Université de Montréal

# Carbon-carbon bond formation: from transition metal catalysis to base-promoted homolytic aromatic substitution

par

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Thèse présentée à la Faculté des études supérieures et postdoctorales
en vue de l'obtention du grade de *Philosophiae Doctor* (Ph.D.)
en chimie

Juin, 2014

Université de Montréal

Faculté des études supérieures et postdoctorales

Cette thèse intitulée:

# Carbon-carbon bond formation: from transition metal catalysis to base-promoted homolytic aromatic substitution

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# Résumé

Cette thèse de doctorat porte sur la catalyse à partir de métaux de transition et sur la substitution homolytique aromatique favorisée par une base visant à former de nouvelles liaisons C–C, et à ainsi concevoir de nouvelles structures chimiques. Au cours des vingt dernières années, des nombreux efforts ont été réalisés afin de développer des méthodologies pour la fonctionnalisation de liens C–H, qui soient efficaces et sélectives, et ce à faible coût et en produisant le minimum de déchets. Le chapitre d'introduction donnera un aperçu de la fonctionnalisation directe de liens C–H sur des centres $sp^2$ et $sp^3$. Il sera également discuté dans cette partie de certains aspects de la chimie radicalaire reliés a ce sujet. Les travaux sur la fonctionnalisation d'imidazo[1,5-*a*]pyridines catalysée par des compleces de ruthénium seront présentés dans le chapitre 2. Malgré l'intérêt des imidazo[1,5-*a*]azines en chimie médicinale, ces composés n'ont reçu que peu d'attention dans le domaine de la fonctionnalisation de liens C–H. L'étendue de la réaction et l'influence des effets stériques et électroniques seront détaillés.

Les cyclopropanes représentent les 10ème cycles carbonés les plus rencontrés dans les petites molécules d'intérêt pharmacologique. Ce sont aussi des intermédiaires de synthèse de choix pour la création de complexité chimique. Malgré de grands progrès dans le domaine de la fonctionnalisation de liens $C(sp^3)$–H, l'étude des cyclopropanes comme substrats dans les transformations directes est relativement nouvelle. Le chapitre trois présentera l'arylation intramoléculaire directe de cyclopropanes. Cette réaction est réalisée en présence de palladium, en quantité catalytique, en combinaison avec des sels d'argent. Des études mécanistiques ont réfuté la formation d'un énolate de palladium et suggéreraient plutôt une étape de métallation - déprotonation concertée. En outre, les cycles de type benzoazepinone à sept chaînons ont été synthétisés par l'intermédiaire d'une séquence d'activation de cyclopropane/ouverture/cyclisation. Une arylation directe intermoléculaire des cyclopropanes a été réalisée en présence d'un auxiliaire de type picolinamide (Chapitre 4).

Les deux derniers chapitres de ce mémoire de thèse décriront nos études sur la substitution homolytique aromatique favorisée par une base. Le mécanisme de la réaction de cyclisation intramoléculaire d'halogénures d'aryle, réalisée en présence de *tert*-butylate de potassium, a été élucidé et se produit via une voie radicalaire (Chapitre 5). La transformation, exempte de métaux de transition, ne nécessite que la présence d’une base et de pyridine comme solvant. Cette réaction radicalaire a été étendue à la cyclisation d'iodures d'alkyle non activés en présence d'un catalyseur à base de nickel et de bis(trimethylsilyl)amidure de sodium comme base (Chapitre 6). Des études de RMN DOSY ont démontré une association entre le catalyseur, la base et le matériel de départ.

**Mots-clés** : catalyse, activation C–H, métal de transition, substitution homolitique aromatique, *tert*-butylate de potassium, phénanthridines, cyclopropanes, imidazo[1,5-*a*]azines.

# Abstract

The dissertation will focus on transition metal catalysis and base-promoted homolytic aromatic substitution as a means of forming new C–C bonds, and thus designing new chemical scaffolds. During the last twenty years, tremenduous efforts have been expended to achieve low-cost, waste-free, efficient and selective C–H bond functionalization methodologies. The introductory chapter will provide an overview of direct functionalization of C–H sp$^2$ and sp$^3$ centers, as well as discuss relevant topics in radical chemistry. Work on the ruthenium-catalyzed functionalization of imidazo[1,5-*a*]pyridines will be presented in Chapter 2. Despite interest from the medicinal chemistry field, imidazo[1,5-*a*]azines have received little attention in the C–H functionalization field. The scope of the reaction and, in particular, the influence of sterics and electronics will be detailed.

Cyclopropanes represent the 10th most encountered rings in small drug synthesis. They are also valuable synthetic intermediates en route to more chemical complexity. Despite great advances in the field of C(sp$^3$)–H functionalizations, the exploration of cyclopropanes as substrates in direct transformations is relatively novel. Chapter three will present the intramolecular direct arylation of cyclopropanes. A combination of palladium catalysis in presence of a silver salt was found to mediate the reaction. Mechanistic studies disproved the formation of a palladium-enolate and pointed towards a concerted metalation-deprotonation pathway. Furthermore, seven-membered benzoazepinone rings were synthesized via a cyclopropane activation/opening/cyclization sequence. An intermolecular direct arylation of cyclopropanes was achieved in presence of a picolinamide auxiliary (Chapter 4).

The last two chapters of the thesis will describe our studies on base-promoted homolytic aromatic substitution. A potassium *tert*-butoxide-promoted intramolecular cyclization of aryl halides was shown to occur through a radical pathway (Chapter 5). The transition metal-free transformation occurred in the sole presence of the base and pyridine as the solvent. The radical process was extended to the cyclization of unactivated alkyl iodides in presence of a nickel catalyst and sodium hexamethyldisilzide as the base (Chapter 6). DOSY NMR studies demonstrated an association between the catalyst, base and starting material.

**Keywords**: catalysis, C–H functionalization, transition metal, homolytic aromatic substitution, potassium *tert*-butoxide, phenanthridines, cyclopropanes, imidazo[1,5-*a*]azines.

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# List of abbreviations

| | |
|---|---|
| Å | Angstrom |
| Ac | acetyl |
| acac | acetoacetate |
| Ad | adamantane |
| 1-AdCO$_2$H | 1-adamantanecarboxylic acid |
| AIBN | azobisisobutyronitrile |
| APPI | Atmospheric Pressure Photoionization |
| Ar | aryl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| BQ | benzoquinone |
| Bu | butyl |
| Bz | benzoyl |
| cat | catalyst |
| Cbz | carboxybenzyl |
| CDC | cross-dehydrogenative coupling |
| CMD | concerted metalation-deprotonation |
| CI | chemical ionization |
| coe | cyclooctene |
| Cy | cyclohexyl |
| Cyp | cyclopentyl |

| | |
|---|---|
| DavePhos | 2-dicyclohexylphosphino-2’-(*N,N*-dimethylamino)biphenyl |
| dba | dibenzylideneacetone |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DG | directing group |
| DMA | dimethylacetamide |
| DMEDA | *N,N*’-dimethylethylenediamine |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| diphos | 1,2-bis(diphenylphosphino)ethane |
| dppf | 1,1'-bis(diphenylphosphino)ferrocene |
| dr | diastereomeric ratio |
| *E* | *entgegen* |
| EDG | electron donating group |
| *ee* | enantiomeric excess |
| $Et_2O$ | diethyl ether |
| EtOAc | ethyl acetate |
| equiv | equivalent |
| Et | ethyl |
| ESI | electrospray ionization |
| EWG | electron withdrawing group |
| FT-IR | Fourier-transform infrared spectroscopy |

| | |
|---|---|
| GC-MS | Gas Chromatography Mass Spectrometry |
| *gem* | geminal |
| h | hour |
| HAS | Homolytic Aromatic Substitution |
| Het | heterocycle |
| HMDS | hexamethyldisilazide |
| HOMO | Highest Occupied Molecular Orbital |
| HMBC | Heteronuclear Multiple Bond Correlation |
| HPLC | High Performance Liquid Chromatography |
| HRMS | High Resolution Mass Spectrometry |
| hυ | light |
| Hz | hertz |
| *i*Bu | *iso*-butyl |
| ICP-AES | Induced Coupled Plasma Atomic Emission Spectrometry |
| *i*Pr | *iso*-propyl |
| *J* | coupling constant |
| kcal | kilo calorie |
| kJ | kilo Joule |
| KIE | kinetic isotope effect |
| L | ligand |
| LC-MS | Liquid Chromatography Mass Spectrometry |
| LRMS | Low Resolution Mass Spectrometry |
| LUMO | Lowest Unoccupied Molecular Orbital |

| | |
|---|---|
| M | metal |
| *m* | *meta* |
| Me | methyl |
| MeCN | acetonitrile |
| $MesCO_2H$ | 2,4,6-trimethylbenzoic acid |
| MHz | megahertz |
| min | minute |
| mp | melting point |
| MS | molecular sieves |
| N/D | not determined |
| NHC | *N*-heterocyclic carbene |
| NMP | *N*-methylpyrrolidone |
| NMR | Nuclear Magnetic Resonance |
| Nu | nucleophile |
| nOe | nuclear Overhauser effect |
| *o* | *ortho* |
| OAc | acetate |
| OPiv | pivalate |
| *p* | *para* |
| Pin | pinacol |
| PivOH | pivalic acid |
| Ph | phenyl |
| PhDavePhos | 2-diphenylphosphino-2'-(*N,N*-dimethylamino)biphenyl |

| | |
|---|---|
| Phen | phenanthroline |
| PhPhen | bathophenanthroline |
| pKa | acid dissociation constant |
| PMB | *p*-methoxybenzyl ether |
| PNP | phenylnorbornylpalladium(II) dimer |
| ppm | parts per million |
| py | pyridine |
| $\rho$ | reaction constant |
| R | substituent |
| rac | racemic |
| rt | room temperature |
| SFC | Supercritical Fluid Chromatography |
| $\mathrm{S_EAr}$ | electrophilic aromatic substitution |
| $\mathrm{S_NAr}$ | nucleophilic aromatic substitution |
| SOMO | Singly Occupied Molecular Orbital |
| *t*Bu | *tert*-butyl |
| TFA | trifluoroacetic acid |
| $\mathrm{Tf_2O}$ | triflic anhydride |
| THF | tetrahydrofuran |
| TLC | Thin Layer Chromatography |
| TMEDA | tetramethylethylenediamine |
| TTMSS | tris(trimethylsilyl)silane |
| *Z* | *zusammen* |

*To my mentors and my friends*

# Remerciements

I would like to express my gratitude to the Chemistry Department at the Université de Montréal for being so welcoming with an anglophone student (merci beaucoup!). The administrative staff has always been nice and helpful and I would like to thank them. I am also grateful to all the members of the NMR team (Dr. Minh Tan Phan-Viet, Dr. Cédric Malveau, Silvie Bilodeau and Antoine Hamel), the Centre for Mass Spectral Analysis (Alexandra Furtos, Karine Venne, Marie-Christine Tang and Christophe Camy), Francine Bélanger-Gariépy for X-ray analysis, Elena Nadezhina for elemental analysis, and the machine shop (Louis Beaumont, Yves Teasdale, Jean-François Myre) for always taking care of Lab D.

My studies would not have been possible without financial assistance from the Natural Science and Engineering Council of Canada, Centre for Green Chemistry and Catalysis, Fonds de recherche Nature et technologies Québec, my supervisor André B. Charette and the Université de Montréal (Faculté des Études Supérieures et Postdoctorales and the Department of Chemistry).

I would like to show my greatest appreciation to my project collaborators: Dr. Yoko Takahashi, Dr. James Mousseau, Dr. Louis-Philippe Bonhomme-Beaulieu, Carolyn Ladd, Frédéric Vallée, and Guillaume Pelletier for your constant dedication on our respective projects, and for having the patience to work with me. One big thank you to my past mentors, for your guidance and your teachings (Dr. Raj Dhiman, Dr. Iain Watson, Dr. James Mousseau and Prof. Frédéric Menard). I've also been lucky to supervise three students (David Gareau, Valentin Poiret and Inna Khazieva) and I hope I've been a good mentor to you.

Thank you to the past and present members of the Charette group for making every day a little more than ordinary – Will, Vince, Scott, Guillaume B., Guillaume P., Sharon, LP, Yoko, Alex, Gérald, Chandra, Sam, Sylvain, Léa, Éric, Max, Pat, Philip, Seb, Dominic, Lucie, Marie-Noelle, Elsa. My Lab D labmates, James, Fred, Jakob, Carolyn, Maria, Callum, thanks for being awesome, but also putting up with my music taste and my constant complaining.

I will be eternally grateful to Barbara Bessis for always being there to answer all my questions, the numerous favours, and for helping me with the formatting of the thesis. Also, I had lots of fun planning parties and events with you!

To my supervisor, André Charette: firstly, thank you for taking a little scared girl from Toronto in your group. Secondly, I appreciate the trust you placed in me, as well as the independence I was given throughout my PhD (for that, you are indeed a unique supervisor). Thirdly, merci for all your encouragement, as well as your critiques, they have made me a better chemist. Lastly, I fondly remember an e-mail from you on Monday, May 16, 2011 with the subject line "Congratulations!! You beat them!" – that was one instant when we beat our scoopers!

Thank you to my parents and brother for always travelling to Montréal to help me through my many moves, as well as your financial and emotional support, and my grandparents in Romania for always thinking about me and sending me lots of presents. I would also like to acknowledge my friends from Toronto, whom I haven't seen too much in the last five years, but I hold you close in my heart (Jenny, Beatriz, Lu, Matt, Amy, Peter, Jon, Andreea). My friends from Montréal (Naïma, Sharon, Antoinette, John, Araceli, Lucie, Lizette, Chouettes Coquettes, Mia San Montréal), I am grateful for spending time outside the lab with you. Herzchen, vielen dank für alles, du bist der beste!

I would like to thank my co-workers Carolyn, Jakob, Guillaume, Éric, Louis and Martin for taking the time to proofread this document. I would like to express my gratitude to my PhD committee members (Profs. Hélène Lebel and Shawn Collins) for your guidance in the last four years. Thank you to Prof. Glenn Sammis for agreeing to read my dissertation.

*Our Stories End*

By Folly & the Hunter

*"Biking home, listening to song birds that signal the dawn up ahead,*
*While these streets are familiar, the Mile End has changed in my head.*
*Like the other ones, you have gone and our story has come to an end,*
*There is seldom an action that create results I intend.*

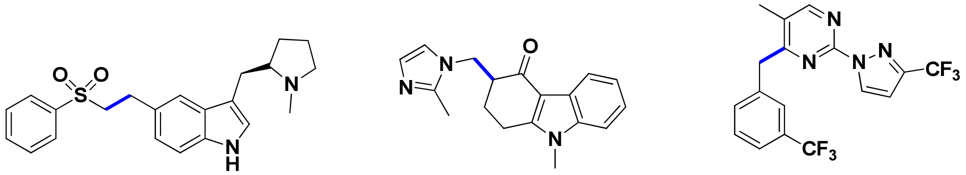
*Strong ideas take so much space that you feel you have died when they've left,*
*But a warmth is replacing the regret held in my chest.*
*Montréal, I wish I could blame you but I'm the one breaking me down,*
*They say you eat your children but people spill blood on the ground.*

*You can't run from the decisions you make in the heat of the sun*
*They led me to the dark while the dominos fell one by one*
*But I'm moving on, as regret fades and the past is now put in its place*
*Cares burn away, so we are all moving on."*

Music and lyrics: Folly & the Hunter (http://www.follyandthehunter.com/wordpress/)
(Link to song on youtube: https://www.youtube.com/watch?v=Bfr2arJ-_eA)

# Chapter 1: C–C bond formation

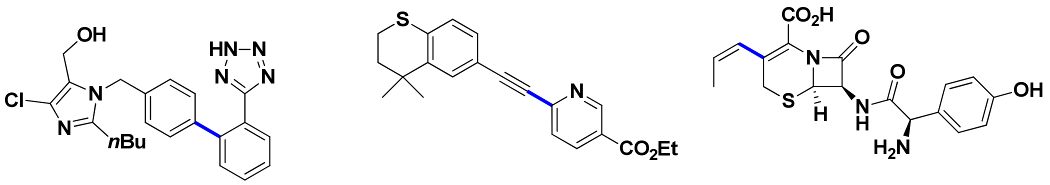
The rapid and efficient assembly of complex chemical structures is highly desired in organic synthesis. In the last two centuries, an enormous number of reactions and reagents have been developed in order to ease the process of chemical synthesis. In particular, carbon-carbon bond forming reactions have played a significant role in shaping organic chemistry. For example, the Grignard,[1] Diels-Alder[2] or Wittig[3] reactions have certainly changed the world of synthesis, and their contribution has been recognized by the Nobel Prize committee.[4] Cross-couplings represent a special category of carbon-carbon bond forming reactions, in which a transition metal, usually in a catalytic amount, is employed to combine two partners, which in some cases require to be synthesized. Cross-couplings have already shown tremendous applications in the synthesis of pharmaceuticals, herbicides, electronics, materials etc. (**Figure 1**).[5] In 2010, the Nobel Prize in chemistry[4] was awarded to three cross-coupling pioneers: Richard Heck, Eichii Negishi and Akira Suzuki.



**Eletriptan (Pfizer)**
**Heck**

**Ondansetron (GlaxoSmithKline)**
**Heck**

**DPX-MY926 (DuPont)**
**Negishi**



**Losartan (Merck)**
**Suzuki-Miyaura**

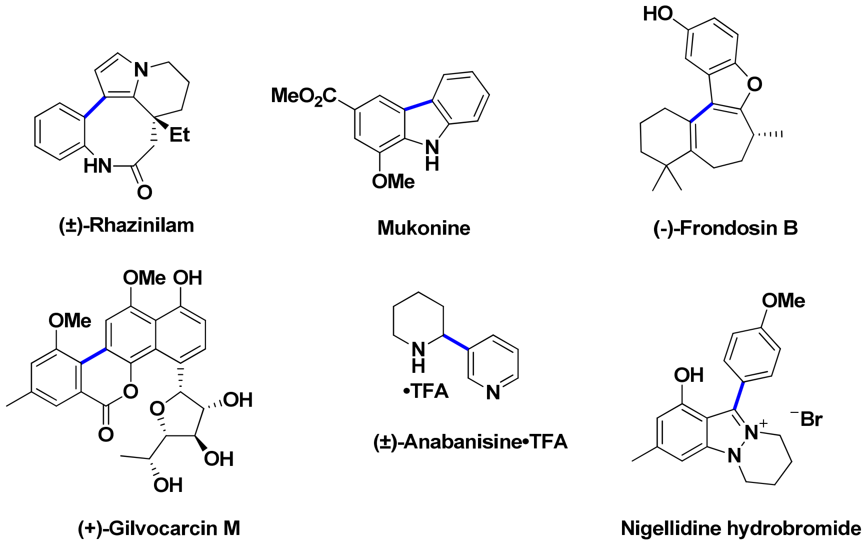
**Tazarotene (Allergan)**
**Sonogashira**

***cis*-Cefropozil (Bristol-Myers Squibb)**
**Stille**

**Figure 1**. Examples of pharmaceuticals that employed a cross-coupling step in their synthesis

Cross-couplings are highly efficient reactions, they are run under mild conditions, and demonstrate excellent functional group tolerance and selectivity. One commonly encountered criticism to cross-couplings (except the Heck reaction) is the need for two pre-activated coupling partners, which is wasteful to the overall atom economy of the process. In addition, the use of stoichiometric amounts of organometallic reagents with moderate to high toxicity (for example, organotin reagents) may affect the applicability of some of the transformations in the pharmaceutical industry. Despite the drawbacks, the number of publications and patents related to carbon-carbon bond formation via cross-couplings is on the rise, with the Suzuki-Miyaura transformation being the most popular in an industrial setting.[6]

Sustainable chemistry, or green chemistry, refers to the design of processes that reduce or eliminate the use or generation of hazardous substances.[7] The twelve principles of green chemistry also underline the importance of atom economy, catalysis and energy efficiency. Based on the principles, the ideal carbon-carbon bond forming reaction should involve the oxidative coupling of two C–H bonds in presence of a reusable catalyst. Oxidative couplings or cross-dehydrogenative couplings (CDC) have already been developed,[8] but most often suffer from issues such as selectivity or high reaction temperature. Considerable effort has instead focused on the functionalization of C–H bonds with a pre-formed coupling partner (most often an aryl or alkyl halide). **Figure 2** contains selected examples of total syntheses where C–H functionalization was applied.[9] Such strategies for C–H functionalization were also the focus of a significant amount of work during the PhD research presented herein and will be further discussed.



(±)-Rhazinilam

Mukonine

(-)-Frondosin B

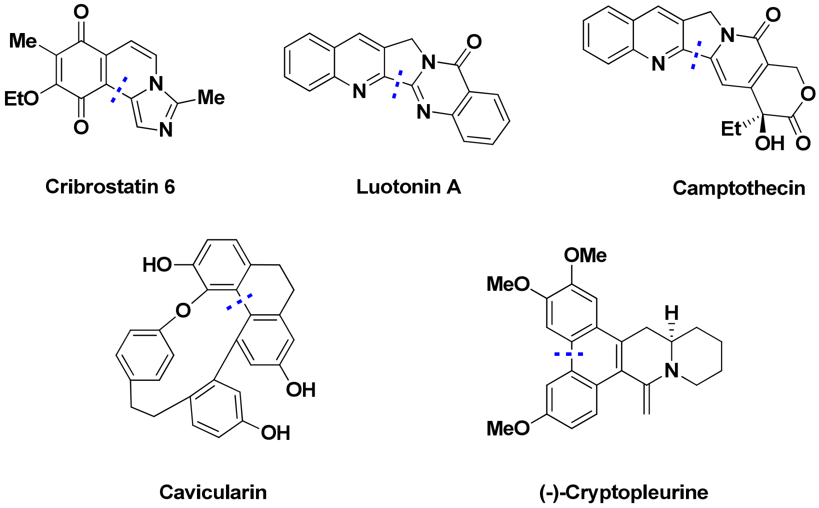
(+)-Gilvocarcin M

(±)-Anabanisine•TFA

Nigellidine hydrobromide

**Figure 2**. Selected examples of C–H activation in total synthesis

A different approach for C–C bond formation is represented by radical reactions. In particular, homolytic aromatic substitution (HAS) has become a common methodology in organic synthesis.[10] A number of natural products and current drug targets have been synthesized via HAS strategies (**Figure 3**).[11] Of late, HAS promoted by a strong base, such as potassium *tert*-butoxide, has gathered a lot of attention in the chemical community,[12] and the last part of the thesis will be dedicated to the advances of the methodology.



Cribrostatin 6

Luotonin A

Camptothecin

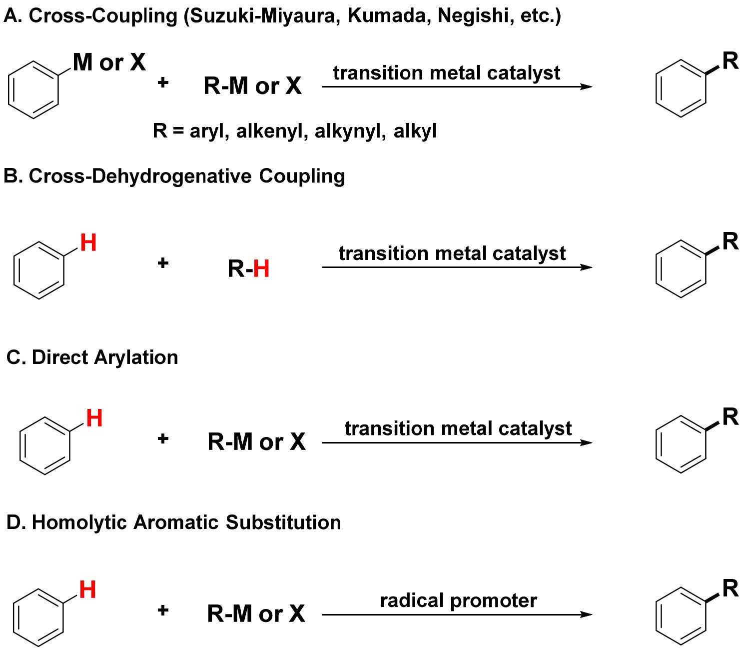
Cavicularin

(-)-Cryptopleurine

**Figure 3**. Examples of natural products synthesized via an HAS reaction

**Scheme 1** provides a short summary of all the C–C bond forming strategies discussed thus far, exemplified by C(sp$^2$)–R (where R = aryl, alkenyl, alkynyl, alkyl, M = metal, and X = halogen) bond formation.

**Scheme 1**. Approaches for the synthesis of C(sp$^2$)–R bonds



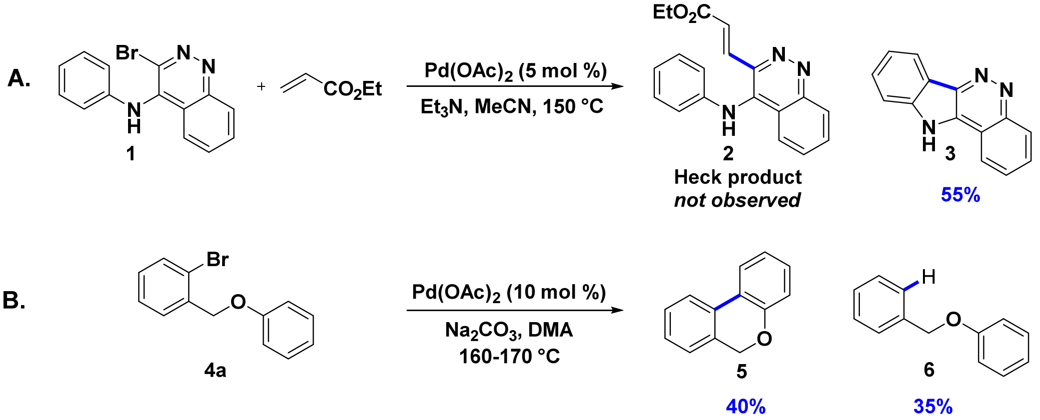
## 1.1 Direct arylation strategies

In recent years, the direct coupling of an aryl C–H bond (bond dissociation energy 113 kcal/mol for benzene)[13] with a pre-activated arene partner has emerged as a reliable and efficient method for the synthesis of biaryl-containing molecules, both inter- and intramolecularly.[14] A particular challenge is site selectivity, which refers to the preferred reaction of one C–H bond in the molecule versus all others. In an intramolecular system, regioselectivity is influenced by the use of a tether, which limits the degree of freedom in the system.[14a] In an intermolecular system a number of factors contribute to site selectivity, such as electronics of the arene, or the use of directing groups.[14a] The next sections will provide an overview of the strategies employed to improve efficiency and selectivity in direct transformations, as well as describe mechanistic considerations.

### 1.1.1 Intramolecular direct arylation

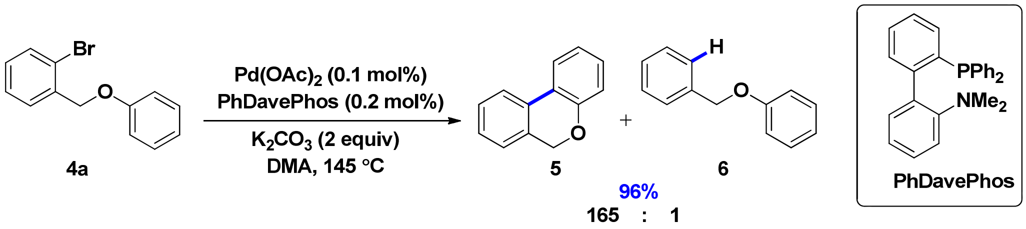
A couple of early examples of intramolecular arylation of a C–H bond were reported by the group of Ames.[15] While attempting to functionalize bromocinnoline scaffold **1** via a Heck reaction, the only product observed was the five-membered ring **3** resulting from direct arylation (55%, **Scheme 2A**).[15a] The former strategy was further applied to the synthesis of benzofurans and benzopyrans (**Scheme 2B**, example for benzopyran **5**).[15b,c] In addition to the low yield, a significant problem with the reaction was the formation of high amounts of debrominated ether **6** (35% yield, **Scheme 2B**).

**Scheme 2**. Ames' early examples of intramolecular direct arylation[15]



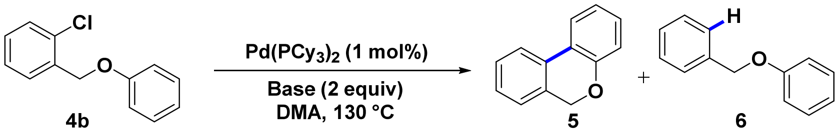
Later, Fagnou's group looked at improving the arylation-to-hydrodehalogenation ratio of Ames' benzopyran system.[16,17] Initial results revealed that the employment of PhDavePhos as a ligand for Pd in presence of the inorganic base potassium carbonate provided the products in 96% yield, with a 165 to 1 ratio of benzopyran **5** to dehalogenated product **6** (**Scheme 3**).[16a]

**Scheme 3**. Fagnou's synthesis of benzopyran[16a]



Even though the system was ideal for the cyclization of aryl bromides, aryl chlorides showed poor reactivity. An in-depth look at ligand effects for the cyclization of aryl chloride **4b** showed that sterically hindered alkyl phosphines such as $PCy_3 \cdot HBF_4$ and $P(tBu)_2Me \cdot HBF_4$ led to higher reactivities than the previously employed aryl phosphines.[17] A significant base effect was also noted and summarized in **Table 1**.[17] $K_2CO_3$ was most effective (entry 1), while other carbonate bases ($Na_2CO_3$ and $Cs_2CO_3$) provided low conversions and decreased selectivities (entries 2 and 3). KOAc provided good selectivity for the benzopyran product, but lower conversions (entry 4), while $K_3PO_4$ resulted in poor conversion and selectivity (entry 5). The strong, non-nucleophilic base KO*t*Bu gave a good conversion, but significant amounts of hydrodehalogenated product **6** (entry 6). Aryl iodides of type **4** could also be cyclized; however, it was found necessary to add a silver additive (such as $Ag_2CO_3$ or AgOTf) in order to sequester the iodide produced. In absence of the silver additive, the iodide had been revealed to inhibit the palladium catalyst, thus shutting down the reaction.[17]

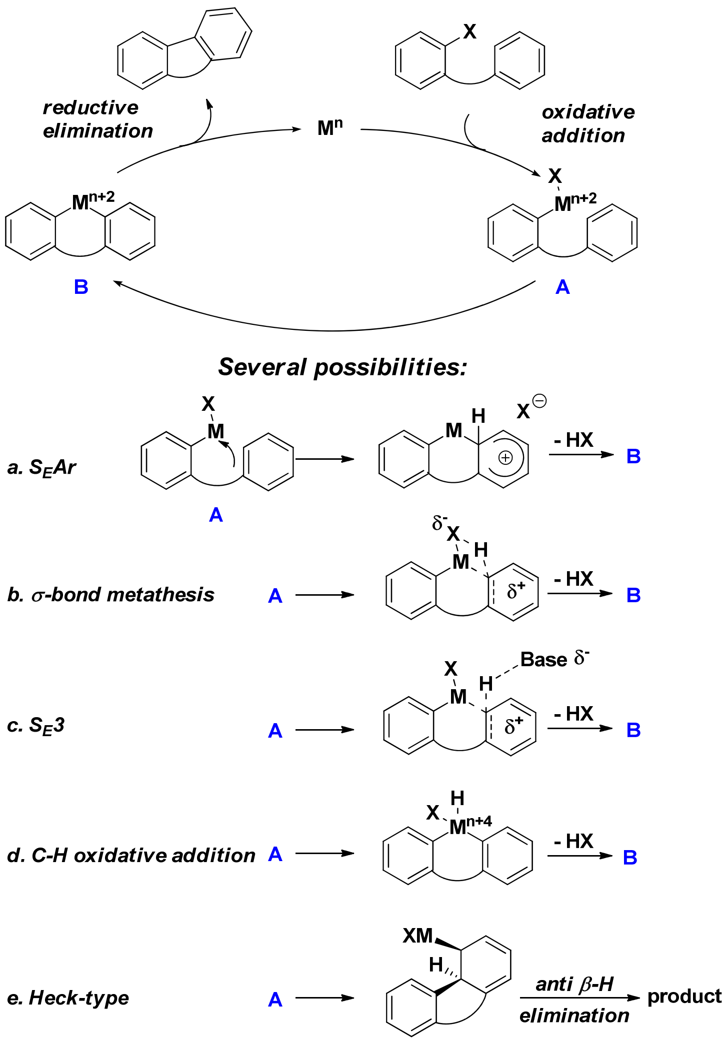
**Table 1**. Base effects in the intramolecular direct arylation of simple arenes[17]



| entry | base | conversion (%) | ratio **5**:**6** |
|---|---|---|---|
| 1 | $K_2CO_3$ | 100 | >99:1 |
| 2 | $Na_2CO_3$ | 11 | 20:1 |
| 3 | $Cs_2CO_3$ | 25 | 15:1 |
| 4 | KOAc | 81 | >99:1 |
| 5 | $K_3PO_4$ | 13 | 5:1 |
| 6 | KO*t*Bu | 84 | 2.3:1 |

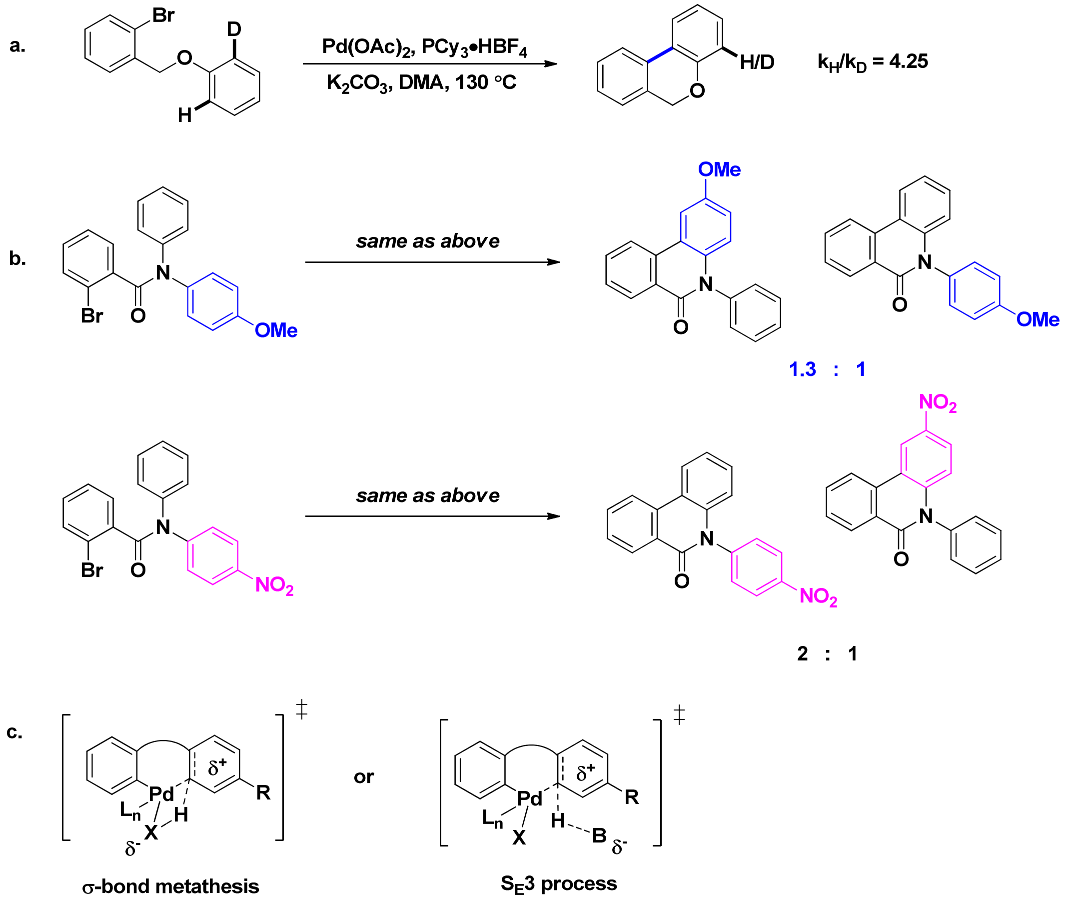
It is worth going over several mechanistic possibilities for direct arylation reactions, as they will repeatedly be discussed throughout the introduction. All the reactions presented thus far follow a classic $Pd^{0/II}$ catalytic cycle, where the first and last steps are always oxidative addition and reductive elimination, while the middle steps have been the target of much debate over the last few decades (**Scheme 4**). Electrophilic aromatic substitution ($S_EAr$, **Scheme 4a**), which involves attack of the arene onto the metal centre has been proposed by Ames in his studies.[15] $S_EAr$ has also been confirmed to occur in several other direct arylation transformations, including the Pd-catalyzed, domino reaction first introduced by Catellani.[18] The concomitant formation of the M–C and X–H bonds is represented by σ-bond metathesis (**Scheme 4b**). DFT calculations have suggested the pathway to be common in direct arylation.[19] A related process, concerted metalation-deprotonation (CMD), implies a simultaneous metalation and intramolecular deprotonation mechanism and will be discussed in Section 1.1.3. An $S_E3$ process is also plausible, where an external base is involved in the arene deprotonation step (**Scheme 4c**).[17] Oxidative addition by two C–H bonds onto the metal centre is another possibility (**Scheme 4d**).[8] Finally, a Heck-type mechanism (**Scheme 4e**) has also been suggested; however, the process implies a rare *anti* β-hydride elimination, or an isomerization followed by a *syn* β-hydride elimination.[9c] A variety of experiments can be employed to provide insights into the reaction mechanism, such as kinetic isotope effect (KIE) determination, labelling and competition studies, Hammett plots, etc. and these will be discussed according to each example presented.

**Scheme 4**. Direct arylation pathways (exemplified in an intramolecular fashion)



Fagnou and co-workers determined a primary kinetic isotope effect of 4.25, and it was incorrectly suggested that the C–H bond breaking event is the limiting step of the transformation (**Scheme 5a**);[17] the observation of a KIE in the intramolecular competition experiment in **Scheme 5a** cannot on its own predict that C–H cleavage is rate-determining.[20] Intramolecular competition experiments revealed a small selectivity for electron-rich rings (**Scheme 5b**), while Echavarren's earlier findings were of no strong electronic bias in direct arylation reactions.[21] A likely proposal for the mechanism is either σ-bond metathesis or an $S_E3$ process, in which the base, potassium carbonate, deprotonates the arene (**Scheme 5c**).

**Scheme 5**. Fagnou's mechanistic studies and transition state proposals[17]



## 1.1.2 Intermolecular direct arylation

In intramolecular transformations, proximity of the two coupling partners induced by the use of a tether aids in product formation. That is not the case in intermolecular reactions, thus several strategies have been explored in order to increase the yields and especially the selectivities. **Figure 4** presents an overview of the strategies, divided into substrate and catalyst based-control.[22] The metal-catalyzed, direct functionalization of simple, unactivated arenes is quite uncommon (due to their low nucleophilicity), hence the presence of a heteroatom in the ring or a substituent that may alter the pKa of the C–H bond to be functionalized plays an important role.[14b] Perhaps the most applied and, at the same time, most useful strategy is the employment of directing groups. The aforementioned strategy can be further divided into "proximal" effects, where, for example, the transformation takes place at the *ortho* position of an arene, or remote functionalizations, where the reaction takes place several bonds away from the directing group.[22a] Catalysts or ligands can also dictate selectivity and influence the reaction outcome.

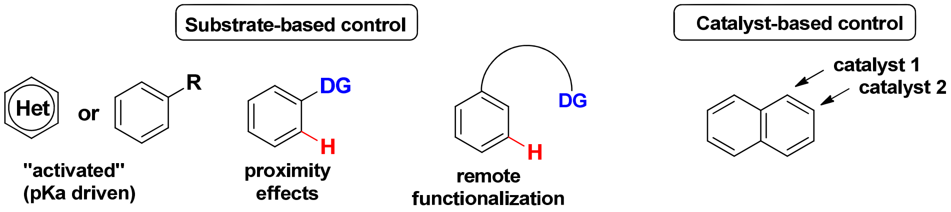
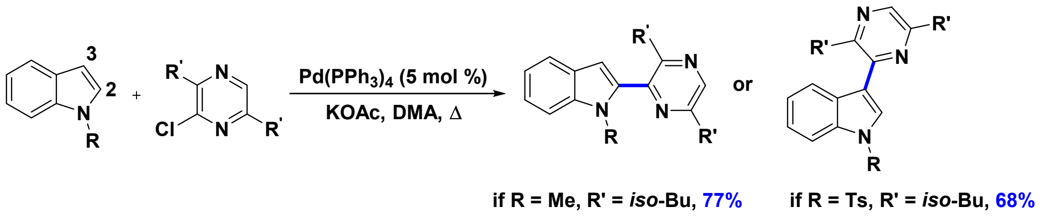


**Figure 4**. Strategies for intermolecular direct functionalizations[22]

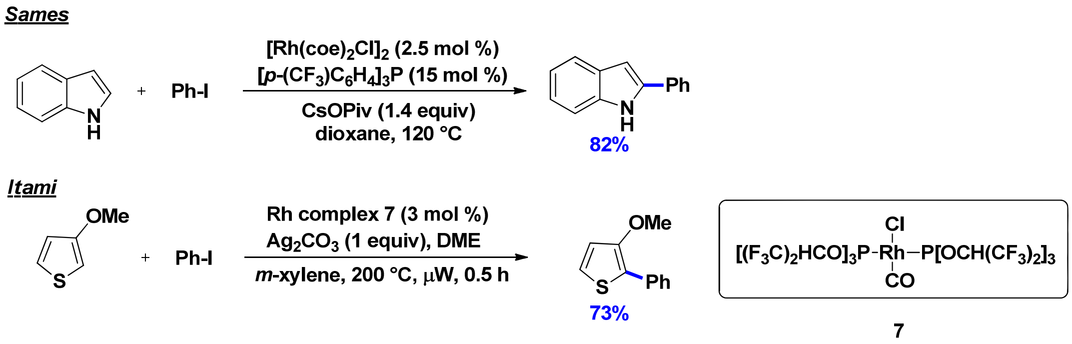
In 1989, Ohta and co-workers reported one of the first examples of heterocyclic direct arylation.[23] Targeting the indole system, it was demonstrated that the *N*-protecting group can dictate the reaction outcome, as one can get a selective arylation at the C-2 position (if R = Me) or the C-3 position (if R = Ts, 50:1 ratio for the C-3 to the C-2 position) (**Scheme 6**).

**Scheme 6**. Ohta's strategy for indole arylation[23]



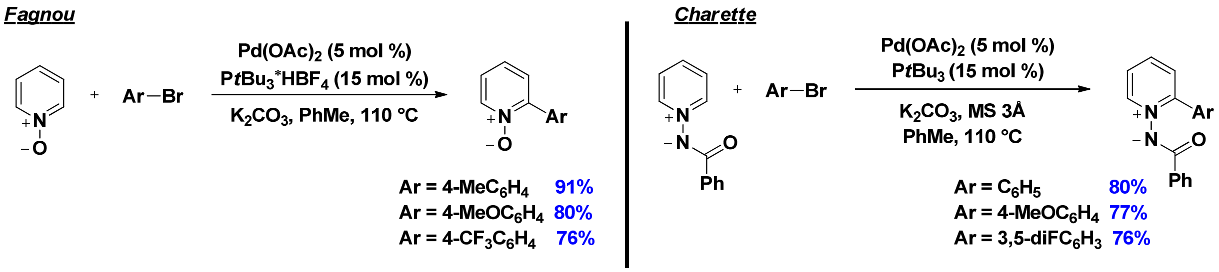
Later, Sames described the Rh-catalyzed arylation of unprotected (free NH) indoles and pyrroles (**Scheme 7**).[24] A selective C-2 arylation occurred in presence of $[Rh(coe)_2Cl]_2$ as the catalyst, triphenylphosphine as the ligand and the weak base cesium pivalate. Other functionalities that were tolerated under the conditions included carbamate, carboxamide, and sulfonamide. The proposed mechanism involved a $Rh^{I/III}$ catalytic cycle, in which CsOPiv activated the catalyst to form a rhodium pivalate species responsible for the C–H activation process.[24] Itami and co-workers also employed a Rh catalyst for the direct arylation of the thiophene core with aryl iodides (**Scheme 7**).[25] In Itami's case, the use of a strongly π-acceptor phosphine ligand, $P[OCH(CF_3)_2]_3$ was key to the transformation. Notably, the reaction is performed under microwave radiation and further arylation of the substrate can be suppressed by the addition of dimethoxyethane.

**Scheme 7**. Rh-catalyzed arylation of heterocycles[24,25]



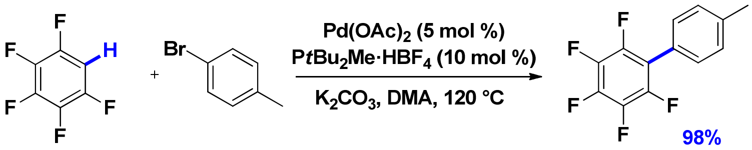
The direct arylation of other electron deficient heterocycles, such as pyridines, is challenging, due to their high Lewis basicity. The Fagnou group developed conditions for the direct functionalization of pyridine *N*-oxides instead (**Scheme 8**).[26] The *N*-oxide functionality decreased the pKa of the 2-position of the heterocycle, and prevented binding of the transition metal to the pyridine nitrogen, which could cause catalyst poisoning. The Charette group explored *N*-iminopyridinium ylides in direct arylation, alkenylation and other transformations.[27] The pyridinium ylide is easily installed in two steps, and its role is both in activating the pyridine ring and as a directing tool for the transition metal. Both the *N*-oxide and pyridinium ylide moieties could be deprotected under reductive conditions.

**Scheme 8**. Arylation of pyridine *N*-oxides and *N*-iminopyridinium ylides[26,27]



C–H bond acidity was further exploited by the Fagnou group in the arylation of pentafluorobenzene with aryl bromides (**Scheme 9**).[28] The Pd-catalyzed transformation exhibited a complete reversal of activity from the S$_E$Ar pathway,[29] as the more electron-deficient arene reacted preferentially during competition experiments. Computational studies demonstrated that the C–H bond breaking event occurred through a concerted metalation-deprotonation pathway, where the bicarbonate ion played an important role.[28]

**Scheme 9**. Fagnou's arylation of pentafluorobenzene[28]



Chemists have turned to the employment of directing groups to tackle the problem of C–H site selectivity. Many such chelating groups have been made popular, including phenols, amides, amines, carbamates, sulfonamides, phosphates, pyridines, oxazoles, etc.[14d,22] The above-mentioned groups are usually located in a proximal position to the site being targeted (for example, in the *ortho* position of the arene) and are strong σ-donors and π-acceptors. In fact, the directing group plays a dual role: it activates the arene, and also guides the transition metal to the desired reaction site. **Figure 5** provides an overview of the most used *ortho*-directing groups in direct arylations.

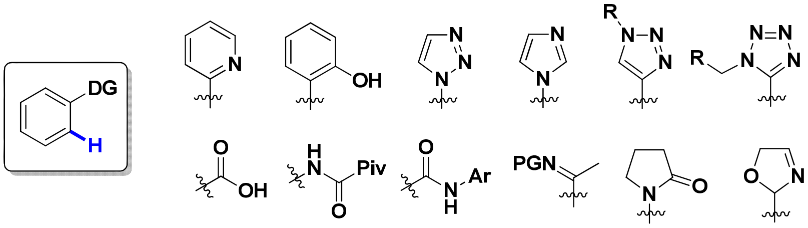


**Figure 5**. An overview of *ortho*-directing groups in direct functionalizations

The inspiration for directing groups originated from the isolation of the first metallacycle species (**Figure 6**). Upon heating azobenzene with dicyclopentadienylnickel, Kleiman and Dubeck isolated the first metallacycle in 1963.[30] Two years later, Cope and Siekmann isolated the corresponding Pd and Pt metallacycles.[31]

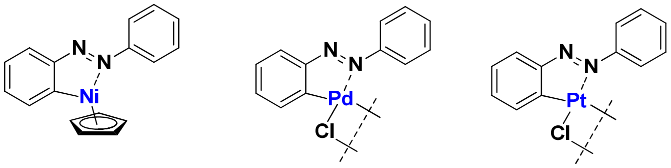
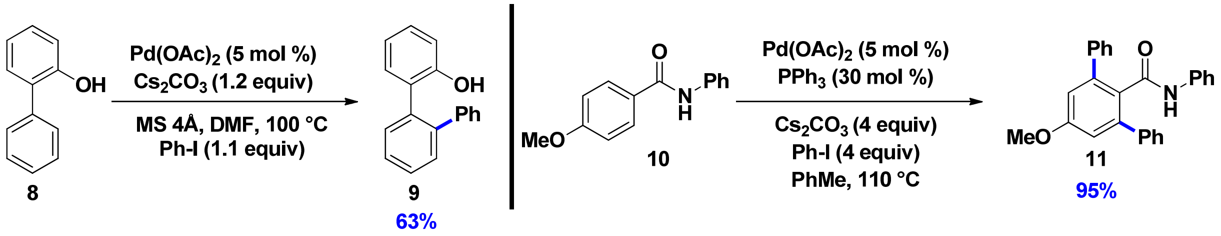


**Figure 6**. First isolated azobenzene metallocycles (Ni, then Pd and Pt)[30,31]

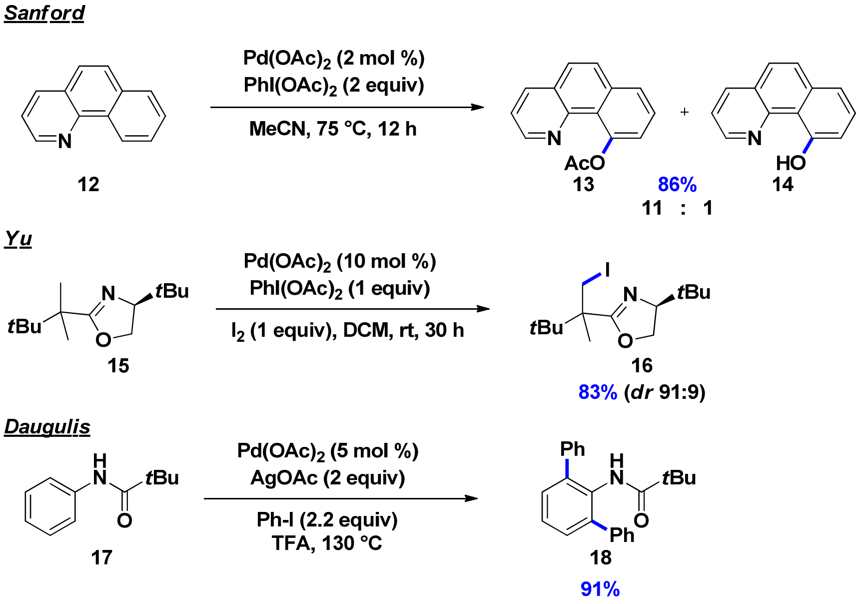
Early work exploiting the just-mentioned findings is scarce;[32] but, in 1997, Miura and co-workers reported the arylation of a phenolic substrate **8** under $Pd^{0/II}$ catalysis (**Scheme 10**).[33a] It was speculated that key to the reaction was the formation of a Pd-phenolate intermediate, responsible for the C–H activation step. A diarylated product could also be obtained if large excess of the aryl iodide was used. The initial findings were followed by another report, where an acetanilide substrate **10** acted as a chelating group for Pd, to provide diarylated products from reaction with aryl triflates or bromides.[33b] Preliminary mechanistic investigations suggested that a free N–H group was important to the reaction outcome, and presumably involved in a chelation with the Pd catalyst.

