701. (c) Schweitzer-Chaput, B.; Sud, A.; Pintér, Á.; Dehn, S.; Schulze, P.; Klussmann, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 13228.

97) (a) Kharasch, M.S.; Fono, A.; Nudenberg, W.; Poshkus, A. C. *J. Org. Chem.* **1950**, *15*, 775. For oxidation of acridines in absence of strong Brønsted acid to form ketone see: (b) Fukuzumi, S.; Ishikawa, M.; Tanaka, T. *J. Chem. Soc. Perkin Trans. II* **1989**, 1037.

98) Pandey, G.; Jadhav, D.; Tiwari, S. K.; Singh, B. *Adv. Synth. Catal.* **2014**, *356* (13), 2813.

99) Pappoport, Z.; Patai, S. *Chemistry of the Cyano Group*, Wiley & Sons, London, 1970. (b) Fleming, F.F.; Wang, Q. *Chem. Rev.* **2003**, *103*, 2035.

100) Mowry, D. T. *Chem. Rev.* **1948**, *42*, 189.

101) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902.

102) Reviews on nitrile synthesis: (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. (c) Wen, Q.; Jin, J.; Zhang, L.; Luo, Y.; Lu, P.; Wang, Y. *Tetrahedron Lett.* **2014**, *55*, 1271. (d) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137. (e) Bisseret, P.; Duret, G.; Blanchard, N. *Org. Chem. Front.* **2014**, *1*, 825. (f) López, R.; Palomo, C. *Angew. Chem. Int. Ed.* **2015**, *54*, 13170.

103) (a) Yang, Y.; Tang, S.; Liu, C.; Zhang, H.; Sun, Z.; Lei, A. *Org. Biomol. Chem.* **2011**, *9*, 5343. (b) Nambo, M.; Yar, M.; Smith, J. D.; Crudden, C. M. *Org. Lett.* **2015**, *17*, 50.

104) (a) Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824. (b) Jinzaki, T.; Arakawa, M.; Kinoshita, H.; Ichikawa, J.; Miura, K. *Org. Lett.* **2013**, *15*, 3750.

105) (a) Yeung, P. Y.; Chung, K. H.; Kwong, F. Y. *Org. Lett.* **2011**, *13*, 2912. (b) Shang, R.; Ji, D. S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem. Int. Ed.* **2011**, *50*, 4470. (c) (d) Recio, III, A.; Heinzman, J. D.; Tunge, J. a. *Chem. Commun.* **2012**, *48*, 142. (d) Yin, L.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 9610.

106) (a) Kosugi, M.; Kiryu, T. F.; Migita, G. Y.; Sano, H. **1984**, *Chem. Lett.* **1984**, 1511. (b) Kashin, A. N.; Tulchinsky, M. L.; Beletskaya, I. P. *J. Organomet. Chem.* **1985**, *292*, 205.

107) Arseniyadis, S.; Kyler, K.S.; Watt, D.S. *Org. React.* **1984**, *31*, 1.

108) (a) Bradamante, S.; Pagani, G. A. *J. Chem. Soc. Perkin Trans. II* **1986**, 1035. (b) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327. (c) Richard, J. P.; Williams, G.; Gao, J. *J. Am. Chem. Soc.* **1999**, *121*, 715. (d) Carlier, P. R.; Lo, C. W. S. *J. Am. Chem. Soc.* **2000**, *122*, 12819s.

109) Kumagai, N.; Matsunage, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632.

110) Ishikawa, T. *Superbases for Organic Synthesis*, John Wiley & Sons, UK, **2009**.

111) Kisanga, P.; McLeod, D.; D'Sa, B.; Verkade, J. *J. Org. Chem.* **1999**, *64*, 3090.

112) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295.

113) Bunlaksananusorn, T.; Rodriguez, A. L.; Knochel, P. *Chem. Commun.* **2001**, *8*, 745.

114) (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757.

115) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632.

116) Fan, L.; Ozerov, O. V. *Chem Commun* **2005**, *35*, 4450.