**Scheme 10**. Miura's direct arylation of phenols and acetanilides[33]

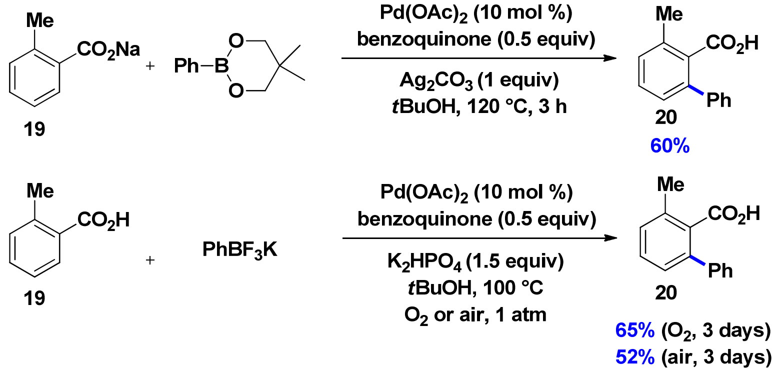


Interest in these types of transformations sparked when Sanford[34] and Yu[35] disclosed a direct acetoxylation and iodination, respectively (**Scheme 11**). In presence of two equivalents of the oxidant diacetoxyiodobenzene, benzo[*h*]quinoline **12** was functionalized via Pd catalysis. No over-oxidation was observed, but a mixture of acetoxylated and phenol products were isolated (**13**:**14**, 11:1).[34] Employing a chiral oxazole auxiliary **15** derived from (*S*)-*tert*-leucinol, the Yu group were successful in obtaining the iodinated product **16** in presence of one equivalent diacetoxyiodobenzene, iodine and catalytic palladium acetate.[35] Daugulis and Zaitsev later disclosed an arylation utilizing an anilide chelating group (**Scheme 11**).[36] Arene **17** was arylated twice via Pd catalysis in presence of stoichiometric silver acetate, acting as a base. The previous three reactions are all presumed to occur via a Pd$^{II/IV}$ catalytic cycle (**Scheme 16**, *vide infra*), although a Pd$^{II/III}$ catalytic cycle cannot be excluded.[37]

**Scheme 11**. Direct functionalizations employing chelating groups[34,35,36]



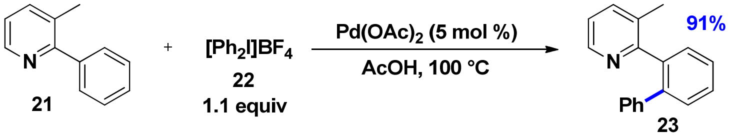
**Scheme 12**. Yu's use of carboxylic acids as directing groups[38]



The employment of carboxylic acids as directing groups for palladium was first disclosed by the group of Yu.[22a] An initial report looked at the functionalization of aryl carboxylates **19** with boronic esters as coupling partners, but the yields were modest and the substrate scope limited;[38a] a subsequent report by the same group improved the yields by utilizing potassium aryltrifluoroborates as coupling partners, while the reaction was promoted by air or oxygen, thus avoiding the use of a silver oxidant (**Scheme 12**).[38b] The reaction time (3 days) could be decreased if increased pressures of oxygen (20 atm) were applied. The reaction pathways were proposed to involve a Pd$^{II/0}$ cycle (**Scheme 16**, *vide infra*).

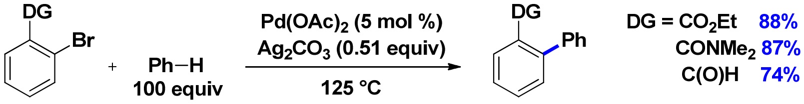
In analogy to the oxygenation reactions employing PhI(OAc)$_2$, the Sanford group sought to explore other iodine-based reagents for direct functionalizations.[39] Iodonium (III) salts, such as **22**, were found to be successful arylating agents for a variety of heterocyclic directing groups including pyridines, quinolines, pyrrolidinones and oxazolidinones (**Scheme 13**). The iodonium salts were predicted to promote a Pd$^{IV}$ species during the catalytic cycle, the step later being proved to be rate-limiting.[39b] Additionally, the reaction conditions showed high functional group tolerance, good regioselectivity and relatively mild conditions (the reaction could also be run under air). However, the disadvantage lies in synthesizing the iodonium arylating agents, as many of these are not commercially available.

**Scheme 13**. Iodonium arylating agents in direct functionalizations[39]



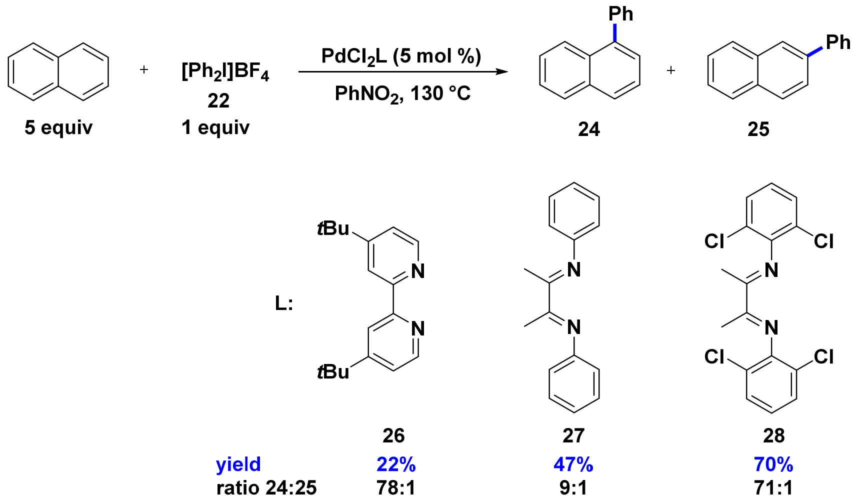
In 2010, our group disclosed an Umpolung direct arylation (**Scheme 14**).[40] The reaction exhibited an unusual reverse in polarity, whereby, in contrast with the reports described above, the aryl bromide was placed *ortho* to the directing group in order to aid with oxidative addition of the transition metal. As such, unactivated arenes (such as benzene or toluene) could be added in high yields to aryl bromides containing sensitive functional groups such as esters, amides, aldehydes and ketones. A key feature of the reaction was the requirement of catalytic acetate, the reaction shutting down in its absence. The reaction mechanism was presumed to occur via a Pd$^{II/IV}$ cycle, where the silver additive aided in the oxidative addition step.[40]

**Scheme 14**. Charette's Umpolung direct arylation[40]



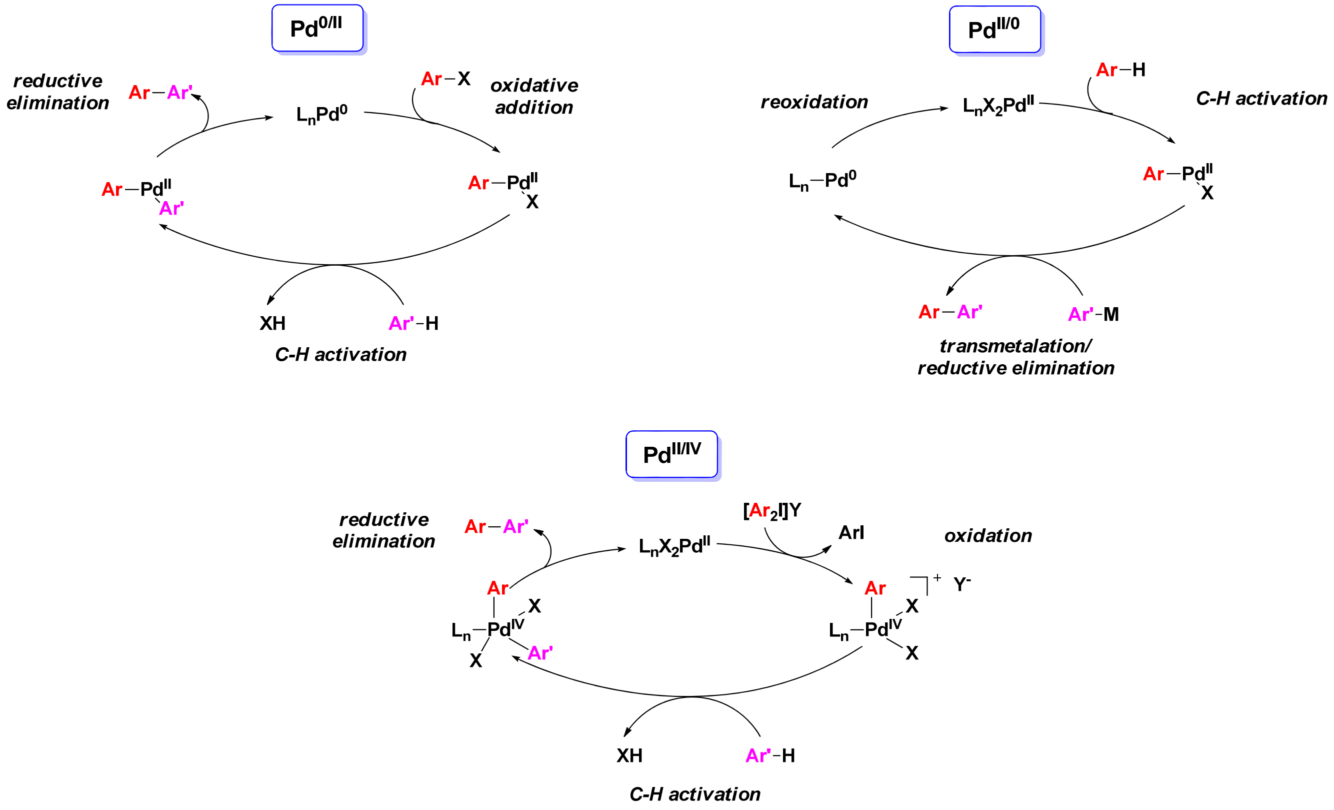
Site-selective direct arylation of unactivated arenes was achieved by the Sanford group through catalyst-based control.[41] Upon exploring a variety of diamine-ligated Pd catalysts in combination with iodonium salts for the arylation of naphthalene, a significant ligand effect was observed (**Scheme 15**). For example, diamine **26** gave excellent selectivity for product **24**, but a low yield, while the Cl-substituted diimine **28** provided both good yields and selectivites. No significant correlation was found between the regioselectivities and the electronics or sterics of the ligands; however, studies into the mechanism supported a Pd$^{II/IV}$ pathway, with oxidative addition being the rate limiting step (the KIE obtained was 1.0, thus C–H activation was not the rate-limiting step).[41]

**Scheme 15**. Regioselective arylation of naphthalene[41]



Many of the intermolecular reactions discussed in the current section occurred through catalytic cycles different from the classical $Pd^{0/II}$ cross-coupling reaction. **Scheme 16** depicts a summary of the proposed mechanistic pathways for many of the functionalization reactions described throughout the introduction. In **Scheme 16**, the details of the C–H activation step were omitted, as the possibilities were already depicted in **Scheme 4**. In-depth discussion about these mechanisms, as they relate to the work in the present thesis, will take place in later chapters.

**Scheme 16**. Catalytic cycles involving palladium catalysts



## 1.1.3 Carboxylate-assisted direct arylation

It has been long established that acetate bases promote the formation of Ir, Pt or Pd cyclometalated complexes.[42] Acetate-assisted reactions have also been the target of extensive mechanistic and computational work, especially probing the nature of the transition state for C–H bond metalation.[43] For the *ortho*-palladation of *N,N*-dimethylbenzylamines with palladium acetate, a reaction initially explored by Ryabov and co-workers, an electrophilic mechanism was proposed.[44] The key features of the mechanism were: (i) the formation of a Wheland-like intermediate and (ii) the implication of an acetate group, coordinated to the Pd centre, in the deprotonation of the arene (**Figure 7**). Later, computational studies favoured agostic interactions in the transition state, over the Wheland-like intermediate (**Figure 7**).[19]

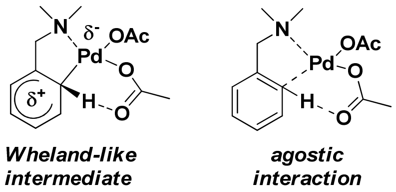
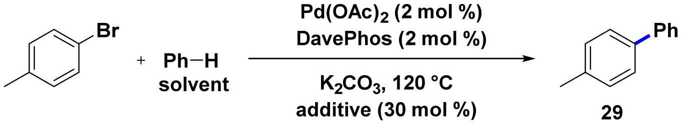


**Figure 7**. Proposed intermediates by Ryabov[44] and Davies[19]

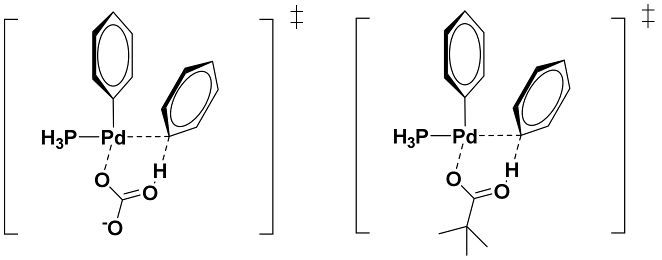
In their arylation reaction with pentafluorobenzene (**Scheme 9**, *vide supra*), the Fagnou group determined that arene nucleophilicity was not important for reactivity, but the acidity of the C–H bond was.[28] The observation led them to the application of carboxylic acids for C–H bond functionalization.[45] The Pd-catalyzed coupling of benzene with 4-bromotoluene did not occur in the absence of an additive (**Table 2**, entry 1); per contra, the addition of 30 mol % acetic acid resulted in 20% conversion (entry 2). Moreover, catalytic pivalic acid provided 100% conversion and 82% yield of the desired biaryl **29** (entry 3). Increasing the steric bulk of the additive (adamantyl carboxylic acid, entry 4) gave inferior results. Use of the base KOPiv in stoichiometric quantities (with the omission of $K_2CO_3$ and PivOH) led to the formation of toluene (through dehalogenation) and the homocoupled side product.[45] DFT calculations determined that transition state **30**, involving deprotonation by a bicarbonate ion, is higher in energy than transition state **31** with pivalic acid (26.2 versus 24.9 kcal/mol, **Scheme 17**).[45]

**Table 2**. Screen of additives for the coupling of benzene with 4-bromotoluene[45]



| entry | additive | conversion | yield **29** (%) |
|---|---|---|---|
| 1 | --- | <5 | 0 |
| 2 | AcOH | 20 | 11 |
| **3** | **PivOH** | **100** | **82** |
| 4 | 1-$AdCO_2H$ | 60 | 36 |

**Scheme 17**. Comparison of transition state energies[45]

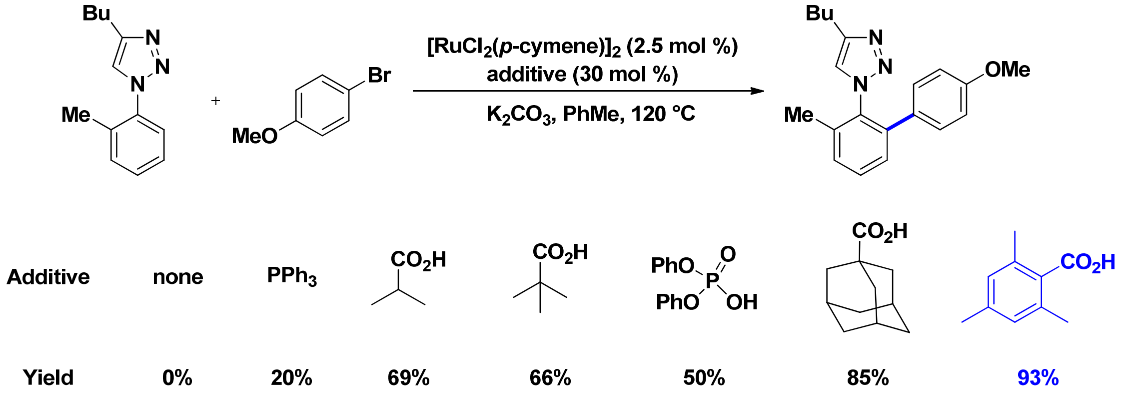


**30**
**26.2 kcal/mol**

**31**
**24.9 kcal/mol**

The beneficial effect of pivalic acid was applied to an intramolecular system,[46] where Fagnou and co-workers were able to lower the reaction temperature to 45 °C, while still providing 100% conversion of **4a** (**Scheme 3**, *vide supra*); it should be noted that the phosphine ligand used was P(*p*-FPh)$_3$. Again, the result could be rationalized through the formation of a Pd-pivalate species, which could undergo the concerted metalation-deprotonation step. A wide range of heterocycles such as thiophene, benzothiophene, furan, pyrrole, thiazole, triazole, imidazole, etc. also underwent direct arylation with aryl bromides in presence of catalytic pivalic acid at 100 °C; notably, only one equivalent of the heteroarene partner was used in the reaction.[47] A great number of palladium-catalyzed direct arylations employing pivalic acid as an additive have now been reported in the literature.[43]

**Scheme 18**. Use of carboxylates in Ru-catalyzed direct arylation[48]

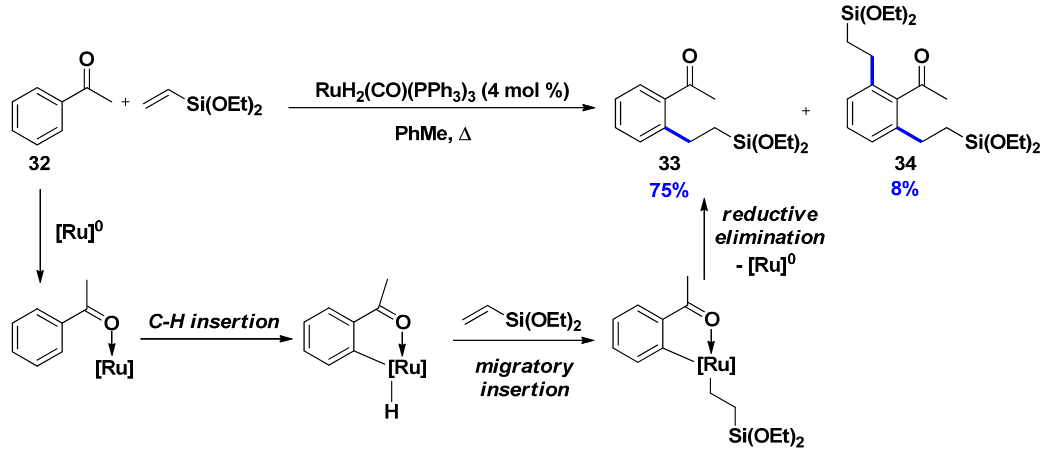


Ackermann promoted the use of carboxylates for ruthenium-catalyzed direct functionalizations (**Scheme 18**).[48] While the majority of Ru-catalyzed reactions up to that point took place in the highly polar solvent *N*-methylpyrrolidinone (NMP), the implementation of carboxylates allowed for the use of non-polar solvent toluene. Ruthenium-catalyzed C–H functionalization is discussed in detail in the next section.

## 1.2 Ruthenium-catalyzed C–H functionalization

With the use of palladium and rhodium catalysts for C–H functionalizations being well documented in synthesis, many groups initiated a search into the reactivity of other transition metals for these types of transformations. In 1993, the Chatani group reported a direct alkylation of aromatic ketone **32** in presence of $RuH_2(CO)(PPh_3)_3$ as the catalyst (**Scheme 19**).[49] The above-mentioned catalyst was a stable precursor of a $Ru^0$ species[49b] which mediated the addition of a variety of olefins to the *ortho*-position of aromatic ketones. The reaction proceeded with remarkable efficiency; traces of dialkylated products **34** were also isolated in cases where the second *ortho*-position was also sterically accessible. In terms of reaction pathway, it was proposed that coordination of the metal to the carbonyl enabled the activation of the C–H bond, followed by migratory insertion of the alkene, then reductive elimination (**Scheme 19**).[49b,50]

**Scheme 19**. Ru-promoted alkylation of aromatic ketones[49,50]



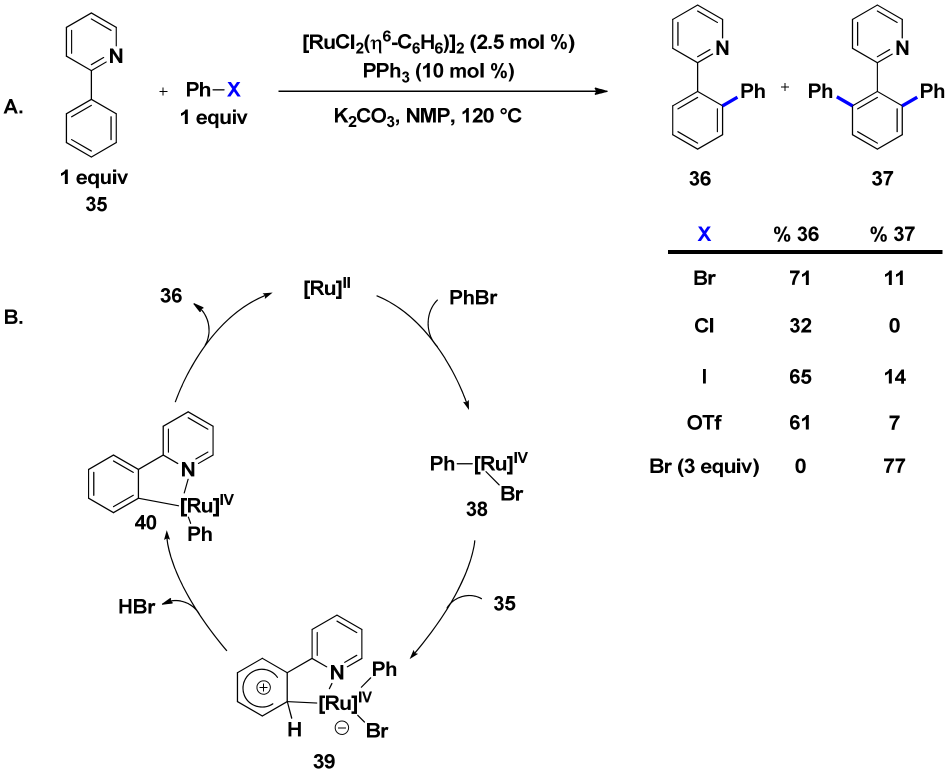
### 1.2.1 Catalysis with $Ru^{II}$ and phosphine ligands

Within the last decade, $Ru^{II}$ catalysis has been vastly explored in relation to C-H bond activation.[51,52] $Ru^{II}$ catalysts are generally more stable to air than moisture than their $Ru^0$

counterparts; in addition, their mechanism of C–H activation is similar to Pd$^{II}$ catalysts, in terms of having a ligand on the metal or a base to perform the deprotonation step.

Inoue and Oi first reported the efficient functionalization of 2-phenylpyridine **35** with aryl halides in presence of a Ru$^{II}$ catalyst.[53] The reaction employed triphenylphosphine as the ligand (two per Ru atom), potassium carbonate as the base and occurred in the highly polar solvent NMP (**Scheme 20**). When only one equivalent of aryl halide was added, the major product was monoaryl **36**; arylation of both *ortho* positions was observed when excess (three equivalents) of aryl halide were added, thus providing diaryl **37** in 77% yield. Aryl bromides, iodides or triflates provided good yields of the corresponding products, presumably due to easier oxidative addition into a Ru(II) complex, while chlorobenzene reacted poorly (**Scheme 20A**). The rate of addition of the aryl halide corresponded to the trend: ArBr>ArI>ArOTf>>ArCl. The initial proposed mechanism involved oxidative addition to give ruthenate species **38**, followed by an electrophilic addition to the arene to provide zwitterionic intermediate **39**, then loss of HBr to provide **40**, and finally reductive elimination to release the product and the Ru$^{II}$ active species (**Scheme 20B**).

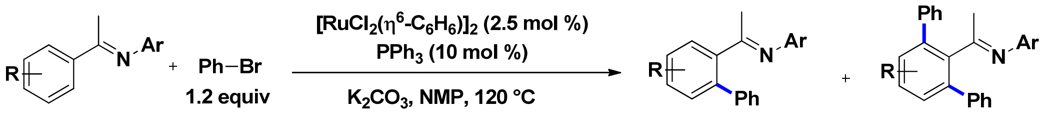
**Scheme 20**. A. Inoue and Oi's arylation of 2-phenylpyridine. B. Proposed mechanism[53]



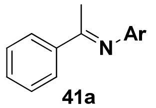
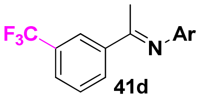
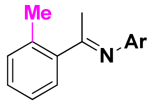
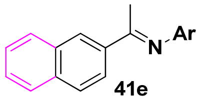
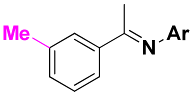
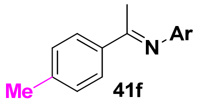
| X | % 36 | % 37 |
|---|---|---|
| Br | 71 | 11 |
| Cl | 32 | 0 |
| I | 65 | 14 |
| OTf | 61 | 7 |
| Br (3 equiv) | 0 | 77 |

Inoue and Oi next looked at using an imine group as a chelator for Ru.[54] Employing the same catalyst as in their previous reaction, the influence of substitution on the arylimine moiety **41** for the ratio of mono **42** versus diarylation **43** was now explored (**Table 3**). The ratio was roughly 4:1 for monoaryl **42**, when no substitution was present on the arylimine (**41a**), in presence of 1.2 equivalents bromobenzene. Interestingly, *ortho*-substitution (**41b**) led to a low 17% yield, which was explained through steric clash between the *ortho*-Me and the methyl on the imino group. *Meta*-substitution (Me, $CF_3$ and naphthyl, **41c-e**) offered exclusively monoaryl **42** in good to excellent yields, while the presence of a *para*-Me (**41f**) provided **42** in a modest 2:1 ratio. For the *para*-substitution, the diarylated product **43** could be targeted exclusively with excess aryl bromide. The above studies concluded that the Ru-catalyzed direct arylation was highly influenced by sterics.

**Table 3**. Influence of arene substitution on the reaction outcome[54]

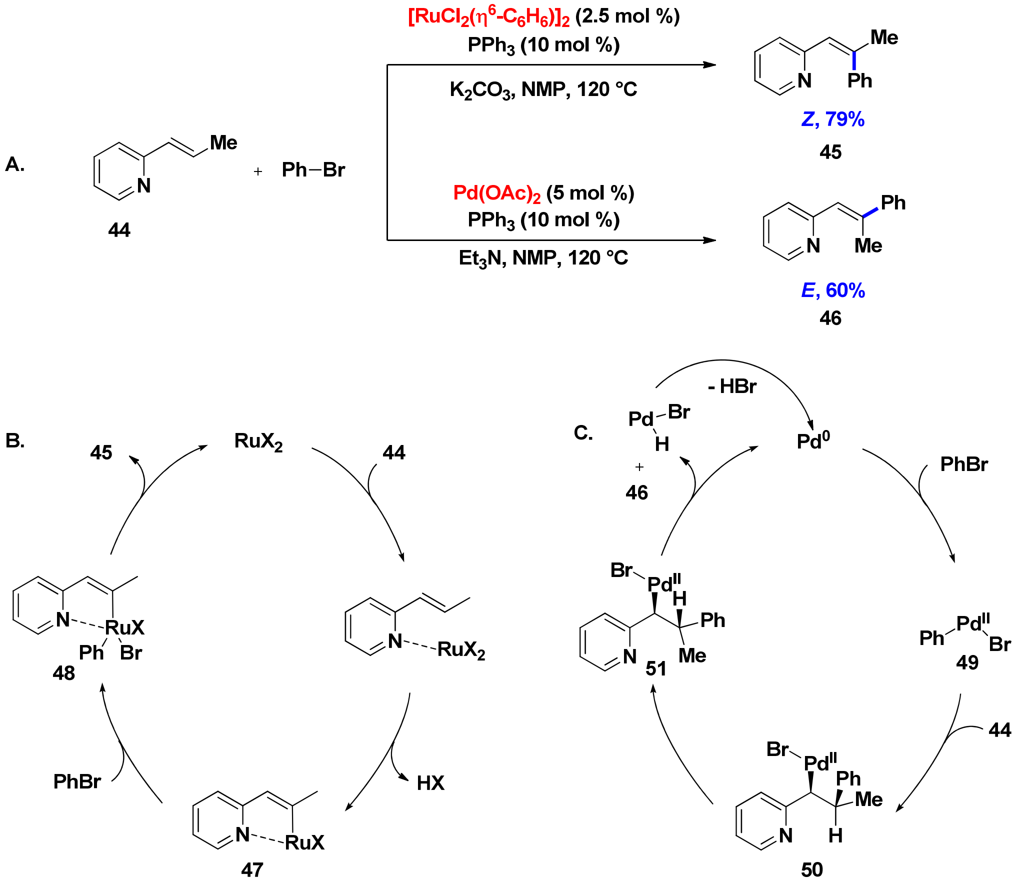


41 42 43

| Imine 41 | yield | ratio 42:43 | Imine 41 | yield | ratio 42:43 |
|---|---|---|---|---|---|
|  **41a** | 90% | 81 : 19 |  **41d** | 93% | 100 : 0 |
|  **41b** | 17% | 100 : 0 |  **41e** | 40% | 100 : 0 |
|  **41c** | 83% | 100 : 0 |  **41f** | 81% | 67 : 33 |

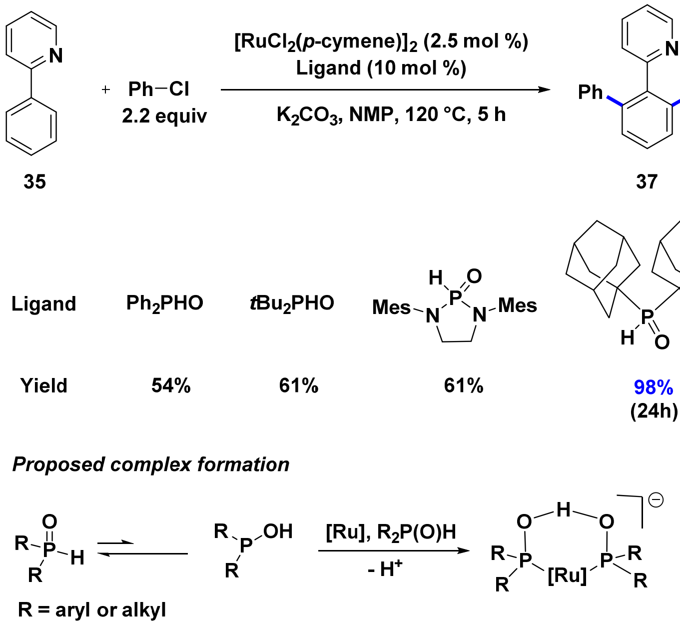
To further expand the applicability of ruthenium catalysis in organic synthesis, Inoue and Oi developed a variant of the Mizoroki-Heck reaction.[55] Intriguingly, the *Z* geometry of the isolated product **45** was in stark contrast to the *E*-alkene **46** produced via the classic Pd-catalyzed Mizoroki-Heck reaction (**Scheme 21A**). The results were rationalized through the chelating effect of the pyridine nitrogen to the ruthenium centre (**Scheme 21B**), which enabled a β-*cis*-ruthenation step to provide intermediate **47**. The intermediate then underwent oxidative addition to give **48**, followed by reductive elimination to afford the product. In contrast, the Pd-catalyzed Mizoroki-Heck reaction commenced with oxidative addition to provide **49**, followed by *syn* migratory insertion (**50**), and rearrangement to enable *syn-β*-hydride elimination (**Scheme 21C**).

**Scheme 21**. A. Comparison between Pd- and Ru-catalyzed Mizoroki-Heck reactions. B. Mechanism for the Ru-catalyzed reaction. C. Mechanism of the Pd-catalyzed transformation[55]



In 2005, Ackermann reported that through the use of a secondary phosphine oxide ligand, less reactive aryl chlorides could also be used as coupling partners for the direct arylation of 2-phenylpyridine **35** in presence of a ruthenium catalyst (**Scheme 22**).[56] Aryl chlorides are less expensive and more widely available than the corresponding aryl bromides, so the research represented a critical discovery. After screening a series of secondary phosphine oxides of different sizes and electronics, the best yield was obtained with the bulky diadamantyl phosphine oxide after heating for 24 h at 120 °C. In general, the latter system advanced by Ackermann was more efficient than the former $PPh_3/Ru^{II}$ system. The role of the secondary phosphine oxide was denoted as simply a ligand precursor, giving rise to a bimolecular bidentate ligand system through self-assembly (**Scheme 22**).[57]

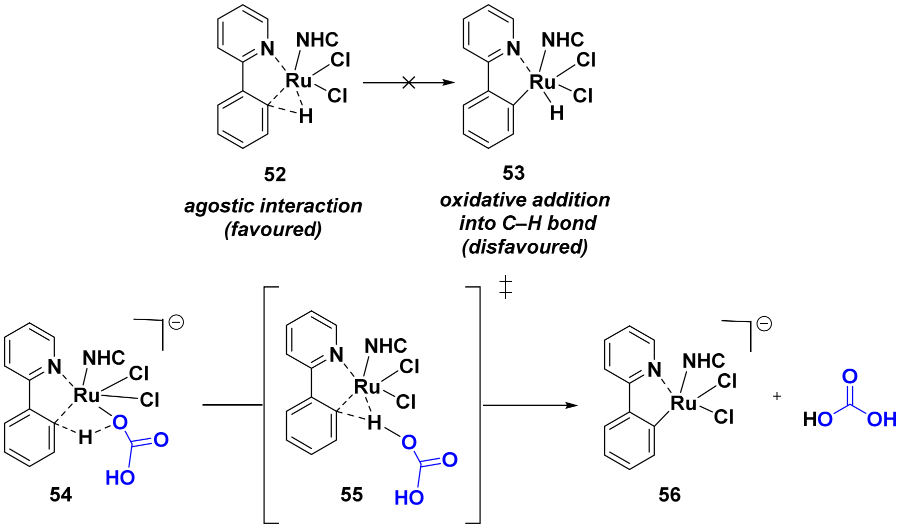
**Scheme 22**. Use of secondary phosphine oxides for the coupling of aryl chlorides[56]



## 1.2.2 Carboxylate-assisted $Ru^{II}$ catalysis

The mechanism of direct arylation through Ru-catalysis was investigated computationally (DFT calculations) by Bruneau and Dixneuf.[58] 2-Phenylpyridine **35** was chosen as the starting material, and its interaction with a $RuCl_2$(NHC) catalyst, and afterwards a base, was studied (**Scheme 23**). To start with, the cleavage of the C–H bond was examined. An agostic interaction between the catalyst and the aryl C–H bond (complex **52**) was found 28.2 kcal/mol lower in energy than $Ru^{IV}$ complex **53**, formed by direct oxidative addition of the arene C–H bond to a $Ru^{II}$ species. To continue, the addition of a carbonate anion resulted in the favourable formation of a Ru adduct (**54**). Then, adduct **54** formed complex **56** through transition state **55**, where the carbonate base was directly involved in the deprotonation step. Transition state **55** was calculated to have a barrier of 13.9 kcal/mol, while the overall transformation from **54** to **56** was exothermic by 13.7 kcal/mol. The DFT studies demonstrated similarities between the mechanisms of arene C–H activation of Ru and Pd catalysts. In consequence, it paved the way to the exploration of carboxylates as additives for Ru, as they had been previously shown to be successful in Pd catalysis (Section 1.1).

**Scheme 23**. Dixneuf's DFT calculations[58]



As early as 2008, Ackermann demonstrated the utility of carboxylates as ligands for Ru (**Scheme 18**, *vide supra*). In particular, 2,4,6-trimethylbenzoic acid ($MesCO_2H$) was shown to be effective for direct arylations with a variety of arenes containing directing groups (**Figure 8**).[48,59,60] In addition, the use of $MesCO_2H$ allowed for a change in solvent from the high boiling NMP (202 °C) to toluene (110 °C).

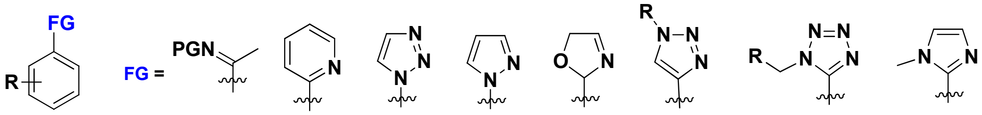


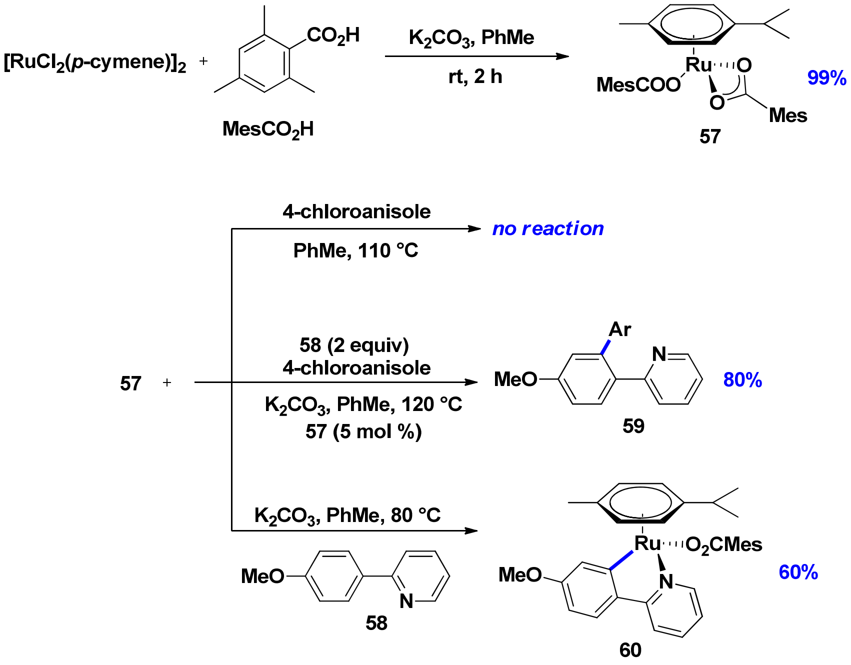
**Figure 8**. Directing groups for the carboxylate-assisted Ru activation

The working mode of the carboxylate-assisted Ru catalysis was also elucidated by the Ackermann group (**Scheme 24**).[59] Firstly, Ru-carboxylate complex **57** was prepared and its structure confirmed by X-ray crystallography. Secondly, complex **57** was proven to be a competent catalyst in the arylation reaction with 2-arylpyridine **58**, providing product **59** in 80% yield. Thirdly, upon heating **57** in presence of 4-chloroanisole, no reaction was detected.

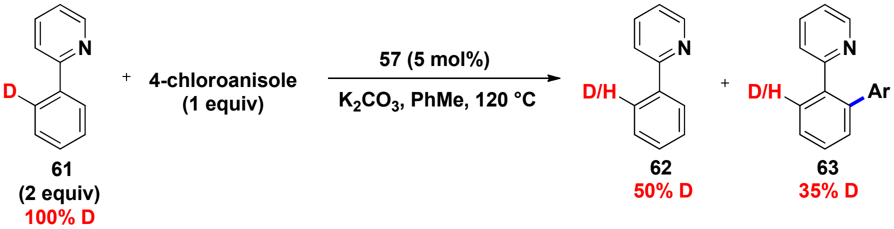
In contrast, upon reacting **57** with 2-arylpyridine **58**, but no aryl chloride, the corresponding ruthenacycle complex **60** was isolated in 60%.[59]

Deuterium experiments were also carried out; when reacting deuterated 2-phenylpyridine, a D/H exchange in both the starting material and the product was clearly observed at 120 °C (**Scheme 25**).[59] The result supported their hypothesis that the C–H activation (ruthenation step) was reversible. In addition, competition experiments with excess heteroarenes (not shown here) favoured the addition of an aryl chloride containing an electron withdrawing versus an electron donating group in either NMP or toluene as solvents, suggesting that oxidative addition is the rate-limiting step.[59]

**Scheme 24**. Synthesis of complex **57** and its competence in arylation reactions[59]

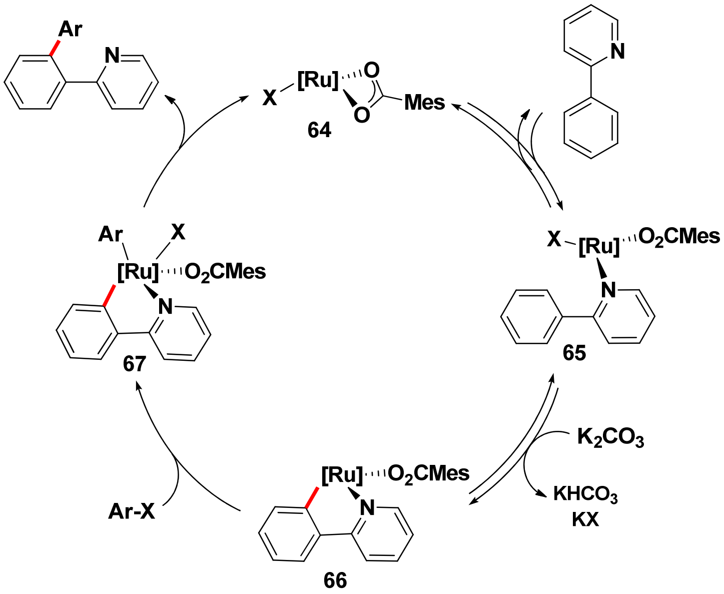


**Scheme 25**. Ackermann's D/H exchange experiment[59]



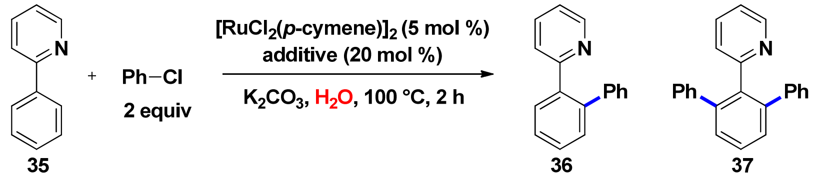
Based on experimental results, the following mechanism was proposed for the Ru-catalyzed direct arylation (**Scheme 26**). Once formed *in situ*, complex **64** undergoes a reversible cyclometalation with 2-phenylpyridine, mediated by the carbonate base, and aided by the carboxylate, to provide complex **66**. Rate-limiting oxidative addition provides $Ru^{IV}$ complex **67**, followed by reductive elimination to give the desired arylated product and release the active catalyst. The mechanism contrasts with the earlier proposed mechanism by Inoue and Oi,[53] where oxidative addition preceded C–H ruthenation (**Scheme 20**, *vide supra*).

**Scheme 26**. Ackermann's proposed catalytic cycle[59]



Dixneuf and co-workers have shown that ruthenium catalysis could also tolerate water as solvent; interestingly, the reaction was more efficient in water than the previously used NMP.[61] In presence of potassium pivalate as an additive, diarylation of 2-phenylpyridine **35** with chlorobenzene was obtained as the sole product at 100 °C in only 2 h (**Scheme 27**). In contrast, potassium acetate or carbonate provided a mixture of mono and diarylation. The order of reactivity of the aryl coupling partner was PhCl>PhBr>PhI, correlating well with their water solubilities. The ability to perform catalysis in water without the use of a surfactant was a great step forward towards developing more environmentally friendly procedures.

**Scheme 27**. Water as solvent in Ru catalysis[61]

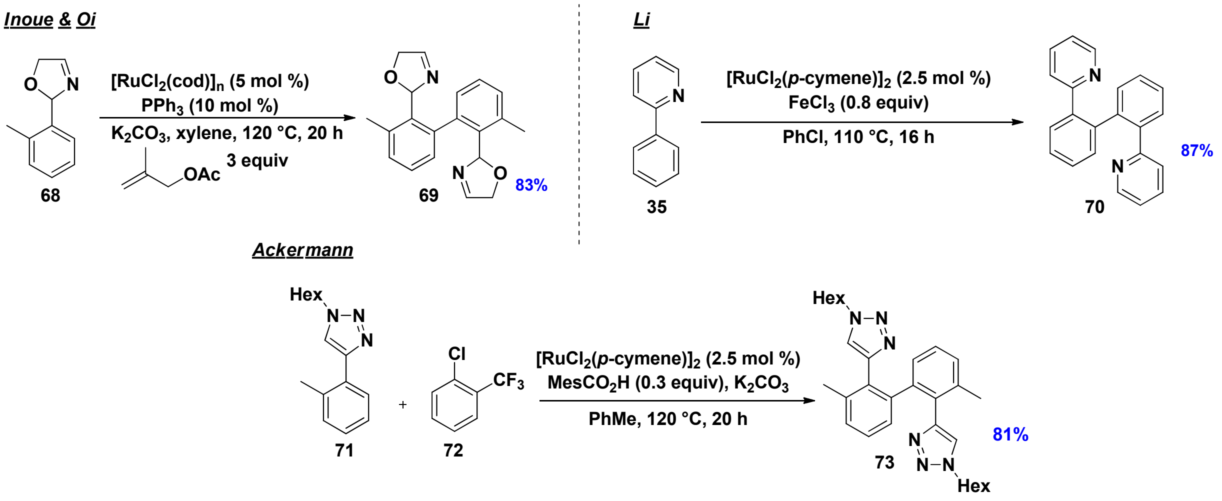


| Additive | Yield | Ratio 36:37 |
|---|---|---|
| $K_2CO_3$ | 97% | 21 : 79 |
| KOAc | 100% | 26 : 74 |
| KOPiv | 100% | 0 : 100 |

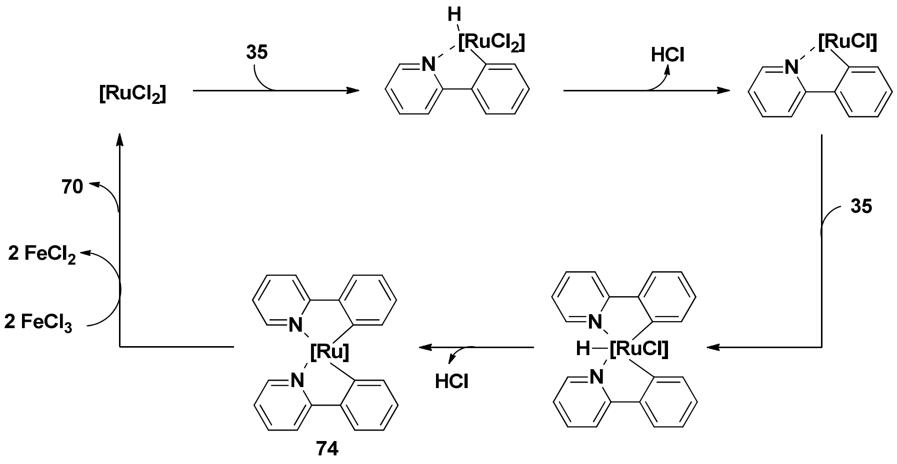
### 1.2.3 Other Ru-catalyzed reactions

Ruthenium(II) complexes have shown to be versatile catalysts for a plethora of transformations, including direct arylations, alkenylations, alkylations, as well as annulations with alkynes and alkenes.[52] In addition, a few intriguing reports appeared in the literature describing oxidative homocoupling (**Scheme 28**). Inoue and Oi showed that, in presence of 2-methylallyl acetate, 2-aryloxazolines **68** reacted with each other in 83% yield.[62] The conditions were amenable to the dehydrogenative coupling of similar *ortho*-substituted imidazole, thiazole or indazole substrates. The group of Li disclosed the homocoupling of several substituted 2-phenylpyridines in presence of a Ru catalyst and $FeCl_3$ as a substoichiometric oxidant.[63] The mechanism proposed consisted of two sequential cyclometalations of 2-phenylpyridine (**35**) via a chelation-directed C–H activation step, with loss of two molecules of HCl (**Scheme 29**). Reductive elimination of complex **74** provided the homocoupled product, while $Ru^0$ was oxidized back to $Ru^{II}$ by ferric chloride. It was suggested that traces of oxygen present in the reaction might also be involved in the re-oxidation of $Ru^0$ to $Ru^{II}$.[63] Finally, Ackermann noticed homocoupling of substituted triazole **71** when *ortho*-substituted aryl halides (for example **72**) were employed as coupling partners (**Scheme 28**).[60a] It was suggested that the sterically hindered aryl halide acted as a sacrificial oxidant.

**Scheme 28**. Ru-catalyzed oxidative homocoupling



**Scheme 29**. Li's proposed oxidative homocoupling mechanism[63]



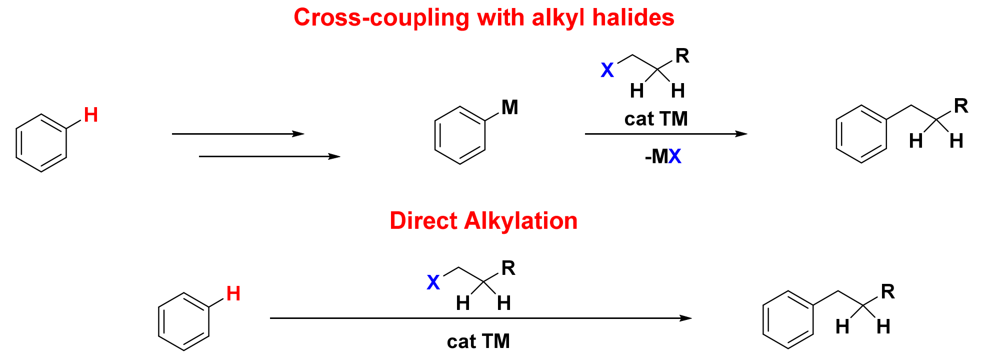
# 1.3 Functionalization at sp$^3$ centers

The following section will look at C–C bond formation at sp$^3$ centers from two points of view: direct alkylation (the coupling of alkyl halides with arene C–H bonds), and direct C(sp$^3$)–H functionalization, focusing on recent approaches featuring cyclopropanes.

## 1.3.1 Direct alkylation

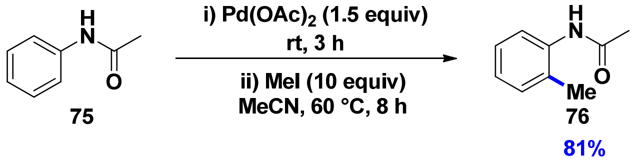
The transformation of sp$^2$ C–H bonds has received great attention from the organic synthetic community, with direct arylation (Sections 1.1 and 1.2), alkenylation[64] and alkynylation[65] reactions being widespread. A less common activation mode is direct alkylation,[66] due to the difficulty of alkyl halides to undergo oxidative addition and their propensity for undesired side reactions such as *β*-hydride elimination. In comparison, conventional cross-coupling strategies rely on the pre-formation of nucleophilic substrates as organometallic reagents, followed by the transition-metal catalyzed addition of an alkyl halide (**Scheme 30**). The disadvantages of the method have already been underlined at the start of the dissertation. Consequently, synthetic efforts are directed towards the development of appropriate conditions that allow for direct alkylation to occur.

**Scheme 30**. Cross-coupling with alkyl halides versus direct alkylation[66]



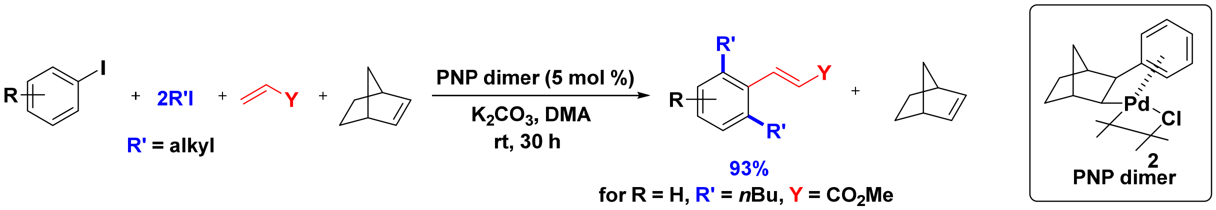
In 1984, Tremont and Rahman reported the alkylation of acetanilides in presence of excess $Pd(OAc)_2$ (**Scheme 31**).[67a] The reaction was proposed to first undergo a directed *ortho*-metalation, most likely followed by oxidative addition of methyl iodide, and reductive elimination to give the desired product. The only alkyl halides tested were methyl, ethyl and allyl iodide. A subsequent report from the same group looked at aryl imines as chelating groups for Pd in direct alkylations.[67b]

**Scheme 31**. Tremont's direct alkylation with excess $Pd(OAc)_2$[67a]



A widely studied example of direct alkylation is the Catellani reaction,[18] whose mechanism was fully elucidated by the pioneering work of Marta Catellani.[68] In the reaction, norbornene acts as a scaffold on which the molecule is built and can be recovered at the end of the reaction (**Scheme 32**). Three new C–C bonds result from this reaction, out of which two are C(sp$^2$)–C(sp$^3$).

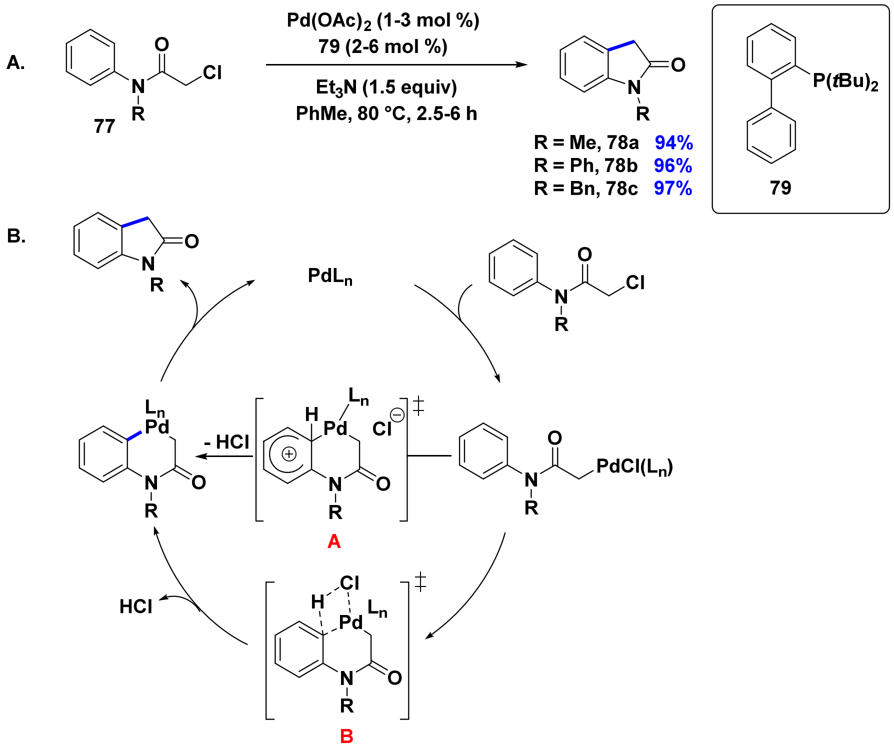
**Scheme 32**. The Catellani reaction[18]



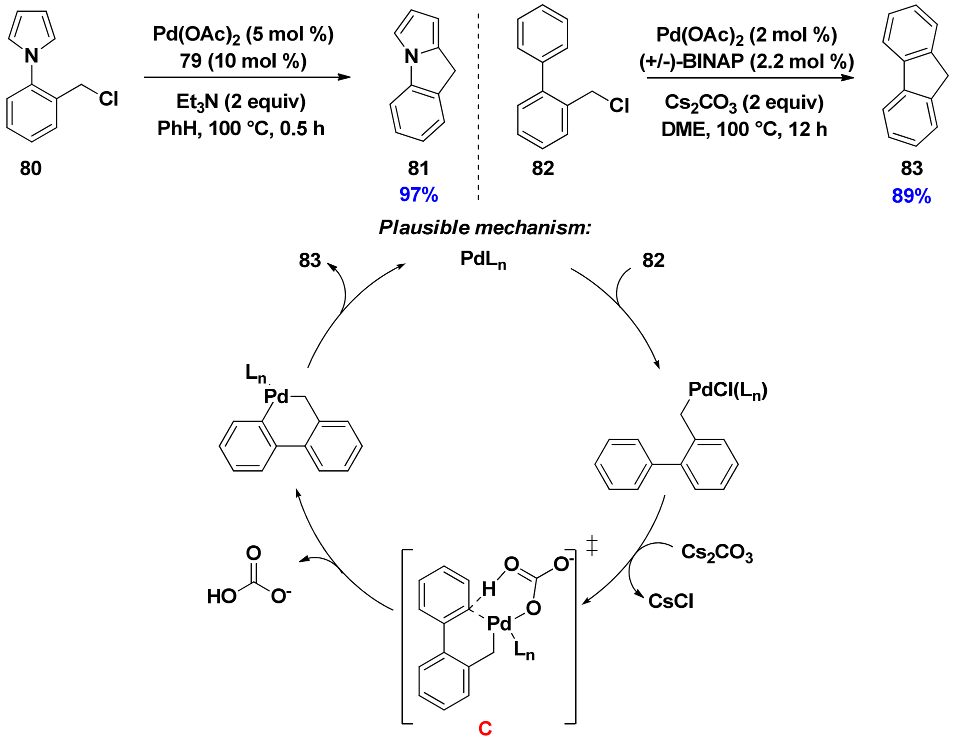
The oxindole scaffold, a motif widely found in medicinal chemistry, was easily accessed by a Pd-catalyzed cyclization of α-chloroacetanilides **77**, in a report by Buchwald and Hennessy (**Scheme 33A**).[69] Protection of the amide group was necessary, and both alkyl and aryl groups could be employed to provide good yields of the corresponding products **78a-c**. Investigations into the reaction mechanism revealed an intermolecular KIE of 1, while the intramolecular value was 4. After oxidative addition of Pd$^0$ into the alkyl chloride bond to give a Pd enolate, two possible pathways are possible, one involving electrophilic substitution (**A**), and the other σ-bond metathesis (**B**) (**Scheme 33B**).

Chang and co-workers disclosed an intramolecular direct alkylation employing benzyl chlorides for the synthesis of pyrrole-containing heterocycles (**Scheme 34**).[70] The calculated KIE values were 1.4 (intramolecular) and 1.7 (intermolecular), implying a C–H activation or electrophilic substitution type mechanism. Furthermore, the transformation could be extended to the synthesis of fluorenones **83** by changing the ligand and base in the reaction (**Scheme 34**).[71] Hammett studies revealed a 0.42 ρ value, predicting a build-up of negative charge during the transition state, thus excluding an electrophilic pathway. The corresponding intermolecular KIE value was 2.1, and the reaction was found to be sensitive to base. Based on all these observations, the proposed mechanism involved a base-assisted deprotonation, as shown in transition state **C** (**Scheme 34**).[71]

**Scheme 33**. A. Buchwald's synthesis of oxindoles. B. Possible mechanisms[69]

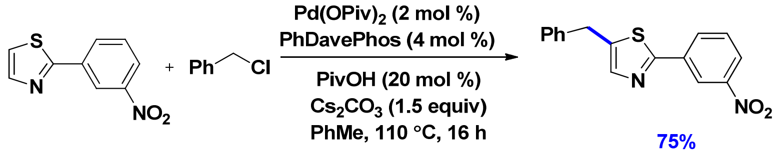


**Scheme 34**. Chang's intramolecular direct alkylation[70,71]



An intermolecular Pd-catalyzed benzylation was disclosed by Fagnou (**Scheme 35**).[72] Under the reaction conditions, a wide range of electron-deficient heterocycles (e.g. thiophenes, thiazoles, furans, indolizines etc) which proved difficult to alkylate under Friedel-Crafts type conditions, were reacted with benzyl chlorides to give the corresponding products in good to excellent yields.

**Scheme 35**. Intermolecular benzylation of thiazoles[72]



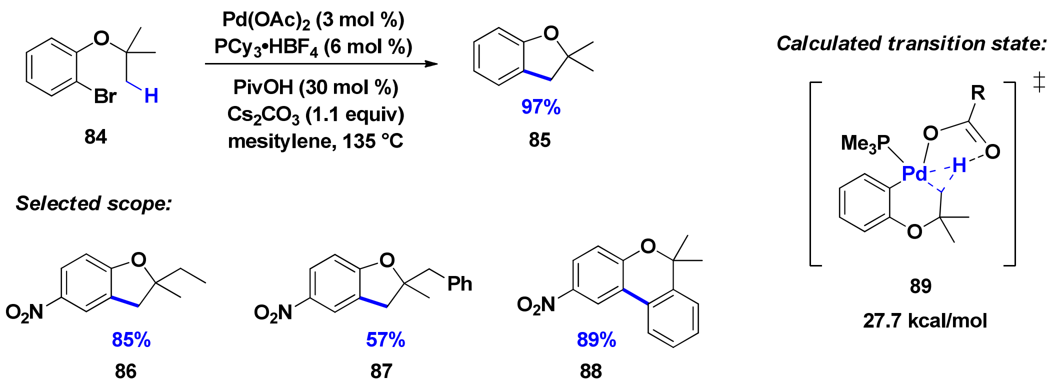
## 1.3.2 Direct functionalization of C($sp^3$)–H Bonds

The direct functionalization of challenging C($sp^3$)–H bonds has attracted many chemical efforts.[73] Although both $sp^2$ and $sp^3$ C–H bonds have high bond dissociation energies (BDE's) (105 kcal/mol for methane, 113 kcal/mol for benzene),[13] $sp^3$ C–H centers lack π-groups which may aid in interacting with transition metal centers. The direct oxidation of allylic or benzylic C–H bonds is much easier,[13] due to the lower BDE values of these bonds (88.8 kcal/mol for allyl and 89.8 kcal/mol for benzyl C-H), but also as a result of interaction of the π-bonds to the metal centre. It should be noted that BDE is a measure of enthalpy change when a bond is cleaved in a homolytic fashion,[13] thus it may not accurately depict the difficulty of C–H bond cleavage upon activation by a transition metal. Due to the ubiquity of C–H bonds in nature, site selectivity is also a major issue, thus chemists have again turned to directing groups to help them overcome the problem.

### *1.3.2.1 Direct C-C bond formation*

In 2007, Fagnou and co-workers disclosed a pivalic acid-mediated, intramolecular $sp^3$ C–H activation in the synthesis of dihydrobenzofuran **85** (**Scheme 36**).[74] High selectivity for a C–H methyl functionalization to form a five-membered ring was observed (compounds **86** and **87**), with one exception: when one of the substituents was an arene, there was a preferential reaction at the $sp^2$ C–H bond to form a six-membered ring (compound **88**). DFT calculations were performed to suggest a mechanistic pathway. The formation of a $Pd^{IV}$ species (not depicted here) was excluded, due to its high energy (47.7 kcal/mol). The value of the computed KIE was 3.6, coinciding well with the experimentally determined value of an intramolecular experiment (KIE 5.4 ± 0.3); however, the intramolecular KIE experiment could not support the conclusion that C–H bond cleavage is rate-limiting. Based on the DFT calculations and experimental evidence, a catalytic cycle involving a $Pd^{0/II}$ cycle seemed more plausible than a $Pd^{II/IV}$ pathway (**Scheme 16**, *vide supra*). After oxidative addition, a concerted metalation-deprotonation step mediated by pivalic acid would take place. Transition state **89** involving an agostic, three-center, two-electron interaction was calculated to be lowest in energy (27.7 kcal/mol). Reductive elimination would provide the desired product and regenerate the $Pd^0$ catalyst. The selective preference for a methyl versus ethyl (compound **86**) was also supported by DFT calculations: activating an ethyl C–H bond proved to be 5.5 kcal/mol higher in energy than the corresponding methyl C–H bond. Although high-yielding, the transformation was restricted to the use of aryl bromides and the presence of an α-quaternary centre.[74]

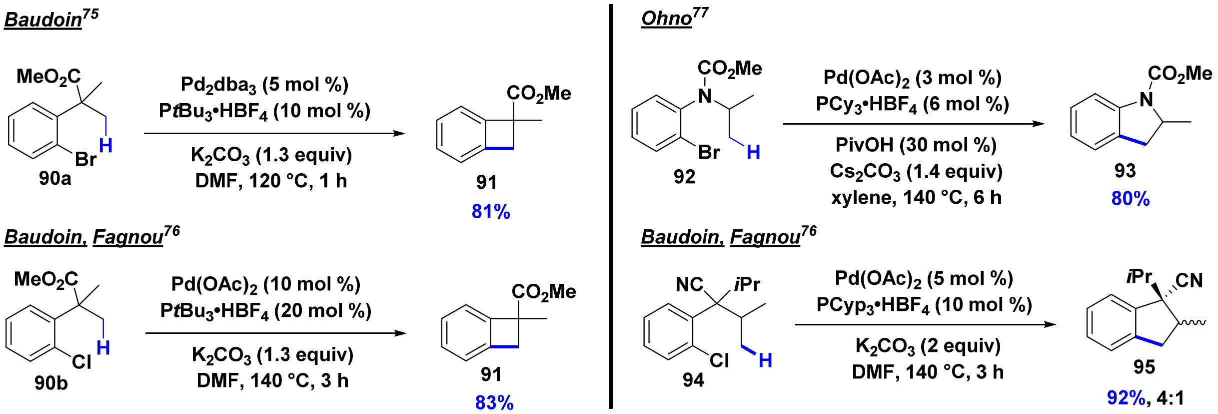
**Scheme 36**. Fagnou's intramolecular $C(sp^3)$–H activation[74]



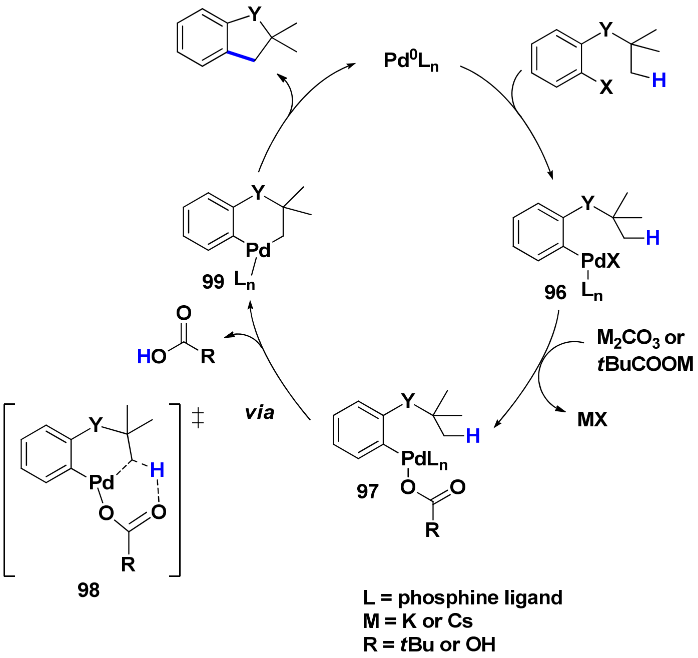
The synthesis of benzocyclobutene **91** was disclosed by the group of Baudoin (**Scheme 37**).[75] Again, the major limitation was the absolute necessity for an α-quaternary centre, due to competing *β*-hydride elimination. A collaborative effort by Baudoin and Fagnou expanded the reaction scope of the intramolecular cyclization to aryl chlorides **90b**, in the synthesis of benzocyclobutenes **91** and indanes **95**.[76] Interestingly, for the synthesis of indanes, α-tertiary centres were viable substrates in presence of the bulky tertiary cyclopentyl phosphine as the ligand.[76] Furthermore, Ohno reported that α-tertiary centres can also be applied in the carboxylate-assisted synthesis of various indolines **93**, in presence of tricyclohexylphosphine.[77]

Based on the experimental and computational evidence provided,[75,76,78] a simplified general mechanism for the intramolecular C(sp$^3$)–H functionalization with aryl halides is presented in **Scheme 38**. The first step is oxidative addition of Pd$^0$ into the aryl halide bond to form **96**. Then, exchange of the halide ligand on Pd by carbonate or pivalate is presumed to occur to give **97**, followed by a concerted metalation-deprotonation step (transition state **98**) to provide a six-membered palladacycle **99**. Reductive elimination provides the desired product and regenerates the Pd catalyst.

**Scheme 37**. Intramolecular C(sp$^3$)-H functionalization with aryl halides



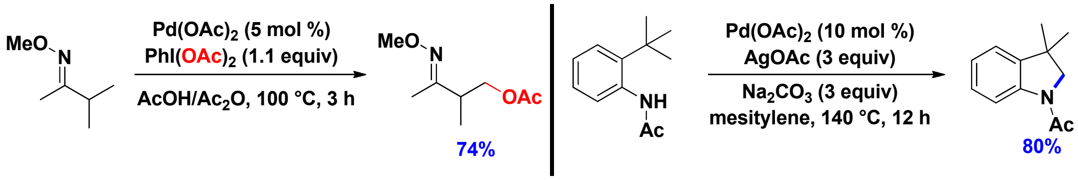
**Scheme 38**. General mechanism for the intramolecular C(sp$^3$)–H arylation



### *1.3.2.2 Direct C-X bond formation*

The direct transformation of C(sp$^3$)–H bonds into C-heteroatom bonds has high synthetic utility (**Scheme 39**). Pioneering work by Melanie Sanford in the palladium-catalyzed acetoxylation reaction[79,14d] has not only provided significant mechanistic understanding of the Pd$^{II/IV}$ catalytic cycle, but also opened the door to the application of the reactivity to other systems. In addition to oxygenations, C–N bond formation has also been studied (**Scheme 39**).[80] Others have shown that C-halide bond synthesis was also possible.[14d,35] More recently, C–F bond formation has become a hot topic in organic synthesis.[81]

**Scheme 39**. Selected examples of C(sp$^3$)–O and C-N bond formation (Sanford,[79] Glorius[80a])

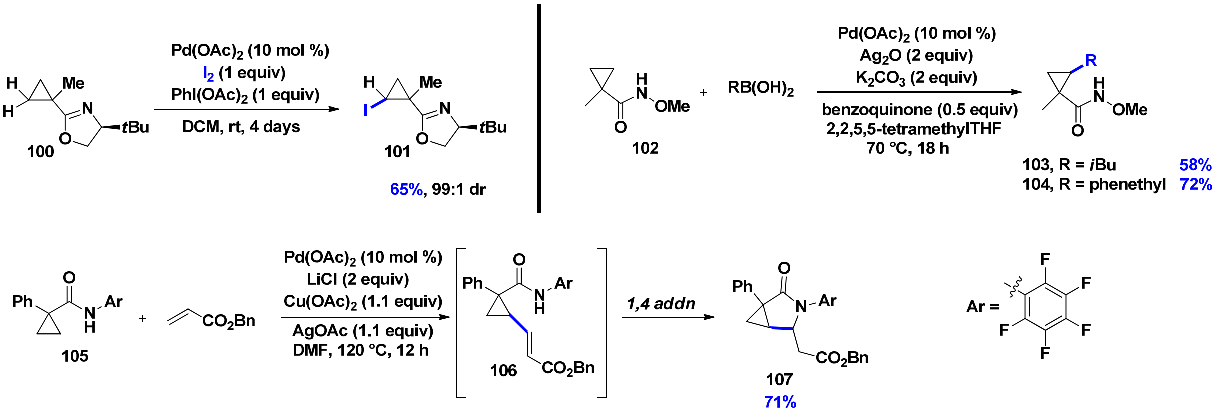


### 1.3.3 Cyclopropyl C–H functionalization

Cyclopropanes have unique physical, chemical and electronic properties as a result of ring strain.[82] The bond angle in a cyclopropane is 60°, while the normal $sp^3$ hybridized bond angle is 109.5°; thus, its carbon atoms display $sp^2$-like properties, which makes them an attractive target for C–H bond functionalization processes.

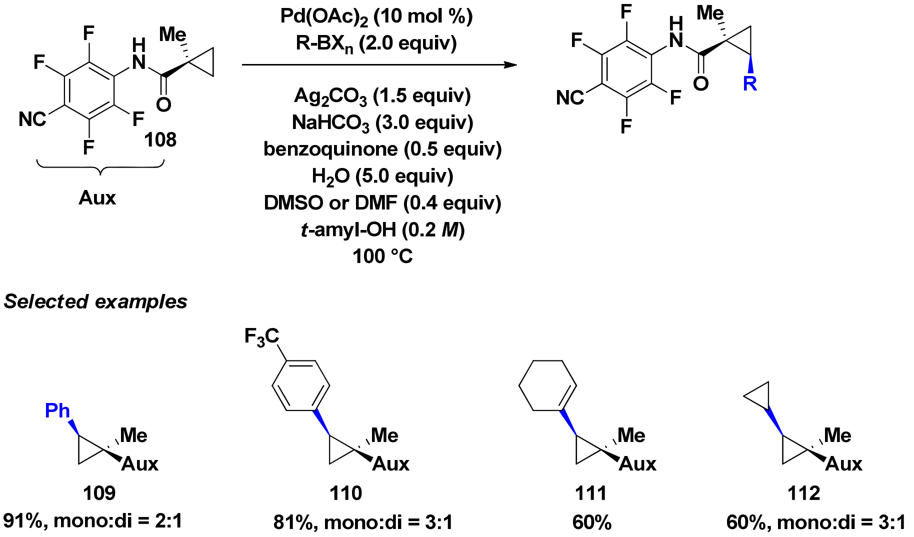
At the start of my PhD, there was little precedent in the literature on the direct functionalization of cyclopropyl C–H bonds. The few scattered examples that existed were from the Yu lab, and are summarized in **Scheme 40**. Diastereoselective iodination of a cyclopropane was possible via palladium catalysis on a substrate containing a cyclopropyl ring directly bound to an oxazoline (**100**), the oxazoline moiety acting as a directing group.[83a] The reaction was performed under mild conditions, at room temperature; however, it required four days for completion. Yu then showed that cyclopropane **102** can be directly coupled with alkyl boronic acids, under Pd catalysis to afford alkylated cyclopropanes **103** and **104** in 58% and 72% yields, respectively.[83b] The use of 2,2,5,5-tetramethyltetrahydrofuran as solvent was key. It was believed that the bulky solvent prevented homocoupling of the boronic acid, as well as $\beta$-hydride elimination. A Pd-catalyzed olefination of $sp^3$ C–H bonds was also disclosed by Yu,[83c] where an amide-directing group was employed, and after the olefination, compound **106** underwent a 1,4-addition to provide the corresponding lactam **107**. A plausible mechanism for the transformation would first involve an amide directed C–H insertion by $Pd^{II}$, followed by carbopalladation of the olefin, and a $\beta$-hydride elimination to provide intermediate **106**. $Pd^0$ would be reoxidized by $Ag^I/Cu^{II}$, while **106** would cyclize to provide to the final product. The main disadvantage of all the cyclopropane-containing substrates (**100, 102** and **105**) was the need for a quaternary centre on the cyclopropane to prevent $\beta$-hydride elimination, or attenuate decomposition pathways of the cyclopropane. The presence of a quaternary centre also resulted in lengthy starting material syntheses.

**Scheme 40**. Yu’s contribution for cyclopropane functionalization up to 2010[83]

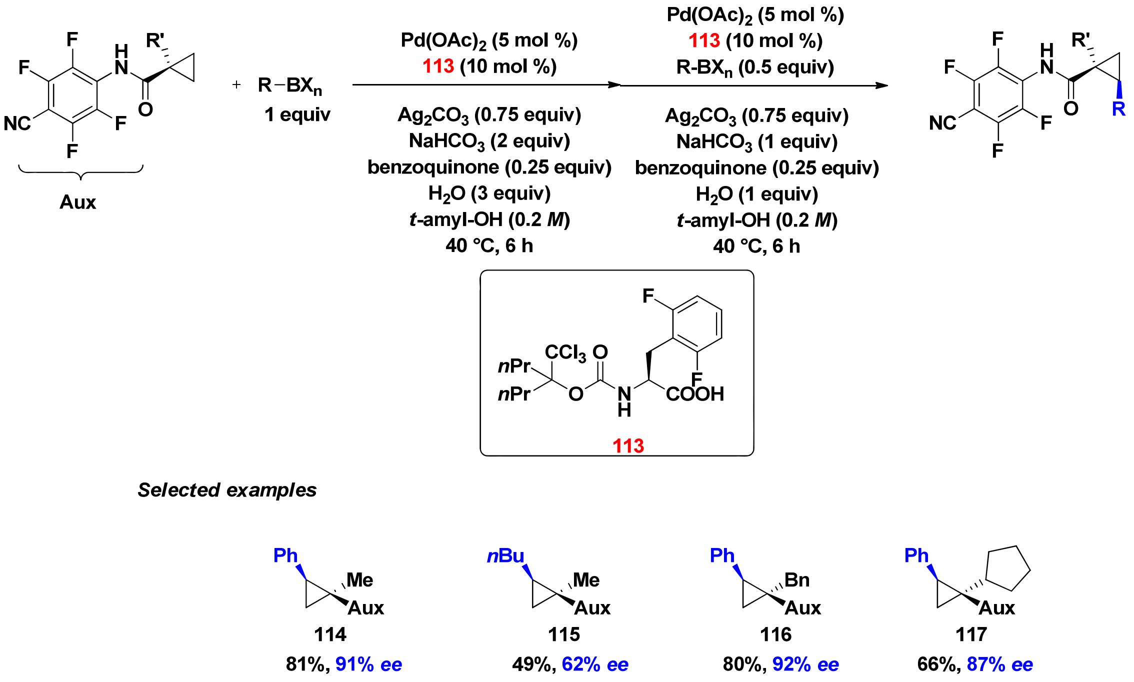


Later, in 2011, the group of Yu disclosed the first enantioselective C–H activation of cyclopropanes.[84] Initially, the optimization of the racemic reaction was performed; usually, a mixture of mono and di-functionalized cyclopropanes was obtained (**Scheme 41**). Then, a thorough screen of amino acids and their derivatives led to the application of chiral ligand **113** in the intermolecular arylation of cyclopropanes **108** (**Scheme 42**). Ph-BPin was the best nucleophile, while the employment of alkyl boronic esters led to generally low yields and enantioselectivities. The conditions were relatively mild, however the necessity for an α-quaternary centre, the employment of an electron-poor amide auxiliary, the use of a double batch method and lack of applicability for large scale synthesis (reactions were ran on 0.1 mmol only) are still major issues that require improvement. Yu followed the report one year later with a more thorough investigation of conditions for the activation of methylene C–H bonds with aryl iodides.[85] After altering the auxiliary and employing a substituted quinoline ligand for Pd, the only cyclopropane example from the scope could be arylated in 86%. Notably, the need for an α-quaternary centre was obviated by the use of the quinoline ligand.

**Scheme 41**. Yu's racemic intermolecular direct functionalization of cyclopropanes[84]

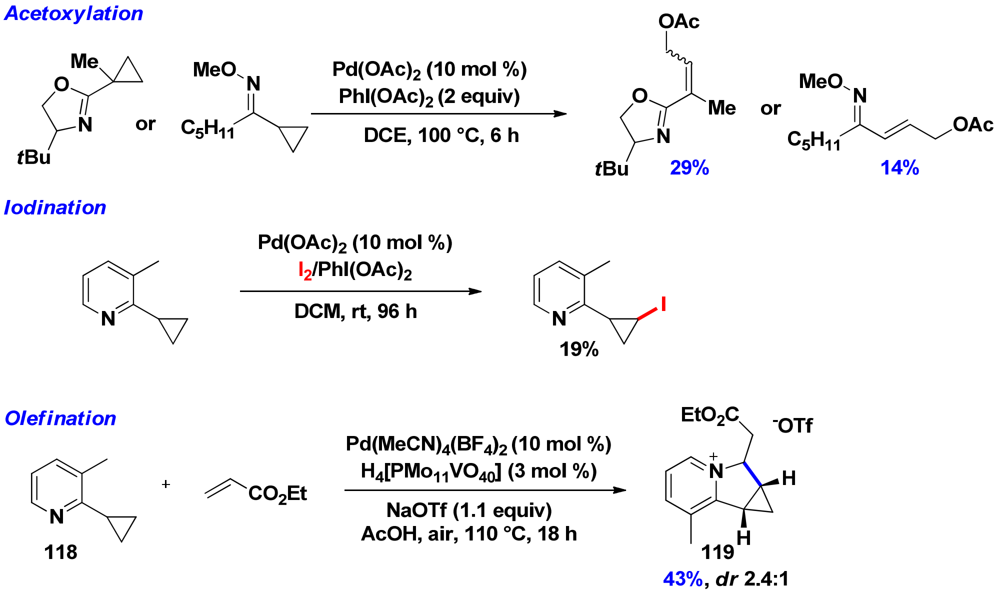


**Scheme 42**. The first enantioselective C–H functionalization of cyclopropanes[84]



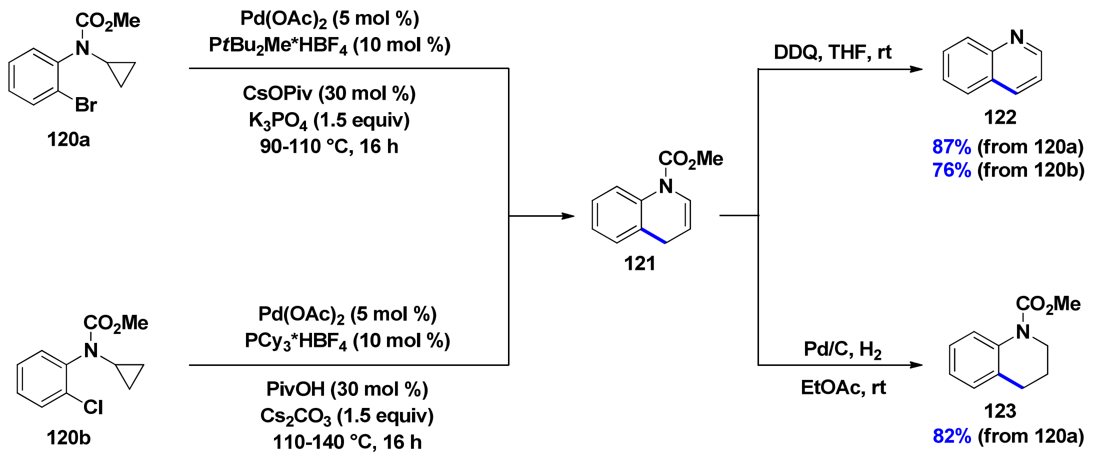
Sanford and Kubota looked at the functionalization of cyclopropanes under oxidative conditions, employing directing groups such as oximes or pyridines (**Scheme 43**).[86a] Their attempted acetoxylation and iodination reactions mainly resulted in opening of the cyclopropane or low yields. A more successful example was the aerobic olefination with ethyl acrylate of 2-cyclopropylpyridine **118**.[86b]

**Scheme 43**. Sanford's efforts towards cyclopropane C–H activation[86]

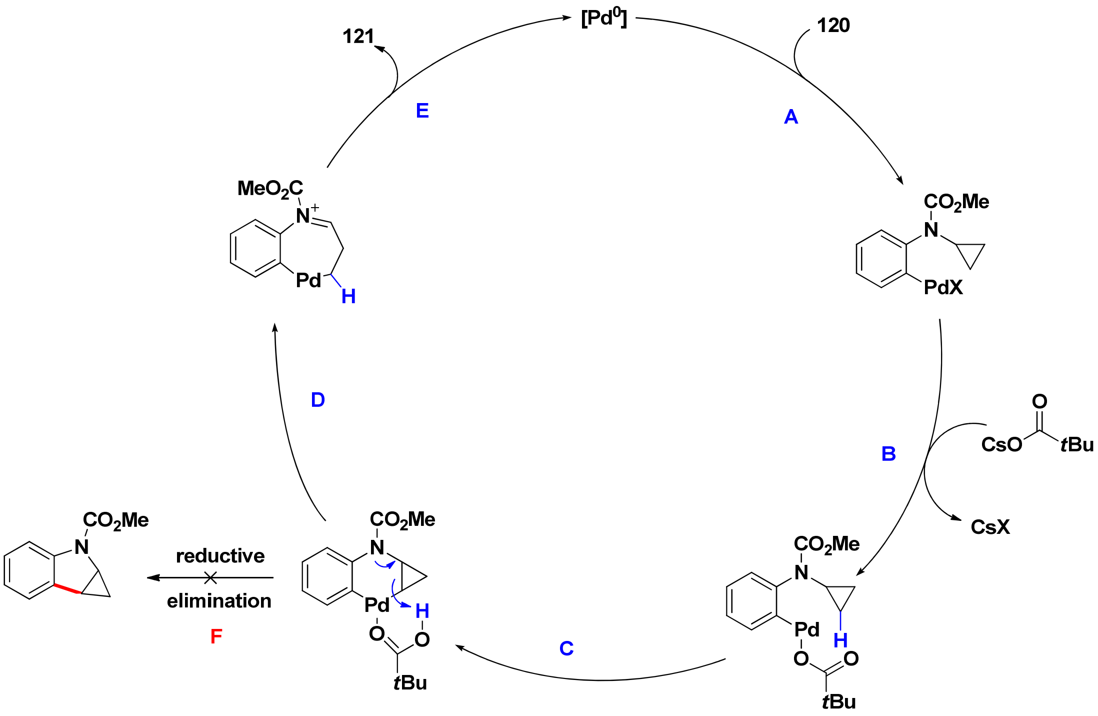


Rousseaux, Liegault and Fagnou reported the elegant formation of quinoline and tetrahydroquinoline derivatives via a C–H activation of cyclopropane.[87] It was found that the resulting dihydroquinolines **121** were prone to decomposition, thus a one-pot aromatization protocol employing DDQ as the oxidant was developed to provide **122** (**Scheme 44**). Alternatively, a one-pot hydrogenation of intermediate **121** to the tetrahydroquinoline species **123** was also a viable alternative. Both aryl bromides and chlorides were feasible substrates, however under slightly different conditions. In particular, the ligand tricyclohexylphosphine worked better with aryl chlorides. Mechanistic studies by the authors have demonstrated that C–H activation of the cyclopropyl bond via a pivalate-assisted concerted metalation-deprotonation step **C** occured prior to the ring opening (step **D**) (**Scheme 45**). Then, deprotonation and reductive elimination (step **E**) would occur to give product **121**. Alternatively, step **F**, the direct reductive elimination was shown not be possible.[87]

**Scheme 44**. Rousseaux and Fagnou's synthesis of quinolones and tetrahydroquinolines[87]



**Scheme 45.** Proposed reaction mechanism for the synthesis of dihydroquinolines **121**[87]



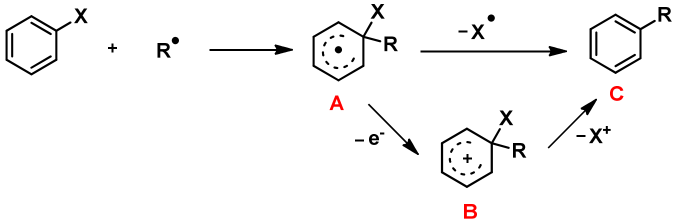
Although some elegant advances in the direct C–H functionalization of cyclopropanes have been achieved, there is still plenty of room for exploration. In particular, the use of directing groups was limited to amides, and only one example of the use of aryl halides for the intermolecular arylation of cyclopropanes was available. Additionally, the full substrate scope of some of the functionalizations (i.e. formation of C–X bonds) has not been fully examined.

## 1.4 Homolytic aromatic substitution

The introduction or replacement of substituents onto an aromatic ring represents a vital transformation in organic synthesis. Aromatic substitution can be divided into four basic mechanisms: 1) electrophilic, 2) nucleophilic, 3) radical, and 4) transition-metal catalyzed.[88] While the previous sections of the introduction looked mostly at numbers 4) and 1), the following section will deal with number 3), in terms of C–C bond forming reaction.

Homolytic aromatic substitution (HAS) is defined as the addition of a radical onto an aromatic ring, with the replacement of a leaving group X (usually H).[10] The general mechanism, pictured in **Scheme 46**, involves initial attack of the radical, followed by the formation of a radical σ-complex **A**, then loss of the leaving group to give the product **C**. In many cases, HAS may involve an oxidative step to obtain a cationic σ-complex **B**, and then loss of $X^+$, which is not well understood in the literature. The most common ways of preparing radical $R^\bullet$ involve the use of tributyltin hydride ($Bu_3SnH$) in presence of 2,2-azobisisobutyronitrile (AIBN) as the initiator; or, tris(trimethylsilyl)silane (TTMSS) with AIBN. In comparison to HAS, the mechanisms for electrophilic and nucleophilic aromatic substitution involve the formation of a cationic or anionic σ-complex, respectively.[88]

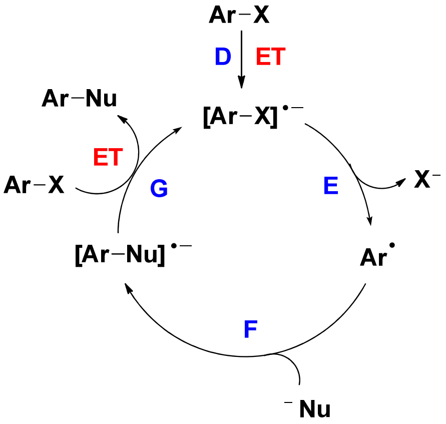
**Scheme 46**. General HAS mechanism[10]



According to studies by Bowman[89] and Russell,[90] the unimolecular radical nucleophilic substitution reaction ($S_{RN}1$) on arenes or heteroarenes can be regarded as HAS.[10] The $S_{RN}1$ reaction on aromatics was first investigated in 1970 by Bunnett and Kim.[91] The proposed mechanism involved a radical chain reaction (**Scheme 47**). The distinctive feature was the initiation, which occurred via an electron transfer (ET) to an aryl halide bond, giving rise to a radical anion (step **D**); fast fragmentation of the species results in an aryl radical and $X^-$ (step

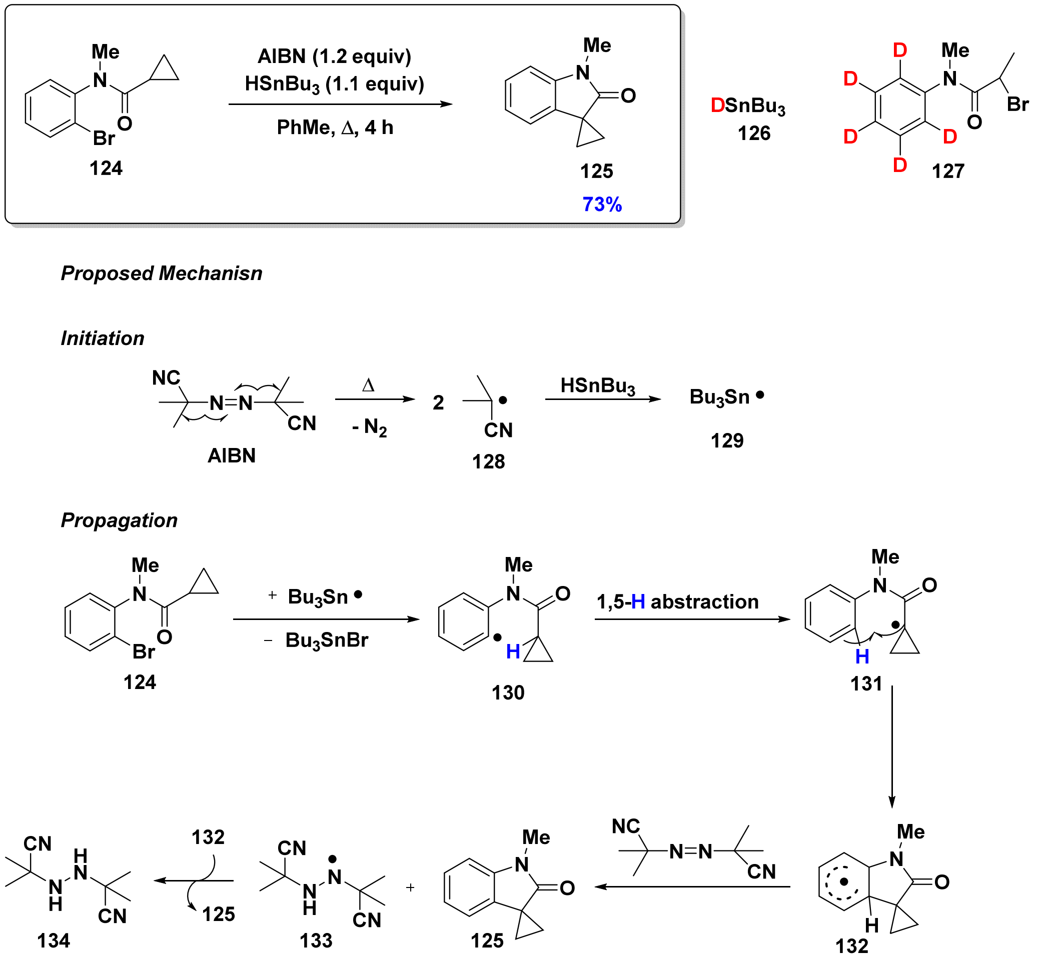
**E**). Attack of a nucleophile generated another radical anion (step **F**), which could transfer an electron to the substrate and propagate the cycle (step **G**).

**Scheme 47**. General $S_{RN}1$ mechanism



As mentioned above, the re-aromatization step of the cyclohexadienyl radical **A** (**Scheme 46**) is a highly debatable topic in HAS chemistry. In most cases, the leaving group **X** is hydrogen, requiring an H-abstraction step. In the synthesis of oxindole product **125**, Bowman and Storey ruled out the involvement of $HSnBu_3$ in this abstraction step by running control experiments with a deuterated tributyltin species.[92] When employing deuterated $DSnBu_3$ **126** in the reaction with **124**, no deuterium incorporation in the product or any HD gas by-product was observed in the reaction (**Scheme 48**). Additionally, no HD gas was produced when **127** was used as precursor, suggesting that $HSnBu_3$ was also not capable of producing a radical anion for a presumed $S_{RN}1$-like initial step. Turning to the role of the initiator, AIBN, only 0.3 equivalents of $N_2$ gas were detected by GC analysis of the gaseous mixture. The fact implied that the rest of 0.9 equivalents of the initiator were consumed elsewhere in the reaction. It was postulated that the initiator acted as an oxidizing agent for the cyclohexadienyl radical by abstracting an H and forming a hydrazyl species, as previously suggested by Curran.[93] To sum up the findings, and the AIBN/$Bu_3SnH$ mechanism, the reaction mechanism for the synthesis of oxindole **125** is shown in **Scheme 48**. In presence of heat, AIBN decomposes to produce nitrogen gas and a tertiary radical **128**; the species abstracts $H^•$ from tributyltinhydride to provide the active $Bu_3Sn^•$ radical **129**, concluding the initiation step. The tin radical **129** abstracts bromide from aryl halide **124** to give aryl radical **130** and $BrSnBu_3$; a 1,5-H abstraction provides a stable cyclopropyl radical **131**. Attack of the cyclopropyl radical onto the arene provides cyclohexadienyl species **132**, from which AIBN abstracts a hydrogen providing the product **125** (in a chain terminating event) and a hydrazyl radical **133**. Radical **133** may undergo another oxidation step (i.e. abstract another H$^{\bullet}$ from another species **132**) or undergo disproportionation. Although hydrazyl **134** derived from AIBN was never isolated, due to its instability under the reaction conditions, other reduced AIBN derivatives have been isolated.[94] The current mechanistic findings were mostly applicable to intramolecular reactions involving aryl bromides; in the case of aryl iodides, a single electron transfer from a radical anion intermediate can cause C–I bond homolysis and propagate the chain.[95]

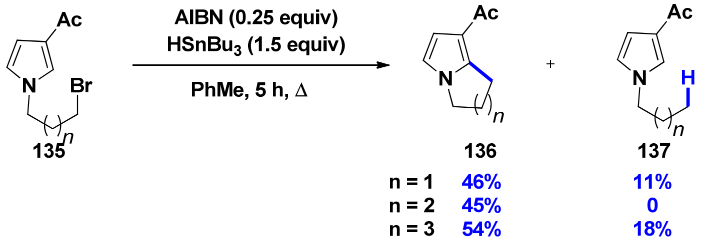
**Scheme 48**. Synthesis of oxindole **125** and proposed mechanism[92]



## 1.4.1 HAS: examples and reagents

Fused pyrroles **136** were synthesized via HAS promoted by AIBN and $Bu_3SnH$ (**Scheme 49**).[89b] The acetyl substituent was necessary to lower the electron density of the electron rich pyrrole, thus enabling attack of the nucleophilic alkyl radical at the electrophilic C-2 position (also β-position with respect to the ketone). In the absence of the acetyl substituent, only reduced product **137** was obtained. Five-, six-, and seven-membered rings were produced, along with significant amounts of reduced starting material **137**.

**Scheme 49**. Synthesis of fused pyrroles via HAS[89b]

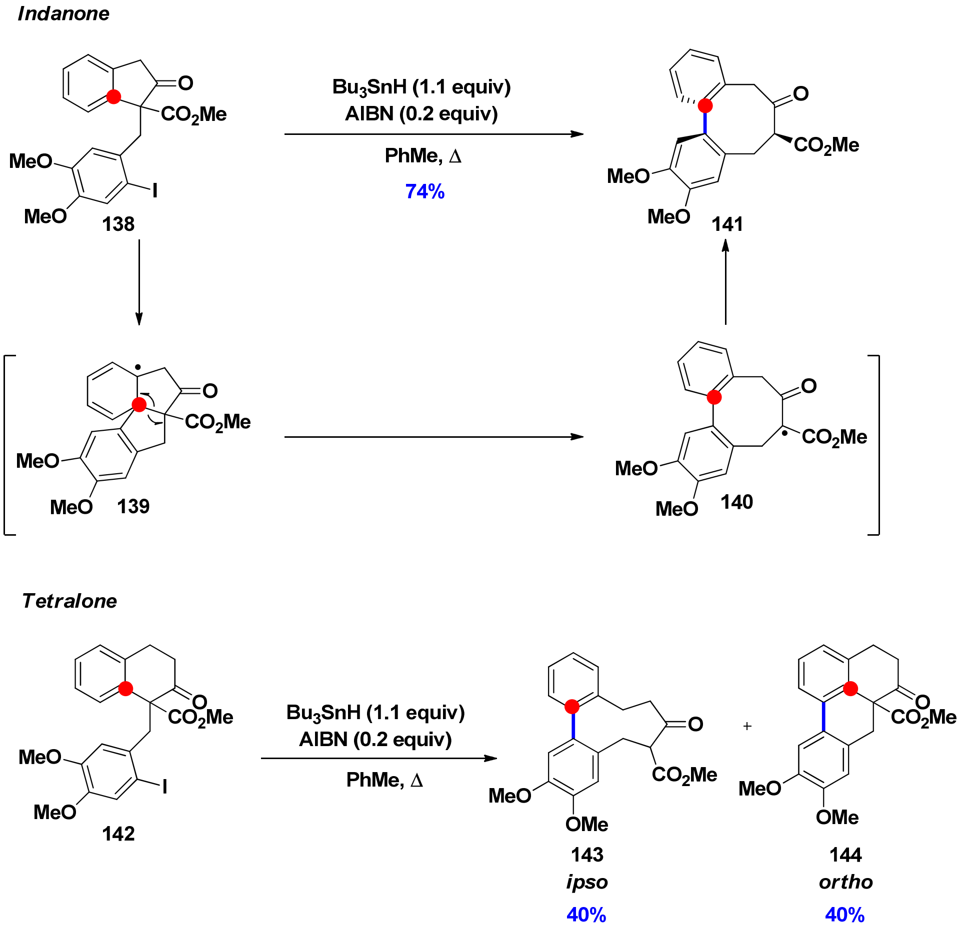


Eight-membered ring **141** was synthesized via an *ipso*-substitution onto an aromatic ring starting from indanone **138** (**Scheme 50**).[96] Generation of an aryl radical from the aryl iodide with the aid of AIBN/$Bu_3SnH$, followed by a 5-*exo*-*trig* cyclization provides intermediate **139**. Radical **139** undergoes a *β*-scission to produce a stable radical **140**. Here, H-abstraction from $Bu_3SnH$ gives rise to the final product **141**, as a single diastereomer after recrystallization. It is worth noting that **141** is the core of the natural product series of steganes.[97] In contrast, tetralone type compounds such as **142** led to a mixture of *ipso*- and *ortho*-substitution (**143** and **144**, **Scheme 53**).[96]

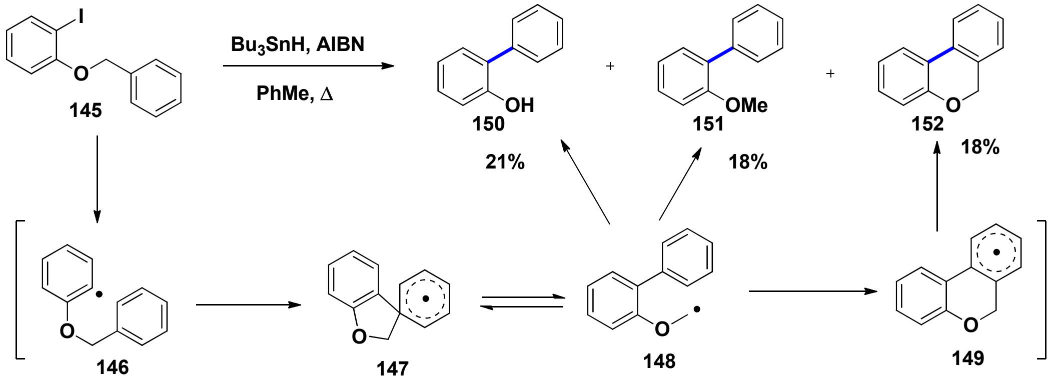
An example that will be more relevant to the topic in Chapter 5 (*vide infra*) and represents a direct comparison to transition metal catalyzed C–H arylation is shown in **Scheme 51**.[98] Harrowven and co-workers studied the intramolecular additions of aryl radicals onto benzyl ethers. Standard radical-forming conditions were employed (AIBN/$Bu_3SnH$) for benzyl ether **145**. After aryl radical **146** was formed, it underwent a *5-exo-trig ipso* cyclization to provide **147**. A number of competing pathways (H-abstraction, bond scission, addition) lead to the formation of three different products in quite low yields. The desired benzopyran **152** was only formed in 18% yield. The radical approach could be compared, for example, with

Fagnou's Pd-catalyzed intramolecular direct arylation strategy, where a similar benzopyran product was isolated in 96% yield (**Scheme 3**, *vide supra*). It was unclear how phenol product **150** was produced in the reaction.[98]

**Scheme 50**. Harrowven's synthesis of eight-membered and nine-membered rings[96]

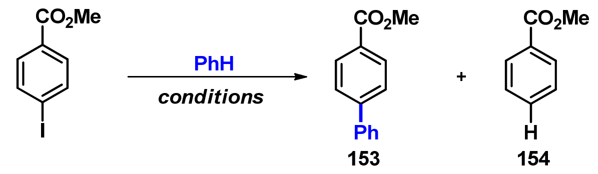


**Scheme 51**. Radical cyclization of iodobenzyl ether **145** leads to mixture of products[98]



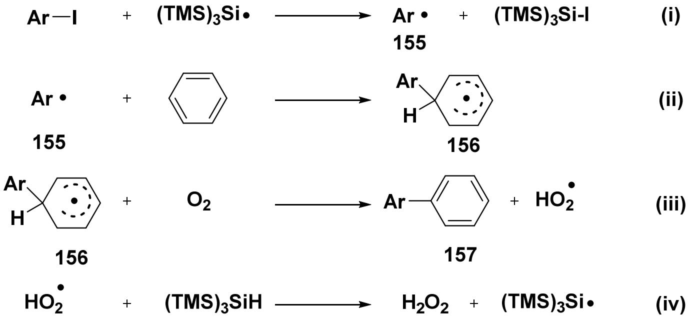
In general, the rise of transition metal-catalyzed cross-couplings and direct functionalizations has superseded the use of HAS in organic chemistry, due to the low yields, side-product formation and poor regioselectivity.[10] In addition, there are concerns associated with the reagents: a. organotin hydrides are known to be highly toxic; b. removal of tin residues after the reaction is problematic, thus limiting its applicability in the pharmaceutical industry; c. AIBN may present an explosion risk.[99] A greener alternative is represented by the use of $(TMS)_3SiH$ in presence of $Et_3B$ or $O_2$ (**Scheme 52**).[100] For the synthesis of biaryl **153**, reduction product **154** was isolated in 10% yield in presence of $HSnBu_3$, while use of $(TMS)_3SiH$ and oxygen as the chain carrier lead to 87% desired product and no dehalogenation product. In addition, the reaction was performed under much milder conditions (room temperature versus 80 °C). The chain carrier mechanism invokes the presence of peroxides (**Scheme 53**) and is proposed to occur in the folloing manner: (i) abstraction of the iodide by $(TMS)_3Si•$, (ii) attack of the resulting aryl **155** onto benzene, (iii) oxidation of cyclohexadienyl species **156** by $O_2$ to give the rearomatized product and a hydroperoxy radical, and (iv) reaction of this hydroperoxy radical with TTMSS to regenerate the $(TMS)_3Si•$ radical.[100]

**Scheme 52**. Comparison between $Bu_3SnH$ and $(TMS)_3SiH$[100]



| | 153 | 154 |
|---|---|---|
| $Bu_3SnH$, AIBN (1 equiv), 80 °C, 18 h | 67% | 10% |
| $(TMS)_3SiH$, AIBN (1 equiv), 80 °C, 14 h | 68% | 6% |
| $(TMS)_3SiH$, $O_2$, rt, 3 h | 87% | 0% |

**Scheme 53**. Proposed mechanism for HAS mediated by $(TMS)_3SiH/O_2$[100]

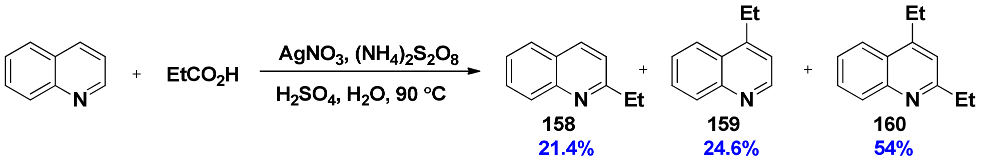


Photolysis of aryl or alkyl iodides has also been used to generate radicals; however, the reaction of aryl or alkyl bromides is sluggish.[101] More recently, the groups of Kellogg, Stephenson, MacMillan and others have advanced the use of visible light in presence of a photoredox catalyst (e.g. $[Ru(bpy)_3]Cl_2$) to generate aryl or alkyl radical from the corresponding bromides.[102]

## 1.4.2 The Minisci reaction

The Minisci reaction is the addition of an alkyl radical onto a protonated heteroarene and is a popular HAS transformation.[103] Substituents on the heteroarene play a significant role in determining reactivity and regioselectivity due to polar and steric effects. For example, addition of an alkyl radical onto quinoline provided a mixture of three products (**Scheme 54**).[104] However, when either the C-2 or C-4 positions are substituted, the reaction provides solely the C-4 or C-2 alkylated products.[105] The general mechanism for the Minisci reaction is similar to HAS (**Scheme 46**), but employs a protonated heterocycle. Another difference is represented by the way the radical is generated in presence of silver salts and persulfate from an alkyl carboxylic acid (**Scheme 54**).[104] The use of carboxylic acids as precursors is successful for a wide variety of linear and cyclic alkyls;[106] however, the reaction fails with aryl carboxylic acids. Recently, Baran disclosed the Minisci reaction of electron deficient heterocyles with aryl boronic acids.[107]

**Scheme 54**. The Minisci reaction and generation of the radical



*Radical formation*

$$2\,Ag^+ + S_2O_8^{2-} \longrightarrow 2\,Ag^{2+} + 2\,SO_4^{2-}$$

$$\text{Alk–COOH} + Ag^{2+} \longrightarrow \text{Alk}\bullet + CO_2 + H^+ + Ag^+$$

## 1.5 Research goals

The research undertaken during my PhD focused on developing novel methodologies for C–C bond formation, reaching from one end of the spectrum (homolytic aromatic substitution) to the other (C(sp$^3$)–H activation). In designing model systems and reaction conditions, my work has always been guided by the green chemistry principles discussed at the beginning of the introduction. A ruthenium-catalyzed C–H arylation of imidazopyridines will be addressed in Chapter 2. The employment of ruthenium catalysis for C–H functionalizations has largely developed in the last 10-12 years, while imidazopyridines have plenty applications in medicinal chemistry and also as fluorescence materials. Significant work also targeted the direct functionalization of cyclopropanes and these projects will be discussed in Chapters 3 and 4. Our group has a long-standing interest in both the synthesis and functionalization of cyclopropanes. Before 2011, there was no full account in the literature on direct C–H cyclopropyl activation; at the moment of writing the thesis, there are over ten such publications. Finally, strong base-promoted homolytic aromatic substitution which will be presented in Chapters 5 and 6 was unheard of in 2009, but became a “hot” and highly debatable topic a year later.