117) Aydin, J.; Conrad, C. S.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 5175.

118) (a) Yazaki, R.; Nitabaru, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 14477. (b) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195. (c) Hyodo, K.; Nakamura, S.; Tsuji, K.; Ogawa, T.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 3385. (d) Hyodo, K.; Nakamura, S.; Shibata, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 10337.

119) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 3195.

120) (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676.

121) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330.

122) You, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5051.

123) Wu, T.; Mu, X.; Liu, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 12578.

124) Wang, G.; Zhou, A.; Wang, J.; Hu, R.; Yang, S-D. *Org. Lett.* **2013**, *15*, 5270.

125) Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7523.

126) (a) Goto, A.; Endo, K.; Saito, S. *Chem. Comn.* **2008**, 2212. (b) Goto, A.; Naka, H.; Noyori, R.; Saito, S. *Chem. Asian J.* **2011**, *6*, 1740.

127) Sureshkumar, D.; Ganesh, V.; Kumagai, N.; Shibasaki, M. *Chem. Eur. J.* **2014**, *20*, 15723.

128) Luo, Y.-R. *Handbook of Bond Dissociation Energy in Organic Compound*, CRC Press, Boca Raton, **2002**

129) (a) Bunescu, A.; Wang, Q.; Zhu, J. *Chem. Eur. J.* **2014**, *20*, 14633. (b) Bunescu, A.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 3132. (c) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 5443. (d) Bunescu, A.; Wang, Q.; Zhu, J. *Org. Lett.* **2015**, *17*, 1890.

130) Chu, X.-Q.; Xu, X.-P.; Meng, H.; Ji, S.-J. *RSC Adv.* **2015**, *5*, 67829.

131) Chu, X.; Xing, Z.; Meng, H.; Xu, X.; Ji, S. *Org. Chem. Front.* **2016**, *3*, 165.

132) Wang, C.; Li, Y.; Gong, M.; Wu, Q.; Zhang, J.; Kim, J. K.; Huang, M.; Wu, Y. *Org. Lett.* **2016**, *18*, 4151.

133) Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. *Chem. Commun.* **2014**, *50*, 15049.

134) Li, Z.; Xiao, Y.; Liu, Z.-Q. *Chem. Commun.* **2015**, *51*, 9969.

135) Yamashita, T.; Yasuda, M.; Watanabe, M.; Kojima, R.; Tanabe, K.; Shima, K. *J. Org. Chem.* **1996**, *61*, 6438.

136) Yamashita, T.; Watanabe, M.; Kojima, R.; Shiragami, T.; Shima, K.; Yasuda, M. J. Photochem. Photobiol. A: Chem. **1998**, *118*, 165.

137) Yoshida, H.; Fujimura, Y.; Yuzawa, H.; Kumagai, J.; Yoshida, T. *Chem Commun* **2013**, *49*, 3793.

138) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948.

139) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020.

140) (a) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149. (b) Bovino, M. T.; Liwosz, T. W.; Kendel, N. E.; Miller, Y.; Tyminska, N.; Zurek, E.; Chemler, S. R. *Angew. Chem, Int. Ed.* **2014**, *53*, 6383.

141) (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (b) Phipps, R. J.; McMurray, L.; Ritter, S.; Duong, H. A.; Gaunt, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 10773.

142) (a) Cahard, E.; Bremeyer, N.; Gaunt, M. J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9284. (b) Cahard, E.; Male, H. P. J.; Tissot, M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2015**, *137*, 7986.

143) (a) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**. *134*, 12462. (b) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. J. *Org. Lett.* **2012**, *14* , 2882. (c) Egami, H.; Shimizu, R.; Sodeoka, M. *Tetrahedron Lett.* **2012**, *53*, 5503. (d) He, Y.-T.; Li, L.-H.; Yang, Y.-F.; Wang, Y.-Q.; Luo, J.-Y.; Liu, X.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 5687. (e) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7841. (f) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1881.

144) Cheng, J. K.; Loh, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 42.