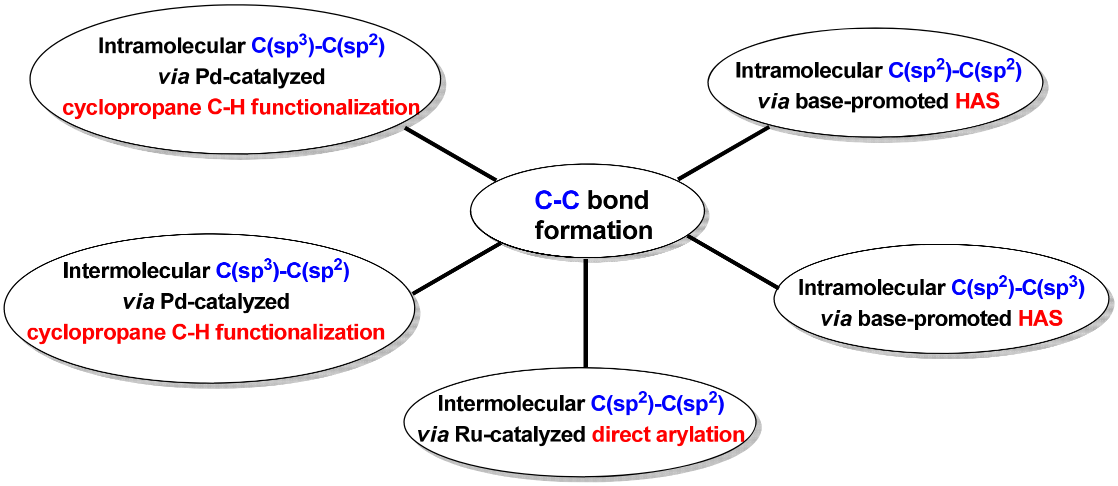


**Figure 9**. C-C bond formation achieved during the PhD

# Chapter 2. Ruthenium catalyzed direct C–H functionalization of imidazo[1,5-*a*]pyridines

## 2.1 Introduction

Nitrogen-containing fused heterocyclic scaffolds represent a special class of biologically relevant compounds. The development of straightforward methodologies for their synthesis and functionalization has consequently gathered a lot of effort from the medicinal and academic organic chemistry community.[108] Among nitrogen-containing pharmacophores, polyfunctionalized units containing a bridgehead "pyridine" nitrogen (as exemplified in **Figure 10**) are particularly challenging to prepare, mainly due to the commercial inaccessibility of the required starting materials.[109]

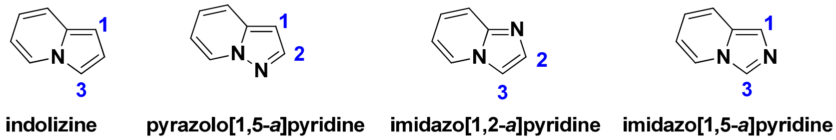
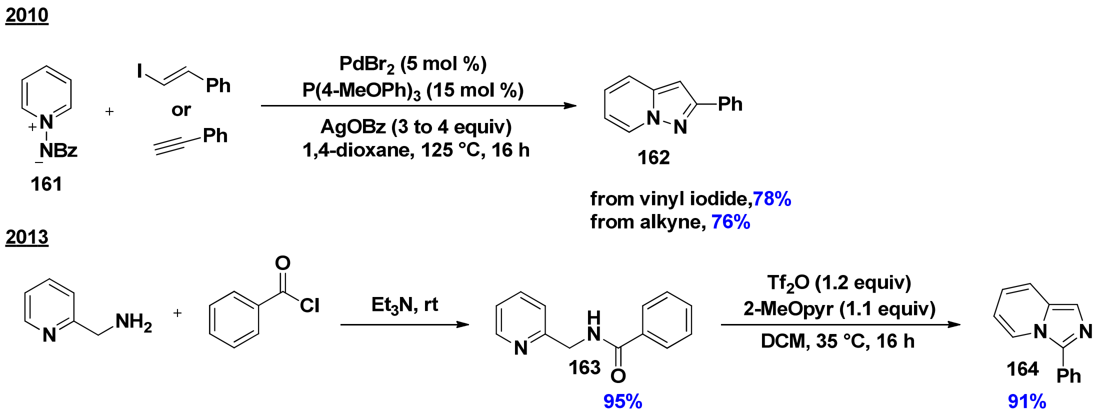


**Figure 10**. Fused bridgehead nitrogen-containing heterocycles

As part of a general program aimed at the development of methodologies for pyridine functionalizations,[110] our group has disclosed an elegant synthesis of pyrazolo[1,5-*a*]pyridines commencing from pyridinium ylide **161**, via a direct functionalization/cyclization sequence (**Scheme 55**).[111,64b] The powerful Pd-catalyzed transformation tolerates a variety of vinyl bromides, iodides or alkynes as coupling partners. Furthermore, the *N*-iminopyridinium ylide **161** is easily accessible from pyridine in two steps.[112] In 2011, David Gareau, a summer student, investigated the functionalization of the C-1 position of pyrazolopyridine **162** by direct arylation, but it proved a difficult task.[113]

Our group published a transition metal free, triflic anhydride mediated synthesis of imidazo[1,5-*a*]pyridines **164** under mild conditions (**Scheme 55**).[114] These compounds could be derived in two steps starting from inexpensive materials (2-aminomethylpyridine and various acyl chlorides) via a Bishler-Napieralski-type cyclization.

**Scheme 55**. Our group's approach for the synthesis of pyrazolo[1,5-*a*]pyridines and imidazo[1,5-*a*]pyridines[111,114]



## 2.1.1 Importance of imidazo[1,5-*a*]pyridines

Imidazo[1,5-*a*]pyridines have several noteworthy applications in medicinal chemistry and material sciences. Lately, an increasing number of compounds with anti-cancer, anti-inflammatory and other medicinal properties containing the imidazo[1,5-*a*]pyridine scaffold have been studied (**Figure 11**).[115] In 2003, the first natural product containing an imidazo[1,5-*a*]quinolone scaffold was discovered by Petit and co-workers in the marine sponge *Cribrochalina* sp.[116] The natural product, named Cribrostatin 6, shows promising anti-cancer and anti-inflammatory activity. Other applications of imidazo[1,5-*a*]pyridines include their use as precursors in the synthesis of *N*-heterocyclic carbenes.[117]

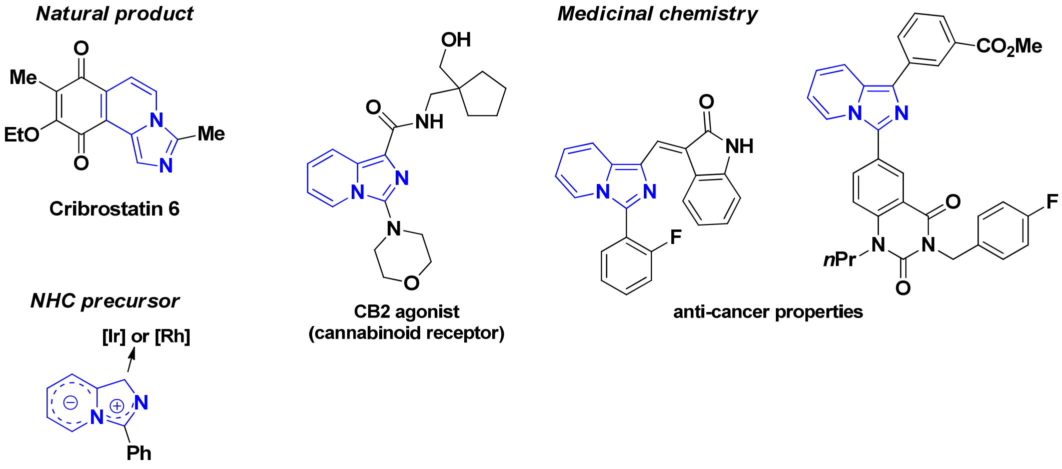
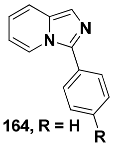
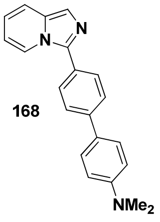
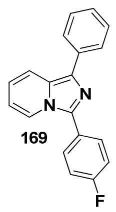
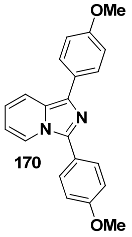


**Figure 11**. Applications of imidazo[1,5-*a*]pyridines

Most interestingly, photophysical studies revealed that certain imidazo[1,5-*a*]azines exhibit high fluorescence efficiencies. **Table 4** shows a few relevant examples along with their UV/Vis and fluorescence properties;[118] special attention should be noted to the quantum yield ($\Phi_F$), as it is a direct measurement of the efficiency of the compound to emit light ($\Phi_F$ is equal to the number of photons emitted divided by the number of photons absorbed).[119] While most aryl substituted imidazo[1,5-*a*]pyridines (entries 1-4) possessed a quantum yield that was equal or less than 0.1, some of the more conjugated systems (structures **168-170**) showed improved light absorbing/emitting properties (entries 5-7). In particular, electron donating groups (OMe, $NMe_2$) influenced positively the quantum yield value.

**Table 4**. UV/Vis and fluorescence properties of some imidazo[1,5-*a*]pyridines

| entry | structure | UV/vis | | fluorescence | |
|---|---|---|---|---|---|
| | | $\lambda_{max}$ (nm) | log ε | $\lambda_{max}$ (nm) | $\Phi_F$ |
| 1 |  **164**, R = H | 317 | 4.25 | 461 | 0.07 |
| 2 | **165**, R = OMe | 306 | 4.05 | 469 | 0.05 |
| 3 | **166**, R = $CF_3$ | 340 | 4.12 | 459 | 0.04 |
| 4 | **167**, R = *t*Bu | N/D | N/D | N/D | 0.04[a] |
| 5 |  **168** | 348 | 4.41 | 488 | 0.32 |
| 6 |  **169** | 304 | 4.11 | 449 | 0.19 |

|  |  |  |  |  |  |
|---|---|---|---|---|---|
| 7 |  170 | 303 | 4.31 | 479 | 0.22 |

---

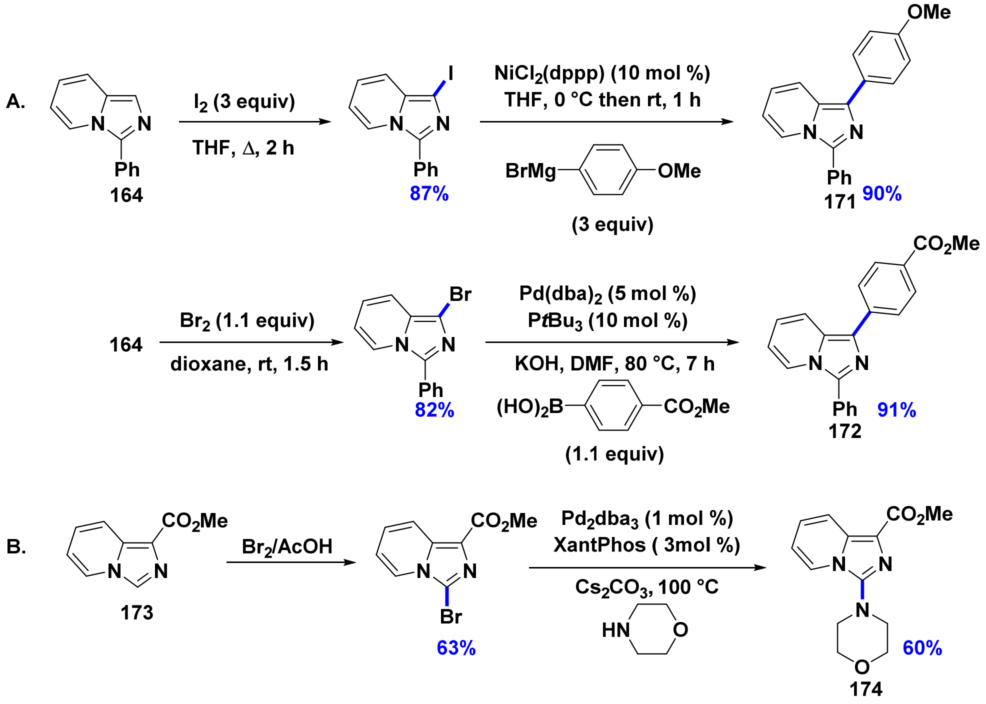
[a] This result was provided by Léa Constantineau-Forget, a former MSc in our group.

## 2.1.2 Direct functionalization of imidazo[1,5-*a*]pyridines

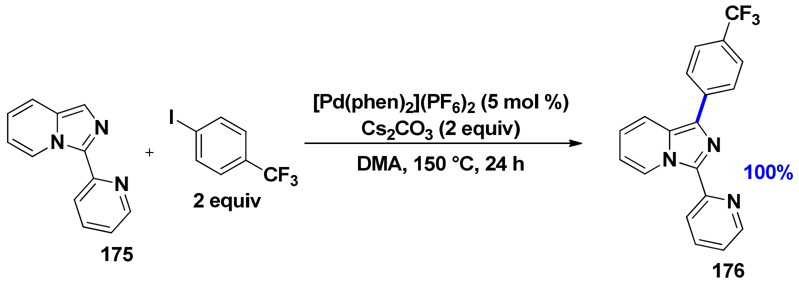
Since aryl groups enhance the photophysical properties of imidazo[1,5-*a*]pyridines,[118b] there is an interest in developing new methodologies for the functionalization of fused *N*-heterocycles.[120] The arylation is usually performed via a two-step sequence: halogenation of the most nucleophilic position of the heterocycle, followed by cross-coupling with an organometallic reagent.[115a,118b] For example, in **Scheme 56**, compound **164** can be either iodinated or brominated at the C-1 position, then coupled to an aryl Grignard reagent or an aryl boronic acid to provide the corresponding products (**171** and **172**) in very good yields over two steps.[118b] If the C-1 position is blocked (heterocycle **173**), then bromination occurrs at the C-3 position, and that position can then be functionalized via a Pd-catalyzed reaction to provide **174** (**Scheme 56B**).[115a]

In 2010, the group of Murai disclosed the catalytic use of a cationic Pd-complex $Pd(phen)_2(PF_6)_2$ in presence of two equivalents cesium carbonate as the base for the direct arylation of the C-1 position of 3-(pyridin-2-yl)imidazo[1,5-*a*]pyridine **175** (**Scheme 57**).[121] The reaction provided the corresponding product **176** in quantitative yield after stirring for 24 h in DMA at 150 °C. Preliminary mechanistic studies suggested against C–H bond breaking as a rate-determining step, and an electrophilic or a radical pathway was proposed.

**Scheme 56**. Multistep functionalizations of imidazo[1,5-*a*]pyridines



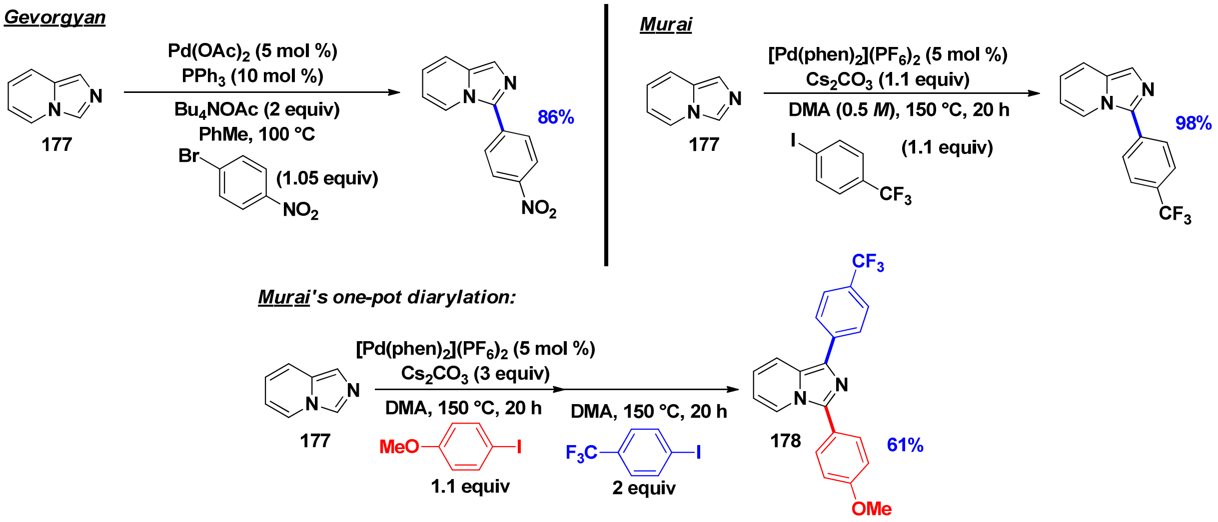
**Scheme 57**. Murai's arylation of the C-1 position[121]



In back-to-back publications, the groups of Gevorgyan and Murai disclosed the first direct arylation of imidazo[1,5-*a*]pyridines at the C-3 position in 2011 (**Scheme 58**).[122,123] More precisely, Gevorgyan employed aryl bromides as coupling partners, palladium acetate as the catalyst, triphenylphosphine as the ligand and tetrabutylammonium acetate as the base.[122] Remarkably, no traces of arylation at the C-1 position were observed. A number of aryl bromides could be successfully coupled; however, electron withdrawing substituents provided better yields. Preliminary mechanistic studies were undertaken and indicated a kinetic isotope effect of 1.0 (calculated via an intermolecular competition reaction in the same flask), which would suggest against a C–H activation step being rate-limiting.

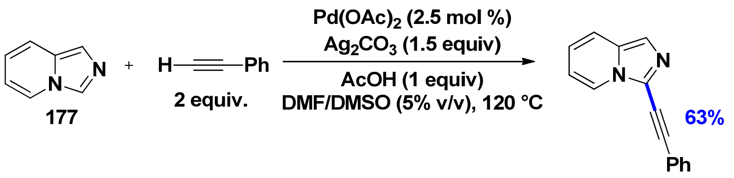
In parallel, Murai and co-workers employed their previously reported conditions[121] to functionalize the C-3 position of **177** with aryl iodides (**Scheme 58**).[123] Expectedy, some arylation at the C-1 position was detected, but could be suppressed by diluting the reaction mixture from 1.0 *M* to 0.5 *M*. Therefore, a second arylation at the C-1 site with a different aryl iodide was possible in a one-pot process (see formation of **178**).

**Scheme 58**. Direct arylation of imidazo[1,5-*a*]pyridines at the C-3 position



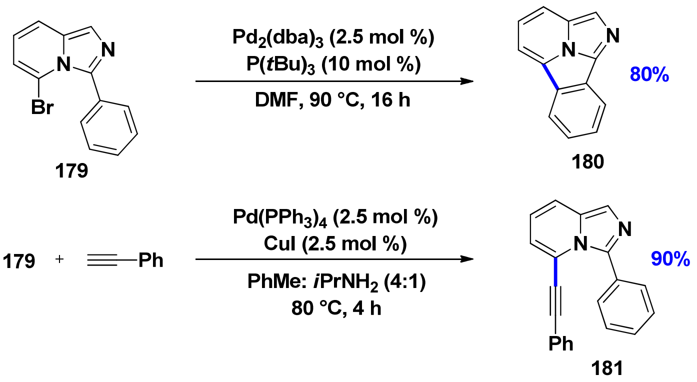
Of late, Murai reported the oxidative coupling of imidazo[1,5-*a*]pyridines with alkynes (**Scheme 59**).[124] The optimized conditions were $Pd(OAc)_2$ as the catalyst, silver carbonate, acetic acid as the additive and a mixture of DMF/DMSO as the solvent. The combination of reagents allowed for selective alkynylation at the C-3 position. Furthermore, slow addition of the alkyne was necessary to prevent its homocoupling. There was no reaction when any of the silver carbonate or acetic acid were omitted, which lead the authors to suggest that a CMD-type pathway is operative. It should be noted that the C-1 position could also be alkynylated, however a two-step sequence involving a bromination, then Sonogashira coupling was necessary.

**Scheme 59**. Oxidative coupling of imidazo[1,5-*a*]pyridines and alkynes[124]



Recently, a couple of direct functionalization examples were also disclosed by the Charette group as part of our studies on the triflic anhydride-mediated synthesis of imidazopyridines (**Scheme 60**).[114] For example, bromoimidazo[1,5-*a*]pyridine **179** could either undergo an intramolecular direct arylation cyclization in presence of a $Pd^0$ source to give **180** or a Sonogashira coupling with phenylacetylene to provide product **181** in very good yields.

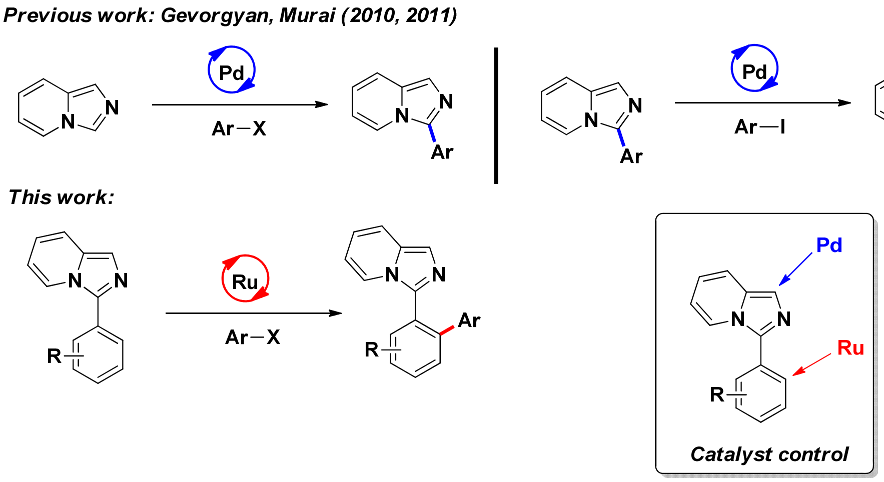
**Scheme 60**. Direct arylation and Sonogashira coupling of imidazo[1,5-*a*]pyridine **179**[114]



## 2.1.3 Research goals

Considering the potential of imidazo[1,5-*a*]azines in medicinal chemistry and their applications as fluorescent materials, as well as our continued interest in direct arylations, we sought to develop novel C–H functionalizations of the substrates. We also had in hand an easy, two-step sequence that would give imidazo[1,5-*a*]pyridines substituted at the C-3 position in high yields.[114] Prompted by the advances in ruthenium-catalyzed direct arylations (Section 1.2), we envisioned that the imidazo[1,5-*a*]pyridine functionality could act as a potential directing group for Ru catalysts. Whereas several nitrogen-containing five-membered heterocycles have been used as chelating groups (**Figure 8**, *vide supra*), fused nitrogen heterocycles of the type shown in **Figure 10** have yet to be tested. Furthermore, the Ru-catalyzed reaction would be complimentary to the Pd-arylation at the C-3 or C-1 positions developed by Murai and Gevorgyan (**Scheme 61**).

**Scheme 61**. Pd- versus Ru-catalyzed direct arylation of imidazo[1,5-*a*]pyridines

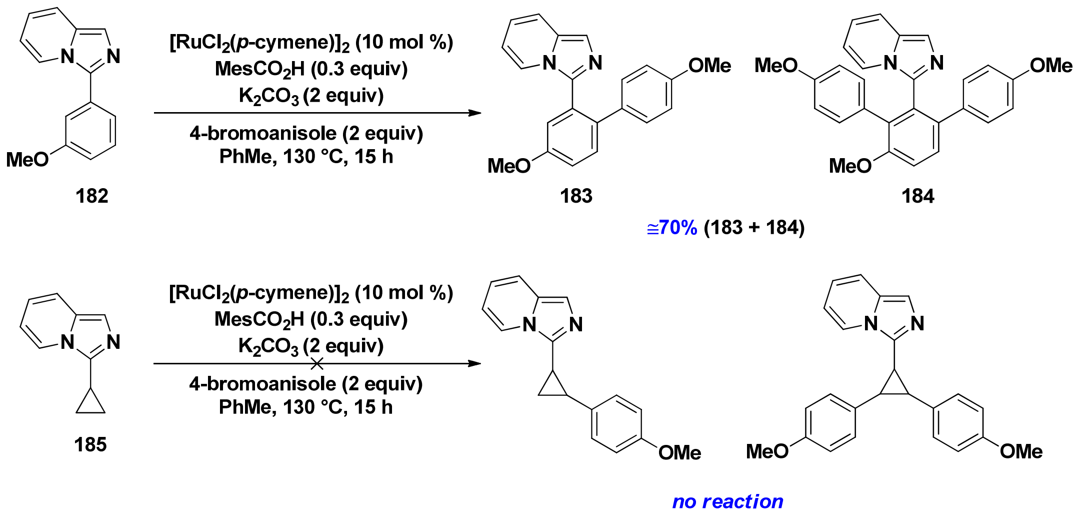


## 2.2 Results and discussion

### 2.2.1 Initial studies

We commenced our studies by adapting Ackermann's previously established conditions for carboxylate-assisted ruthenation to a generic imidazo[1,5-*a*]pyridine template.[48] Imidazopyridine **182** containing a *meta*-OMe group provided monoaryl **183** as the main product, along with traces of **184** in about 70% (**Scheme 62**) when subjected to the reaction conditions.

**Scheme 62**. Preliminary results for the Ru-catalyzed arylation of **182** and **185**

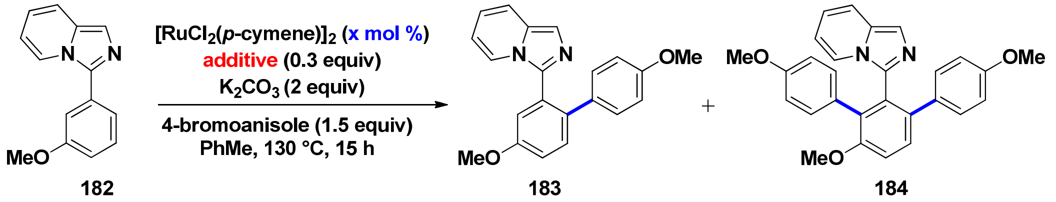


A cyclopropane substituted imidazopyridine **185** was also tested (**Scheme 62**); unfortunately, only starting material was recovered in this case, suggesting that the present conditions were not suitable for cyclopropyl C–H activation. Nonetheless, a promising result with aryl C–H activation led us to pursue this study further.

## 2.2.2 Reaction optimization

An intern from France (Valentin Poiret) helped with the initial optimization of the methodology. A few additives were screened for the reaction of **182** with 4-bromoanisole and the results are disclosed in **Table 5**. In absence of any carboxylate additive, there was no reaction (entry 1), while adding benzoic acid or 2,4,6-trimethylbenzoic acid ($MesCO_2H$) with only 2.5 mol % $[RuCl_2(p\text{-cymene})]_2$ as the catalyst resulted in incomplete conversions (entries 2 and 3). Increasing the catalyst loading to 5 mol % led to complete conversion of the starting material to **183**, and traces of **184**. A higher yield was obtained with the more sterically hindered acid $MesCO_2H$ versus benzoic acid (compare entries 4 and 5). It should be noted that the reaction does not proceed at a lower temperature (≤100 °C). Separating traces of **184** from the product **183** proved to be quite challenging via column chromatography. In addition, using $^1H$ NMR yields for the optimization was also troublesome due to the overlap of the starting material and products peaks in the spectrum.

**Table 5**. Initial optimization with 4-bromoanisole and **182**

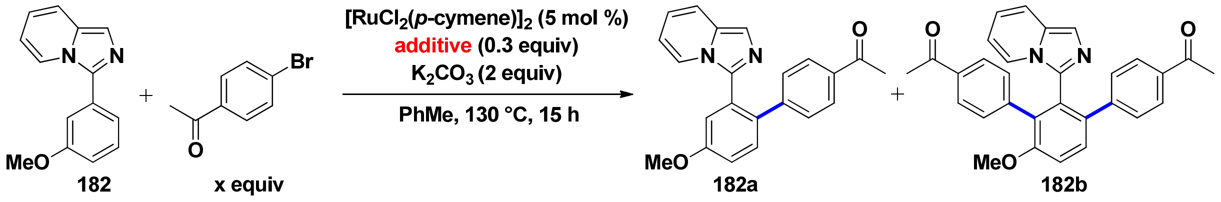


| entry | [Ru] catalyst | additive | comments[a] |
|---|---|---|---|
| 1 | 2.5 mol % | --- | <2% **183** |
| 2 | 2.5 mol % | BzOH | about a 1:1 mixture of **182**:**183** |
| 3 | 2.5 mol % | $MesCO_2H$ | about a 1:1 mixture of **182**:**183** |
| 4 | 5.0 mol % | BzOH | 57% **183** (traces of **184**) |
| 5 | 5.0 mol % | $MesCO_2H$ | 66% **183** (traces of **184**) |

[a] Reactions were run on a 0.3 or 0.4 mmol scale; isolated or estimated yields.

In order to avoid complications due to analytical issues, the optimization of the additive was revisited employing 4'-bromoacetophenone as the coupling partner, as the two products **182a** and **182b** were easily separable by column chromatography (**Table 6**). Both BzOH and $MesCO_2H$ provided good yields of the products, with a similar 2:1 ratio of mono- to diaryl (entries 1 and 2). 1-Adamantyl carboxylic acid ($AdCO_2H$) gave a lower yield (entry 3), while pivalic acid resulted in 33% unreacted starting material (entry 4). Employing potassium acetate as the additive provided a 1:1 mixture of mono and diarylated products.

**Table 6**. Screen of additives

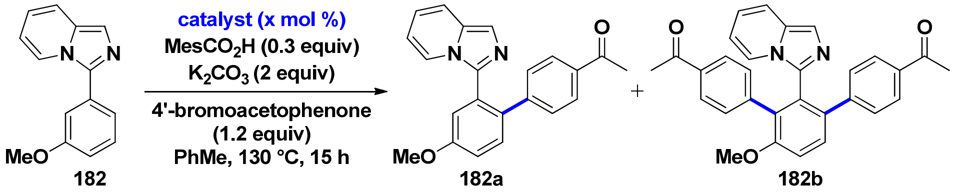


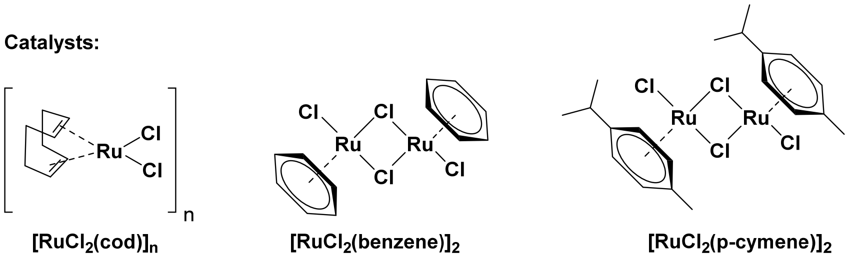
| | | | yield[a] (%) | | |
|---|---|---|---|---|---|
| entry | ArBr (x equiv) | additive | **182** | **182a** | **182b** |
| 1 | 1.5 | BzOH | 0 | 50 | 19 |
| **2**[b] | **1.2** | **$MesCO_2H$** | **0** | **51** | **22** |
| 3[b] | 1.5 | $AdCO_2H$ | 0 | 44 | 20 |
| 4 | 1.5 | PivOH | 33 | 57 | 2 |
| 5 | 1.2 | KOAc | 0 | 34 | 30 |

[a] Reactions were run on a 0.2 mmol scale. Isolated yields. [b] Reaction was run on a 0.4 mmol scale. Isolated yield.

We next looked at other Ru complexes as catalysts. Using 10 mol % of inexpensive $RuCl_3$ hydrate (containing 48-50% Ru, about 5 mol % Ru in the reaction) resulted in no reaction (**Table 7**, entry 1). Other $Ru^{II}$ sources could be successfully employed in the reaction, however incomplete conversions (entry 2) or lower yields (entry 3) were obtained. In the end, the initial $[RuCl_2(p\text{-cymene})]_2$ was the optimal catalyst (entry 4).

**Table 7**. Screen of Ru catalysts





| entry | Ru (mol %) | yield[a] (%) | | |
|---|---|---|---|---|
| | | **182** | **182a** | **182b** |
| 1 | $RuCl_3\cdot xH_2O$ (10) | 87 | 0 | 0 |
| 2 | $[RuCl_2(cod)]_n$ (5) | 42 | 17 | 7 |
| 3 | $[RuCl_2(benzene)]_2$ (5) | 0 | 36 | 26 |
| **4**[b] | **$[RuCl_2(p\text{-cymene})]_2$ (5)** | **0** | **51** | **22** |

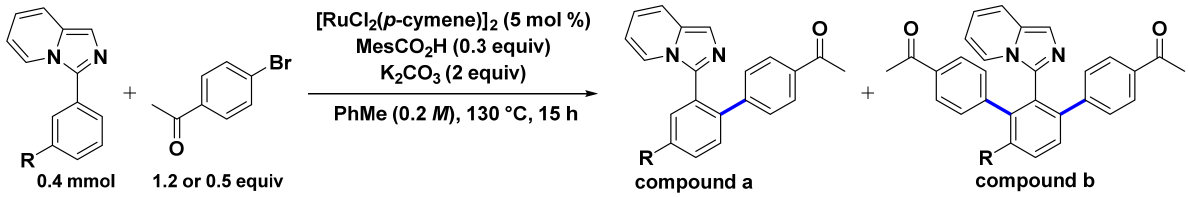
[a] $^1H$ NMR yield using $Ph_3CH$ as internal standard. [b]Isolated yield on a 0.4 mmol scale.

Upon analysis of the reaction mixture by LC-MS, we also observed some higher molecular weight peaks corresponding to dimerization of either the starting material, or the product, or a mixture of both. The dimerization side-reaction is comparable to an oxidative homocoupling Ackermann and co-workers observed when employing *ortho*-substituted aryl halides as coupling partners.[60a] The side-reaction would explain why the product yield reached a plateau of 70-80%, despite observing no unreacted starting material by LC-MS.

### 2.2.3 Scope of the imidazo[1,5-*a*]pyridine partner

Various *meta*-substituted imidazo[1,5-*a*]pyridines were screened in presence of either 1.2 or 0.5 equivalents of 4'-bromoacetophenone as the coupling partner (**Scheme 63**). When the imidazo[1,5-*a*]pyridine was used as the limiting reagent, an electron donating group (OMe) on **182** led to the lowest selectivity for the monoarylated product **182a** (2:1), while both methyl (**186**) and trifluoromethyl (**187**) substituents gave predominantly monoarylation (20:1 and 10:1 respectively). When the reaction was performed employing the aryl bromide as the limiting reagent (1.0 equiv ArBr to 2.0 equiv imidazo[1,5-*a*]pyridine), an almost quantitative conversion of the desired monoarylation products was isolatedNo diarylation was observed; instead, unreacted imidazo[1,5-*a*]pyridine was recovered (20%), along with some dimerization of the starting imidazo[1,5-*a*]pyridine.

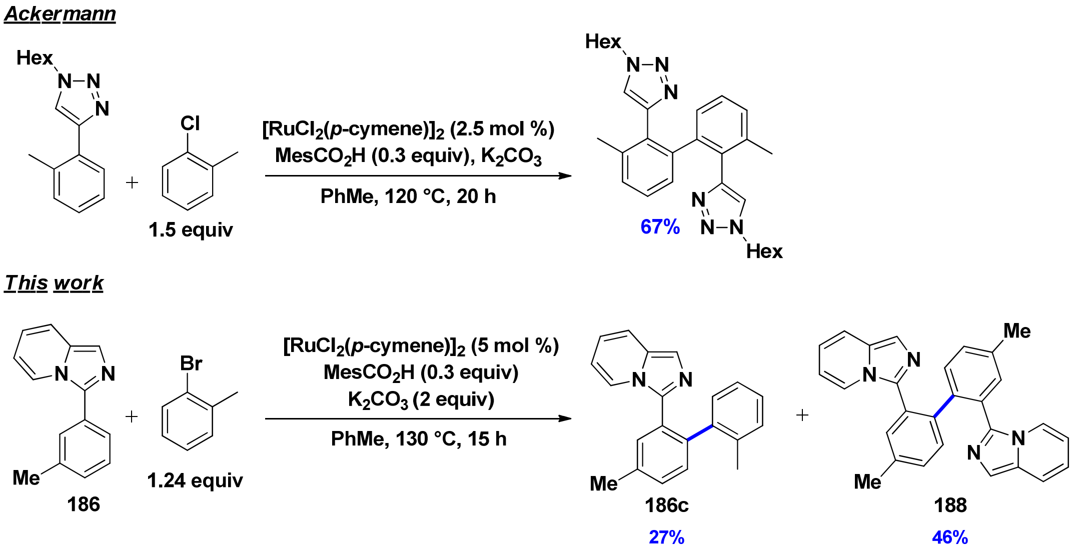
**Scheme 63**. Screen of *meta*-substituted imidazo[1,5-*a*]pyridines



| R = 3-MeO (182) | 182a | 182b | R = 3-Me (186) | 186a | 186b | R = 3-CF$_3$ (187) | 187a | 187b |
|---|---|---|---|---|---|---|---|---|
| 1.2 equiv ArBr | 51% | 22% | 1.2 equiv ArBr | 87% | 4% | 1.2 equiv ArBr | 71% | <5% |
| 0.5 equiv ArBr | 93% | 0 | 0.5 equiv ArBr | 98% | 0 | 0.5 equiv ArBr | >95% | 0 |

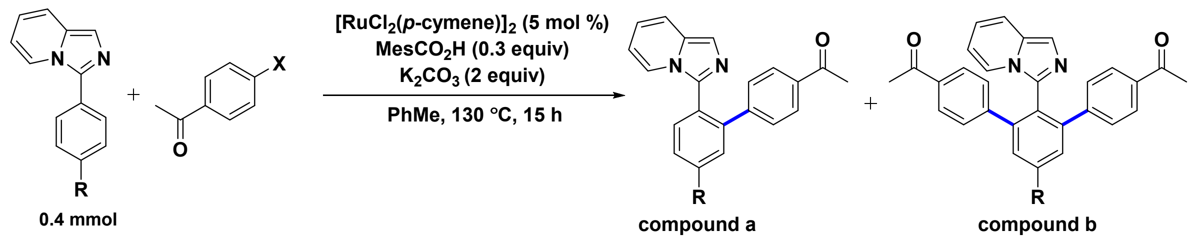
In order to investigate the dimerization further, Ackermann's oxidative homocoupling work was revisited.[60a] In a recently published study, a reaction performed in presence of 2-chlorotoluene as the coupling partner, furnished 67% isolated dimer as the sole product (**Scheme 64**). In the present case, imidazo[1,5-*a*]pyridine **186** was reacted with 2-bromotoluene, and, under our optimized reaction conditions, 27% of direct arylation product **186c** was isolated, along with 46% dimer **188** (the structure of dimer **188** was determined via COSY NMR). Unlike Ackermann's results, where dimerization is observed exclusively, we are able to obtain some direct arylation product with the sterically hindered 2-bromotoluene.

**Scheme 64**. Oxidative homocoupling with *ortho*-substituted aryl halides



Imidazo[1,5-*a*]pyridines containing a *para*-substituent were also tested under the reaction conditions with 1.2 equivalents aryl halides (**Scheme 65**). It was expected that the diarylation products would be more prominent versus the *meta*-series. Indeed, the ratio was roughly 2-2.5:1 for all substituents, similar to what Inoue and Oi had observed (**Table 3**, *vide supra*),[54] while the best overall yield (92%) was obtained for the trifluoromethyl-substituted **166**. A bulky *tert*-butyl substituent did not improve the mono:di ratio significantly (2.5:1). A reaction between 4'-chloroacetophenone and imidazo[1,5-*a*]pyridine **165** was also set up; both the yields and ratios were higher than the corresponding bromide, consistent with the reactivity order ArCl>ArBr.

**Scheme 65**. Screen of *para*-substituted imidazo[1,5-*a*]pyridines



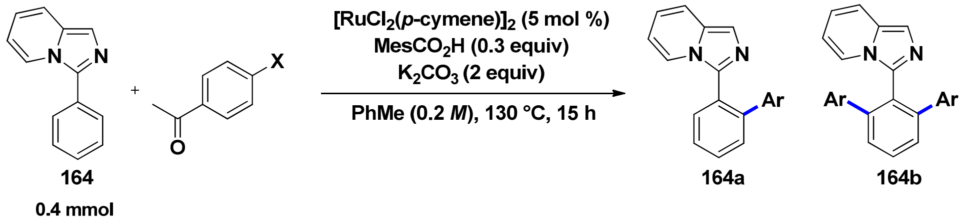
| R = 4-MeO (165) | 165a | 165b |
|---|---|---|
| 1.2 equiv ArBr | 32% | 16% |
| 1.2 equiv ArCl | 49% | 20% |

| R = 4-CF$_3$ (166) | 166a | 166b |
|---|---|---|
| 1.2 equiv ArBr | 59% | 30% |

| R = 4-*t*Bu (167) | 167a | 167b |
|---|---|---|
| 1.2 equiv ArBr | 55% | 22% |

When the unsubstituted imidazo[1,5-*a*]pyridine **164** was submitted to the reaction conditions, a mixture of mono- and diarylation was obtained with all aryl halides tested (**Scheme 66**). Adding excess of the aryl bromide resulted in the formation of diaryl **164b** solely. Therefore, by modulating the amount of the coupling partner, one can obtain either product as major. Again, the reactivity order for different halides was determined to be ArCl>ArBr>ArI.

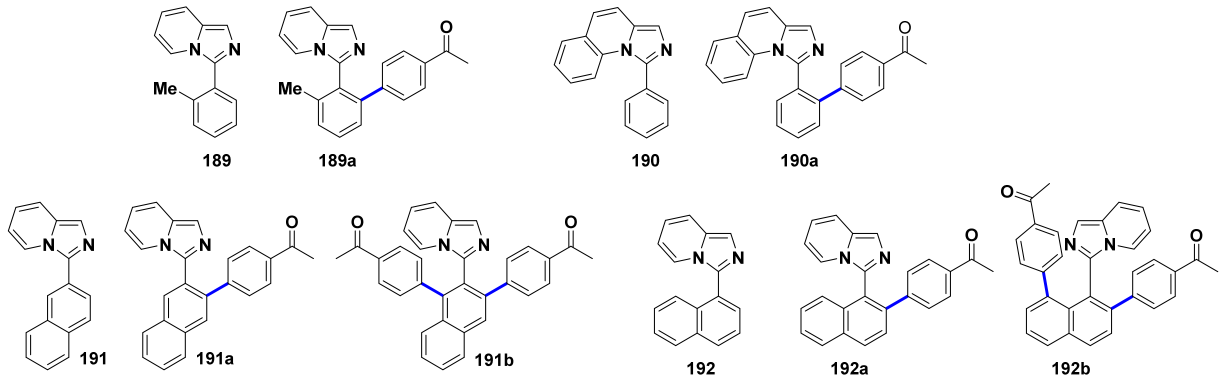
**Scheme 66**. Functionalization of unsubstituted imidazo[1,5-*a*]pyridine **164**



| | | |
|---|---|---|
| 1.2 equiv ArBr | 41% | 23% |
| 3.0 equiv ArBr | 0 | 77% |
| 1.2 equiv ArCl | 50% | 27% |
| 1.2 equiv ArI | 31% | 20% |

Finally, other substituted imidazo[1,5-*a*]pyridines were tested in the reaction (**Table 8**). *ortho*-Methyl **189** led to the formation of the monoaryl product in 63% yield (entry 1). Quinoline substrate **190** provided solely monoaryl **190a** in 66% yield (entry 2); a second arylation did not occur presumably due to a restricted conformation imposed by π,π-stacking between the acetophenone and the quinoline ring. Lower yields were obtained with 2-naphthyl substrate **191** (entries 3-4), while 1-naphthyl **192** led to 57% of the expected monoaryl **192a** (entry 5). Interestingly, the molecular weight of a potential diaryl substrate was observed by LC-MS analysis of the crude mixture, and 19% yield **192b** was isolated. Upon 1D and 2D NMR analysis, it was determined that the second arylation occurred on the naphthyl ring at the C-9' position (see structure **192b**).

**Table 8**. Screen of other imidazo[1,5-*a*]azines



| entry | imidazo[1,5-*a*]azine | 4'-bromoacetophenone | mono, yield[a] | diaryl, yield[a] |
|---|---|---|---|---|
| 1 | **189** | 1.5 equiv | **189a**, 63% | **189b**, 0 |
| 2 | **190** | 1.2 equiv | **190a**, 66% | **190b**, 0 |
| 3 | **191** | 1.2 equiv | **191a**, 32% | **191b**, 20% |
| 4 | **191** | 0.5 equiv | **191a**, 41% | **191b**, 0 |
| 5 | **192** | 1.2 equiv | **192a**, 57% | **192b**,[b] 19% |

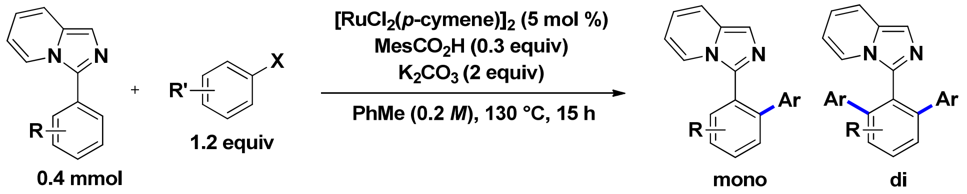
[a] Reaction conditions: imidazo[1,5-*a*]azine (0.4 mmol), 4'-bromoacetophenone (x equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $K_2CO_3$ (2 equiv), PhMe (2 mL), 130 °C, 15 h. Isolated yields. [b] See structure of **192b**.

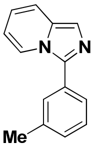
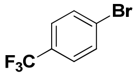
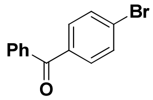
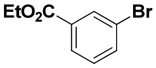
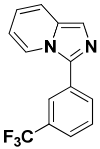
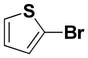
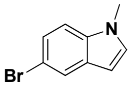
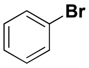
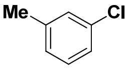
To sum up, the product distribution observed can be correlated to the sterics and electronic influence exerted by the C-3 aryl group of the starting imidazo[1,5-*a*]pyridine. As such, electron neutral and electron withdrawing groups on the C-3 phenyl ring provided better yields and mono- to diarylation ratios than the 3- or 4-MeO-substituted imidazo[1,5-*a*]pyridines. Having the aryl halide as the limiting reagent was also ideal, leading to over 90% yields in almost all cases.

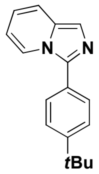
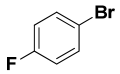
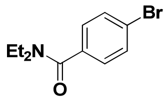
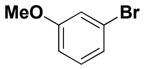
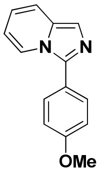
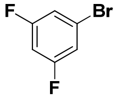
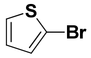
### 2.2.4 Scope of the aryl halide

Following the latter study, we next considered the functional group tolerance of the aryl halide partner (**Table 9**). To have a better understanding of the steric influence versus electronics in the reaction, imidazo[1,5-*a*]pyridines substituted in the *meta* and *para* positions were evaluated. Heterocycles **186** and **187** tolerated a variety of aryl halides containing electron withdrawing ($CF_3$, $MeO_2C$, PhC(O), entries 1-3) or electron neutral groups (entries 6 and 7). Notably, heterocycles such as 2-bromothiophene and 5-bromo-1-methyl-1*H*-indole performed well to provide the monoarylated products in excellent yields (entries 4-5). Most of the products were solely obtained as monoaryl, but in some cases traces of diarylation were also observed (details in the Experimental section). *tert*-Butyl-substituted imidazopyridine **167** also tolerated electron withdrawing (F, $Et_2NC(O)$, entries 8-9) or electron donating groups (3-OMe, entry 10). Lower yields were obtained in the case of imidazo[1,5-*a*]pyridine **165** (entries 11-12) as significant dimerization of products **165c** and **165e** was observed by LC-MS. In addition, when 1-bromo-4(trifluoromethyl)benzene was employed as coupling partner, the corresponding arylated imidazo[1,5-*a*]pyridines had a higher propensity to decompose to unknown by-products, even when stored at -20 °C.[125]

**Table 9**. Scope of the aryl halide



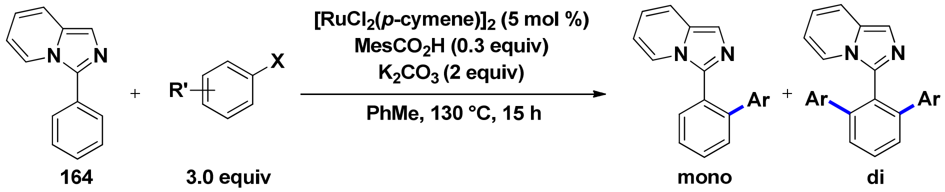
| entry | imidazo[1,5-*a*]pyridine | aryl halide | mono, **yield** | di, **yield** |
|---|---|---|---|---|
| 1 |  **186** |  | **186d, 60%** | **186e, 0** |
| 2 |  |  | **186f, 47%** | **186g, <3%** |
| 3 |  |  | **186h, 48%** | **186i, 0** |
| 4 |  **187** |  | **187c, 77%** | **187d, 6%** |
| 5 |  |  | **187e, 81%** | **187f, <3%** |
| 6 |  |  | **187g, 89%** | **187h, 0** |
| 7 |  |  | **187i, 77%** | **187j, 0** |

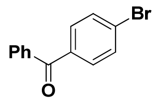
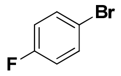
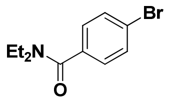
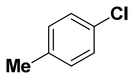
| | | | | |
|---|---|---|---|---|
| 8 | <br>**167** |  | **167c**, **47%** | **167d**, **21%** |
| 9 | |  | **167e**, **69%** | **167f**, **9%** |
| 10 | |  | **167g**, **47%**<br>(**98%**)$^a$ | **167h**, **18%** |
| 11 | <br>**165** |  | **165c**, **40%** | **165d**, **16%** |
| 12 | |  | **165e**, **22%** | **165f**, **10%** |

$^a$0.5 equiv of aryl halide was used.

In order to preferentially obtain diarylated products, the reactions of imidazo[1,5-*a*]pyridine **164** with 3.0 equivalents aryl halides were investigated. In the case of 4'-bromoacetophenone (**Scheme 66**, *vide supra*), the diarylation product was obtained exclusively; however, other aryl halides tested provided the diaryl compound only preferentially (**Table 10**, entries 1-3). The best partner was 4-bromobenzophenone which provided **164d** in 83% (entry 1). 4-Chlorotoluene gave an overall yield of 72%, but an almost 1:1 mixture of mono and di (entry 4). We reasoned that the bulky $MesCO_2^-$ ligand ($MesCO_2H$ is deprotonated *in situ* by $K_2CO_3$) on the Ru centre might significantly encumber the second arylation, so we switched to KOAc as the additive, as the exchange of chloride with acetate easily takes place for [RuCl$_2$(*p*-cymene)]$_2$.[126] Granted, the ratio was improved to 2:1 favouring diarylation, but the yield was not improved (entry 5).

**Table 10**. Direct arylation with excess aryl halide

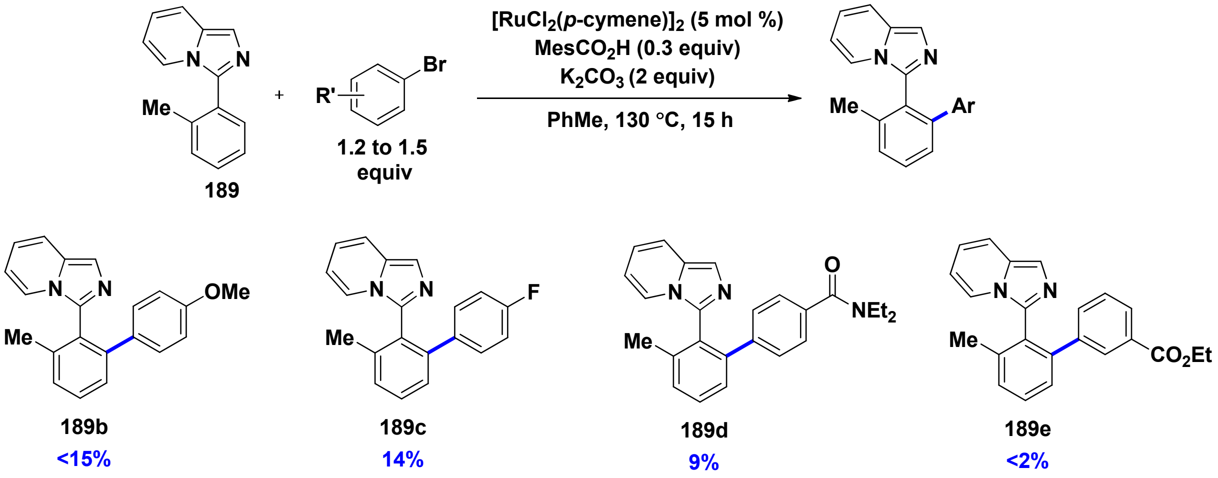


| entry | aryl halide | **mono**, **yield** | **di**, **yield** |
|---|---|---|---|
| 1 |  | **164c, 9%** | **164d, 83%** |
| 2 |  | **164e, 16%** | **164f, 55%** |
| 3 |  | **164g, 10%** | **164h, 43%** |
| 4 |  | **164i, 32%** | **164j, 40%** |
| 5 |  | **164i, 20%**[a] | **164j, 43%**[a] |

[a]KOAc (0.3 equiv) instead of $MesCO_2H$.

The reactivity of *ortho*-tolyl imidazo[1,5-*a*]pyridine **189** proved to be substrate dependant (**Scheme 67**). Whereas 4'-bromoacetophenone provided 63% product (Table 8, entry 1), other aryl halides screened gave very poor conversion; starting material was recovered, and no dimerization of **189** was observed by LC-MS.

**Scheme 67**. Scope of *ortho*-substituted imidazo[1,5-*a*]pyridine ($^1$H NMR yields using triphenylmethane as internal standard)

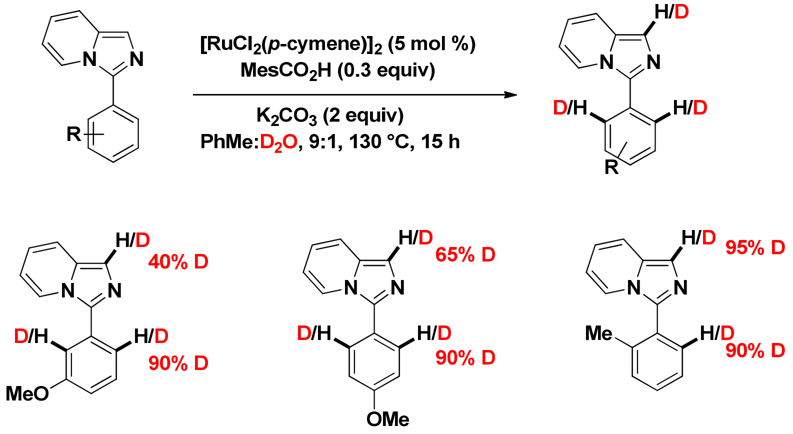


## 2.2.5 Mechanistic investigations

### 2.2.5.1 Deuteration experiments

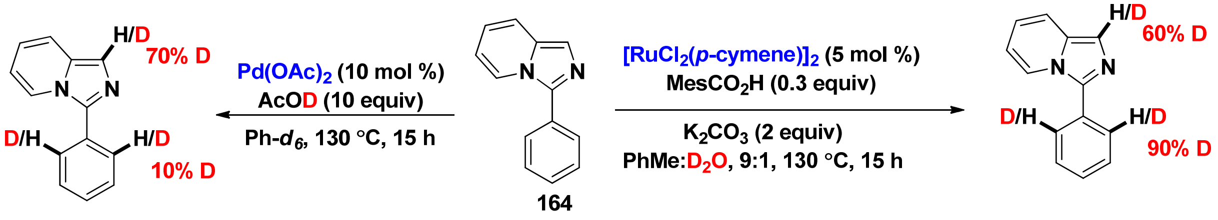
To study the reaction mechanism, control reactions were ran in presence of a 1:9 mixture of $D_2O$ and toluene as the solvent, leading to 90% deuterium incorporation at the *ortho* positions of the 3-aryl-substituted imidazo[1,5-*a*]pyridines (**Scheme 68**), clearly demonstrating the reversibility of the C–H ruthenation step (**Scheme 25**, *vide supra*).[59] Furthermore, the C-1 position was also deuterated in variable amounts, thus implying that arylation at the position should also be possible; however, no C-1 arylation product was observed during the scope exploration.

**Scheme 68**. Deuterium incorporation experiments



An interesting comparison between the site selectivity of Ru versus Pd is shown in **Scheme 69**. Under the Ru deuteration conditions described above, imidazo[1,5-*a*]pyridine **164** underwent exchange at the expected *ortho*-tolyl C–H and C-1 positions. In parallel, heating up the substrate with $Pd(OAc)_2$ and AcOD, incorporated deuterium mainly at the C-1 position, with small traces at the *ortho*-tolyl position.

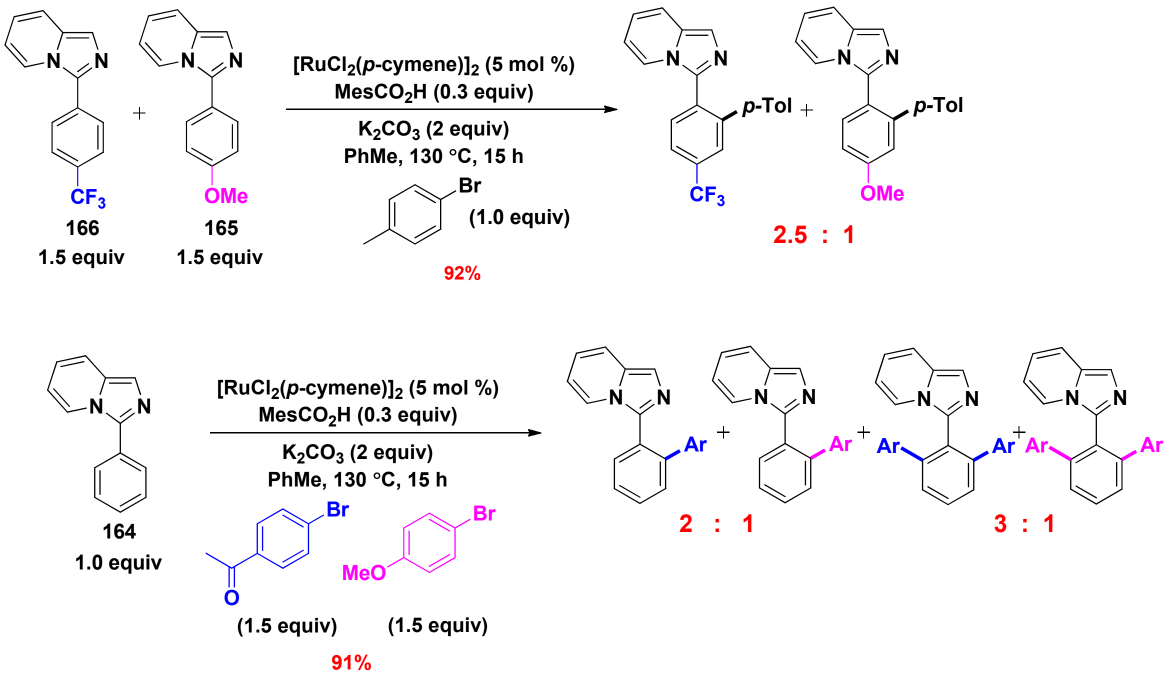
**Scheme 69**. Deuterium incorporation for Pd versus Ru catalysis



### 2.2.5.2 Competition experiments

A competition experiment performed between different electronics on the imidazo[1,5-*a*]pyridines demonstrated a clear preference for arylation on the electron poor imidazo[1,5-*a*]pyridine **166** (**Scheme 70**). The result was consistent with some of the poor yields associated with reactions involving electron rich imidazo[1,5-*a*]pyridines. Moreover, another competition experiment between an electron rich and an electron poor aryl bromide also led to a clear preference for the electron withdrawing acetophenone reactant (**Scheme 72**). The preferences were in accord with the previous work disclosed by Ackermann.[59]

**Scheme 70**. Competition experiments

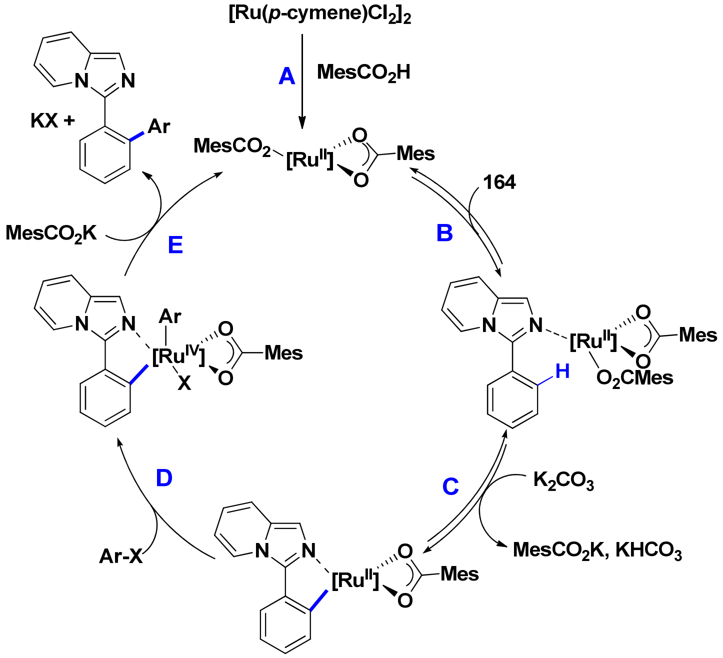


### 2.2.5.3 Proposed mechanism

Based on our preliminary mechanistic investigations, as well as on the previous studies with carboxylate-assisted Ru-catalyzed direct arylations (Section 1.2), a plausible mechanism is depicted in **Scheme 71**. It is generally accepted that the active catalytic species forms *in situ* upon reaction with the carboxylic acid additive (step **A**). Then, coordination of the Ru$^{II}$ species to the nitrogen of the imidazo[1,5-*a*]pyridine (step **B**) is followed by a carboxylate-assisted reversible C–H ruthenation (step **C**), with loss of $MesCO_2K$ (which may form by reaction of

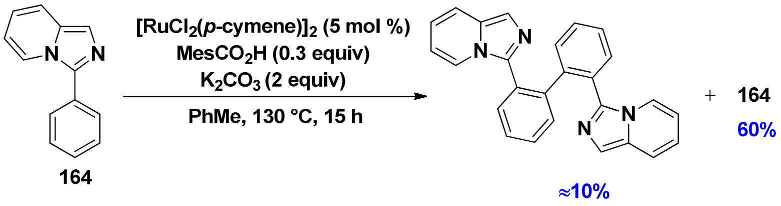
$MesCO_2H$ with $K_2CO_3$). The oxidative addition of the aryl halide (step **D**) gives rise to a $Ru^{IV}$ species, followed by reductive elimination (step **E**) to provide the desired product and regenerate the active $Ru^{II}$ catalyst. The second arylation would take place in a similar manner.

**Scheme 71**. Proposed mechanism for Ru-catalyzed arylation of imidazo[1,5-*a*]azines



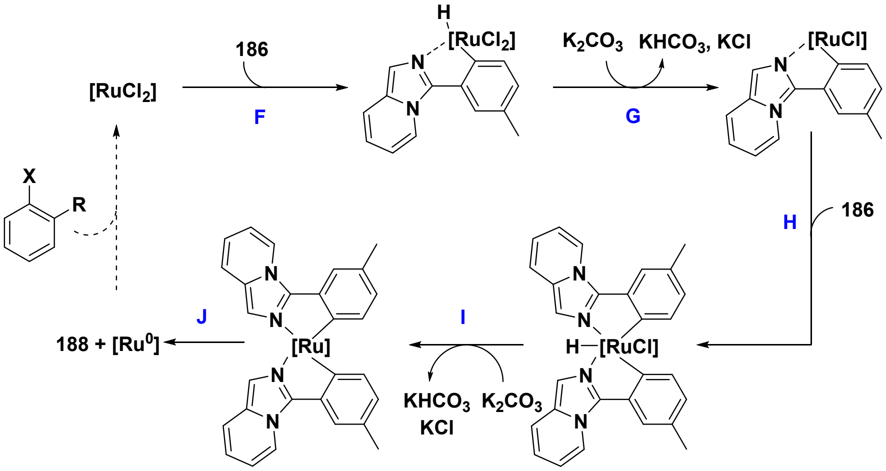
However, the above mechanism does not explain how the dimerization of the starting material occurrs. In a report, Li and co-workers[63] used sub-stoichiometric amounts of iron oxidant and hypothesized that oxygen in the air acted as an extra oxidant (to account for roughly 7% of product, **Scheme 29**). Ackermann proposed that *ortho*-substituted aryl halides acted as sacrificial oxidants.[60a] Indeed, we also observed oxidative homocoupling as the major product in case of 2-bromotoluene (**Scheme 64**). However, traces of dimerization were also observed when other aryl bromides were employed throughout the scope. Performing a control reaction with imidazo[1,5-*a*]pyridine **164** in absence of aryl bromide resulted in roughly 10% dimer (estimated by $^1H$ NMR and LC-MS), along with unreacted **164** (**Scheme 72**), demonstrating that the Ru reagent reacts stoichiometrically in the dimerization. In order to test whether oxygen affects the homocoupling process, the reaction in **Scheme 64** was performed under air. To our surprise, mostly unreacted starting material **186** was recovered at the end of the reaction, with only traces (<5%) of **186c** and **188**, suggesting against a potential re-oxidation of $Ru^0$ to $Ru^{II}$ by $O_2$.

**Scheme 72**. Control reaction in absence of aryl halide



Based on our results, the following mechanism is proposed for the homocoupling **(Scheme 73**). A Ru$^{II}$ species undergoes chelation-assisted oxidative addition into the C–H bond of imidazo[1,5-*a*]pyridine **186** (step **F**), followed by reductive elimination of HCl (step **G**). A subsequent oxidative addition followed by loss of another HCl molecule (steps **H** and **I**), leads to a Ru$^{II}$ intermediate containing two imidazopyridines. Reductive elimination of the latter intermediate provides the homocoupled product **188** and a Ru$^{0}$ species. In presence of an *ortho*-substituted aryl halide, Ru$^{0}$ can oxidatively add into the aryl halide bond to regenerate a Ru$^{II}$ species which can continue the catalytic cycle. The base, $K_2CO_3$, may be involved in quenching the HCl formed in the reaction; the role of the carboxylic acid $MesCO_2H$ remains under investigation.

**Scheme 73**. Plausible mechanism for the formation of homocoupled product **188**



## 2.3 Conclusion

To sum up, we have established that imidazo[1,5-*a*]pyridines can act as directing groups in Ru-catalyzed direct arylations. *Meta*-substituted imidazo[1,5-*a*]pyridines gave the best mono- to diarylated ratios, while electron withdrawing or electron neutral groups on the 3-aryl substitutent proved to be ideal. A variety of aryl chlorides, bromides, and iodides were also tolerated under the reaction conditions. Excess of the aryl coupling partner led to diarylated imidazo[1,5-*a*]pyridines. Preliminary mechanistic studies established that the C–H ruthenation step was reversible; in addition, a plausible mechanism for the dimerization side reaction was proposed. Moreover, a distinctive site selectivity for C–H activation was determined for Ru versus Pd catalysts.

# Chapter 3: Intramolecular direct functionalization of cyclopropanes

<u>References:</u> (a) Ladd, C. L.; Sustac Roman, D.; Charette, A. B. *Org. Lett.* **2013**, *15*, 1350. (b) Ladd, C. L.; Roman, D. S.; Charette, A. B. *Tetrahedron* **2013**, *69*, 4479.

## 3.1 Introduction

The cyclopropyl ring, a three-membered carbocycle, is a versatile building block in organic chemistry. It is widely found in natural products or current drug targets (**Figure 12**). The simplest of these natural products is 1-aminocyclopropane carboxylic acid (ACC), which is synthesized by an ACC synthase enzyme, and then converted to ethylene by an ACC oxidase enzyme.[127] Cyclopropanes can also be part of *trans*-fatty acids, as exemplified by (±)-grenadamide.[128] *Trans*-chrysanthemic acid has applications as an insecticide,[129] while bicyclohumulenone, a sesquiterpene, is used in the perfume industry.[130] U-106305, a potent cholesteryl ester transfer protein inhibitor, contains a total of five cyclopropyl units and has been previously synthesized by our group.[131]A few examples of FDA-approved drugs containing a cyclopropane are also shown; perhaps the most relevant example here is Montelukast (Singulair$^{TM}$), an anti-asthmatic and anti-allergic compound, developed at the former Merck facilities in Montréal.[132] In a recent article, the cyclopropane ring placed in the 10th spot in a Top 100 list of the most frequently used rings in the synthesis of small molecule drugs, thus highlighting its continual relevance in biologically active compounds.[133]

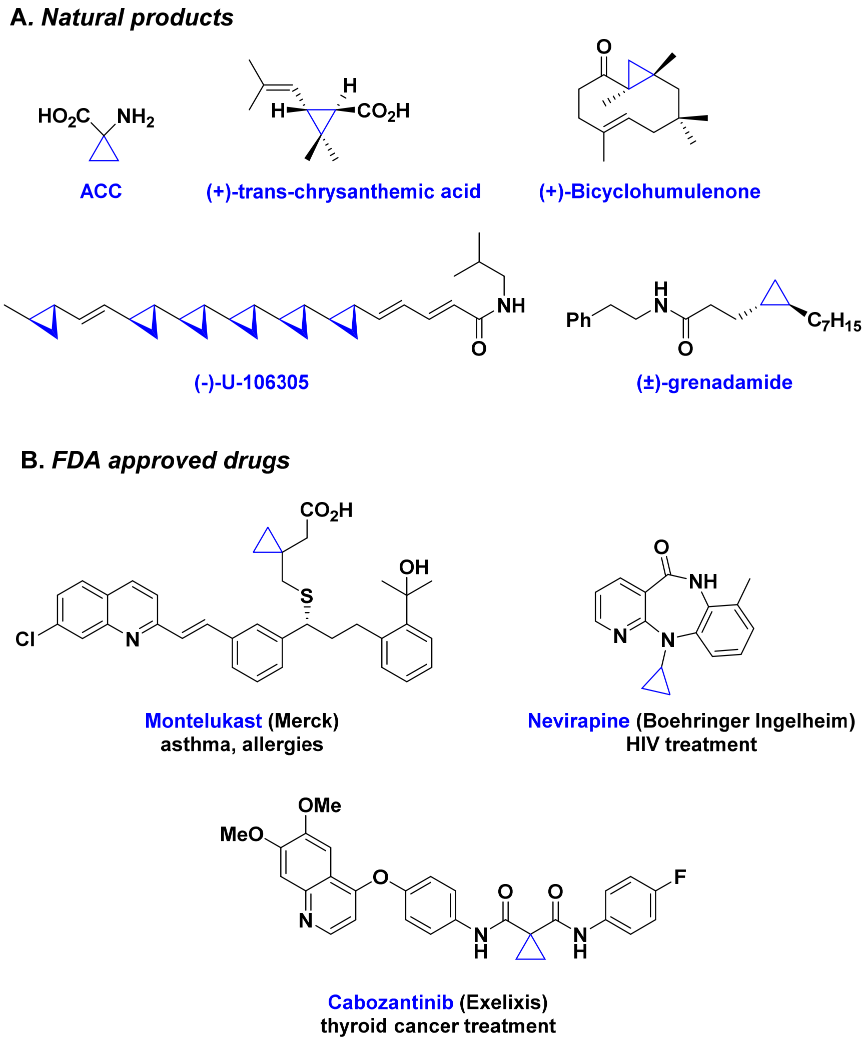
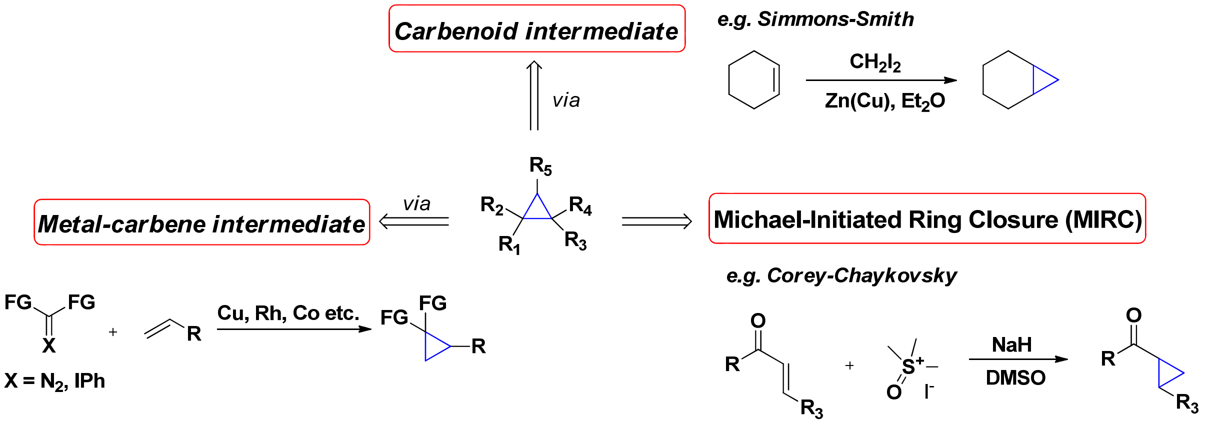


**Figure 12**. Examples of natural products (**A**) and drugs (**B**) that contain a cyclopropyl unit

### 3.1.1 Synthesis and cross-coupling of cyclopropanes

Given the predominance of cyclopropanes in medicinal chemistry and natural product synthesis, a plethora of methods are currently available for their synthesis and functionalization. Nature uses rearrangements (cationic, radical, and metal-catalyzed), redox or photochemical reactions for the biosynthesis of cyclopropanes,[134] which have most certainly inspired current cyclopropane synthesis (**Scheme 74**). Three main synthetic strategies are depicted, all based on a [2+1] cyclization starting from a substituted alkene, either involving a metal carbene or carbenoid, or a Michael-initiated ring closing (MIRC). Two famous named reactions related to the transformations discovered over half a century ago are Simmons-Smith[135] and Corey-Chaykovsky.[136] Our research group has also had a long-standing interest in the asymmetric synthesis of cyclopropanes, developing an enantioselective methodology employing a dioxaborolane chiral auxiliary,[137] based on the original Simmons-Smith reaction. Furthermore, it contributed to the field of "metal carbene" cyclopropanations, looking both at the nature of the diazo and designing new chiral rhodium catalysts.[138]

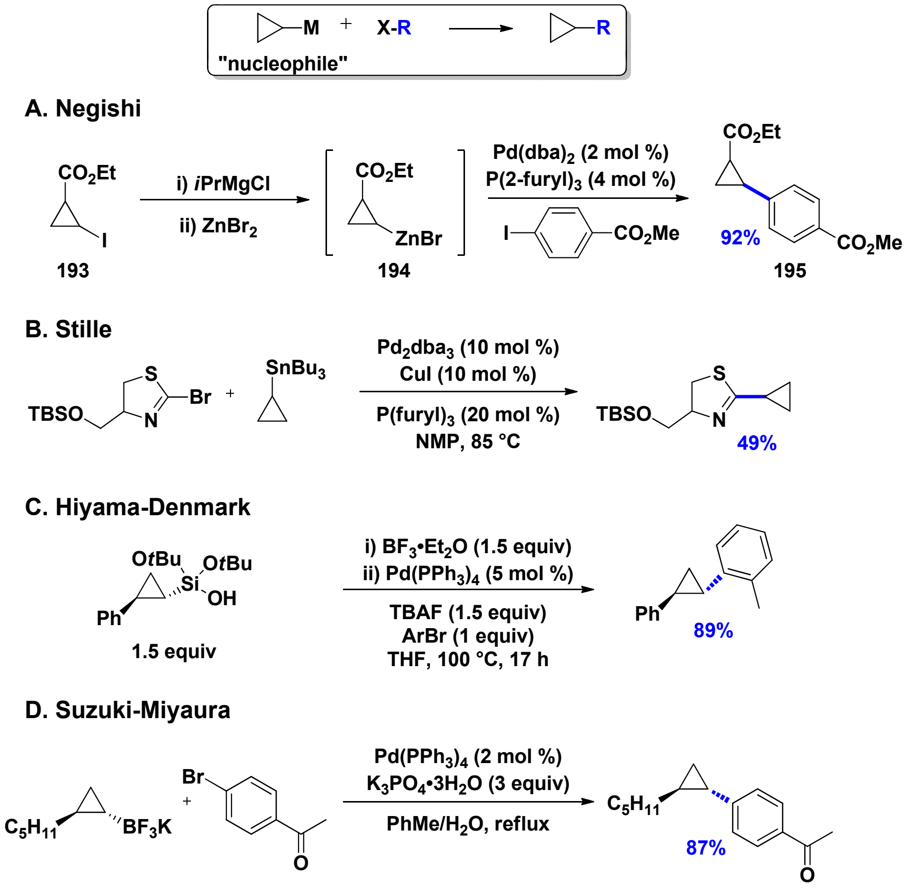
**Scheme 74**. Most common synthetic pathways to accessing cyclopropanes



Cyclopropanes may also act as precursors en route towards accessing more chemical complexity, via involvement in a variety of reactions such as cycloadditions, ring openings or cross-couplings.[82] Cyclopropanes can also be employed as "radical clocks" to test for radical intermediates in mechanistic studies (e.g. cyclopropylmethyl radical undergoes ring-opening with a rate constant of $1.2*10^8$ $s^{-1}$ at 37 °C).[139] Indeed, the applications of the cyclopropane ring and its derivatives in organic synthesis are abundant, therefore, the following brief introduction will concentrate on mainly Pd-catalyzed transformations, as direct C–H functionalizations of cyclopropanes were covered in Section 1.3.3.

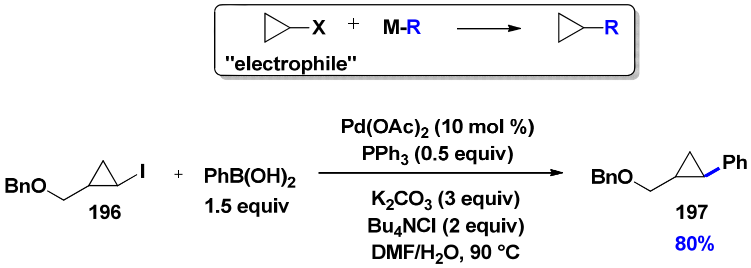
There is ample literature precedence for the functionalization of cyclopropanes via cross-couplings.[82] The cyclopropane can act as either the "nucleophile" (organometallic reagent) or "electrophile" (cyclopropyl halide). Both roles require a number of synthetic steps to achieve the pre-functionalized partners. For example, cyclopropylzinc **194** is derived via halogen-magnesium exchange from iodocyclopropane **193**, followed by transmetalation with $ZnBr_2$; subsequent addition of Pd catalyst, ligand and aryl halide provides the desired product **195** in excellent yield (**Scheme 75**A).[140] Stille-type cross-couplings are less refined; due to the low nucleophilicity and bulkiness of the alkylstannane species, transmetalation to Pd is not very favourable, resulting in low yields (**Scheme 75**B).[141] As a consequence, stannylcyclopropanes are instead employed as precursors to other cyclopropyl organometallics. Of late, our group disclosed a Hiyama-Denmark cross-coupling of cyclopropylsilanols, where the silanol moiety acts both as a directing group, and also mediates the transmetalation (**Scheme 75**C).[142] It may be that the most popular cross-coupling reaction for cyclopropanes is the Suzuki-Miyaura coupling, due to the mild conditions, functional group tolerance, and, most notably, the ease of isolation and stability of cyclopropyl organoboron reagents, combined with straightforward transmetalation to Pd (**Scheme 75**D).[143] Cyclopropylboronic esters can be obtained from the corresponding alkenylboronic esters; and, in 2013, Hartwig published an elegant direct C–H borylation of cyclopropanes employing an iridium catalyst.[144]

**Scheme 75**. Selected examples of cross-couplings where the cyclopropane acts as a "nucleophile" A. Negishi, B. Stille, C. Hiyama-Denmark, D. Suzuki-Miyaura



Cyclopropyl halides can also be employed directly in cross-coupling, however, examples are scarce. In comparison to the use of alkyl halides, the advantage of using the cyclopropane scaffold as an electrophile lies in avoiding *β*-hydride elimination, as it would create a strained cyclopropene species. Consequently, our group developed Suzuki-Miyaura cross-couplings of racemic iodocyclopropane **196** (**Scheme 76**).[145] Recently, an example of a Sonogashira cross-coupling employing a cyclopropyl halide was disclosed by the group of Cossy.[146]

**Scheme 76**. Suzuki-Miyaura coupling of iodocyclopropanes[145a]

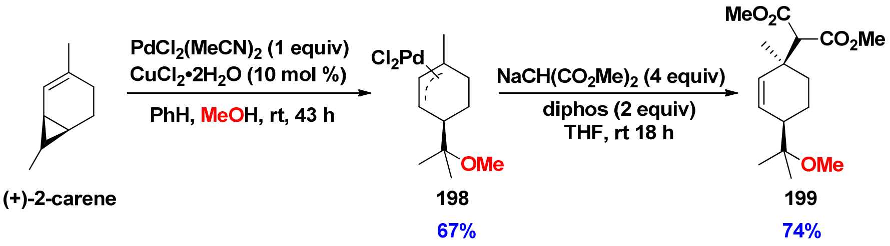


Cross-couplings involving cyclopropyl derivatives suffer from the same disadvantages as aryl cross-couplings, such as, lengthy syntheses of cyclopropyl organometallics or halides, low atom economy, waste generation, as well as toxic concerns with some of the reagents used.

## 3.1.2 Palladium-catalyzed ring-opening of cyclopropanes

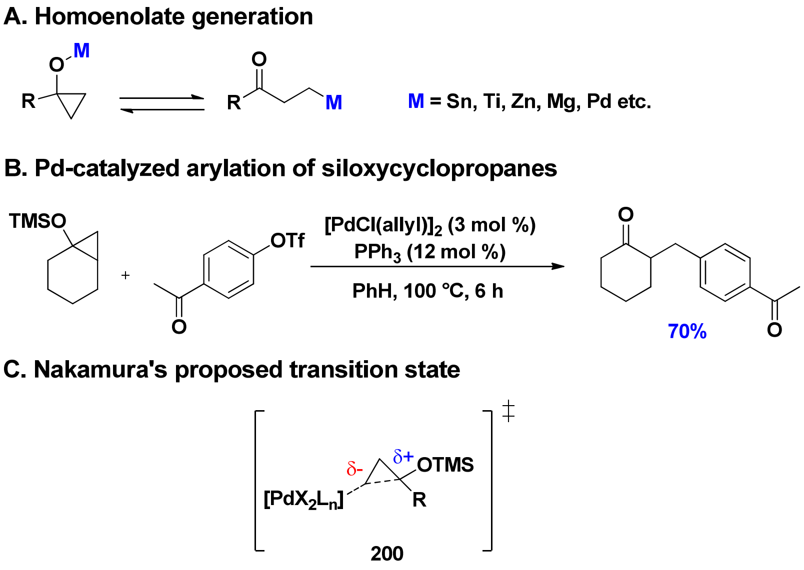
The activation of cyclopropanes resulting in their ring-opening has a lot of synthetic potential in organic chemistry. The strategy can be matched with a subsequent nucleophilic attack, coupling or cycloaddition leading to novel substrates. Vinylcyclopropanes can form π-allyl intermediates in presence of transition metals and undergo transformations similar to a Tsuji-Trost reaction. An early example comes from the group of Bäckvall, who, in 1985, studied the chloropalladation of (+)-2-carene (**Scheme 77**).[147] It was speculated that an initial binding of Pd (used in stoichiometric amounts) to the olefin aided with the opening of the cyclopropane, followed by nucleophilic attack (methanol or other alcohol) to give complex **198**. Complex **198** was then reacted with sodium dimethyl malonate to provide product **199** as one isomer.

**Scheme 77**. Nucleophilic ring-opening of a vinylcyclopropane[147]



Cyclopropane ring-opening can be used to generate a homoenolate, a species containing an anionic carbon β to a carbonyl group (**Scheme 78A**). The opening was routinely performed with a Lewis acid; however, in 1988, Nakamura and Kawajima reported the first catalytic generation of a Pd-homoenolate (**Scheme 78B**).[148] Key to the success of the reaction was electron donation from a C–C σ-bond to an empty orbital onto the metal complex. Siloxycyclopropanes were ideal substrates, as their HOMO is higher in energy in comparison with cyclopropane or ethylene. Equally important was the generation of an electrophilic cationic Pd species, which was only possible when aryl triflates or diazonium salts were employed as the coupling partner (aryl halides were unreactive). Additionally, the use of an electron rich (*p*-methoxy-substituted) aryl triflate resulted in no reaction, also underlying the electrophilic nature of the metal. The proposed mechanism involved a $Pd^{0/II}$ catalytic cycle, while computational and experimental studies revealed that the C–C bond cleavage occurred through a "corner attack" from the electrophilic Pd species, thus forming a positive partial charge at the C-1 position (transition state **200** in **Scheme 78C**).[149] The group of Nakamura extended the Pd-homoenolate methodology to the addition of acyl chlorides, several carbonylative couplings, and use of aryl iodonium salts.[150]

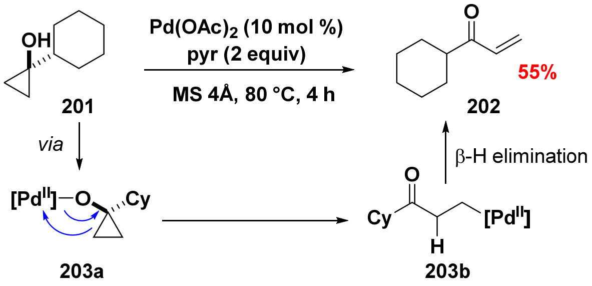
**Scheme 78**. Pd-catalyzed ring-opening of siloxycyclopropanes



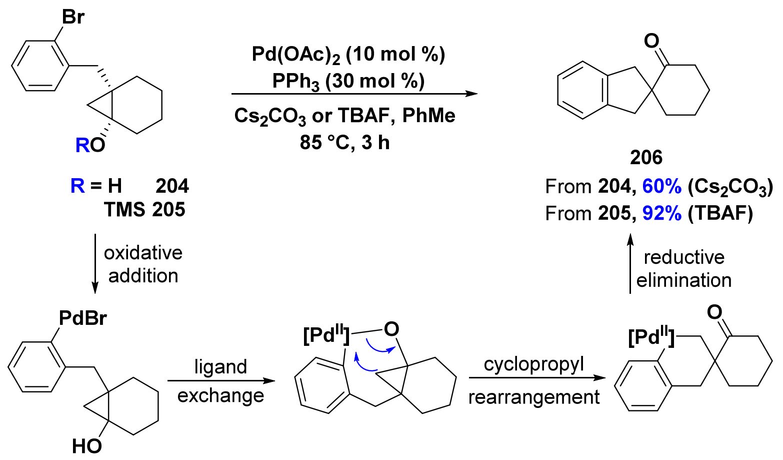
**200**

Later it was shown that hydroxycyclopropanes **201** can also undergo ring-opening (**Scheme 79**).[151] The reaction was proposed to proceed through a Pd-enolate **203a**, followed by opening of the C–C bond and β-hydride elimination to give α,β-unsaturated ketones **202**; when the cyclopropane contained further substitution, the less substituted C–C bond would be cleaved preferentially. Inspired by the latter work, Rosa and Orellana demonstrated the intra- and intermolecular cross-coupling of cyclopropanols with aryl halides (**Scheme 80**).[152] The reaction was viable in presence of an unprotected hydroxyl group (**204**); however, better yields were obtained if the alcohol was protected with a TMS group (**205**) and an *in situ* deprotection with TBAF was performed. The proposed mechanism involved oxidative addition of the Pd catalyst into the aryl bromide bond, followed by ligand exchange, Pd-homoenolate formation via a cyclopropyl rearrangement and reductive elimination (**Scheme 80**).

**Scheme 79**. Pd-catalyzed ring-opening of hydroxycyclopropanes[151]

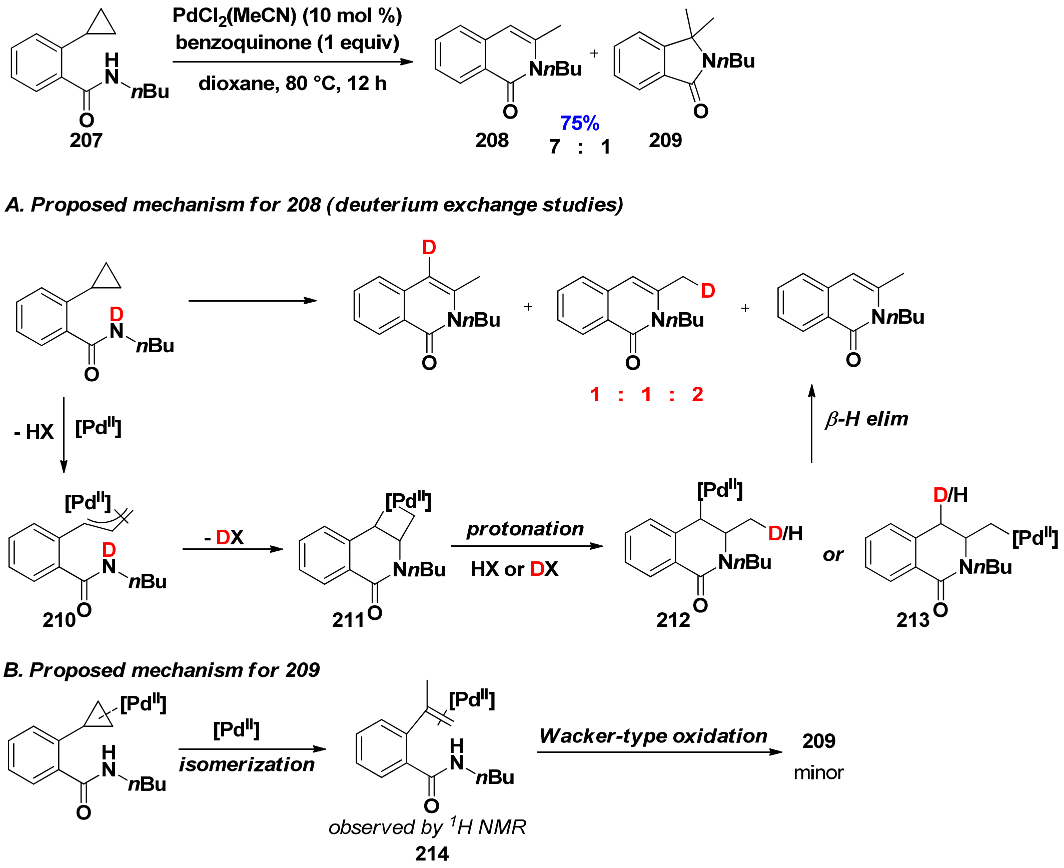


**Scheme 80**. Pd-catalyzed cross-coupling of cyclopropanols with aryl halides[152]



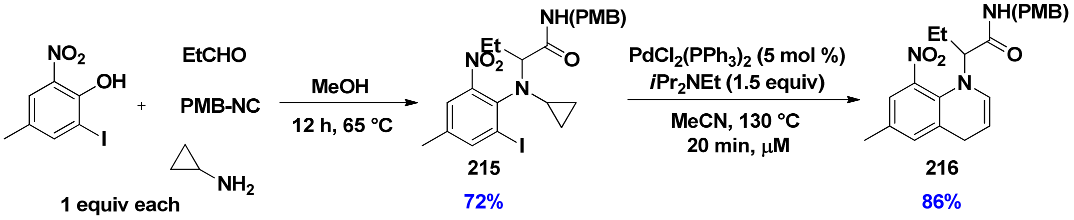
He and Yudin explored the ring expansion of arylcyclopropanes bearing a heteroatom substitution in the *ortho*-position of the aryl ring (**Scheme 81**).[153] The intramolecular Pd-catalyzed process was amenable to amides, carboxylic acids and phenols in presence of oxidants such as copper chloride or benzoquinone. Although the mechanistic picture was not fully elucidated, plausible mechanisms based on NMR observations and deuterium scrambling were proposed. In case of amide **207**, based on deuterium exchange experiments, π-allyl **210** was proposed as an intermediate (**Scheme 81A**). A subsequent amide attack on the central carbon would provide **211**, containing a four-membered palladacycle. Then, protonation of **211** by either HX or DX would give **212** and **213**, respectively. *β*-Hydride elimination of the latter intermediates would provide the major product **208**. Formation of the minor product **209** would occur via methylstyrene **214** and a subsequent Wacker-type oxidation (**Scheme 81B**).

**Scheme 81**. Yudin's Pd-catalyzed oxidative opening of arylcyclopropanes A. Proposed mechanism for **208**, **B.** Proposed mechanism for **209**



Shortly after Fagnou reported on the Pd-catalyzed opening of cyclopropanes (described in Section 1.3.3),[87] another report surfaced in the literature. The work involved the preparation of different arylaminocyclopropanes (such as **215**) via a Ugi-Smiles condensation (**Scheme 82**).[154] Then, the cyclopropyl substrates were submitted to microwave irradiation in presence of 5 mol % $PdCl_2(PPh_3)_2$ and 1.5 equivalents Hunig's base to obtain dihydropyridines in good yields (**216**, 86%). The reaction required no source of acetate and pivalate, and no experimental evidence was proposed to support a CMD pathway. Additionally, only aryl iodides could be used as substrates. Nonetheless, the work provided easy access to some biologically relevant cyclized enamines.

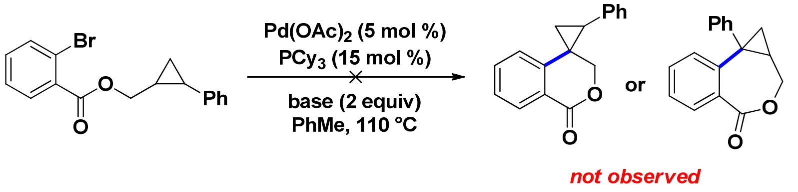
**Scheme 82**. Ugi-Smiles condensation followed by aminocyclopropane cyclization[154]



## 3.1.3 Project origin and research goals

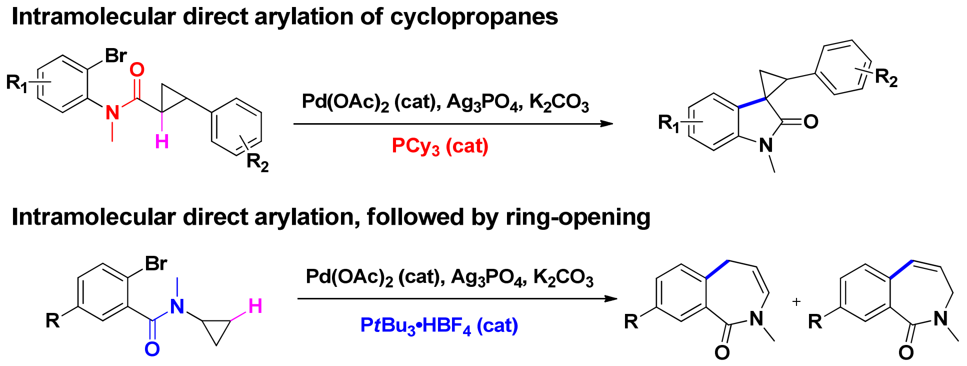
Given the prevalence and significance of cyclopropanes in the various areas of biological chemistry, natural product synthesis and other applications, our group sought to develop methodologies for their direct functionalization. A former PhD student in the group, James Mousseau, briefly looked at developing an intramolecular C–H arylation of cyclopropanes employing an ester tether (**Scheme 83**).[155] None of the desired six- or seven-membered rings were obtained even after screening several reaction conditions. The only product isolated was coupling of the aryl bromide with the toluene solvent when the base employed was silver carbonate.[40] In retrospect, perhaps the formation of a seven- or eight-membered palladacyle intermediate would have been too difficult; or, the ester was not such a good chelator for Pd. However, the work was a great inspiration for the development of the current project.

**Scheme 83**. James Mousseau's attempt at intramolecular cyclopropane arylation



An additional inspiration was also some of the more recent literature employing amides as directing groups for performing C($sp^3$)–H arylation.[156] Along with an MSc student in the group, Carolyn Ladd, we embarked on the challenging task of developing conditions for an intramolecular arylation of cyclopropyl C–H bonds. Indeed, it was discovered that biologically relevant cyclopropyl oxindoles could be synthesized starting from bromoanilides under Pd catalysis (**Scheme 84**). Moreover, the ring-opening of cyclopropyl amides was also explored as a complementary reaction to our system. Mechanistic studies supporting direct activation of the C–H cyclopropyl bond by Pd will also be described.

**Scheme 84**. Proposed direct arylation of cyclopropanes


Intramolecular direct arylation of cyclopropanes

Intramolecular direct arylation, followed by ring-opening

## 3.2 Palladium-catalyzed, silver-mediated intramolecular direct arylation of cyclopropanes

### 3.2.1 Importance of cyclopropyl oxindoles

A simple search in Reaxys for the 3,3'-cyclopropyl oxindole motif (allowing for all atom substitutions in the query) provided over 2000 compounds with bioactivity/ecotox data. Furthermore, even protection of the amide moiety with a methyl group still gave about 200 compound results, strongly supporting the utility of the motif in medicinal chemistry, and also in other fields such as agriculture. A few examples of such compounds are depicted below (**Figure 13**).[157]

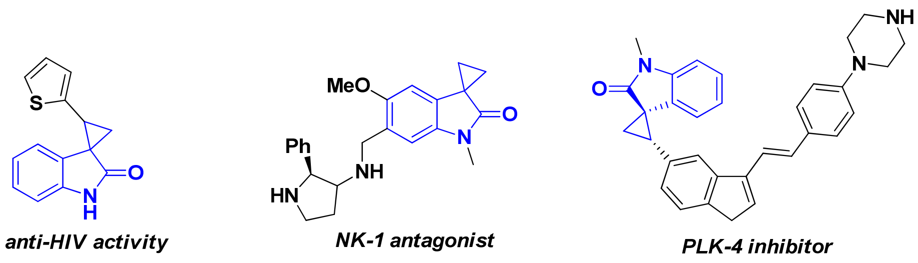
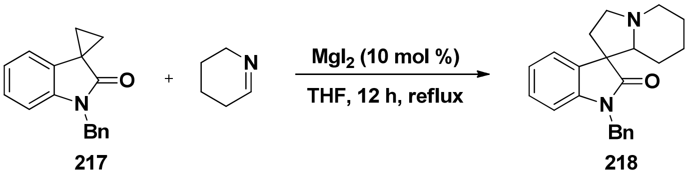


**Figure 13**. 3,3'-Cyclopropyl oxindoles possessing bioactivity

As described before (Section 3.1.2), ring-opening of cyclopropanes is also a useful reaction leading to novel compounds. For example, the group of Carreira disclosed an elegant ring expansion of 3,3’-cyclopropyl oxindole **217** with aldimines in presence of the Lewis acid $MgI_2$ (**Scheme 85**).[158] The strategy was later exploited for the total syntheses of (±)-strychnofoline,[159] (±)-horsfiline,[160] and (-)-spirotryprostatin B[161] by the same group.