145) (a) DeBernardis, J. F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. *J. Med. Chem.* **1987**, *30*, 178. (b) Strobel, G. A.; Ford, E.; Worapong, J.; Harper, J. K.; Arif, A. M.; Grant, D. M.; Fung, P.; Chau, R. M. W. *Phytochemistry* **2002**, *60*, 179. (c) X. Xu, F. Song, S. Wang, S. Li, F. Xiao, J. Zhao, Y. Yang, S. Shang, L. Yang and J. Shi, *J. Nat. Prod.* **2004**, *67*, 1661. (d) Y.-J. Kwon, M.-J. Sohn, C.-J. Kim, H. Koshino and W.-G. Kim, *J. Nat. Prod.* **2012**, *75*, 271.

146) Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. *Tetrahedron* **2003**, *59*, 2471.

147) Bigler, A. J.; Bøgesø, K. P.; Toft, A.; Hansen, V. Eur. J. Med. Chem. **1977**, *12*, 289.

148) Inoue, T.; Kusumi, I.; Yoshioka, M. Curr. Drug Targets: CNS Neurol. Disord. **2002**, *1*, 519.

149) Andrews, S. W.; Guo, X.; Zhu, Z.; Hull, C. E.; Wurster, J. A.; Wang, S.; Wang, E. H.; Malone, T. *U.S. Pat. Appl. Publ.* **2006**, US 20060004084 A1 20060105.

150) Praveen, C.; Iyyappan, C.; Girija, K.; Kumar, K. S.; Perumal, P. T. J. Chem. Sci. **2012**, *124*, 451.

151) (a) DeBernardis, J. F.; Arendsen, D. L.; Kyncl, J. J.; Kerkman, D. J. J. Med. Chem. **1987**, *30*, 178. (b) Houlihan, W. J.; Nadelson, J. *U.S. Patent* 37,45,165, **1973**. (c) Feichtinger, H.; Linden, H. (Ruhrchemie A.-G.), *U.S. Patent* US31,76,024, **1965**.

152) Karmakar, R.; Pahari, P.; Mal, D. *Chem. Rev.* **2014**, *114*, 6213.

153) Kobayashi, K.; Shikata, K.; Fukamachi, S.; Konishi, H. *Heterocycles* **2008**, *75*, 599.

154) Parmar, D.; Rueping, M. *Chem. Commun.* **2014**, *50*, 13928.

155) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778.

156) Hewitt, J. F. M.; Williams, L.; Aggarwal, P.; Smith, C. D.; France, D. J. *Chem. Sci.* **2013**, *4*, 3538.

157) (a) Demyanovich, V. M.; Shishkina, I. N.; Kuznetsova, A. A.; Potekhin, K. A.; Chesnova, A. V. Russ. J. Org. Chem. **2006**, *42*, 986. (b) Zhang, L.; Zhang, W.; Liu, J.; Hu, J. *J. Org. Chem.* **2009**, *74*, 2850. (c) Panda, B.; Sarkar, T. K. Tetrahedron Lett. **2008**, *49*, 6701. (d) Mihara, M.; Ishino, Y.; Minakata, S.; Komatsu, M. Synlett **2002**, 1526.

158) Eildal, J. N. N.; Andersen, J.; Kristensen, A. S.; Jørgensen, A. M.; Bang-Andersen, B.; Jørgensen, M.; Strømgaard, K. *J. Med. Chem.* **2008**, *51*, 3045.

159) (a) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767. (b) Lu, D.; Zhou, Y.; Li, Y.; Yan, S.; Gong, Y. J. Org. Chem. **2011**, *76*, 8869. (c) Brinkmann, C.; Barrett, A. G. M.; Hill, M. S.; Procopiou, P. A.; Reid, S. Organometallics **2012**, *31*, 7287.

160) Eds. Brandrup, J; Immergut, E.H.; Grulke, E.A. "*Polymer Handbook*", 4th Edition, John Wiley, New York, **1999**, II/2-69.

161) (a) Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 5915. (b) Zou, Y.; Qin, L.; Ren, X.; Lu, Y.; Li, Y.; Zhou, J. *Chem. Eur. J.* **2013**, *19*, 3504.