**Scheme 85**. Carreira’s ring expansion strategy[158]



217

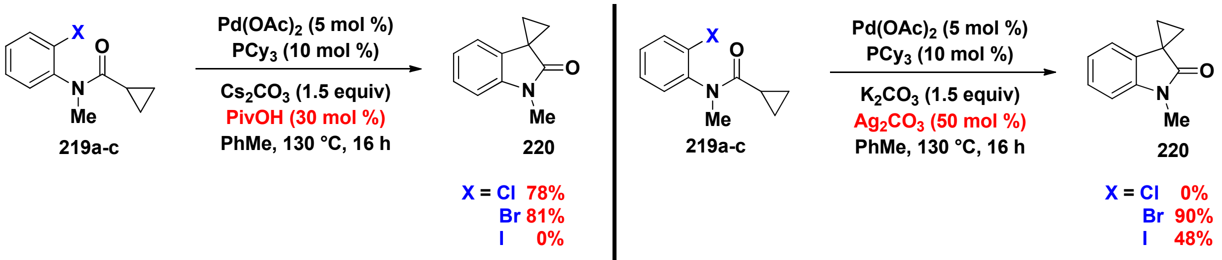
218
68%, 6:1 dr

## 3.2.2 Reaction optimization

Cyclopropylbromoanilide **219** was chosen as the model substrate for the intramolecular cyclopropane arylation, due to its straightforward (two-step) synthesis from commercially available 2-bomoaniline and cyclopropanecarbonyl chloride. The optimization experiments were carried out by Carolyn Ladd and were described in her MSc thesis.[162] Only a brief summary will be provided here.

Initially, Fagnou-type conditions employing a pivalic acid additive were tested;[45] gratifyingly, the reaction proceeded well for aryl chlorides and bromides, but failed with aryl iodides (**Scheme 86**). As previously encountered in the literature, it was believed that accumulation of iodide anions in the reaction mixture had a detrimental effect on the activity of the Pd catalyst (known as catalyst poisoning). In such cases, some bases, and especially silver sources, can be employed to sequester iodide.[163] For example, Fagnou and co-workers employed silver carbonate to sequester iodide.[17] Moreover, in Fagnou’s case, silver sources were found to accelerate reaction times and lower the temperature. Upon adding silver carbonate to the model cyclization, improved yields were observed for aryl iodides and bromides, while the chloride failed to react (**Scheme 89**).

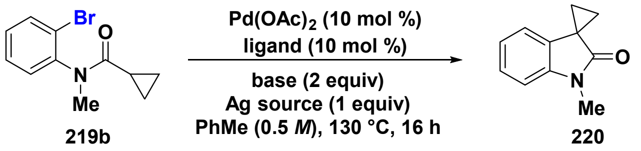
**Scheme 86**. Initial studies with PivOH and $Ag_2CO_3$[a]



[a] $^1$H NMR yields employing trimethoxybenzene as internal standard.

The optimization was further pursued utilizing an aryl bromide in presence of a silver salt, and some modifications to the reaction conditions in **Scheme 86** are presented in **Table 11**. Both Pd$^0$ and Pd$^{II}$ sources could be applied to the reaction and an acetate source was not required (not shown). A sterically demanding ($P\textit{t}Bu_3{\cdot}HBF_4$) or a bidentate phosphine (BINAP) gave poor conversions (entries 1 and 2). Triphenylphosphine provided the product in a modest 62% yield (entry 3). $K_2CO_3$ and $Cs_2CO_3$ gave the best conversions, and inexpensive $K_2CO_3$ was chosen as the optimal base (entry 4). NaO*t*Bu, a much stronger base resulted in decomposition (entry 6), while another weaker base, $K_3PO_4$, provided a lower yield (entry 5). Silver acetate gave a low 30% yield (entry 7), while other silver sources such as $Ag_3PO_4$ and $AgNO_3$ were effective in promoting the reaction (entries 8 and 9). It was important that only one equivalent of cationic silver was employed, as increasing or decreasing that amount significantly inhibited the reaction.[162] Finally, the amount of base could be reduced to 1.5 equivalents, and reaction was complete in 3 h at 130 °C (entry 10). It should be noted that the reaction could also be performed at 110 °C with minimum loss of yield (85%). A series of control reactions were also performed by omitting each reaction component; it was found that the silver source, the base, the catalyst and the ligand were all necessary for the reaction to occur.

**Table 11**. Summary of the reaction optimization



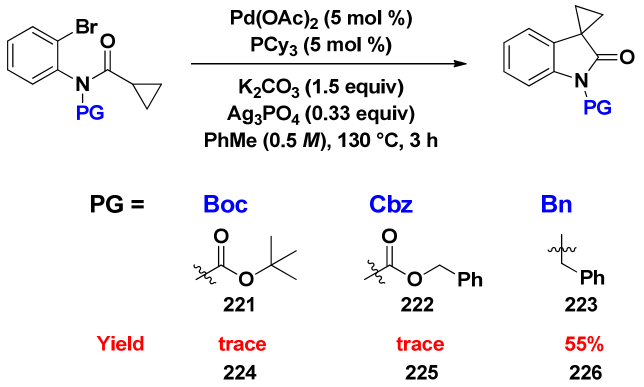
| entry | ligand | base | Ag source | yield **220**[a] |
|---|---|---|---|---|
| 1 | *rac*-BINAP | $K_2CO_3$ | $Ag_2CO_3$ | 25% |

| | | | | |
|---|---|---|---|---|
| 3 | P*t*Bu$_3$·HBF$_4$ | K$_2$CO$_3$ | Ag$_2$CO$_3$ | trace |
| 3 | PPh$_3$ | K$_2$CO$_3$ | Ag$_2$CO$_3$ | 62% |
| 4 | PCy$_3$ | Cs$_2$CO$_3$ | Ag$_2$CO$_3$ | 89% |
| 5 | PCy$_3$ | K$_3$PO$_4$ | Ag$_2$CO$_3$ | 61% |
| 6 | PCy$_3$ | NaO*t*Bu | Ag$_2$CO$_3$ | 25% |
| 7 | PCy$_3$ | K$_2$CO$_3$ | AgOAc | 30% |
| 8 | PCy$_3$ | K$_2$CO$_3$ | Ag$_3$PO$_4$ | 90% |
| 9 | PCy$_3$ | K$_2$CO$_3$ | AgNO$_3$ | 89% |
| **10**[b] | **PCy$_3$** | **K$_2$CO$_3$** | **Ag$_3$PO$_4$** | **90%** |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard. [b] Optimal conditions: Pd(OAc)$_2$ (5 mol %), PCy$_3$ (5 mol %), K$_2$CO$_3$ (1.5 equiv), Ag$_3$PO$_4$ (0.33 equiv), PhMe (0.5 *M*), 130 °C, 3 h.

Carolyn Ladd explored several amide protecting groups (**Scheme 87**). In absence of any protecting group, the substrate decomposed, while anilides protected with a Boc **221** or Cbz **222** produced only traces of product. A benzyl protecting group was found to be compatible (**223**), providing 55% of the desired product **226**. It is necessary to note that no cyclization onto the phenyl group was detected, thus highlighting the fact that the conditions are selective for C(sp$^3$)–H functionalization.

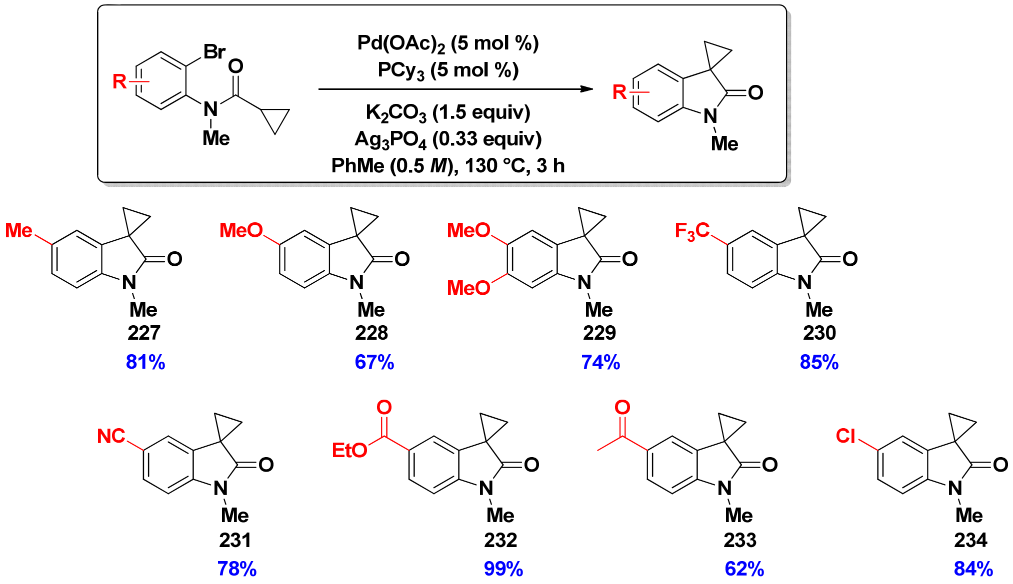
**Scheme 87**. Screen of anilide protecting groups



## 3.2.3 Reaction scope

The scope was pursued by exploring substitution on the aryl moiety. The substrates were synthesized by Carolyn Ladd using various synthetic operations and submitted to the optimized conditions (**Scheme 88**). Pleasingly, a variety of functional groups were tolerated, including methoxy (**228**, **229**), trifluoromethyl (**230**), nitrile (**231**), ester (**232**), and ketone (**233**). Also, a chloro substituent was viable (**234**), thus allowing for further functionalizations.

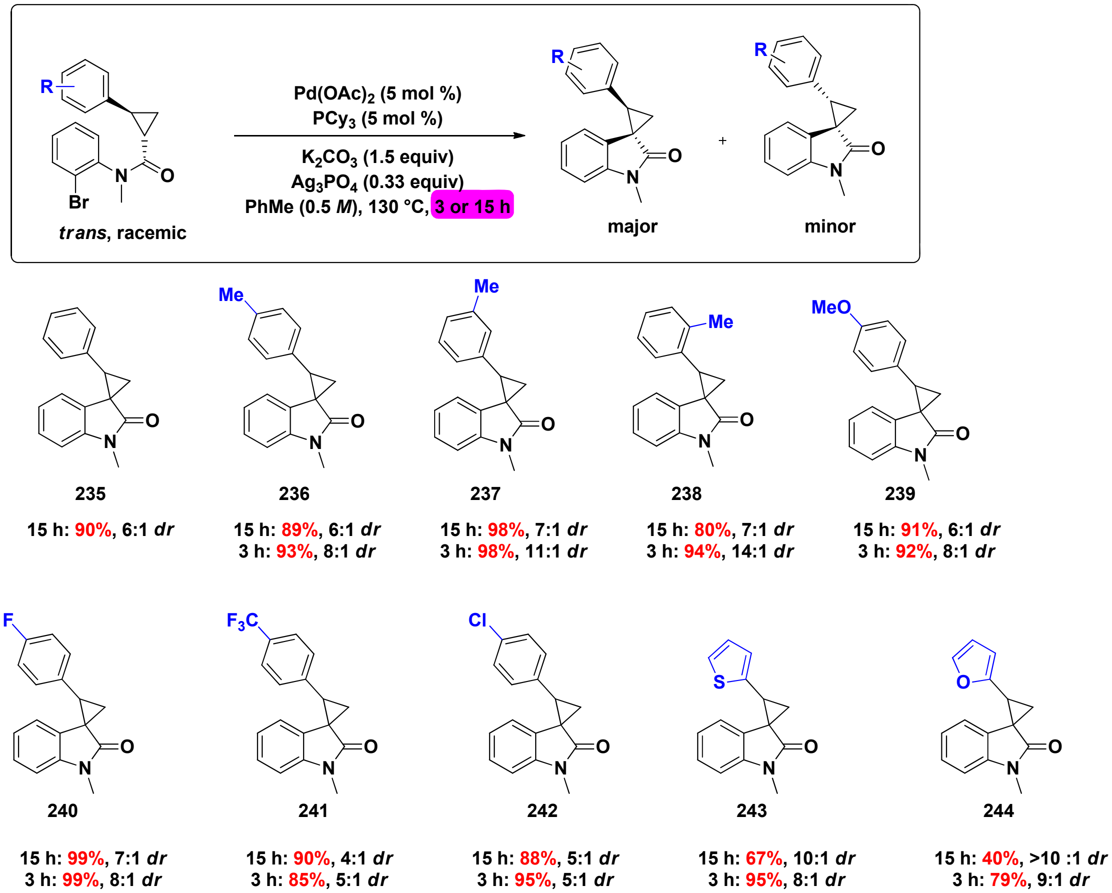
**Scheme 88**. Probing substitution on the aryl moiety[a]



[a]Reactions were performed on 0.5 mmol scale. Isolated yields.

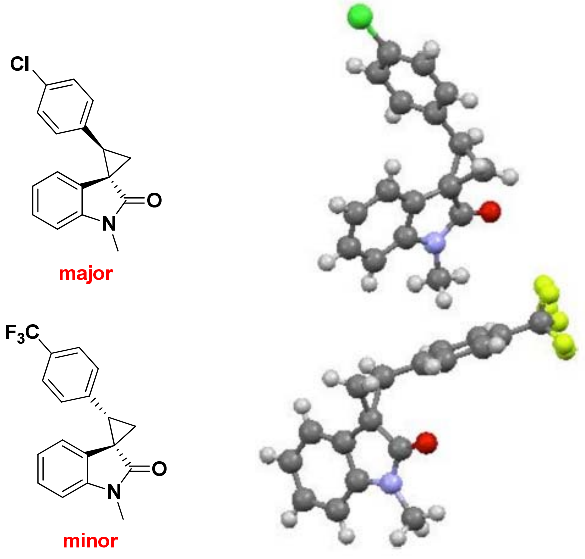
Next, the scope with respect to substitution on the cyclopropane was explored (**Scheme 89**). A multitude of *trans*, racemic, aryl-substituted cyclopropanes were synthesized via a Corey-Chaykovsky/amide formation/methylation sequence and then tested under the reaction conditions. A mixture of two diastereomers was produced, which were separable in some cases. The structure of the diastereomers was determined via X-ray crystallography (**Scheme 90**). Initially, the reactions were performed for 15 h at 130 °C to afford good to excellent yields, but modest diastereoselectivities. It was later found by Carolyn Ladd that the yields and diastereoselectivities could be improved when the reaction was performed the reaction for only 3 h. The reaction could tolerate *ortho*, *meta* and *para* substitution (**236-238**), as well as many functional groups including methoxy (**239**), fluoro (**240**), trifluoromethyl (**241**), and chloro (**242**) in the *para* position. In addition, heterocycles such as thiophene (**243**) and furan (**244**) gave good yields and diastereoselectivities (>8:1). In general, the reaction was not found to be highly sensitive to either sterics or electronics; however, better *dr*'s were obtained in case of electron donating substituents.

**Scheme 89**. Effect of arylcyclopropane substitution[a]



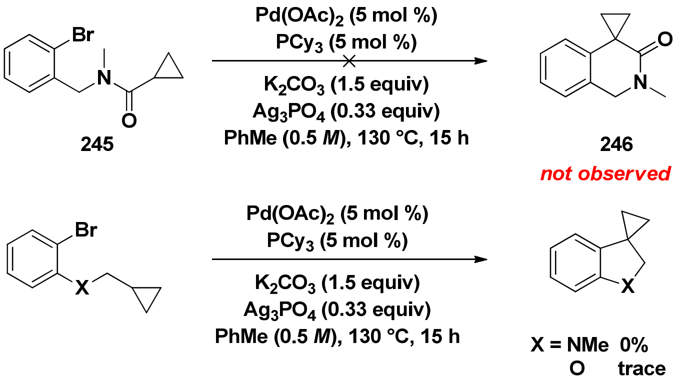
[a]Reactions were perfomed on a 0.5 mmol sclae. Isolated yields. For compounds **240, 241** and **242** the diastereomers were separable.

**Scheme 90.** X-Ray structures of diastereomers



It should be noted that for all the substrates above, only the five-membered spirooxindole ring was isolated; no trace of the six-membered ring was observed. We attempted to form a six-membered ring by cyclizing amide **245**, which contained a longer tether (**Scheme 91**). Unfortunately, none of the desired product was observed, and only unreacted starting material and traces of the aryl bromide coupling with the toluene solvent was detected. The results were reminiscent of James Mousseau's initial attempt at intramolecular arylation of cyclopropanes (**Scheme 83**, *vide supra*), implying that a potential seven-membered palladacycle is not feasible. Additionally, changing the amide tether to an ether or methyl-protected amine was also unsuccessful, resulting in unreacted starting material or dehalogenation (**Scheme 91**).

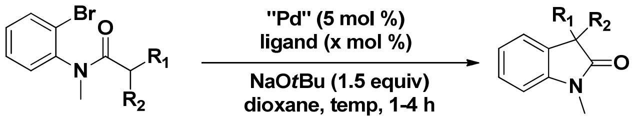
**Scheme 91**. Attempts at forming other spiro products

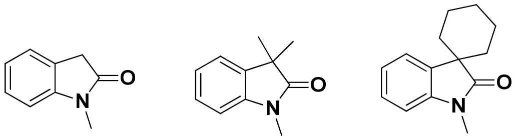


## 3.2.4 Mechanistic studies

We wanted to probe whether the reaction was occurring through a CMD-type pathway or enolate arylation. Hartwig and co-workers had previously investigated α-arylation of amides on bromoanilide substrates in presence of the strong base NaO*t*Bu (**Scheme 92**).[164] In 2001, the same group disclosed improved conditions for the arylation: use of the less sterically demanding $PCy_3$ allowed for lower temperatures (even room temperature in some cases) and the employment of aryl chlorides at 70 °C (**Scheme 92**).[165] It was argued that the steric demand of the bromoamide starting material accounted for the need to use $PCy_3$, that is, a smaller [$Pd^0$] species would be able to insert faster into the Ar-X bond.

**Scheme 92.** Hartwig's $\alpha$-arylation of amides[164-165]

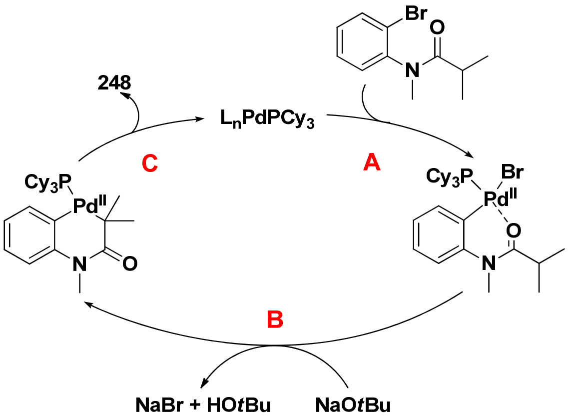




| | 247 | 248 | 249 |
|---|---|---|---|
| with Pd(dba)$_2$, BINAP (7.5 mol %), 100 °C | 60% | 75% | 82% |
| with Pd(OAc)$_2$, PCy$_3$ (5 mol %), 50 °C | 62% | 92% | 93% |

Mechanistic studies on the relative rates of each step determined that oxidative addition was the rate-determining step, while deprotonation of the amide occurred rapidly. The proposed mechanism is shown in **Scheme 93**: rate-limiting oxidative addition (step **A**); deprotonation and formation of an arylpalladium intermediate (step **B**); and finally, reductive elimination (step **C**) to provide the oxindole product **248** and a [Pd$^0$] species.

**Scheme 93**. Proposed mechanism for $\alpha$-arylation of amides

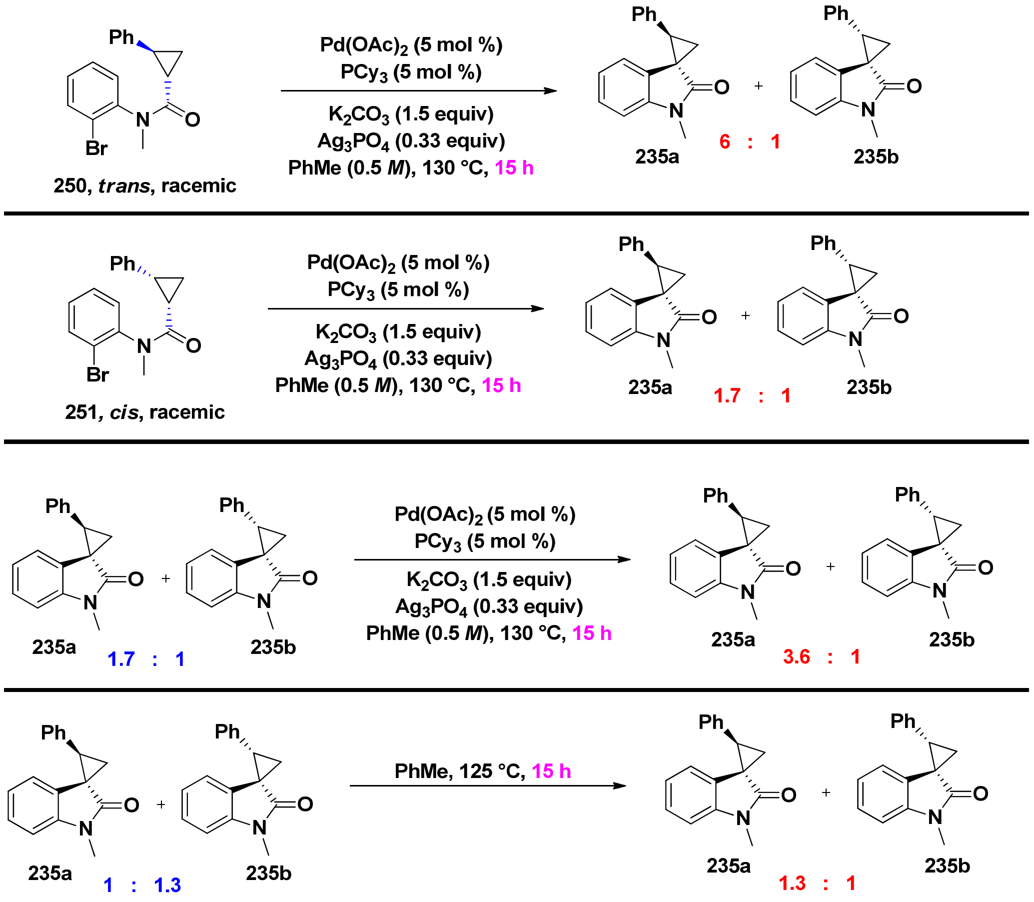


In contrast with Hartwig's system, our optimized reaction conditions employed mild $K_2CO_3$ and $Ag_3PO_4$ as bases, while use of NaO*t*Bu resulted in decomposition of the starting material. Nonetheless, the preceding observations are not enough evidence to discount the enolate pathway. As we were also intrigued by the fact that different diastereoselectivities were obtained for different reaction times, we decided to pursue other studies that would shed light on the behaviour.

### 3.2.4.1 Isomerization and epimerization studies

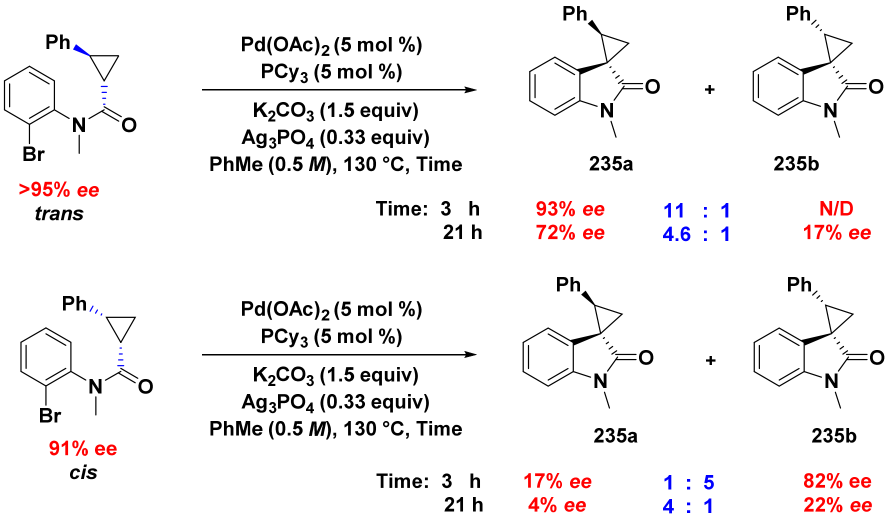
Initially, the behaviour of a racemic *trans* versus *cis* substituted arylcyclopropane **250** or **251** was investigated (**Scheme 94**). When submitting **250** to the optimized reaction conditions for 15 h, a 6:1 mixture of diastereomers was recovered, while repeating the same experiment with **251**, a 1.7:1 mixture was recovered. The major diastereomer was **235a** in both cases. Upon taking the 1.7:1 mixture obtained above and resubmitting to the same reaction conditions, a mixture of 3.6:1 favouring **235a** was obtained. Additionally, a control reaction in toluene demonstrated some isomerization also occurred. Thus, the minor diastereomer **235b** slowly isomerizes to the major **235a** over time.

**Scheme 94**. Studies on the isomerization of arylcyclopropanes



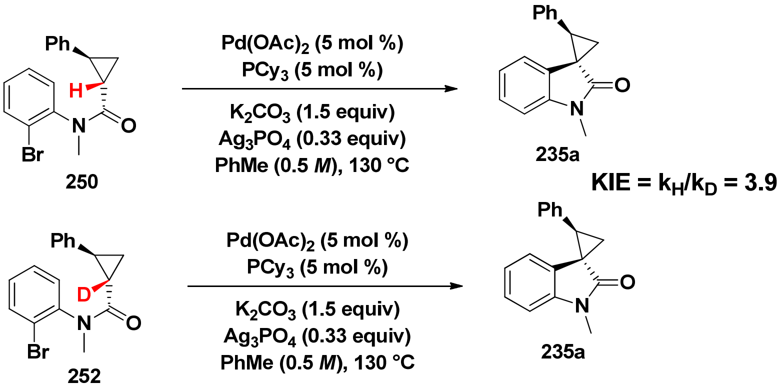
In order to determine if a potential enolate was forming during the reaction, the epimerization of the arylcyclopropane was investigated. Two enantiopure starting materials **250** and **251** (95% and 91% *ee*) were prepared using the standard Simmons-Smith methodology developed in our group.[166] After three hours the reaction was complete and little erosion in enantioselectivities for both substrates was observed (**Scheme 95**). The observation is not consistent with an enolate mechanism, where complete epimerization of the product is expected at the end of the reaction. However, the enantioselectivity does erode over time, but as a result of the isomerization of the product.

**Scheme 95**. Epimerization studies of enantiopure cyclopropyl starting materials



### 3.2.4.2 Kinetic isotope effect

**Scheme 96**. Kinetic isotope effect study



A deuterated cyclopropane **252** was prepared and the kinetic isotope effect of the cyclization was measured. Two parallel reactions were set up and the relative rates of conversion were analysed via NMR spectroscopy (details in the experimental section).[20] The KIE was calculated to be 3.9, which indicated C–H cleavage to be rate-limiting (**Scheme 96**).

### 3.2.4.3 Proposed mechanism

At the end of the mechanistic investigations, an enolate pathway was rejected based on the following arguments:

- In contrast to Hartwig's system where a strong base NaO*t*Bu was employed, we could use a mild base $K_2CO_3$, while NaO*t*Bu gave mainly decomposition;
- Little erosion of enantioselectivity was observed when the reaction was complete, thus suggesting against an enolate mechanism;
- C–H cleavage was determined to be rate-determining, while Hartwig determined the oxidative addition to be rate-limiting for the α-arylation of amides.

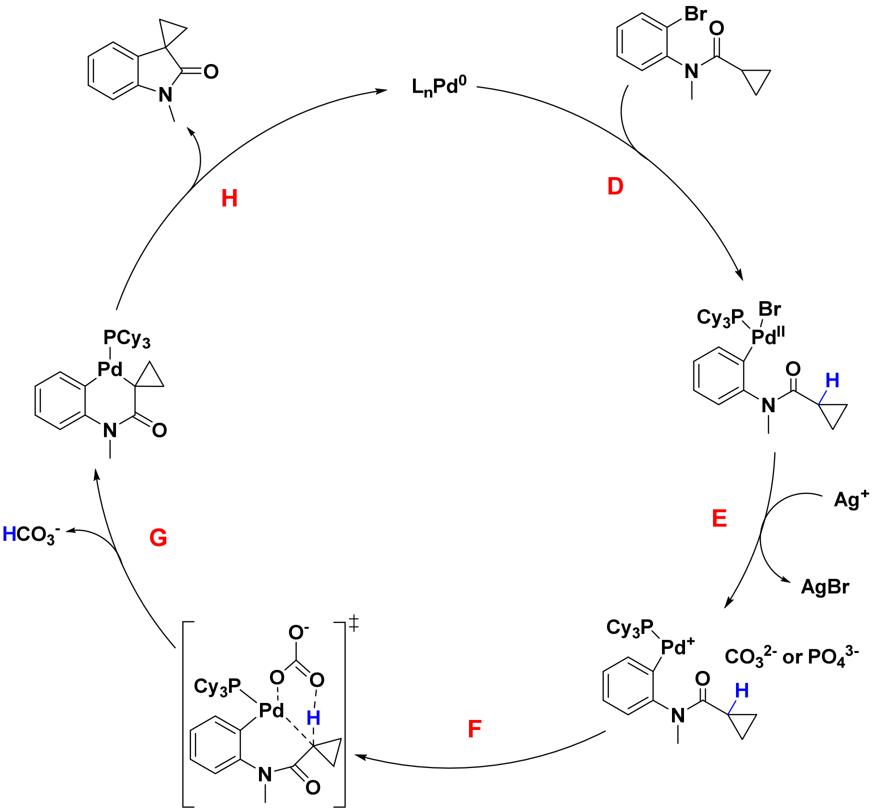
A direct functionalization pathway was deemed plausible, based on the KIE observed. In addition, the role of the reactants in the concerted metalation-deprotonation step was carefully examined and the following could be concluded:

- Catalytic acetate was not necessary for the reaction, as $PdBr_2$ was also an effective catalyst;
- Either carbonate or phosphate could be the base involved in the CMD step;
- The silver salt could sequester halide, but it is also well known that $Ag^I$ can abstract halide from a Pd intermediate to provide a cationic Pd species.[167]

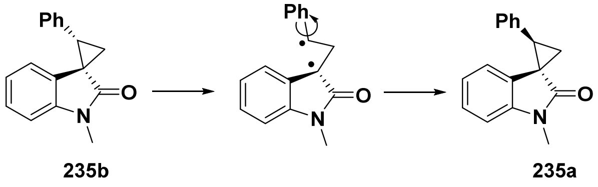
Based on all the observations, the mechanism shown in **Scheme 97A** was proposed. An initial oxidative addition step **D** is followed by bromide abstraction by $Ag^+$ to give a cationic Pd species (step **E**), which can undergo the concerted metalation-deprotonation mediated by carbonate (or phosphate, **F** and **G**). The six-membered palladacycle then undergoes reductive elimination (step **H**) to give the product and regenerate the $Pd^0$ catalyst.

It is known in the literature that cyclopropanes rearrange via homolytic cleavage of the most substituted bond, followed by bond rotation and then re-bonding (**Scheme 97B**).[168] It is possible that the pathway is also viable in our case, and is responsible for the thermal *cis/trans* isomerization observed. Opening of the cyclopropane would also explain why the enantioselectivity drops so significantly over time, especially for the *cis* substrate. However, besides the loss of enantioselectivity, there is currently no other experimental evidence in its support.

**Scheme 97**. Proposed reaction mechanism



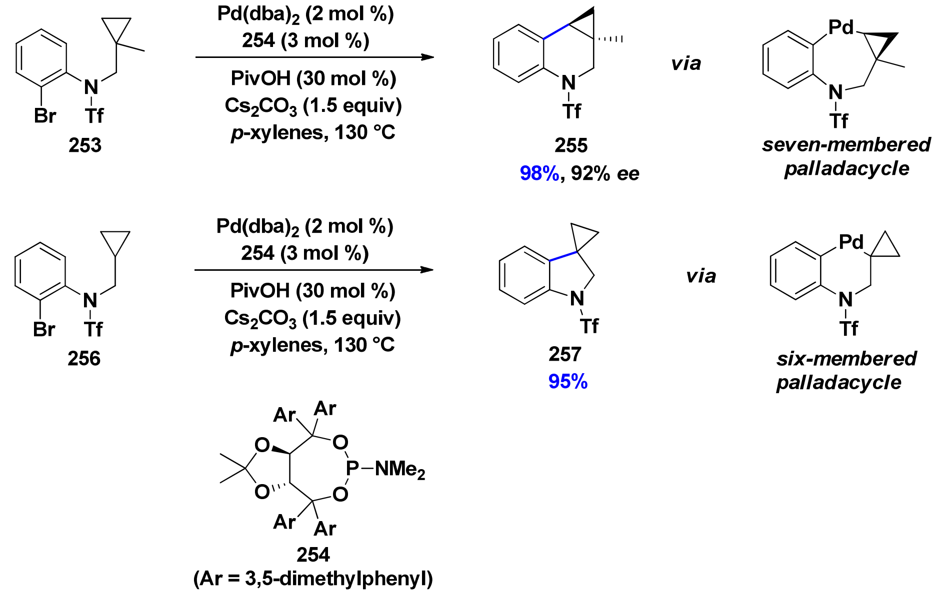
**B. Possible isomerization mechanism**



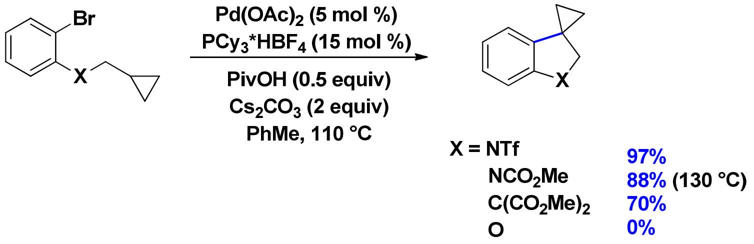
## 3.2.5 Related work

During our manuscript preparation, two related examples appeared in the literature that are worthwhile mentioning here. Namely, the group of Cramer first disclosed an enantioselective, intramolecular cyclopropyl C–H arylation to form tetrahydroquinolines of type **256** (**Scheme 98**).[169] In a Pd-catalyzed, pivalic acid-promoted cyclization, aryl bromides containing a triflyl protected amine tether could be cyclized in excellent yields and enantioselectivities. The chiral ligand **254** was TADDOL-derived. Of note is the use of an alkyl (or aryl) substituent on the cyclopropane to induce a seven-membered palladacycle; in its absence, a six-membered palladacycle would be formed which would reductively eliminate to give spiroindoline **257** in 95% yield (**Scheme 99**).[170] Interestingly, improved conversions were observed when $PCy_3$ was used as a ligand, while the overall conditions were somewhat reminiscent of Fagnou's previous work on direct arylation.[47]

**Scheme 98**. Cramer's enantioselective, intramolecular arylation of cyclopropanes[169]



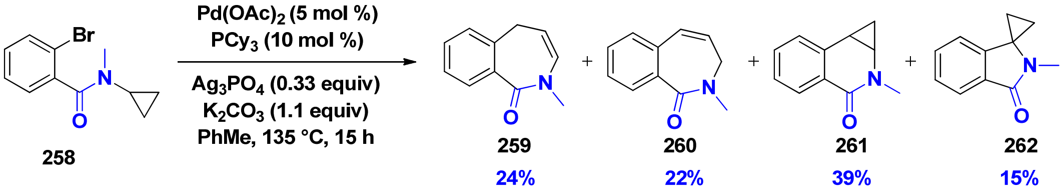
**Scheme 99**. Cramer's synthesis of spiroindolines[170]



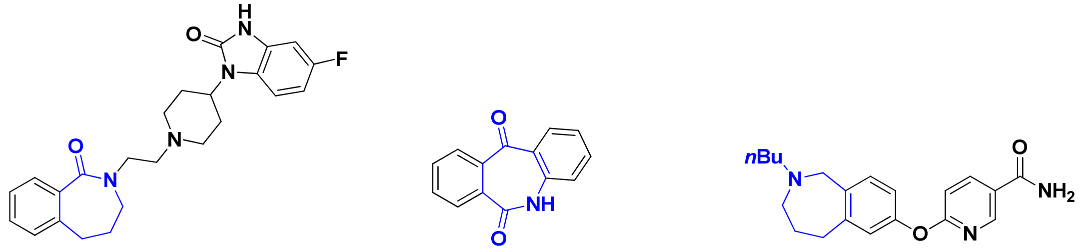
## 3.3 Palladium-catalyzed ring-opening of cyclopropyl benzamides

While the project discussed above was still ongoing in our lab, we pursued a complementary reaction. Our goal was to induce C–H activation of cyclopropane, followed by ring-opening. We hypothesized that a neighbouring nitrogen lone pair could facilitate the opening. Indeed, upon submitting amide **258** to our previously optimized conditions, we observed full conversion of the starting material and detected about 46% product resulting from cyclopropane opening, under the form of two isomers **259** and **260** (**Scheme 100**). The rest of the material consisted of five-membered and six-membered spirooxindoles **261** and **262**. The reaction also represented the first instance we were able to produce a six-membered ring **261** with an intact cyclopropane.

**Scheme 100**. Initial studies on amide **258**



The seven-membered aza-heterocycles formed are formally referred to as benzo[*c*]azepine-1-ones and are compounds of significant bioactivity, used in a range of medicinal chemistry applications (**Figure 14**).[171] Additionally, compounds of type **259** or **260** could be used as precursors for more complex aza-heterocycle-containing molecules.[171d-e]



***5-HT$_7$ receptor antagonist***

***anti-convulsant activity***

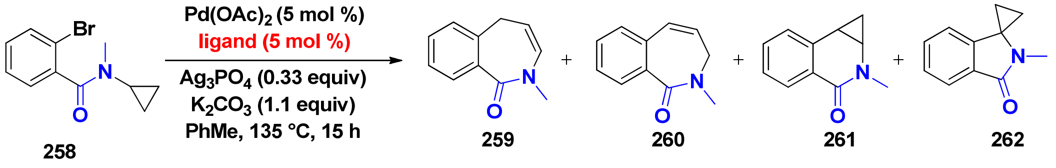
***opioid receptor antagonist***

**Figure 14**. Benzazepine type compounds in medicinal chemistry

## 3.3.1 Reaction optimization

The reaction optimization was commenced by a phosphine ligand screen (**Table 12**). A significant ligand effect was observed; bulky P*t*Bu$_3$·HBF$_4$ provided exclusively the benzazepinone products **259** and **260** (entry 2), while phosphines such as PPh$_3$, DavePhos or JohnPhos also provided the desired products, albeit in low yields (entries 3-5). Thus, P*t*Bu$_3$·HBF$_4$ appeared to have the optimal steric (Tolman cone angle 182° versus PCy$_3$ 170°)[172] and electronic properties for the C–H activation and cyclopropane opening.

**Table 12**. Ligand screen

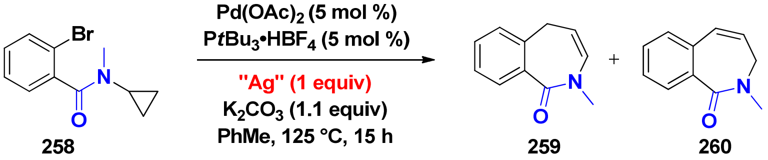


| entry | ligand | yield[a] (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | **258** | **259** | **260** | **261** | **262** | Total product |
| 1 | PCy$_3$[b] | 0 | 24 | 22 | 39 | 15 | 100 |
| **2** | **P*t*Bu$_3$·HBF$_4$** | **0** | **66** | **26** | **0** | **0** | **92** |
| 3 | PPh$_3$ | 27 | 18 | 15 | 0 | trace | 33 |
| 4 | DavePhos | 21 | 43 | 9 | 0 | trace | 52 |
| 5 | JohnPhos | 10 | 37 | 12 | 12 | 19 | 80 |

[a] $^1$H NMR yields using trimethoxybenzene as internal standard. [b] Isolated yield with 10 mol % PCy$_3$.

Next, the role of the silver salt in the reaction was investigated. Silver salts such as carbonate, acetate or bromide provided complete conversion, but lower yields of the desired products (**Table 13**, entries 1-3). Silver triflate provided complete decomposition of the starting material (entry 4). Furthermore, my colleague Carolyn Ladd screened the stoichiometry of silver phosphate in the reaction and discovered that, similarly to the previous section, exactly one equivalent of cationic silver was required; increasing the amount of Ag resulted in lower yields.[162]

**Table 13**. Screen of silver salts

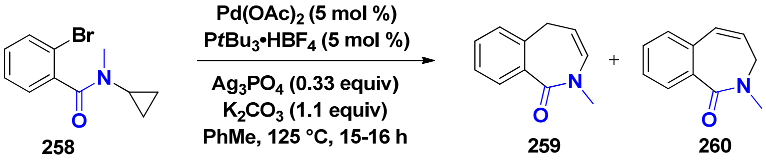


| entry | "Ag" source | yield[a] (%) | | |
|---|---|---|---|---|
| | | **259** | **260** | Total product |
| 1 | Ag$_2$CO$_3$ | 58 | 11 | 69 |
| 2 | AgOAc | 44 | 9 | 53 |
| 3 | AgBr | 31 | 41 | 72 |
| 4 | AgOTf | 0 | 0 | 0 |

[a] $^1$H NMR yields using trimethoxybenzene as internal standard.

A number of control reactions were also performed to determine the necessity for each reaction component (**Table 14**). In absence of the Pd catalyst, there was no reaction (entry 1). Omitting the ligand or the base did result in some product formation (entries 2-3). Omitting the silver source provided only traces of product (entry 4). Replacing $K_2CO_3$ by the weaker base $K_3PO_4$ provided the products in a total yield of 6% (entry 5). The ideal temperature for the reaction was 125 °C, and lowering it to 100 °C resulted in significant loss of yield (entry 6). It should be noted for all the reactions, the rest of the mass balance was recovered starting material **258**.

**Table 14**. Control reactions



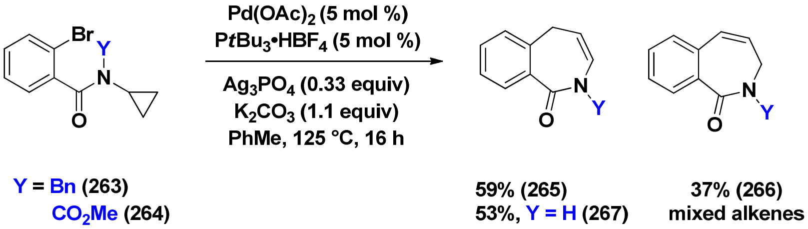
| entry | variation from standard conditions | yield[a] (%) **259** | **260** | Total product |
|---|---|---|---|---|
| 1 | no Pd | 0 | 0 | 0 |
| 2 | no P*t*Bu$_3$·HBF$_4$ | 17 | 3 | 20 |
| 3 | no $K_2CO_3$ | 27 | 18 | 45 |
| 4 | no $Ag_3PO_4$ | trace | trace | trace |
| 5 | no $Ag_3PO_4$, $K_3PO_4$ instead of $K_2CO_3$ | 5 | 1 | 6 |
| 6 | at 100 °C | 34 | 8 | 42 |

[a] $^1$H NMR yields using trimethoxybenzene as internal standard.

## 3.3.2 Reaction scope

The scope of the reaction was mainly explored by Carolyn Ladd, who synthesized all starting materials and submitted them to the cyclization, except for **Scheme 103**.[162]

**Scheme 101**. Protecting group screen

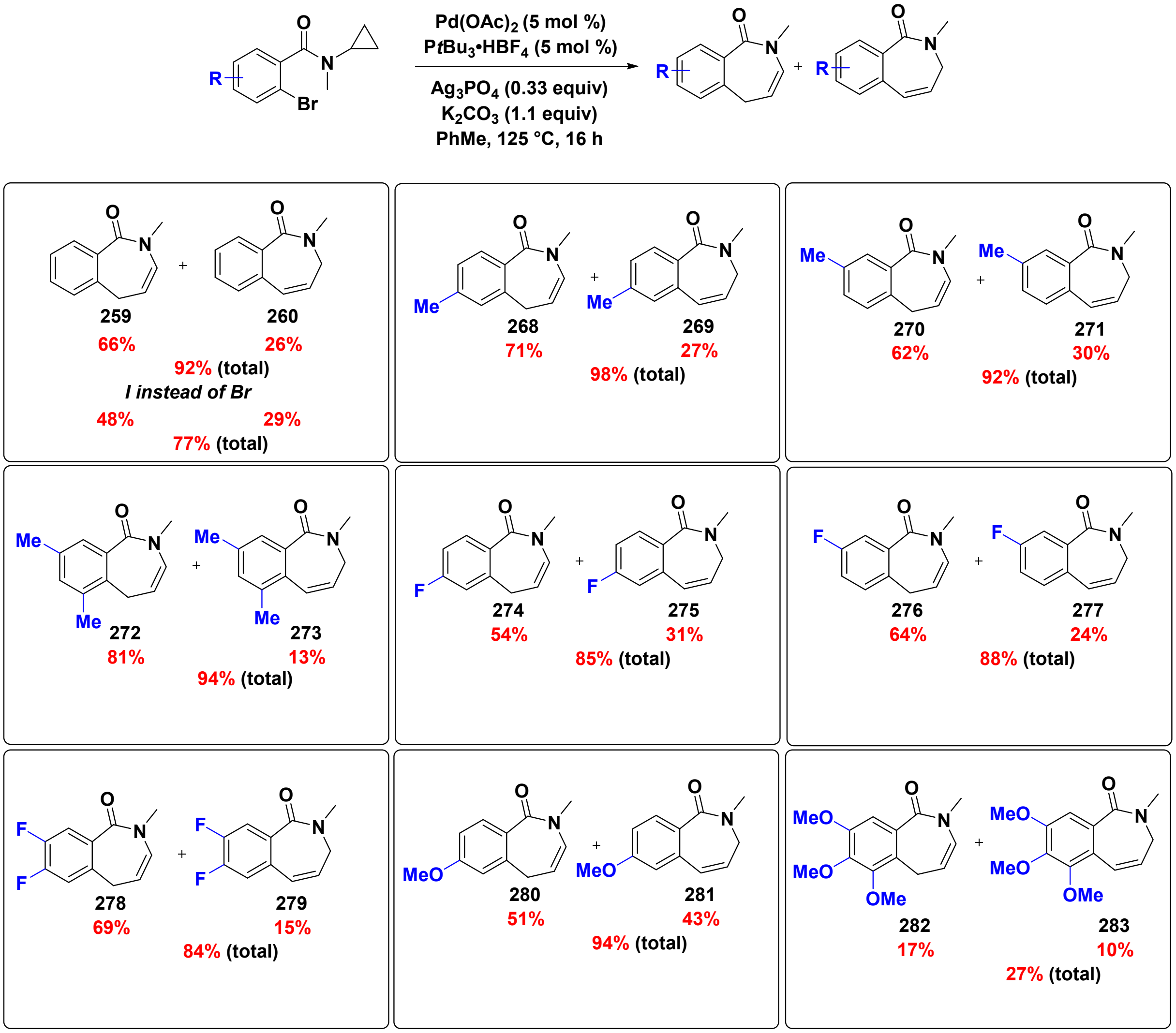


Upon changing the amide protecting group, it was discovered that benzyl **263** was also suitable (**Scheme 101**). In the cyclization of **263**, a total product yield of 96% was obtained, and the cyclization was specific for C(sp$^3$)–H bonds; none of the aryl cyclization was observed. A carbamate protected substrate **264** was highly labile and underwent deprotection during the reaction to provide **267** in 53% yield along with a mixture of unknown alkenes.

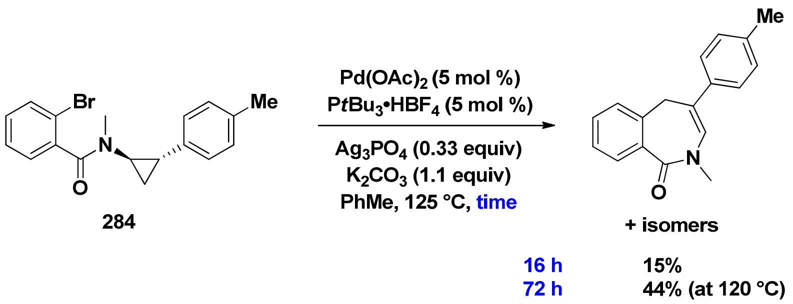
The scope was further investigated with substrates bearing a substitution on the aromatic ring (**Scheme 102**). Aryl iodides were also reactive (77% overall yield), but aryl chlorides gave no conversion (not shown). Furthermore, methyl, dimethyl, fluoro and difluoro substituents all provided the desired products in excellent yields; importantly, a methyl group *ortho* to the bromide did not seem to hinder the reaction, benzazepinones **272** and **273** being isolated in 94% yield. Additionally, a methoxy substituent was also tolerated, as **280** and **281** were obtained in a total yield of 94%, in about a 1:1 ratio. Unfortunately, the reaction was sensitive to a very electron rich substrate bearing three methoxy substituents (27% overall yield) and unreacted and dehalogenated starting material were also isolated.

A substrate bearing aryl substitution was also tested under the ring-opening conditions (**Scheme 103**). Compound **284** bearing a *p*-tolyl substituent was quite unreactive and even after 72 h of heating at 120 °C only 44% yield of the desired products (the exact structure was not assigned) were obtained, along with other unidentified alkenyl products. It was concluded that a substituted cyclopropane was not suitable for the transformation, perhaps as a result of steric interaction with the bulky P*t*Bu$_3$·HBF$_4$.

**Scheme 102**. Scope with respect to the aryl halide

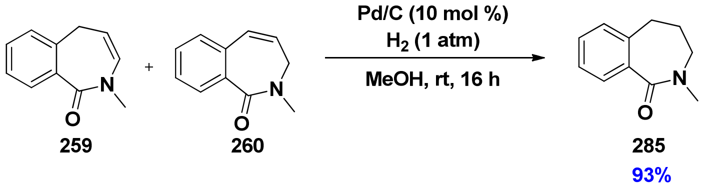


**Scheme 103**. Ring-opening of a substrate bearing an aryl-substituted cyclopropane



As an application, it was demonstrated that the mixture of products can be easily hydrogenated to give one product **285** in 93% yield (**Scheme 104**), thus providing easy access to a benzolactam product.