162) (a) Baldwin, D.; Johnson, F. N. Rev. Contemp. Pharmacother. **1995**, *6*, 315. (b) Keller, M. B. J. Clin. Psychiatry **2000**, *61*, 896. (c) Dorell, K.; Cohen, M. A.; Huprikar, S. S.; Gorman, J. M.; Jones, M. Psychosomatics **2005**, *46*, 91.

163) Tu, H. M.; Wang, Q.; Zhu, J. *Chem. Commun.* **2016**, *4*, 11100–11103.

164) (a) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, **1991**; Vol. 1, pp 476. (b) Bandichhor, R.; Nosse, B.; Reiser, O. Top. Curr. Chem. **2005**, *243*, 43. (c) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. Angew. Chem., Int. Ed. **2009**, *48*, 9426.

165) (a) Koch, S. S. C.; Chamberlin, A. R. J. Org. Chem. **1993**, 58, 2725. (b) Koch, S. S. C.; Chamberlin, A. R. Stud. Nat. Prod. Chem. **1995**, 16, 687. (c) Collins, I. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1377.

166) (a) J. B. Bush, Jr., H. Finkbeiner, *J. Am. Chem. Soc*. **1968**, *90*, 5903. (b) E. I. Heiba, R. M. Dessau, W. J: Koehl, Jr., *J. Am. Chem. Soc*. **1968**, *90*, 5905. (c) E. I. Heiba, R. M. Dessau, P. G: Rodewald, *J. Am. Chem. Soc*. **1974**, *96*, 7977;

167) Corey, E. J.; Gross, A. W., *Tetrahedron Lett.* **1985**, *26*, 4291.

168) (a) Fristad, W. E.; Hershberger, S. S., *J. Org. Chem.* **1985**, *50*, 3143. (b) Ito, N.; Nishino, H. Kurosawa, K., *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3527.

169) Wu, L.; Zhang, Z.; Liao, J.; Li, J. *Chem. Commun.* **2016**, *52*, 2628.

170) Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652.

171) Wei, X. J.; Yang, D. T.; Wang, L.; Song, T.; Wu, L. Z.; Liu, Q. *Org. Lett.* **2013**, *15*, 6054.

172) a) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc*. **1972**, *94*, 843; b) Zhang, B.; Studer, A. *Org. Lett*. **2014**, *16*, 1790. For a recent review: c) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem.* **2011**, *123*, 11256; *Angew. Chem. Int. Ed*. **2011**, *50*, 11062.

173) Niggemann, M.; Meel, M. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 3684.

174) (a) Morris, G. E.; Oakley, D.; Pippard, D. A.; Smith, D. J. H. *J. Chem. Soc. Chem. Commun.* **1987**, 411. (b) Gephart III, R. T.; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc*. **2012**, *134*, 17350.

175) (a) Vederas, J. C. *J. Am. Chem. Soc*. **1980**, *102*, 374. (b) Odabachian, Y.; Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2013**, *52*, 10878. (c) Buyck, T.; Wang, Q.; Zhu, J. *J. Am. Chem. Soc*. **2014**, *136*, 11524.

176) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624.

177) (a) Gan, L.-S.; Yang, S.-P.; Fan, C.-Q.; Yue, J.-M. *J. Nat. Prod.* **2005,** *68*, 221. For the synthesis of (±)-Sacidumlignan D: (b) Pandey, D. S. K.; Ramana, C. V. *J. Org. Chem.* **2011**, *76*, 2315. (c) Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 1566. (d) Zhang, J.-J.; Yan, C.-S.; Peng, Y.; Luo, Z.-B.; Xu, X.-B.; Wang, Y.-W. *Org. Biomol. Chem.* **2013**, *11*, 2498. (e) Xie, C.; Bai, D.; Huang, S.-H.; Jia, X.; Hong, R. *Asian J. Org. Chem*. **2014**, *3*, 277.

178) Ha, T. M.; Chatalova-Sazepin, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 9249.

179) Lefemine, D. V.; Dann, M.; Barbatschi, E.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohnos, N. *J. Am. Chem. Soc.* **1962**, *34*, 3184.

180) Kasai, M.; Kono, M. *Synlett.* **1992**, 778.

181) Vega-Pérez, J. M.; Palo-Nieto, C.; Vega-Holm, M.; Góngora-Vargas, P.; Calderón-Montaño, J. M.; Burgos-Morón, E.; López-Lázaro, M.; Iglesias-Guerra, F. *Eur. J. Med. Chem.* **2013**, *70*, 380.

182) Deecher, D. C; Abou-Gharbia, M. A. *US20060019966A1*.

183) (a) Tanner, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 599. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.

184) Degenaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881.

185) (a) Trost, B. M.; Fleming, J. E. G. I. *Comprehensive Organic Synthesis*, Pergamon, Oxford, **1991**, Vol. 7, p 467; (b) Gribble, G. W.; Gilchrist, T. L. *Progress in Heterocyclic Chemistry*, Pergamon Elsevier Science, Oxford, **2000**; Vol. 12, Chapter 4.1, p.57.

186) (a) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328. (b) Li, Z.; Conser, K. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (c) Atkinson, R. S. Tetrahedron, **1999**, *55*, 1519. (d) Pellissier, H. *Adv. Synth. Catal.* **2014**, *356*, 1899.

187) (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1995**, *34*, 676. (b) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc. Perkin Trans.* 1, **1999**, 2293.

188) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed*. **2009**, *48*, 7224.

189) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2013**, *52*, 7841.

190) Kawamura, S.; Egami, H.; Sodeoka, M. *J. Am. Chem. Soc.* **2015**, *137*, 4865.

191) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem. Eur. J.* **2013**, *19*, 6209.

192) Fort, D. A.; Woltering, T. J.; Nettekoven, M.; Knust, H.; Bach, T. *Chem Commun* **2013**, *49*, 2989.

193) Wu, K.; Liang, Y.; Jiao, N., *Molecules* **2016,** *21*, 352

194) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.

195) (a) Kolb, H. C.; Sharpless, K. B. *Drug Discov. Today* **2003**, *8*, 1128. (b) Meldal, M.; Tomøe, C. W. *Chem. Rev.* **2008**, *108*, 2952.

196) Huryn, D. M.; Okabe, M. *Chem. Rev.* **1992**, *92*, 1745.

197) Bräse, S.; Banert, K. *Organic Azides, Wiley-VCH*, Weinheim, **2010**.

198) (a) Chen, Z.-M.; Zhang, Z.; Tu, Y.-Q.; Xu, M.-H.; Zhang, F.-M.; Li, C.-C.; Wang, S.-H. *Chem. Commun.* **2014**, *50*, 10805. (b) Lu, M. Z.; Wang, C. Q.; Loh, T. P. *Org. Lett.* **2015**, *17*, 6110. (c) Yuan, Y. A.; Lu, D. F.; Chen, Y. R.; Xu, H. *Angew. Chem. Int. Ed.* **2016**, *55*, 534.

199) (a) Online, V. A.; Xu, L.; Mou, X.; Chen, Z.; Wang, S. *Chem. Commun.* **2014**, *50*, 10676. (b) Wu, Z.; Ren, R.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10821.

200) Xu, J.; Li, X.; Gao, Y.; Zhang, L.; Chen, W.; Fang, H.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 11240.

201) (a) Valiulin, R. A.; Mamidyala, S.; Finn, M. G. *J. Org. Chem.* **2015**, *80*, 2740. (b) Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *J. Org. Chem.* **2016**, *81*, 4020. (c) Chen, L.; Xing, H.; Zhang, H.; Jiang, Z.-X.; Yang, Z. *Org. Biomol. Chem.* **2016**, *14*, 7463.

202) (a) Renaud, P.; Ollivier, C.; Panchaud, P. *Angew. Chem. Int. Ed.* **2002**, *41*, 3460. (b) Weidner, K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511.