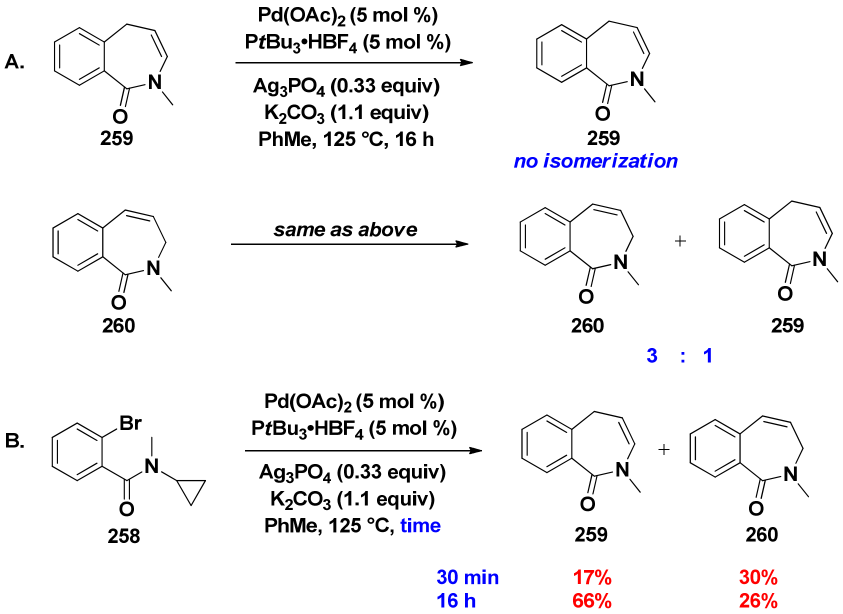
**Scheme 104**. Hydrogenation of benzazepinones



## 3.3.3 Mechanistic investigations

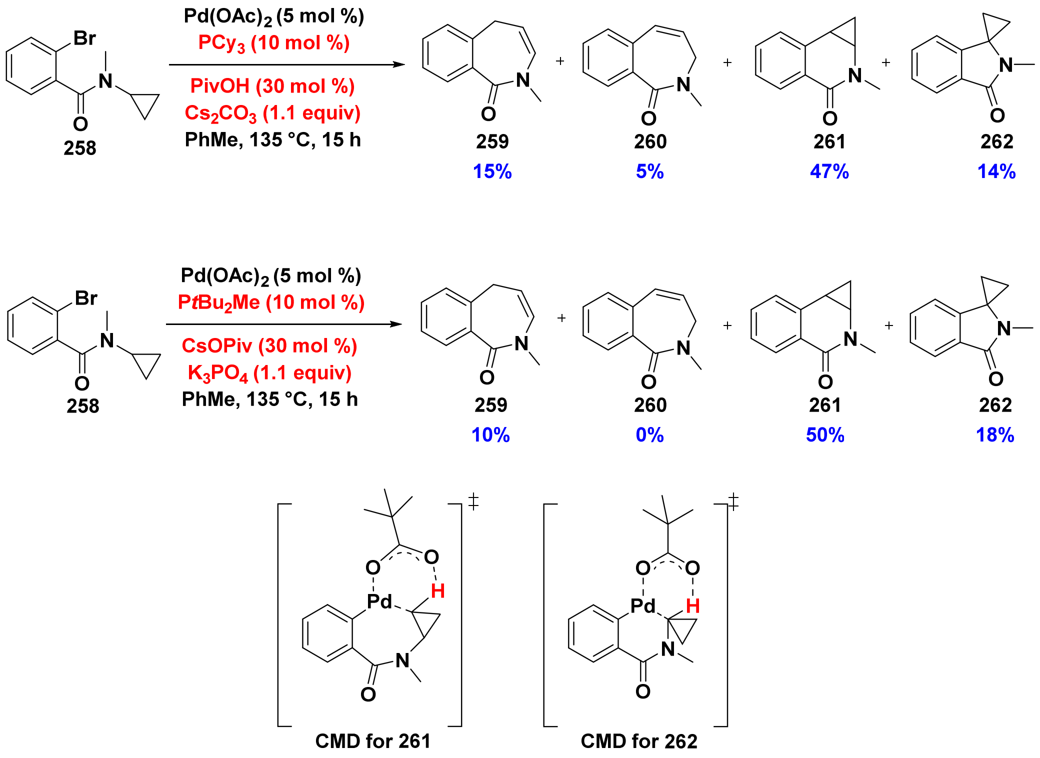
To gain an understanding into the formation of each product, each alkene isomer was separately re-submitted to the reaction conditions (**Scheme 105A**). The major benzoazepinone product **259** remained unchanged, while minor **260** provided a 3:1 mixture of **259**:**260**. What is more, when the reaction was tested after only 30 min, formation of minor **260** was predominant (30% versus 17%), while at the end of the 16 h reaction time, **259** was formed in majority, with about a 2.5:1 ratio to **260** (**Scheme 105B**). The results suggest that **260** was the kinetic product and **259** was the thermodynamic product.[162]

**Scheme 105**. Isomerization studies of **A. 259-260** and **B. 258**

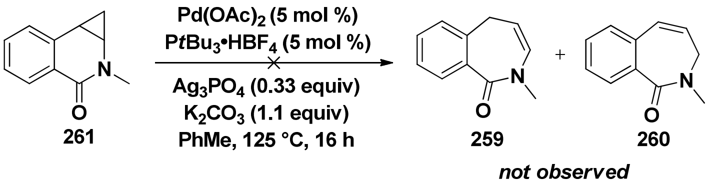


Next, we wished to investigate whether the cyclopropyl C–H activation occurred prior to the cyclopropane opening. Benzamide **258** was submitted to the reaction conditions previously disclosed by Fagnou *et al*,[87] and under both conditions dihydroisoquinoline **261** was the major product (47% or 50% yield), along with spirooxindole **262** (**Scheme 106**). Benzoazepinone products were also isolated, albeit in much lower yields. Products **261** and **262** are believed to form via a pivalate-mediated CMD transition state to give either a six- or seven-membered palladacycle, followed by reductive elimination. It was hypothesized that perhaps **261** was prone to ring-opening during the reaction, and led to the formation of **259** and **260**; however, **261** was fully recovered at the end of 16 hours (**Scheme 107**).

**Scheme 106**. Screen of pivalate conditions

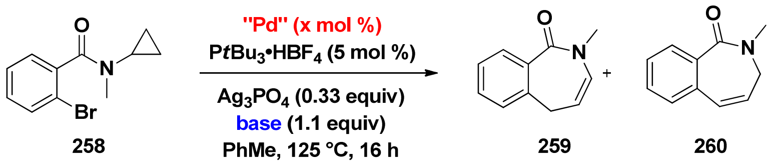


**Scheme 107**. Control reaction with **261**



For the cyclopropane arylation presented in Section 3.2, it was found that both $Pd^{II}$ and $Pd^{0}$ sources were reactive, and that catalytic acetate was not necessary for the CMD step. For the ring-opening transformation, when $Pd_2(dba)_3$ was evaluated as catalyst, a low conversion was observed; upon adding acetate in the reaction (1.1 equiv KOAc instead of $K_2CO_3$), most of the reactivity was restored (**Table 15**). The result suggested the necessity of acetate during the CMD step.

**Table 15**. Influence of acetate on the reaction outcome



| entry | "Pd" | base | yield[a] (%) | | |
|---|---|---|---|---|---|
| | | | **259** | **260** | Total product |
| 1 | $Pd_2(dba)_3$ (2.5 mol %) | $K_2CO_3$ | 8 | 6 | 14 |
| 2 | $Pd_2(dba)_3$ (2.5 mol %) | **KOAc** | **52** | **11** | **63** |

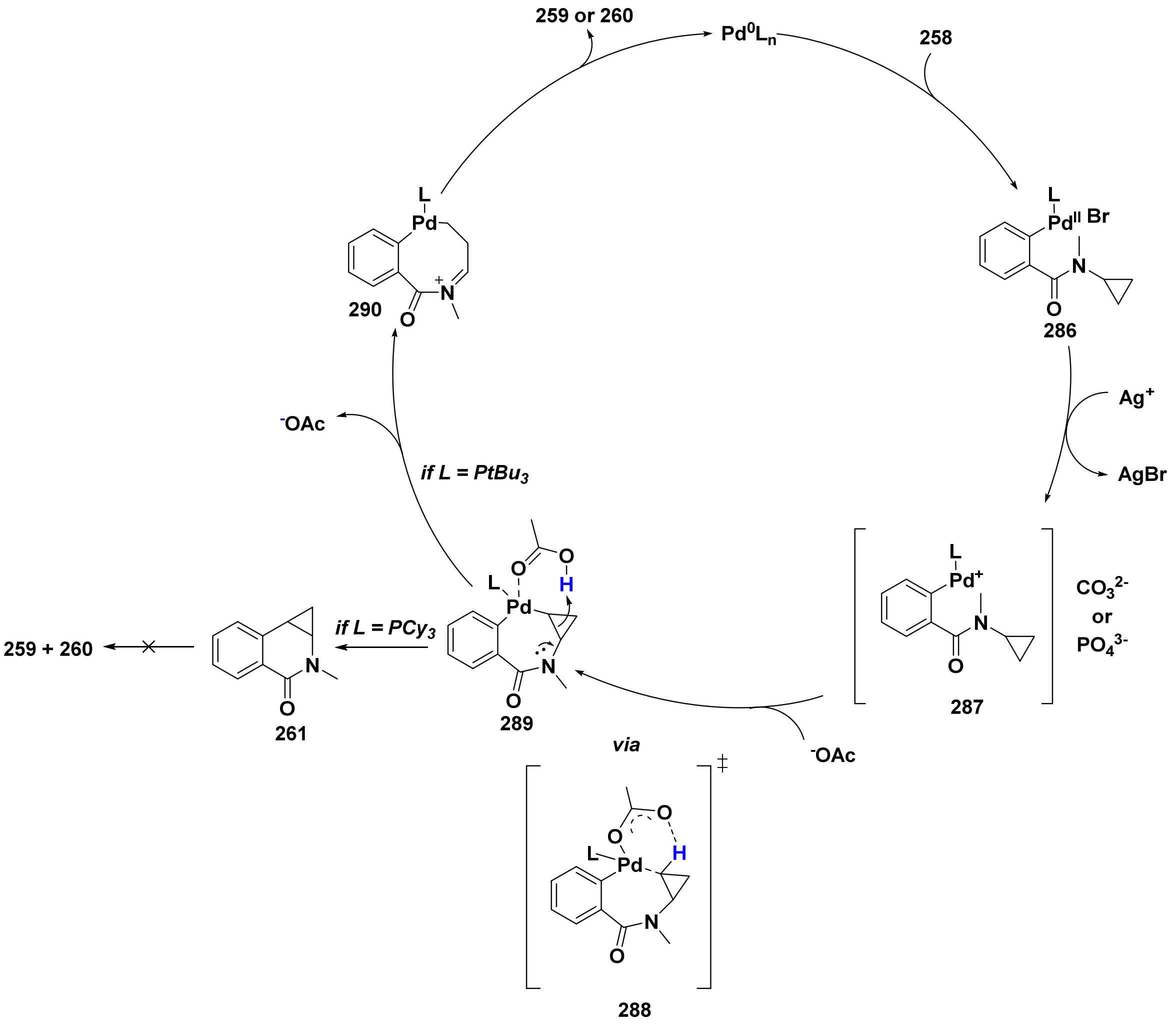
[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

A short summary of all mechanistic investigations and observations is presented below:

- C–H activation of cyclopropane does not require the presence of pivalate (compare the formation of dihydroisoquinoline **261** in **Scheme 100** and **Scheme 106**);
- Dihydroisoquinoline **261** does not undergo ring-opening under the reaction conditions;
- Acetate is responsible for proton abstraction during the CMD step (**Table 15**);
- Exactly one equivalent of $Ag^+$ was found necessary for the cyclization;
- It is speculated that the silver source may be involved in halide abstraction and formation of a cationic Pd species;
- A sterically hindered ligand was important for formation of the ring-opened products.

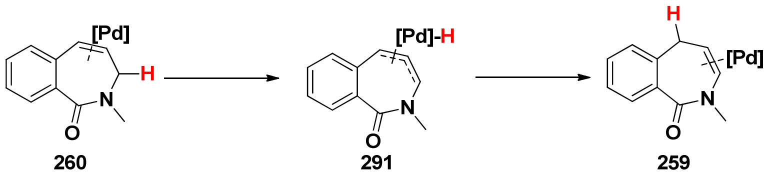
Based on the observations, the following plausible catalytic cycle was proposed (**Scheme 108**). Initial oxidative addition forms complex **286**, followed by halide abstraction by the cationic silver to produce cationic Pd intermediate **287**. A seven-membered palladacycle **289** forms via an acetate-mediated CMD transition state **288**. When $PCy_3$ is employed as ligand, reductive elimination gives rise to dihydroisoquinoline **261**, which was shown to not undergo any ring-opening. In presence of sterically hindered P*t*$Bu_3$ ring-opening occurs, aided by both Pd and the nitrogen lone pair to give **290** which may undergo deprotonation and then reductive elimination to provide either product.

**Scheme 108**. Plausible catalytic cycle



A plausible mechanism for the alkene isomerization is shown in **Scheme 109**. It is well known that double bond migration can be promoted by a variety of transition metals, including Ru, Rh, Pd, Fe etc.[173] Coordination of Pd to the alkene is followed by a π-allyl formation via a 1,3-H shift to give **291**, then reductive elimination to produce the more stable enamide-type structure.

**Scheme 109**. Possible isomerization mechanism



## 3.4 Conclusion

In summary, two novel intramolecular C–H functionalizations of cyclopropanes were developed. In the first project, cyclopropyl spirooxindoles were synthesized starting from easily available bromoanilides. It was demonstrated that the reaction mechanism followed a CMD-type pathway, and not enolate arylation, through epimerization experiments and determination of the KIE. In the second project, benzoazepinone-type products were synthesized starting from benzamides. It was demonstrated that a bulky ligand such as P*t*Bu$_3$ resulted in cyclopropane opening, while a less hindered ligand such as PCy$_3$ provided mainly cyclization of the intact cyclopropane. Mechanistic studies and comparison to the Fagnou conditions led us to conclude that C–H activation of the cyclopropyl bond via a CMD pathway occurred previous to ring-opening.

The projects added to the few known examples in the literature of direct cyclopropane functionalization, demonstrated the use of Ag in generating a reactive cationic species and opened the door to the development of other activation cyclopropanes methodologies.

# Chapter 4: Auxiliary-enabled, Pd-catalyzed, intermolecular arylation of cyclopropanes

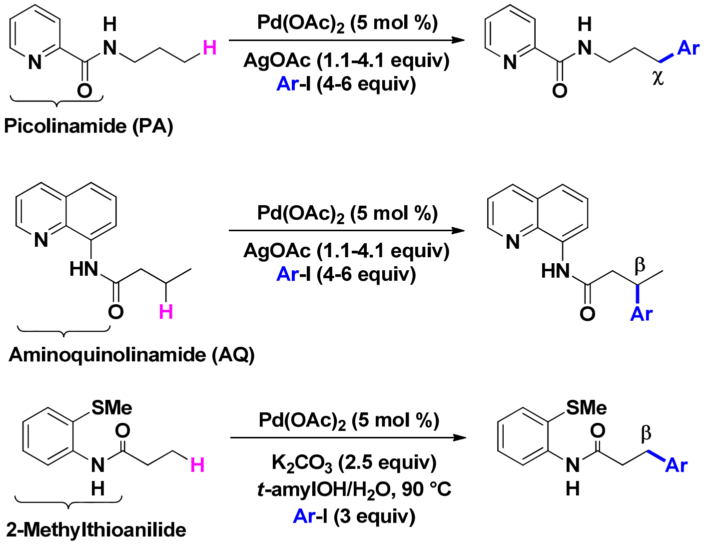
Reference: Sustac Roman, D.; Charette, A. B. *Org. Lett.* **2013,** *15*, 4394.

The introductory chapter provided an overview of monodentate directing groups used in transition metal catalysis. The current chapter will present a brief overview of amide-based bidentate groups for Pd catalysis, and applications to the functionalization of cyclopropanes. In comparison to monodentate coordination, bidentate groups maintain a higher degree of stereochemical control around the metal centre, which enables the formation of more rigid cyclometalated species.

## 4.1 *N,N*-Bidentate directing groups

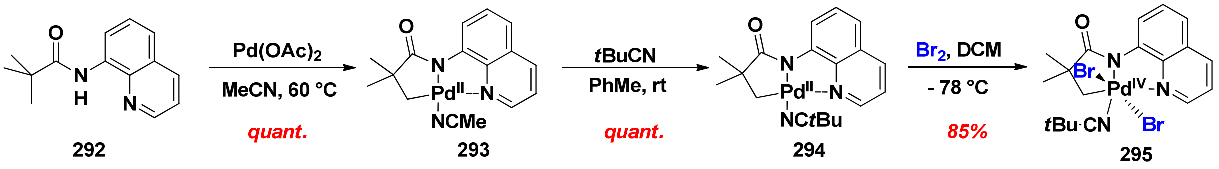
The concept of bidentate coordination being able to promote $sp^2$ or $sp^3$ C–H activation has been well known in the literature, with most of the early work employing stoichiometric transition metal.[174] A breakthrough in the field came in 2005, when Daugulis *et al* introduced the picolinamide and aminoquinolinamide auxiliaries for Pd-catalyzed direct arylation of $C(sp^2)$–H and $C(sp^3)$–H centers with aryl iodides (**Scheme 110**).[175a] The reaction took place in presence of $Pd(OAc)_2$ (5 mol %), AgOAc (1.1 to 4.1 equiv), in absence of any solvent between 130-150 °C. The authors followed up the initial communication with a full paper in which the scope and mechanism were fully investigated.[175b] Key to a successful bidentate auxiliary was the presence of an acidic NH group, as well as a nitrogen or sulfur (derived from 2-methylthioaniline) coordinating group; it was suggested that the bidentate coordination mode would retard *β*-hydride elimination (**Scheme 110**). Either β-arylation of carboxylic acids or γ-arylation of amines could be performed, depending on the type of auxiliary used. Additionally, alkylation with alkyl iodides or benzyl bromides could also be achieved. The reactions conditions could also be modified to avoid the use of stoichiometric silver, using instead $K_2CO_3$ as the base and a mixture of *t*-amylOH and $H_2O$ as the solvent (**Scheme 110**). The bidentate auxiliary derived from 8-aminoquinoline could be removed in refluxing sulfuric acid.

**Scheme 110**. Daugulis' auxiliaries for C(sp$^3$)–H arylation[175]



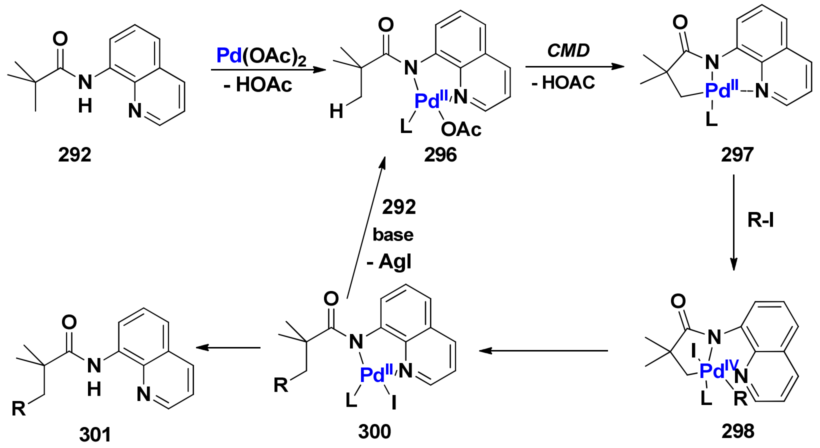
In terms of mechanistic studies, several complexes related to reaction intermediates have been isolated and characterized by Shabashov and Daugulis (**Scheme 111**).[175b] Upon stirring aminoquinolinamide **292** in acetonitrile with stoichiometric Pd(OAc)$_2$ the corresponding cyclometalated complex **293** was formed. The complex underwent replacement of the labile nitrile solvent with *t*BuCN to form **294**. At – 78 °C, complex **294** oxidatively added bromine to provide Pd$^{IV}$ complex **295**, which was characterized by NMR and X-ray crystallography. It also represented one of the first examples of alkyl-Pd$^{IV}$ complexes isolated. Attempts at replacing the bromine with other substituents were unsuccessful.

**Scheme 111**. Isolation of reaction intermediates[175b]



Based on all the experimental evidence, a generalized mechanism for bidentate-directed C–H functionalization was proposed (**Scheme 112**).[175b] Initial formation of a palladium amide species **296** is followed by a fast concerted metalation-deprotonation to give complex **297**, containing a five-membered kinetically favoured palladacycle. Complex **297** undergoes oxidative addition to provide a Pd$^{IV}$ complex **298**. At which point, the authors could not discount the formation of a bimetallic Pd$^{III}$ species.[37] Reductive elimination, followed by ligand exchange provides the desired product **301** and regenerates the Pd catalyst. The silver salt's role is in sequestering the iodide produced as an insoluble salt.

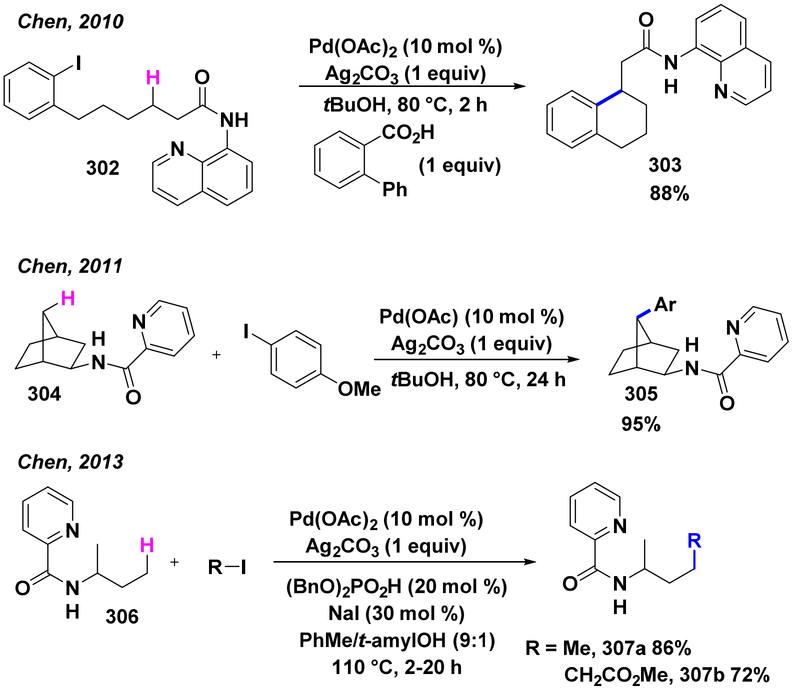
**Scheme 112**. Daugulis' proposed mechanism[175]



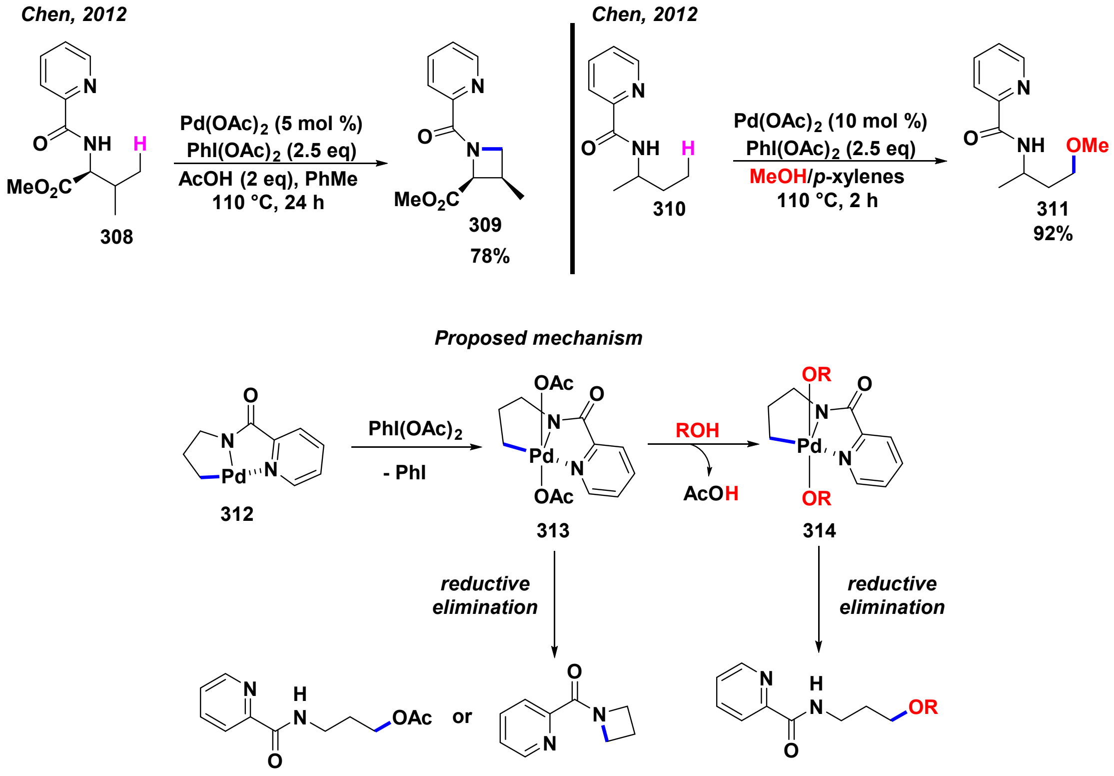
The reports by Daugulis were followed by many other publications, all employing either the picolinamide or aminoquinolamide auxiliaries to perform various C–H functionalizations.[176] Selected examples using Pd catalysis are shown in **Scheme 113**. The group of Chen disclosed an intramolecular arylation using the aminoquinoline auxiliary.[177] An extensive screen of aliphatic and aryl carboxylic acids revealed *o*-phenyl benzoic acid as the best ligand for Pd to promote the reaction, obtaining **303** in 88% yield. The same group achieved the monoarylation of cyclohexane (not shown) and *exo*-norbornane **304**.[178] The methodology was also applied to alkylation reactions of **306** employing primary alkyl iodides.[179] Catalytic amounts of an organic phosphate, acting as a solid-to-solution phase-transfer catalyst, were found necessary to control the concentration of $Ag^+$ cations in solution.

Furthermore, C–heteroatom bond formation was also possible (**Scheme 114**). Intramolecular picolinamide-directed C–H amination to provide azetidine **309** was achieved in presence of the oxidant iodosobenzene diacetate.[180] Other *N*-heterocycles such as pyrrolidine or indoline could also be synthesized. An acetoxylation by-product was observed during the cyclization, which the Chen group explored in a subsequent publication to form ether products of type **311** in good yields.[181] The proposed mechanism implicated oxidation of palladacycle **312** by $PhI(OAc)_2$. Subsequently, $Pd^{IV}$ complex **313** can undergo reductive elimination to provide either C–N or C–O bond formation. However, it was hypothesized that the OAc ligand may dissociate and be replaced by other nucleophiles, such as an alcohol to give complex **314** which reductively eliminates to give the desired ether product.

**Scheme 113.** Selected examples of C–C bond formation using an *N,N*-bidentate auxiliary

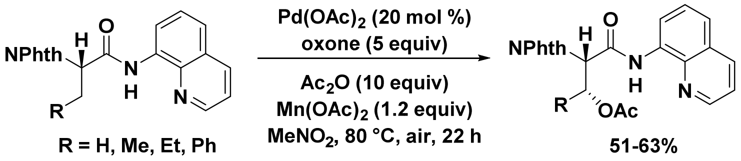


**Scheme 114**. Selected examples of C-heteroatom bond formation using an *N,N*-bidentate auxiliary



Corey first demonstrated in 2006 that unnatural amino acids can be accessed via aminoquinolinamide-directed Pd-catalyzed acetoxylation (**Scheme 115**).[182]

**Scheme 115**. Corey's synthesis of unnatural amino acids[182]



The reaction conditions and choice of auxiliary were later improved by several groups and employed to access unnatural amino acids or lactams via alkylation, oxidation, or amidation reactions (**Figure 15**).[183] Besides Pd-catalyzed reactions, Chatani, Daugulis, Nakamura and others have shown that other transition metals such as Ru, Ni, Cu or Fe can form bidentate metalacycles and give rise to C–C (aryl, alkenyl, alkynyl or alkyl) or C–heteroatom (O, N, F, S) bonds.[184,185,186,187] From the brief introduction, it can be concluded that *N,N*-bidentate auxiliaries are reliable directing groups for C–H transformations with a variety of metals, as well as electrophiles and nucleophiles.

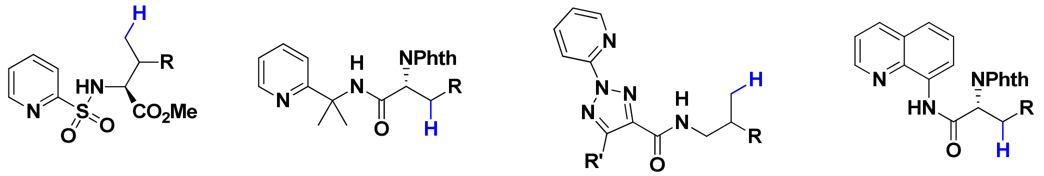
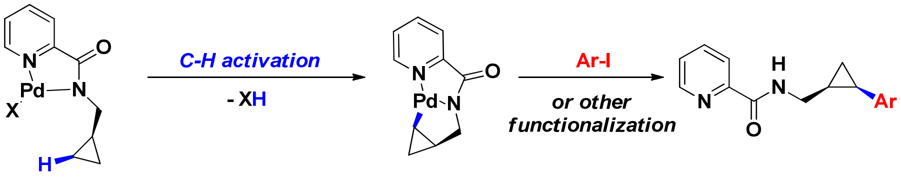


**Figure 15**. Examples of other related auxiliaries

## 4.1.1 Project goal

An efficient and practical methodology for the intermolecular functionalization of cyclopropanes was the goal of our project. Cognizant of the previous work from the Yu group (Section 1.3), where an expensive, tetrafluorobenzonitrile amide auxiliary was employed as directing group, we embarked upon finding other reaction conditions and systems to achieve cyclopropane C–H arylation. Use of a bidentate system consisting of an amide moiety and another coordinating atom appeared attractive, given the plethora of transformations utilizing picolinamide or aminoquinoline-based auxiliaries described above. It was hypothesized that the proximity effect induced by a bidentate auxiliary could be exploited for activation of a cyclopropyl C–H bond, mediated by a Pd catalyst (**Scheme 116**). Then, oxidative addition of an aryl halide followed by reductive elimination could produce a disubstituted cyclopropane. Furthermore, in order to achieve a successful transformation, the auxiliary should be inexpensive and easily cleavable. The resulting *cis*-cyclopropyl amines (after cleavage of the picolinamide auxiliary) or carboxylic acids (after cleavage of the aminoquinoline auxiliary) possess interesting pharmacological properties.[188]

**Scheme 116**. Desired C–H functionalization of cyclopropanes

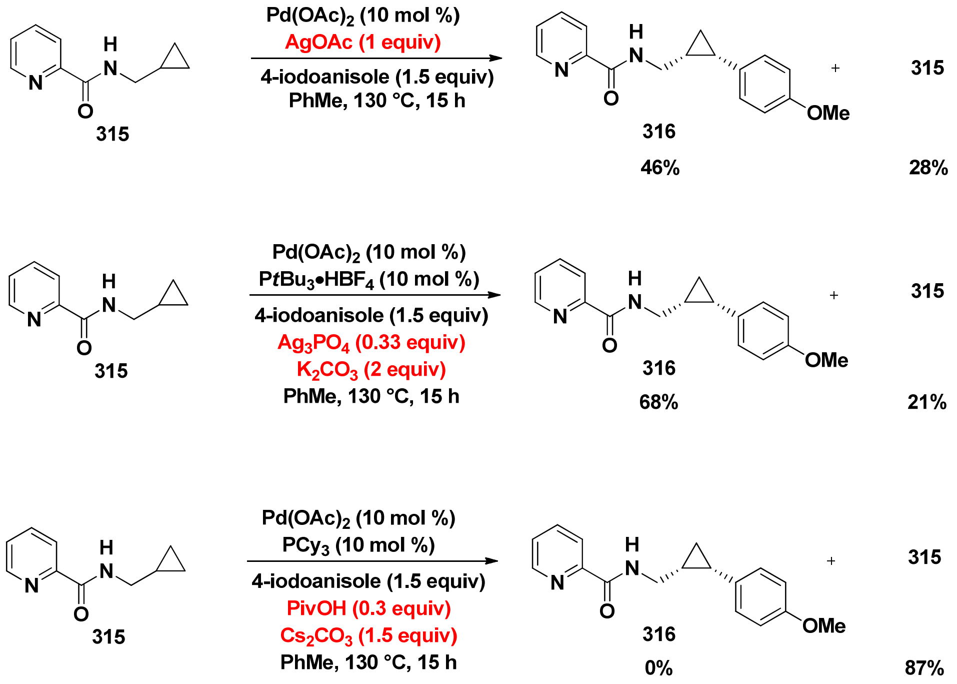


## 4.2 Reaction optimization

### 4.2.1 Initial studies

The picolinamide auxiliary was chosen as a model substrate (**Scheme 117**). Picolinamide **315** was synthesized in two steps starting from cyclopropanecarbonitrile and 2-picolinic acid. Gratifyingly, when substrate **315** was submitted to Daugulis-type conditions,[175] 46% of the desired product **316** (one diastereomer) was observed, along with 28% unreacted starting material. In addition, submitting **315** to the conditions previously developed in Chapter 3 for the intramolecular arylation of cyclopropanes, 68% arylated product **316** was observed, along with 21% unreacted **315**. Traces of a diarylated product were also observed by LC-MS. Employing other conditions for cyclopropane arylation with pivalic acid and cesium carbonate, no desired product was isolated. It was decided to continue the optimization with the picolinamide auxiliary in presence of a silver salt. Interestingly, a sterically hindered phosphine ligand was tolerated in the reaction; its role would be investigated later on.

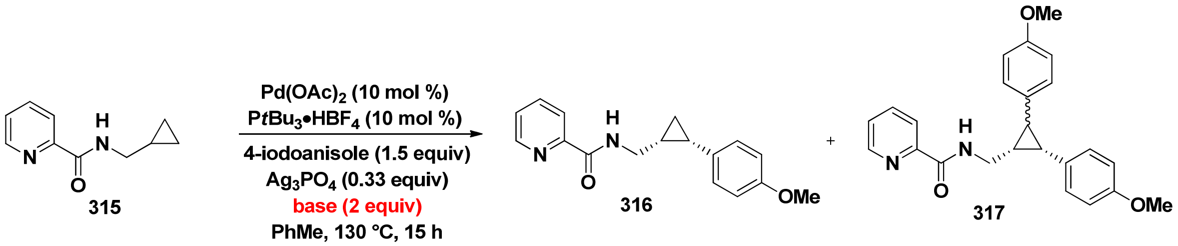
**Scheme 117**. Initial studies with a picolinamide auxiliary



## 4.2.2 Optimization of reaction conditions using a silver salt

As the conditions employing $Ag_3PO_4/K_2CO_3/PtBu_3{\cdot}HBF_4$ provided the best yield in the initial screen (**Scheme 117**), they were considered a good starting point for further optimizing the reaction. Firstly, other carbonate bases were screened (**Table 16**). Sodium carbonate (entry 2) gave a better yield than the corresponding potassium base (entry 1), while cesium carbonate, although more soluble in the toluene solvent, was less reactive (entry 3). Significant amounts of the diaryl **317** were also observed. Compound **317** was found to have mainly a *trans* configuration, although in some cases traces of *cis* were also observed.

**Table 16**. Base screen for the intermolecular arylation of cyclopropanes

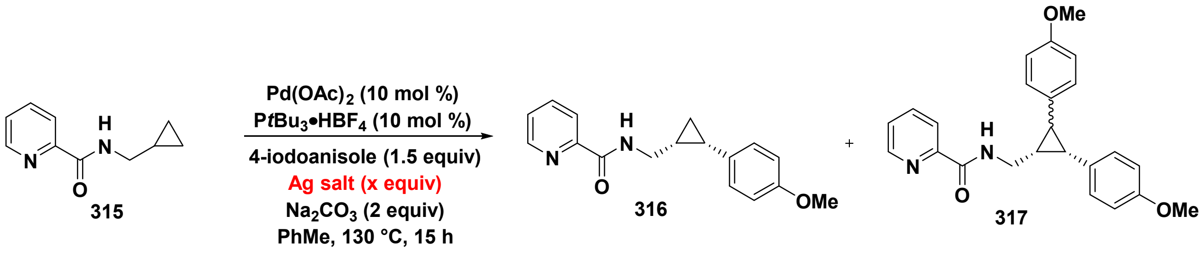


| entry | base | yield[a] (%) | | |
|---|---|---|---|---|
| | | **315** | **316** | **317** |
| 1 | $K_2CO_3$ | 13 | 59 | 10 |
| 2 | $\mathbf{Na_2CO_3}$ | 15 | **75** | <5 |
| 3 | $Cs_2CO_3$ | 71 | 17 | <1 |

[a] $^1H$ NMR yield using trimethoxybenzene as internal standard.

Secondly, the silver source was investigated (**Table 17**). Silver phosphate (either 0.4 or 0.5 equivalents) provided the best yield of the monoarylated product **316** (entries 1 and 2), while silver bromide the worst (entry 5). Silver carbonate also gave complete conversion and 77% overall yield (entry 3), while silver acetate only provided 45% yield desired product **316** (entry 4).

**Table 17**. Silver source screen for the intermolecular arylation of cyclopropanes

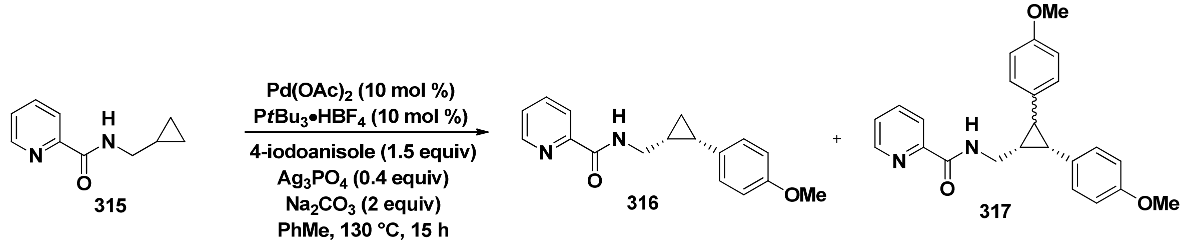


| entry | Ag salt (x equiv) | yield[a] (%)<br>**315** | **316** | **317** |
|---|---|---|---|---|
| 1 | $Ag_3PO_4$ (0.5 equiv) | <2 | 71 | 5 |
| 2 | $Ag_3PO_4$ (0.4 equiv) | <2 | 65 | 14 |
| 3 | $Ag_2CO_3$ (0.75 equiv) | <1 | 61 | 16 |
| 4 | AgOAc (1.5 equiv) | <2 | 45 | 11 |
| 5 | AgBr (1.5 equiv) | 57 | 12 | 0 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

Thirdly, control reactions were run in order to determine the requirement for each reaction component (**Table 18**). The Pd loading could be decreased to 5 mol % (entry 1). In absence of the silver salt, only 5% yield product **316** was observed (entry 2), while omitting the base gave about 20% yield desired monoaryl **316** (entry 3). Removing the Pd catalyst resulted in no reaction (entry 4). Omitting the ligand had no impact on the transformation (entry 5). The result suggested that the sterically hindered ligand was probably not present on the metal centre during the course of the reaction; the picolinamide moiety acts as both substrate and ligand for the reaction.[175] Consequently, developing an enantioselective version of the reaction with a phosphine ligand would not be viable.

**Table 18**. Control reactions for the intermolecular arylation of cyclopropanes

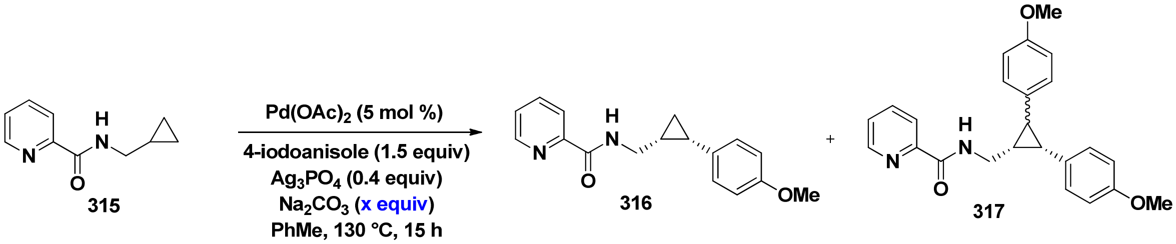


| entry | variation | yield[a] (%)<br>**315** | **316** | **317** |
|---|---|---|---|---|
| 1 | 5 mol % Pd | <2 | 67 | 22 |
| 2 | no $Ag_3PO_4$ | 94 | 5 | 0 |
| 3 | no $Na_2CO_3$ | 54 | 20 | <2 |
| 4 | no $Pd(OAc)_2$ | 94 | 0 | 0 |
| 5 | no $PtBu_3\cdot HBF_4$ | 6 | 68 | 16 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

Lastly, the stoichiometry of base was investigated in the reaction, in the absence of the ligand (**Table 19**). It was shown that good yields could be obtained even when using substoichiometric amounts of carbonate base (entries 1-4), while increasing the base loading slightly decreased the yields (entries 6-7). For ease of manipulation, 0.3 equivalents of dry $Na_2CO_3$ were chosen as ideal.

**Table 19**. Base loading screen for the intermolecular arylation of cyclopropanes



| entry | $Na_2CO_3$ equiv. | yield[a] (%) | | |
|---|---|---|---|---|
| | | **315** | **316** | **317** |
| 1 | 0.1 | 25 | 65 | 10 |
| 2 | 0.2 | 9 | 75 | 15 |
| **3** | **0.3** | **5** | **71** | **22** |
| 4 | 0.5 | 5 | 73 | 10 |
| 5 | 1.0 | 6 | 70 | 10 |
| 6 | 1.5 | 7 | 64 | 9 |
| 7 | 2.0 | 6 | 68 | 16 |

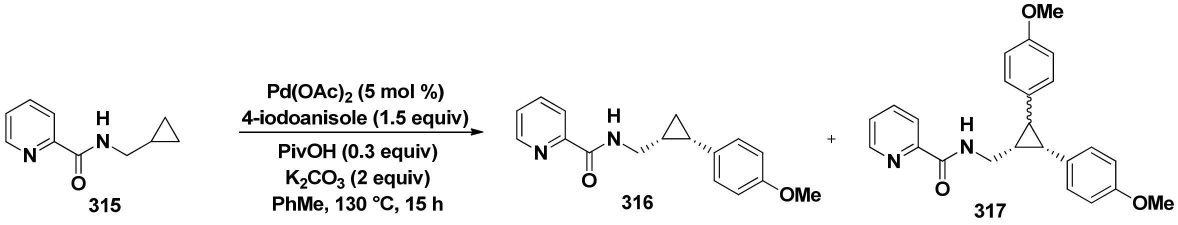
[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

Additionally, lowering the temperature to 110 °C significantly decreased the yield to 50%. The reactions were run for 15 h, as there were still traces of unreacted starting material after that time.

### 4.2.3 Optimization of the reaction conditions using pivalic acid

During the initial studies, no conversion was observed when pivalic acid was employed as an additive in the reaction in presence of cesium carbonate (**Scheme 117**). However, when the same reaction was now performed using $K_2CO_3$ as base and in absence of any ligand, 75% desired product **316** was observed, along with traces of diarylation and unreacted starting material (**Table 20**, entry 1). It is not surprising, as the group of Daugulis also reported conditions for the C(sp$^3$)–H arylation employing employing a bidentate auxiliary trimethylacetic acid.[175b] Changing the base to $Na_2CO_3$ led to only traces of product (entry 2), highlighting the importance of the carbonate counter ion. In the absence of pivalic acid, there was little product formation (entry 3), while increasing the amount of pivalic acid dramatically affected the conversion (entry 4).

**Table 20**. Reaction optimization using pivalic acid



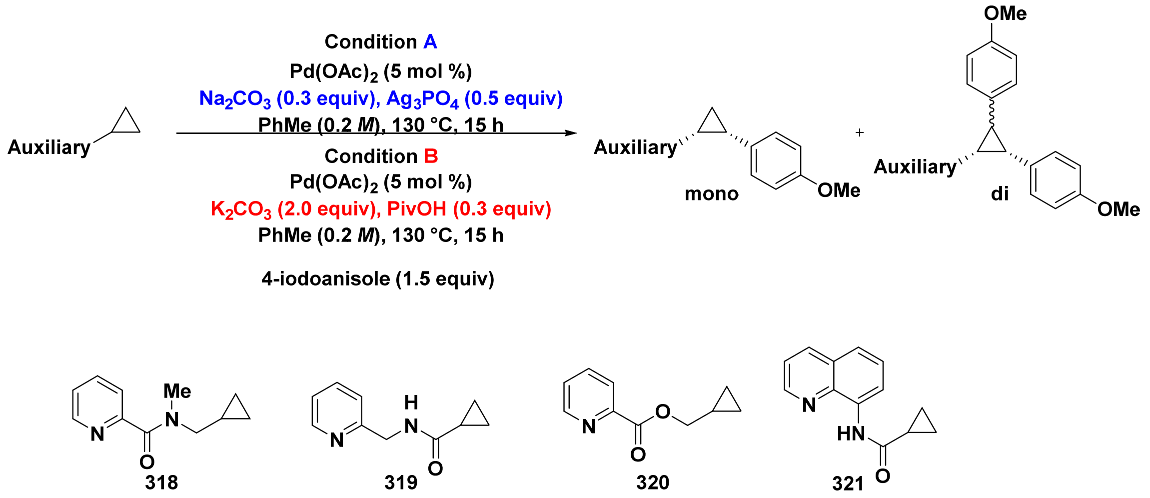
| entry | variation | yield[a] (%) | | |
|---|---|---|---|---|
| | | **315** | **316** | **317** |
| **1**[b] | **none** | **6** | **75** | **15** |
| 2 | $Na_2CO_3$ instead of $K_2CO_3$ | 82 | <1 | <1 |
| 3 | no PivOH | 78 | <5 | <1 |
| 4 | PivOH (0.5 equiv) | 74 | 20 | <1 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard. [b] Isolated yield on 0.5 mmol.

## 4.2.4 Screen of other auxiliaries

With two different reaction conditions in hand, other auxiliaries were investigated (**Scheme 118**). Protecting the amide with a methyl group (compound **318**) resulted in no reaction, highlighting the importance of the secondary amide moiety for coordination to the metal centre. A substrate **319** containing the amide moiety next to the cyclopropane resulted in low yields and decomposition of the starting material. Replacing the amide entirely by an ester (**320**) did not provide any desired product. The auxiliary derived from 8-aminoquinoline, **321**, provided only traces of product under both conditions.

**Scheme 118**. Screen of other auxiliaries[a]



**318**
A: no reaction

**319**
A: 33% mono, 5% di
B: 20% mono, <1% di

**320**
A: no reaction

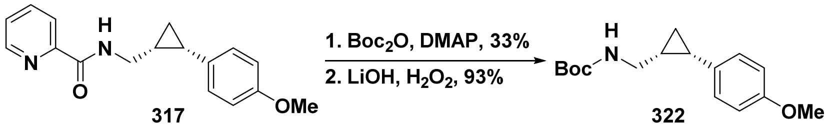
**321**
A: traces mono
B: traces mono

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

### 4.2.5 Auxiliary cleavage

The picolinamide auxiliary was removed in two steps: 1) protection of the amide with a Boc group, followed by 2) oxidative cleavage under basic conditions (**Scheme 119**). Other attempts at reducing the amide to the corresponding amine with $NaBH_4$ or $Tf_2O/Et_3SiH$ resulted in unreacted starting material, while $LiAlH_4$ provided some desired product, along with decomposition.

**Scheme 119**. Two-step auxiliary removal



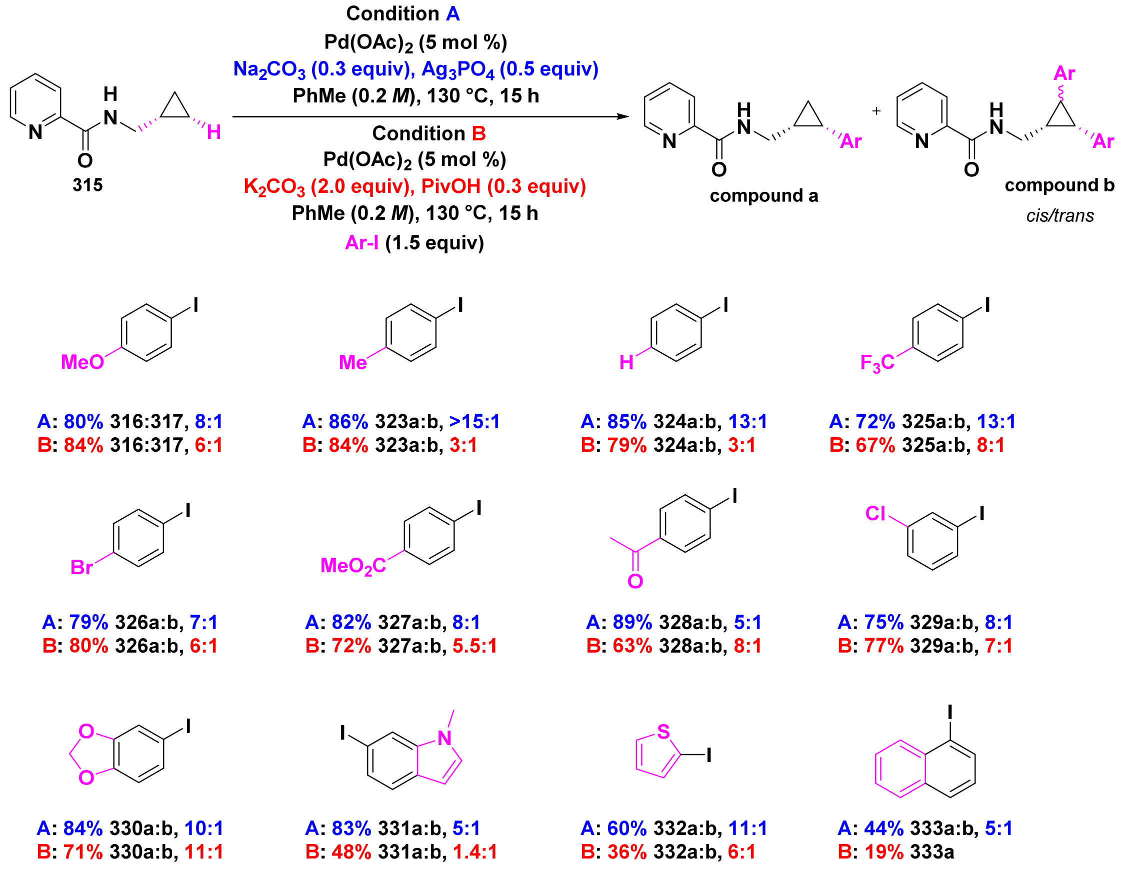
**317** **322**

## 4.3 Reaction scope

Aryl iodides were found reactive under reaction conditions **A** and **B** (**Scheme 120**); aryl bromides or chlorides failed to react under either conditions (not shown). It is hypothesized that oxidative addition onto a Pd$^{II}$ complex to provide a Pd$^{IV}$ complex is much more difficult for Ar-Br and Ar-Cl. Thus, the scope was explored employing aryl iodides (**Scheme 120**). A variety of substituents were tolerated at the *para* position, including electron donating (methoxy), electron neutral (H, methyl) and electron withdrawing (trifluoromethyl, ester, ketone) groups. Bromo (**326**) and chloro (**329**) provided the desired products in 79% and 77%, respectively, under conditions **A**. The Br and Cl groups allow for further functionalizations via other cross-couplings. Heterocycles were also viable coupling partners, the corresponding cyclopropanes being obtained in 83% (indole, **331**) and 60% (thiophene, **332**) yields under the silver conditions, while the pivalic acid conditions provided much lower yields and selectivities (83% versus 48% for indole **331**, 5:1 versus 1.4:1 mono:di selectivity). The reaction was found to be sensitive to sterics, as 1-iodonaphthalene only gave 44% total yield of **333** (conditions **A**) or 19% **333a** (conditions **B**). In all cases, the monoarylated product was exclusively the *cis* diastereomer, thus providing a robust method for the synthesis of aryl and heteroaryl *cis*-substituted cyclopropanes. The diarylated product had mainly a *trans* configuration for compounds **317**, **331b** and **333b**, probably due to sterics for the latter two; a *cis/trans* mixture for **317**, **327b** and **328b**, and a *cis* configuration for the rest.