203) Lapointe, G.; Kapat, A.; Weidner, K.; Renaud, P. *Pure Appl. Chem.* **2012**, *84*, 1633.

204) Wang, F.; Qi, X.; Liang, Z.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 1881.

205) (a) Carboni, A.; Dagousset, G.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 1240. (b) Dagousset, G.; Carboni, A.; Magnier, E.; Masson, G. *Org. Lett.* **2014**, *16*, 4340.

206) (a) Fristad, W.; Brandvold, T.; Peterson, J.; Thompson, S. *J. Org. Chem.* **1985**, *50*, 3647. (b) Snider, B. B.; Lin, H. *Synth. Commun.* **1998**, *28*, 1913.

207) Liwosz, T. W.; Chemler, S. R., *Chem. Eur. J.* **2013,** *19*, 12771.

208) Li, Y.; Studer, A., *Angew. Chem. Int. Ed.* **2012**, *51*, 8221.

# Curriculum Vitae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## EDUCATION

**06/2012-present** **PhD,** École Polytechnique Fédérale de Lausanne EPFL, Switzerland
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**09/2009-08/2010** **PhD**, Faculty of Chemistry, Hanoi University of Science - Vietnam National University, Hanoi (**unfinished**)

**09/2005-06/2009** **BS,** *Talented Student Program*, Faculty of Chemistry, Hanoi University of Science - Vietnam National University, Hanoi
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## WORK EXPERIENCES

**06/2012-present** **Research Assistant,** laboratory of Synthesis and Natural Product LSPN, EPFL
**Supervisor:** Prof. Dr. Jieping ZHU
"Development of chemical transformation in difunctionalization of C-C multiple bonds by palladium and copper catalysis"

**03/2011-06/2011** **Research Assistant,** laboratory of Dr. René GRÉE, UMR6226, Rennes, France
***"****Towards to total synthesis of Isodunnianin, a natural product with neurotrophic properties"*
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**07/2009-02/2010** **Research Assistant,** Organic Synthesis Laboratory No.3**,** Faculty of Chemistry, Hanoi University of Science - Vietnam National University Hanoi
*"Synthesis and investigation of the characteristics of biodiesel fuel from Fish Oil and Jatropha oil in Vietnam"*
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**06/2007-06/2009** **Research Assistant**, Organic Synthesis Laboratory No.3, Faculty of Chemistry, Hanoi University of Science - Vietnam National University Hanoi
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*"Synthesis and investigation of the characteristics of 5-(4-acetamido-2-halogen-phenyl)-1,3,4-oxadizol-2-thiol"*

## TEACHING EXPERIENCE

**Spring 2015** **Teaching Assistant** in **Organic chemistry laboratory work** (CH-233) – Practical course for 2nd year bachelor students, *EPFL*

**Autumn 2014** **Teaching Assistant** in **Organic chemistry laboratory work** (CH-233) – Practical course for 2nd year bachelor students, *EPFL*

**Autumn 2014** **Teaching Assistant** in **Organic functions and reactions II** (CH-233) – Theoretical course for 2nd year bachelor students, *EPFL*

**Spring 2014** **Teaching Assistant** in **Total synthesis of natural products** (CH-438)– Theoretical course for master students, *EPFL*

**Spring 2014** **Teaching Assistant** in **Preparative chemistry I** (CH-239) – Practical course for 2nd year bachelor students, *EPFL*

**Autumn 2013** **Teaching Assistant** in **Organic functions and reactions II** (CH-233) – Theoretical course for 2nd year bachelor students, *EPFL*

**2010-2012** **Private Tuition** for high school student in chemistry courses, Vietnam

## POSTERS AND PRESENTATIONS

1. **Oral presentation and Poster:** *"Synthesis of tetracyclic Indole-containing compounds by Pd(II)-catalyzed diamination of alkynes and retro-Michael reaction"*, NCCR Chemical Biology retreat, June **2013**, Villars, Switzerland.
2. **Poster presentation:** *"Synthesis of Indolo[3,2-b]quinolinone derivatives by simple acid-mediated reactions"*, NCCR Site Visit, Octobor **2014**, EPFL, Switzerland.
3. **Poster presentation:** *"Synthesis of Aziridines by Copper catalyzed amino-cyanomethylation of unactivated alkenes"*, NCCR Chemical Biology retreat, June **2015**, Villars, Switzerland.
4. **Poster presentation:** *"Copper catalyzed cyanomethylation of unactivated alkenes"*, NCCR Chemical Biology retreat, June **2016**, Villars, Switzerland.

## HONORS AND AWARDS

**2012-16** NCCR (National Centre of Competence in Research, Switzerland) doctoral fellowship

**2008** **Third Prize** in the **Student's Research Contest**, Vietnam Ministry of Education and Training
**Third Prize** of **VIFOTEC** (Viet Nam Fund for Technology Creation)
**Second Prize** in the **Student's Research Contest**, Vietnam National University Hanoi

**2005** **First prize** at the **National Contest of Chemistry** for excellent high school students, Ministry of Education and Training

**2004** **Bronze Medal** at the 36th **International Chemistry Olympiad (IChO)**
**First prize** at the **National Contest of Chemistry** for excellent high school students, Ministry of Education and Training

**2004** & **2006** **Outstanding student and promotive scientist honor**, Vietnam National University Hanoi

**2004** & **2006** **Recontres du Vietnam Scholarship** for Academic Excellent, Recontres du Vietnam Organization

## SKILLS/ABILITIES

**Fluent in English**

**Computer Proficient** (Microsoft Windows All versions, Microsoft Word, Excel, Power Point, etc)

**Technical Proficient** (Organic synthesis, Purification techniques, Schlenk and Glove-box technique, NMR, MS, IR, …)

## PUBLICATIONS

1. **T. Ha**, Y. Bo, Q. Wang, J. Zhu, "2‑(Methoxycarbonyl)ethyl as a Removable N‑Protecting Group: Synthesis of Indoloisoquinolinones by Pd(II)-Catalyzed Intramolecular Diamination of Alkynes", *Organic Letters* **2015**, *17*, 1750-1753 (T. Ha and Y. Bo contributed equally).

2. **T. Ha**, Y. Bo, Q. Wang, J. Zhu, "Sulfonamide and Tertiary Amine as Nucleophiles in Pd(II)-Catalyzed Diamination of Alkynes: Synthesis of Tetracyclic Indolobenzothiazine S,S-Dioxides", *Organic Letters* **2015**, *17*, 5256-5259.

3. **T. Ha**, C. Chatalova-Sazepin, Q. Wang, J. Zhu, "Copper-Catalyzed Formal [2+2+1] Heteroannulation of Alkenes, Alkylnitriles and Water to γ-Butyrolactones: Development and Application to a Total Synthesis of (±)-Sacidumlignan D", *Angew. Chemie Int. Ed.* **2016**, 55, 9249 – 9252.

4. **T. Ha**, Q. Wang, J. Zhu, "Copper-Catalysed Cyanoalkylative Cycloetherification of Alkenes to 1,3-Dihydroisobenzofurans: Development and Application to the Synthesis of Citalopram", *Chem. Comm.* **2016**, *accepted*, DOI: 10.1039/C6CC06356J.

5. A. Bunescu, **T. Ha**, Q. Wang and J. Zhu, "Copper-Catalyzed Intermolecular Carboamination of Unactivated Alkenes with Alkyl Nitriles and azide: Efficent route to access β-aminoacids", *manuscript in preparation* (A. Bunescu and T. Ha contributed equally).

6. **T. Ha**, Q. Wang and J. Zhu, "Synthesis of aziridines by Copper catalyzed amino-cyanomethylation of unactivated alkenes", *manuscript in preparation*.

7. **T. Ha**, Q. Wang and J. Zhu, "Synthesis of Indolo[3,2-b]quinolinone derivatives by simple acid-mediated reactions", *manuscript in preparation.*

## REFERENCES

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