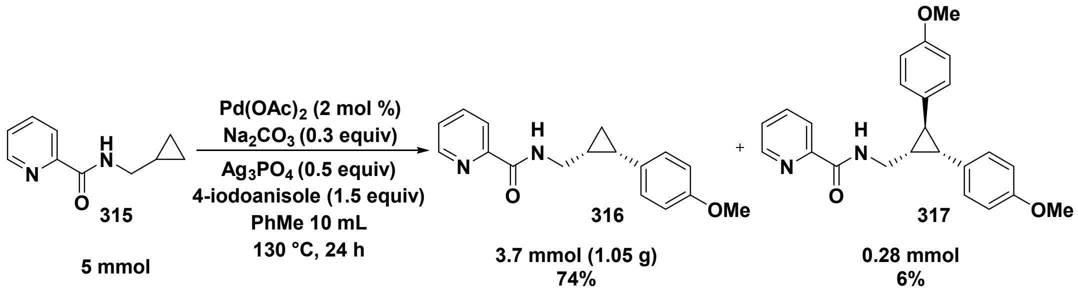
To prove the practicality and robustness of the methodology, the reaction was scaled up on 5 mmol in presence of 2 mol % Pd(OAc)$_2$ to provide the desired product **316** in 74% yield, along with 6% diarylation **317** (**Scheme 121**).

**Scheme 120**. Scope of aryl iodides[a]



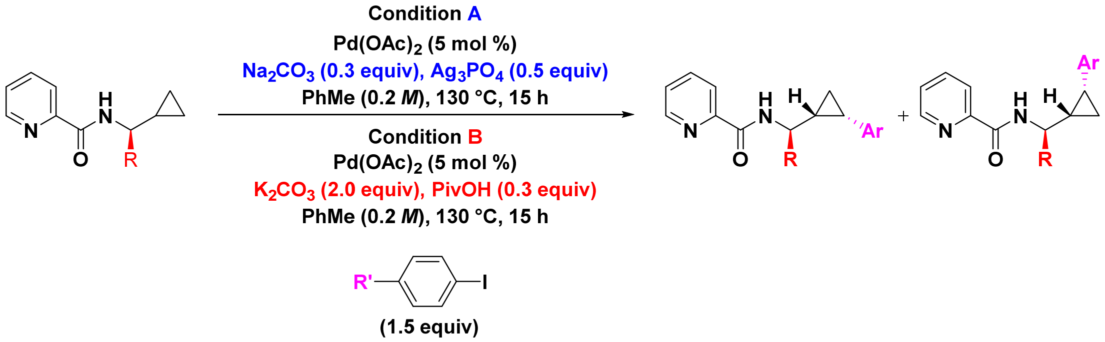
[a] Isolated yield on 0.5 mmol. [b] The reaction was run for 45 h. [c] 0.4 equiv Ag$_3$PO$_4$. [d] Reported as $^1$H NMR yield using trimethoxybenzene as an internal standard. [e] 10 mol % Pd(OAc)$_2$.

**Scheme 121**. Scale up of the reaction



To further prove the applicability of the transformation, a diastereoselective arylation of cyclopropanes was also achieved (**Table 21**). A picolinamide derivative, **334**, substituted in the α-position by a methyl group and synthesized via a four-step sequence starting from Ellman's auxiliary,[189] was arylated under conditions **A** in good yield and diastereoselectivities (entries 1 and 2). Traces of diarylation were also observed. Lower yields were obtained under condition **B** (entry 3), while replacing the methyl with a bulky isopropyl group shut down the reaction (entry 4), demonstrating the sensitivity of the reaction to steric hindrance.

**Table 21**. Diastereoselective arylation of cyclopropanes

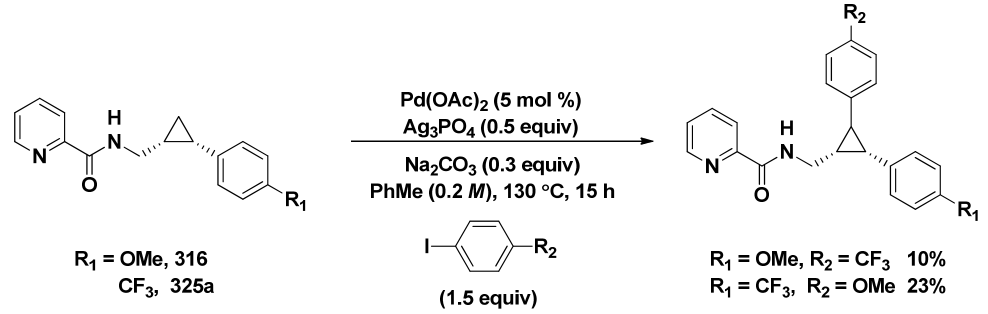


| entry | R | R’ | condition | total yield[a] (selectivity) |
|---|---|---|---|---|
| 1 | Me, **334** | 4-OMe | A | 81% (7:1) |
| 2 | Me, **334** | 4-$CF_3$ | A | 69% (8:1) |
| 3 | Me, **334** | 4-OMe | B | 45% (N/D)[b] |
| 4 | *i*Pr, **335** | 4-OMe | A | <1% |

[a] Isolated yields on 0.2 mmol. [b] Reported as $^1$H NMR yield using trimethoxybenzene as an internal standard.

Since in some cases significant diarylation product was isolated, it was envisioned that a second arylation with a different aryl iodide could lead to synthetically useful trisubstituted cyclopropanes. Unfortunately, neither disubstituted cyclopropane **316** or **325a** bearing an electron donating or electron withdrawing group, respectively, were very reactive under the reaction conditions (**Scheme 122**). Interestingly, the yields obtained (10% and 23%) roughly coincide with the amounts of diarylation observed in **Scheme 120**. The *cis* configuration of the starting disubstituted cyclopropane may sterically prevent the oxidative addition of another aryl iodide. Perhaps the conversion can be improved if the starting cyclopropane were *trans*.

**Scheme 122**. Attempts at cyclopropane diarylation[a]

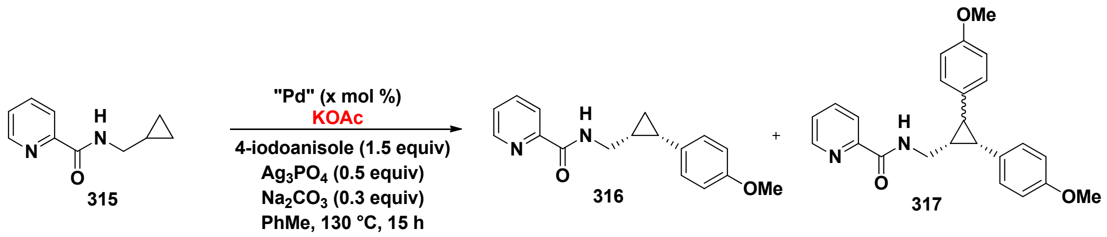


[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

## 4.4 Mechanistic studies

In order to elucidate the role of the acetate ligand in the reaction mechanism, several control experiments were run in presence of Pd$^0$ or Pd$^{II}$ sources (**Table 22**). $Pd_2(dba)_3$ provided 43% desired product **316** in absence of an acetate source (entry 2), while upon addition of 10 mol % KOAc the reactivity was re-established (entry 3). Another Pd$^0$ source, $Pd(PPh_3)_4$, was ineffective either in the presence or absence of catalytic acetate (entries 4-5). The difference between the two Pd$^0$ sources can be explained through the easier dissociation of the dibenzylideneacetone versus triphenylphosphine ligand. A Pd$^{II}$ source, $PdBr_2$, provided monoaryl **316** in 28% (entry 6), while addition of catalytic acetate restored the activity (entry 7). $Pd(TFA)_2$ was also tested, and the reaction was completely inhibited (entry 8). Again, reactivity was restored in presence of 10 mol % KOAc (51%, entry 9). The results support the direct involvement of the acetate ligand in a concerted metalation-deprotonation step.[40,190] Trifluoroacetic acid (p$K_a$ 0.5 versus 4.8 for AcOH) was a less effective proton shuttle. It is hypothesized that the carbonate or phosphate bases may be involved in regulating the pH of the reaction, by trapping the equivalent of "H$^+$" generated.[40]

**Table 22**. Screen of Pd sources and additives under conditions **A**

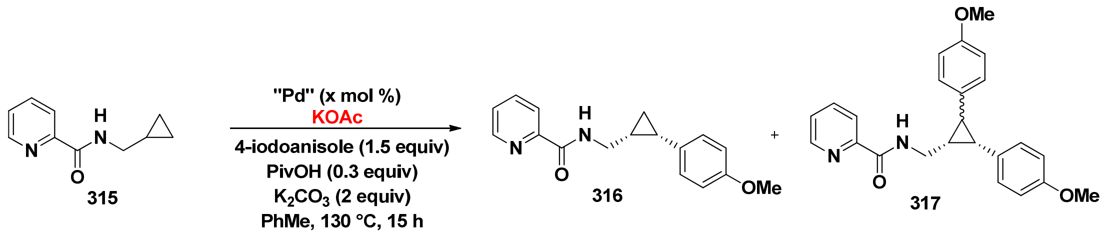


| entry | Pd (x mol %) | KOAc | yield[a] (%) | | |
|---|---|---|---|---|---|
| | | | **315** | **316** | **317** |
| 1 | Pd(OAc)$_2$ (5) | --- | 8 | **78** | 5 |
| 2 | Pd$_2$(dba)$_3$ (2.5) | --- | 53 | **43** | <1 |
| 3 | Pd$_2$(dba)$_3$ (2.5) | 10 mol % | 8 | **76** | 14 |
| 4 | Pd(PPh$_3$)$_4$ (5) | --- | 95 | **<1** | 0 |
| 5 | Pd(PPh$_3$)$_4$ (5) | 10 mol % | >90 | **<1** | 0 |
| 6 | PdBr$_2$ (5) | --- | 56 | **28** | <1 |
| 7 | PdBr$_2$ (5) | 10 mol % | 5 | **63** | 3 |
| 8 | Pd(TFA)$_2$ (5) | --- | 98 | **<1** | 0 |
| 9 | Pd(TFA)$_2$ (5) | 10 mol % | 25 | **51** | 5 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

Additionally, Pd$^0$ and Pd$^{II}$ sources were also tested under conditions **B** (**Table 23**). Some reactivity was observed in presence of Pd$_2$(dba)$_3$ (29%, entry 2), while the yield increased to 51% when catalytic acetate was added (entry 3). Both acetate and pivalate have previously been shown to be effective proton transfer agents.[45] PdBr$_2$ gave similar reactivity to Pd(OAc)$_2$ (entries 1 and 4).

**Table 23**. Screen of Pd sources and additives under conditions **B**

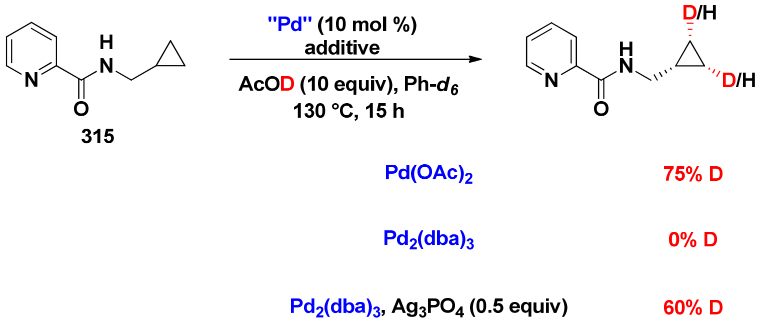


| entry | Pd (x mol %) | KOAc | yield[a] (%) | | |
|---|---|---|---|---|---|
| | | | **315** | **316** | **317** |
| 1 | Pd(OAc)$_2$ (5) | --- | 6 | **75** | 15 |
| 2 | Pd$_2$(dba)$_3$ (2.5) | --- | 66 | **29** | <1 |
| 3 | Pd$_2$(dba)$_3$ (2.5) | 10 mol % | 46 | **51** | <1 |
| 4 | PdBr$_2$ (5) | --- | 18 | **72** | 10 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

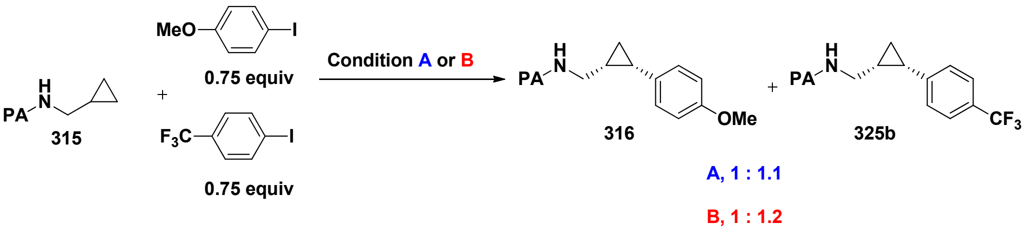
Perhaps the surprising result in **Tables 22** and **23** was the fact that the reaction worked in presence of a Pd$^0$ source. All previous examples of activation employing auxiliaries discussed at the beginning of Section 4 involved the use of a Pd$^{II}$ source (Section 4.1). To gain more understanding into the reaction mechanism, cylopropyl picolinamide **315** was submitted to a deuterium exchange experiment (**Scheme 123**). In presence of 10 mol % Pd(OAc)$_2$ and 10 equivalents AcOD, 75% D/H exchange was observed on the cyclopropyl moiety. When the catalyst was exchanged for $Pd_2(dba)_3$, no deuteration was observed. Upon addition of 0.5 equivalents of $Ag_3PO_4$ to the experiment, 60% D incorporation was detected. Based on the results, the following can be concluded: 1) C–H activation of the cyclopropane bond in presence of $Pd(OAc)_2$ occurs prior to oxidative addition, 2) $Pd^0$ alone is not able to perform the C–H activation step, and 3) $Ag_3PO_4$ may be involved in oxidizing $Pd^0$ to $Pd^{II}$. Additionally, oxidative addition of aryl iodide may occur before the C–H insertion step in case of $Pd^0$, which could explain the results in absence of a silver source (**Table 23**, entries 2 and 3).

**Scheme 123**. Deuterium incorporation experiments



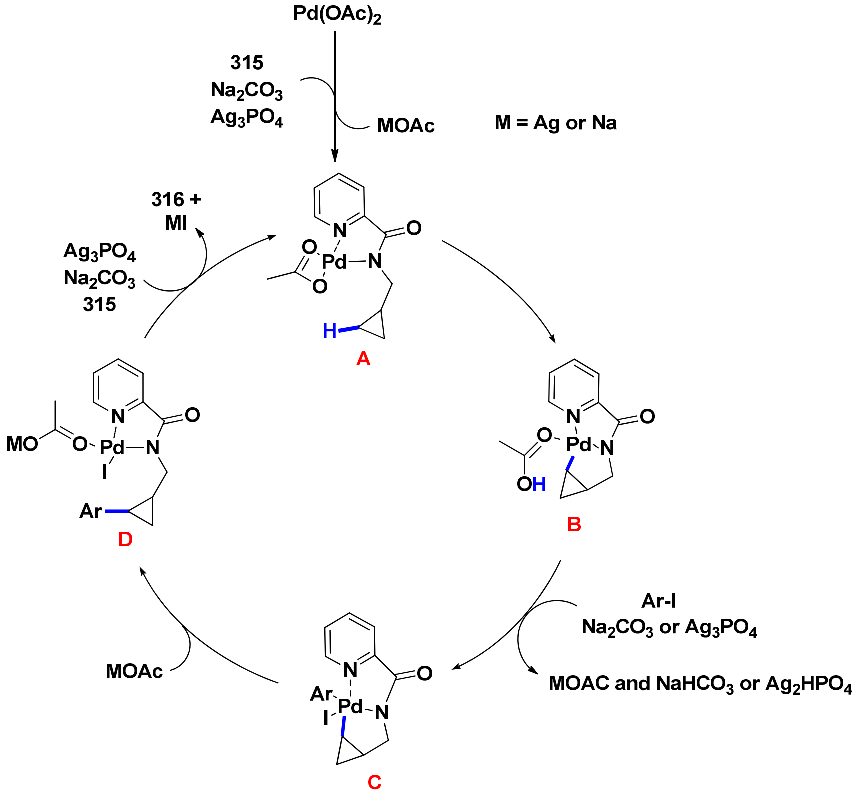
Moreover, a competition experiment between an electron donating and electron withdrawing *para*-substituted aryl iodide showed no significant preference for either product **316** or **325b** (**Scheme 124**).

**Scheme 124**. Competition experiment for the arylation of picolinamide **315**



Based on all the experimental results, as well previous mechanistic work from Daugulis[175] and Chen,[178] the following $Pd^{II/IV}$ mechanism was proposed for conditions **A** (**Scheme 125**). Coordination of $Pd(OAc)_2$ to the picolinamide **315** to give complex **A** occurs with loss of one acetate molecule. Then, the acetate-mediated concerted metalation-deprotonation provides complex **B**. Oxidative addition of the aryl iodide gives rise to a highly unstable $Pd^{IV}$ complex **C**, which undergoes reductive elimination to provide complex **D**. Loss of iodide mediated by $Ag_3PO_4$ or $Na_2CO_3$, product dissociation and coordination of $Pd^{II}$ to another picolinamide molecule closes the catalytic cycle. A $Pd^{II/III}$ pathway cannot be excluded.[37] A similar mechanism can be envisioned for condition **B**, except with pivalate instead of acetate, and $K_2CO_3$ as the base. Additionally, the silver salt may act as a base, halide sequester, oxidant (in case of $Pd^0$ sources), or form a bimetallic species with Pd.[191]

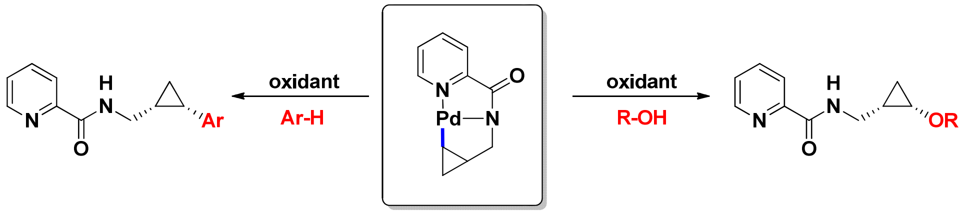
**Scheme 125**. Plausible mechanism



## 4.5 Further functionalizations

We sought to extend the current methodology to the formation of C-heteroatom bonds, as well as a direct oxidative coupling, as many of these reactions employing a cyclopropane are unreported or scarce in the literature (**Scheme 126**).[83]

**Scheme 126**. Proposed cyclopropane functionalizations

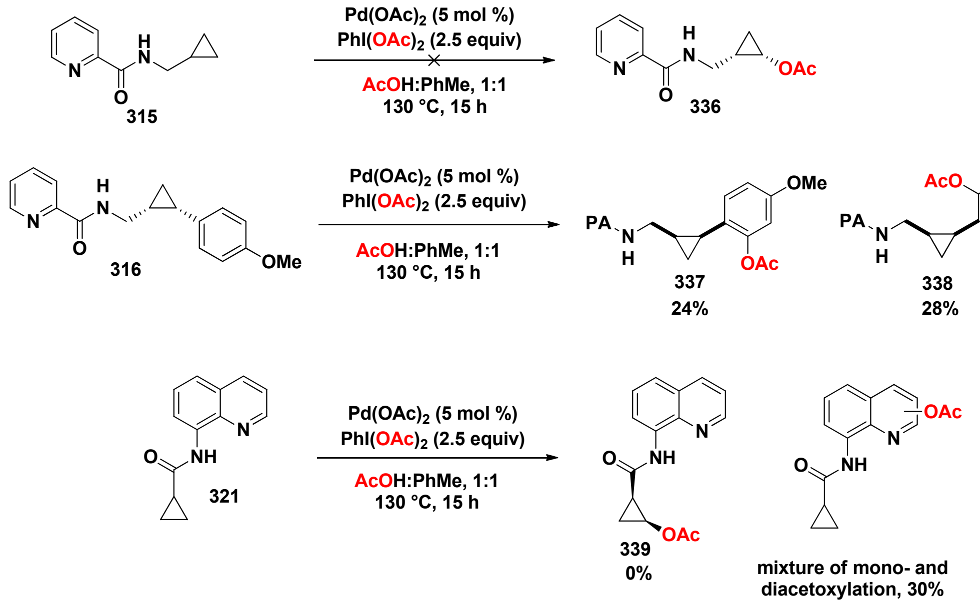


## 4.5.1 Formation of C–heteroatom bonds

C–H bond oxidation is an attractive area of research.[192] In particular, the development of general methods for the oxidation of $C(sp^3)$–H bonds has been the target in recent years.[14] Challenges associated with the type of transformation include regioselectivity and high potential for over-oxidation. Chen already established an oxidation protocol for a picolinamide-directed $C(sp^3)$–H bond oxidation using $PhI(OAc)_2$ as the oxidant (**Scheme 114**).[181] Under certain conditions, an oxidation followed by an intramolecular C–N bond formation also occurred. Earlier work from the Sanford group exploring the functionalization of cyclopropanes under oxidative conditions resulted in low yields, decomposition and lack of desired reactivity.[86a]

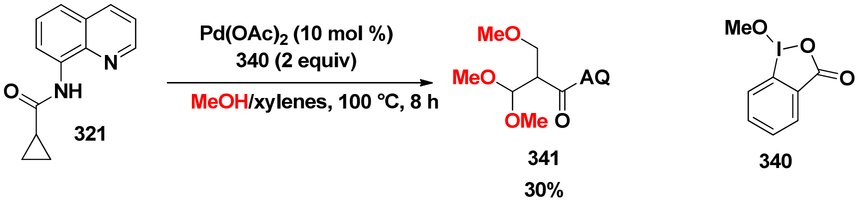
Inspired by Chen[181] and Sanford's[86a] work, the oxidation of cyclopropyl substrate **315** was pursued (**Scheme 127**). Unfortunately, extending the oxidation methodology to cyclopropanes proved challenging. No desired acetoxylation product was observed using $PhI(OAc)_2$ as the oxidant. Other oxidants (oxone, benzoquinone, potassium persulfate, Selectfluor) provided only unreacted starting material, while cerium ammonium nitrate gave mainly decomposition. Interestingly, when monoarylated cyclopropane **316** was submitted to the same oxidation conditions, mono and di-acetoxylation of the aryl ring were observed as the only products (**Scheme 127**). Moreover, attempts at acetoxylation of aminoquinoline **321** yielded a mixture of mono- and diacetoxylation of the quinoline ring in about 30%. The results clearly demonstrate how much more facile $sp^2$ versus $sp^3$ oxidation is.

**Scheme 127**. Attempts at acetoxylation of cyclopropane **315**



Furthermore, a recent publication by the group of Rao explored oxidations of similar picolinamide substrates employing cyclic hypervalent iodide reagents.[193] Although the reaction was robust for alkyl or cyclic alkyl substrates, employment of a cyclopropane resulted in ring-opening to provide **341** in 30% yield (**Scheme 128**).

**Scheme 128**. Oxidation of cyclopropane resulting in ring-opening

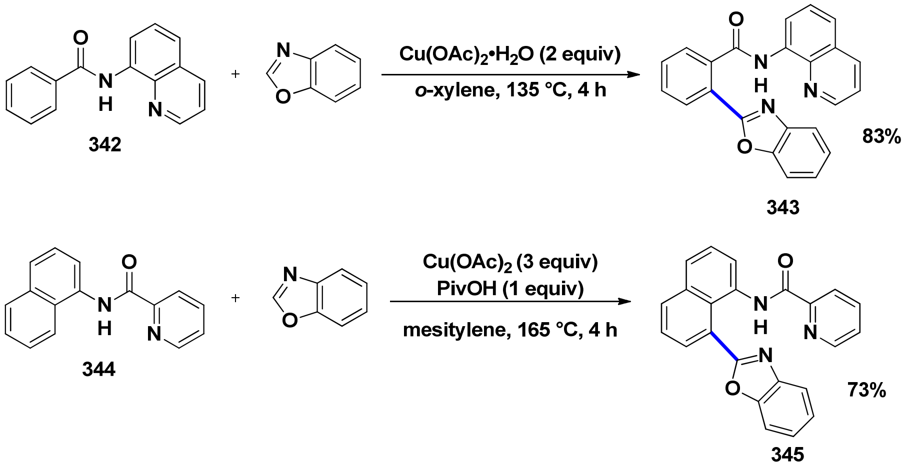


## 4.5.2 Cross-dehydrogenative coupling

From the point of view of atom economy, one drawback of the above methodology was the use of an aryl halide (a pre-functionalized coupling partner). The direct oxidative coupling between a cyclopropane C–H bond and an aryl C–H bond would be ideal. Such a reaction has been long established for the formation of aryl-aryl bonds,[8] but has yet to be reported for cyclopropanes. The use of the bidentate auxiliary in presence of a transition metal should facilitate the process through chelation to the metal centre and thus stabilization of cyclometalation intermediates. Moreover, the directing group should dictate the regioselectivity of the reaction; the reaction site is often problematic in the absence of a pre-functionalized coupling partner.

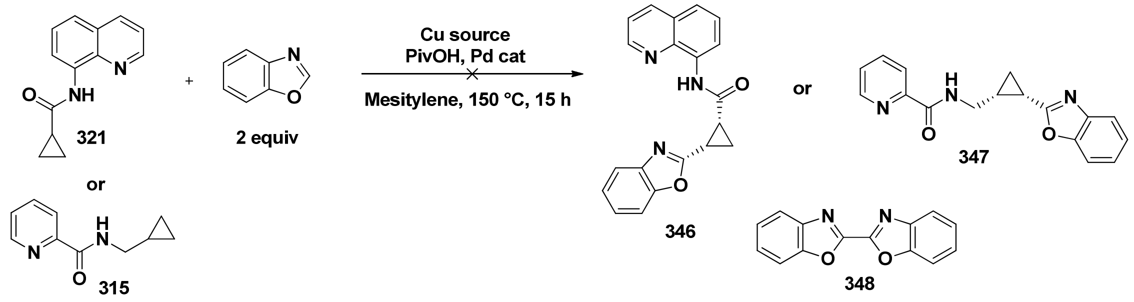
In 2013, Miura disclosed aminoquinolinamide **342** and picolinamide **344** directed cross-dehydrogenative coupling employing aryl C–H bonds only (**Scheme 129**).[194] The reactions employed copper acetate as the excess oxidant at high temperatures. The scope included azole-type heterocycles, due to the presence of an acidic hydrogen, thus avoiding regioselectivity issues.

**Scheme 129**. Miura's CDC using the aminoquinolamide auxiliary[194]



Attempting the reaction with the cyclopropyl substrates **315** and **321** under a variety of reaction conditions: various copper salts ($Cu(OAc)_2$, $Cu(OTf)_2$), additives (PivOH), catalysts ($Pd(OAc)_2$) never led to any desired product formation, even when heating to 150 °C for extended periods of time (**Scheme 130**). The only product detected was the benzoxazole dimer **348**. Additionally, no coupling with the toluene solvent was observed by LC-MS.

**Scheme 130**. Attempts at CDC on cyclopropanes

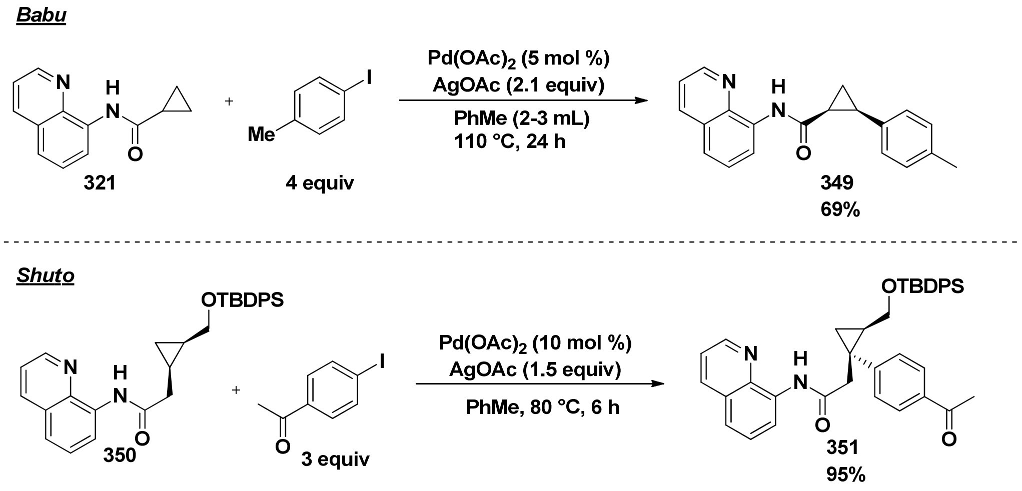


Overall, the oxidation of cyclopropyl C–H bonds has proven a more ambitious project than initially anticipated. Cyclopropanes did not behave as their alkyl or aryl counterparts under similar reaction conditions, thus underlying the difficulty of developing conditions for cyclopropane functionalizations.

## 4.5.3 Related work

During the preparation of our manuscript, a similar publication appeared in *Organic Letters*. The group of Babu showed that the aminoquinoline auxiliary **321** could be employed for C–H activation of cyclopropanes with excess aryl iodide under palladium catalysis (**Scheme 131**).[195] Later, the group of Shuto demonstrated that quaternary centers could be synthesized in good yields in presence of the bidentate aminoquinoline auxiliary **349** (**Scheme 131**).[196]

**Scheme 131**. Babu and Shuto's intermolecular direct arylation of cyclopropanes



## 4.6 Conclusion

In summary, a methodology for the intermolecular arylation of cyclopropanes was established. Two reaction conditions were developed, involving either $Ag_3PO_4$ and $Na_2CO_3$ or PivOH and $K_2CO_3$ in presence of catalytic $Pd(OAc)_2$. Key to the reactivity was the employment of a *N,N*-bidentate auxiliary which formed a kinetically-favoured five-membered cyclometalated complex able to activate the cyclopropane bond via concerted-metalation deprotonation. The deuteration studies suggested that the C–H activation step occurred prior to oxidative addition of the aryl halide for $Pd^{II}$ sources. $Pd^0$ sources with easily dissociative ligands could also be employed as catalysts; it was hypothesized that either the silver salt acted as an oxidant for Pd, or oxidative addition occurred initially. The reaction was compatible with a variety of aryl and heteroaryl iodides. Moreover, extension of the oxidative conditions for $sp^3$ centers to cyclopropanes was not successful, demonstrating the requirement for novel approaches for cyclopropane C–H functionalization.

# Chapter 5: Potassium *tert*-butoxide mediated intramolecular homolytic aromatic substitution

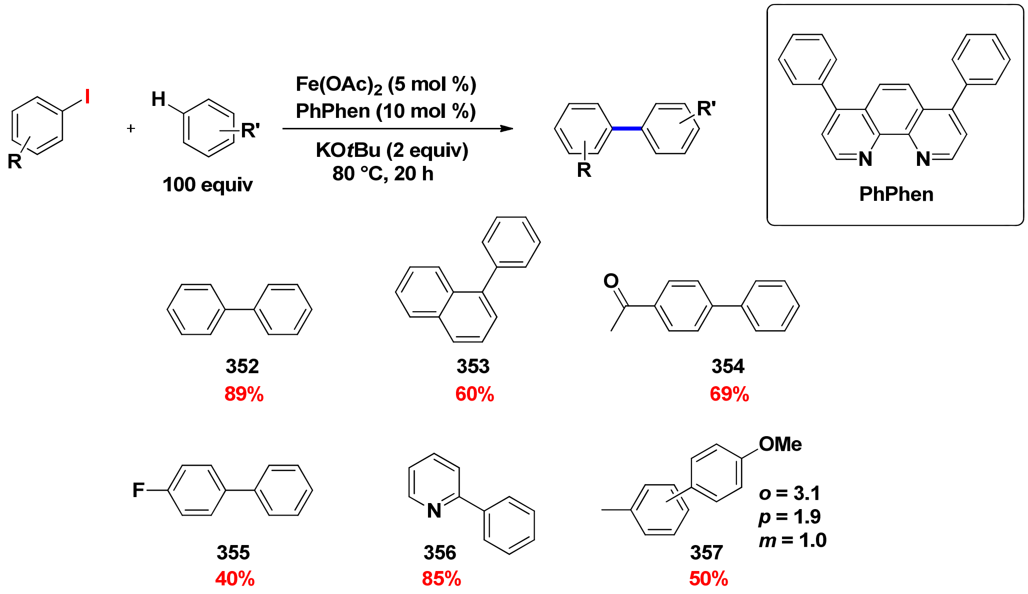
Reference: Sustac Roman, D.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3242.

## 5.1 Introduction

### 5.1.1 Fe-catalyzed direct arylation

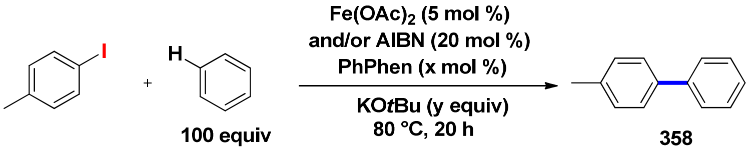
In an effort to develop more eco-friendly methodologies for direct functionalizations, the Charette group disclosed an iron-catalyzed intermolecular biaryl formation.[197] Iron is the most abundant element in the Earth's crust, is inexpensive and possesses low toxicity.[198] While iron catalysis in cross-couplings is well-established,[199] its use in direct transformations is relatively unexplored.[187] Thus, in the presence of 5 mol % $Fe(OAc)_2$, 10 mol % bathophenanthroline (PhPhen) and two equivalents KO*t*Bu at 80 °C, aryl iodides could be coupled with a variety of arenes in good to excellent yields (**Scheme 132**). If the arene was unsymmetrical, a mixture of *ortho*, *meta*, and *para* biaryls **357** were isolated, with *ortho* substitution being the major product.

**Scheme 132**. Selected scope of Fe-catalyzed arylation[197]



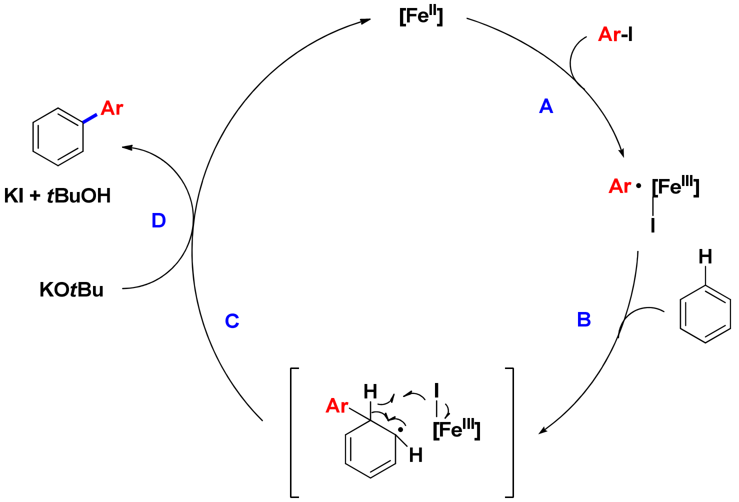
The intermolecular KIE of the reaction was determined to be 1.04, suggestive of a radical pathway.[197] The addition of radical scavengers such as TEMPO or galvinoxyl shut down the reaction. Control reactions determined no conversion in the absence of the iron catalyst (**Table 24**, entry 2). Additionally, replacing the catalyst with the known radical initiator AIBN (20 mol %) gave an almost stoichiometric amount of product, relative to AIBN (entry 3). In absence of the base, but presence of iron salt and AIBN, there was no reaction (entry 4), highlighting the necessity of the base for radical generation and propagation.

**Table 24**. Control reactions[197]



| entry | catalyst | PhPhen (x) | KO*t*Bu (y) | yield **358** (GC-MS) |
|---|---|---|---|---|
| 1 | $Fe(OAc)_2$ | 10 | 2 | 91% |
| 2 | none | 10 | 2 | <1% |
| 3 | AIBN | none | 2 | 17% |
| 4 | $Fe(OAc)_2$ + AIBN | 10 | none | <1% |

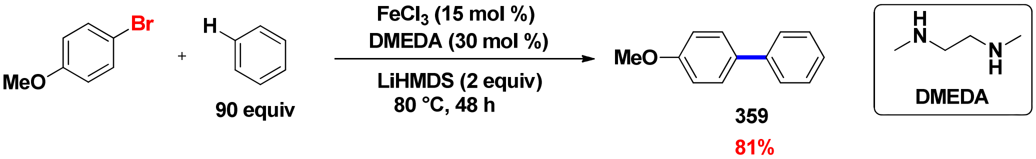
**Scheme 133**. Plausible mechanism for Fe-catalyzed biaryl formation[197]



Based on all the observations, the above mechanism was proposed for the reaction (**Scheme 133**).[197] A one-electron oxidation from the metal centre activates the aryl halide to form a radical arene, presumably associated to an $Fe^{III}$ species (step **A**). Then, the radical attacks the unactivated arene (step **B**). Rearomatization occurs by proximal proton abstraction of the iodine (step **C**), releasing HI, which may be quenched by the base (step **D**), and regeneration of the iron catalyst. However, a different role for the butoxide base could not be ruled out.

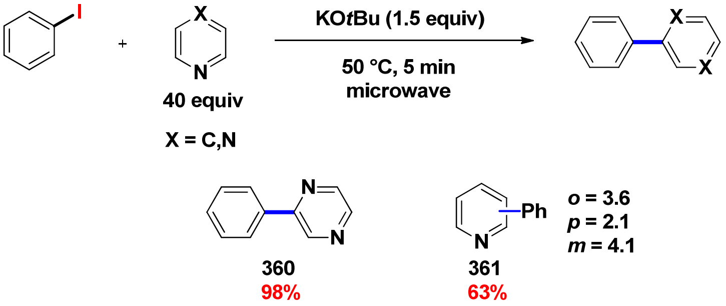
Shortly after, a similar publication appeared from the group of Lei.[200] In their case, aryl iodides, bromides and even chlorides could be coupled with excess unactivated arenes in presence of 15 mol % $FeCl_3$, 30 mol % DMEDA (dimethylenediamine) and two equivalents LiHMDS as the base at 80 °C (**Scheme 134**). The authors ruled out a benzyne pathway based on the regiochemistry of the reaction. A KIE of 1.7 was calculated for the transformation.

**Scheme 134**. Lei's Fe-catalyzed arylation of aryl bromides[200]



Prior to our investigation of the current project, there was one other intriguing report in the literature which employed a strong base for biaryl synthesis. In 2008, the group of Itami disclosed KO*t*Bu-mediated coupling of aryl halides with excess electron-deficient heteroarenes under microwave conditions (**Scheme 135**).[201] The authors hypothesized a radical mechanism, HAS or $S_{RN}1$ (discussed in Section 1.4), as performing the reaction in the presence of well-known radical scavengers provided no product.

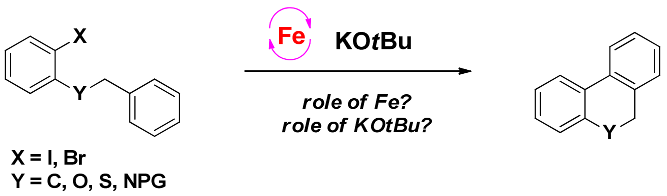
**Scheme 135**. Itami's KO*t*Bu-mediated arylation of heteroarenes[201]



## 5.1.2 Research goal

Several arylation strategies have already been presented in this thesis, all employing rather expensive Pd or Ru catalysts (Chapters 2-4). In order to develop a more sustainable process, a transformation employing a more available and less costly catalyst was investigated. After the development of the Fe-catalyzed biaryl formation by former group members Frédéric Vallée and James Mousseau,[197] an intramolecular version of the reaction was pursued (**Scheme 136**). The reaction would be complimentary to some of Fagnou's Pd-catalyzed work (**Scheme 3**, *vide supra*). Another goal was to elucidate the role of the iron catalyst and the *tert*-butoxide base.

**Scheme 136**. Development of an intramolecular arylation reaction



Additionally, the resulting cyclized products (benzopyran, phenanthrene, phenanthridine, phenanthridinone) have many applications in medicinal chemistry and materials synthesis. In particular, phenanthridine and phenanthridinone motifs are part of the core of many alkaloid natural products, including nitidine and fagaronine (anti-cancer properties), parnafungin A (anti-fungal properties), or as the core of current medicinal chemistry targets (**Figure 16**).[202]

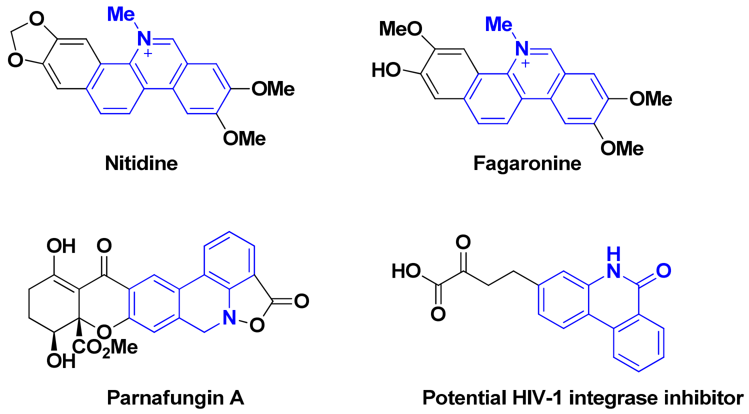


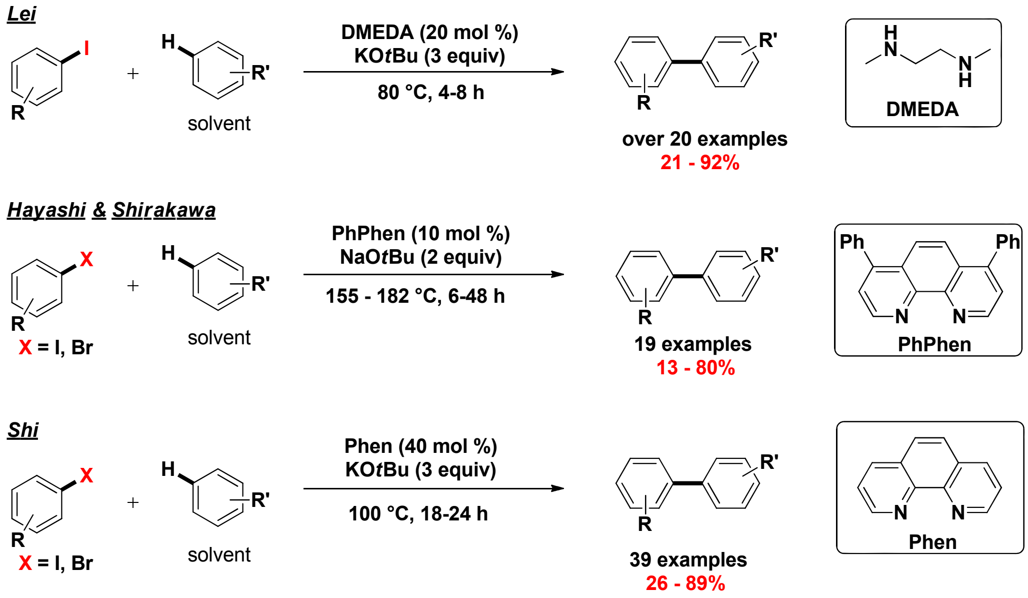
**Figure 16**. Bioactive phenanthridines and phenanthridones[202]

### 5.1.3 Concomitant work

Before launching into the results and discussion of the project, it is necessary to describe some of the related work that appeared in the literature concomitant with our own studies. Undoubtedly, the results presented below have greatly influenced the direction of the current project.

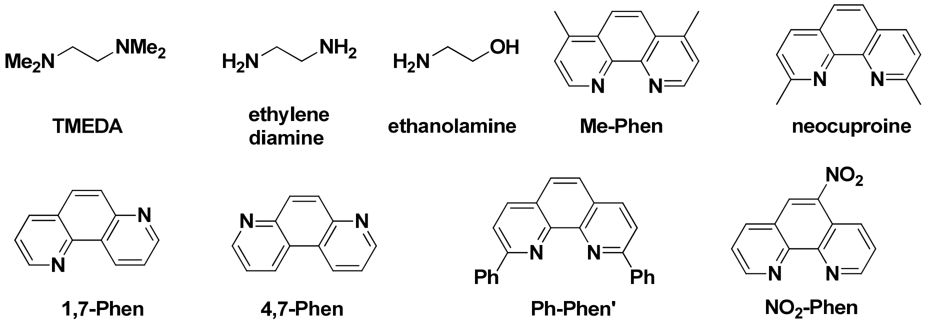
After disclosing the Fe-catalyzed biaryl formation (**Scheme 134**), the group of Lei described a similar transition metal-free transformation occurring in the presence of 20 mol % DMEDA and three equivalents KO*t*Bu as the base at 80 °C (**Scheme 137**).[203] The authors referred to the transformation as "organocatalysis" and "a striking breakthrough to the frame of traditional cross-coupling/C–H functionalizations."[203] Hayashi and Shirakawa also disclosed biaryl formation in the presence of two equivalents NaO*t*Bu and 10 mol % bathophenanthroline at high temperatures (155 °C).[204] The group of Shi revealed biaryl synthesis in presence of 0.4 equivalents phenanthroline and three equivalents KO*t*Bu at 100 °C.[205] The latter authors also described the reaction in terms of organocatalysis. Compared to the earlier conditions developed by our group,[197] each of these transition metal-free reactions employed either higher temperatures or larger loadings of the base/organocatalyst.

**Scheme 137**. Transition metal-free arylations[203-205]



A summary of the catalyst and base screen from the three reports above is given in **Table 25**. The strong base KO*t*Bu (pKa of conjugate acid 17) was highly reactive in all three cases, although NaO*t*Bu was chosen by Hayashi and Shirakawa.[204] Interestingly, Lei's work reports no reaction with NaO*t*Bu,[203] while Shi's paper does not report a base screen.[205] Weaker bases (such as $Na_2CO_3$, or KOAc) and even other stronger bases (LiO*t*Bu, LiHMDS, NaH, NaOH, KOH) were found unreactive, implying a special role for the *tert*-butoxide anion and $K^+$ or $Na^+$ as counterions. In terms of organocatalysts, *N*-based, bidentate ligands worked best. Lei reports that pyridine or pyrazine did not work, while both Lei and Hayashi found bipyridine and TMEDA (tetramethylethylenediamine) unreactive.[203,204] Shi's group reports no reactivity with DMEDA and aryl bromides,[205] while DMEDA was the catalyst of choice for Lei's work with aryl iodides.[203] Hayashi and Shirakawa screened phenanthroline derivatives having nitrogens at the 1,7 or 4,7-positions, but these were found ineffective.[204]

**Table 25**. Summary of catalyst and base screen for transition metal-free arylations[203-205]

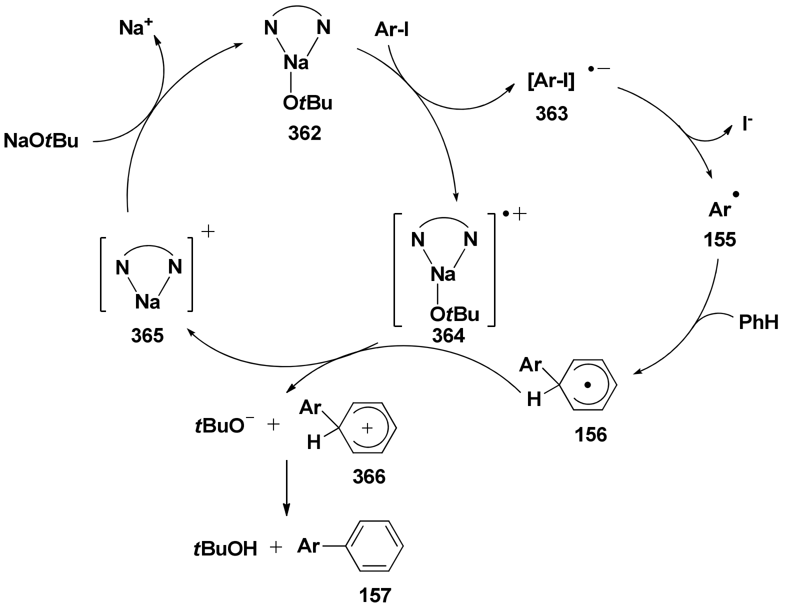


| Group | Organocatalyst (+)[a] | Organocatalyst (-)[a] | Base (+)[a] | Base (-)[a] |
|---|---|---|---|---|
| Lei[203] | **DMEDA**<br>L-proline<br>ethylene diamine<br>ethanolamine<br>*cis*-cyclohexane-1,2-diol | bipyridine<br>TMEDA<br>pyridine<br>pyrazine | **KO*t*Bu** | NaO*t*Bu<br>LiO*t*Bu<br>LiHMDS<br>NaH, KOH<br>$Na_2CO_3$ |
| Hayashi & Shirakawa[204] | **PhPhen**<br>Phen<br>Me-Phen | bipyridine<br>TMEDA<br>1,7-Phen<br>4,7-Phen<br>Ph-Phen' | **NaO*t*Bu**<br>KO*t*Bu | LiO*t*Bu<br>NaOH<br>$Na_2CO_3$<br>$Bu_3N$ |
| Shi[205] | **Phen**<br>PhPhen<br>neocuproine | DMEDA<br>$NO_2$-Phen | **KO*t*Bu** | N/A |

[a] (+): >30% yield, (-): <30% yield (or unreactive)

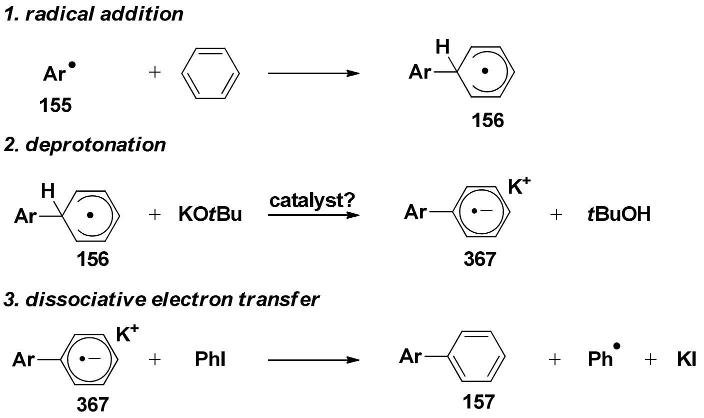
Furthermore, running the reaction in presence of radical scavengers provided no product in all three cases. Hayashi determined a KIE of 1.07,[204] and Shi of 1.1.[205] In cases where a mixture of biaryl isomers was possible, the major isomer was *ortho*. All of the observations led the authors to suggest a radical mechanism for the transformation. A plausible mechanism for the reaction via a homolytic aromatic substitution pathway was proposed by Hayashi and Shirakawa (**Scheme 138**).[204] Interaction between the base and catalyst was thought to provide complex **362**, responsible for a single-electron transfer to the aryl iodide, giving rise to a radical anion **363** and a radical cation **364**. After loss of iodide, aryl radical **155** added to benzene, to give cyclohexadienyl radical **156**. A single-electron oxidation of radical **156** by the radical cation **364** produced aryl cation **366**. Intermediate **366** was deprotonated by *tert*-butoxide to give the product, **157**, and *tert*-butanol. Complex **362** was regenerated through reaction of **365** (or free PhPhen) with NaO*t*Bu.[204] An interaction between the base, phenanthroline catalyst and benzene substrate was also suggested by Shi and co-workers; π-π or $K^+$-π interactions were proposed to promote the reaction.[205]

**Scheme 138**. Hayashi and Shirakawa's proposed HAS mechanism for transition metal-free arylation[204]



Studer and Curran discussed the findings in a subsequent essay.[12] The authors suggested that instead of referring to the transformations as "organocatalysis," a better explanation was "base-promoted homolytic aromatic substitution" via a chain mechanism (**Scheme 139**). The propagation mechanism involves attack of an aryl radical **155** onto an arene to give cyclohexadienyl radical **156** (step 1), which gets deprotonated by KO*t*Bu to give a radical anion **367**, a powerful reducing agent (step 2). Radical anion **367** is able to transfer an electron to another aryl iodide to provide the biaryl product **157**, aryl radical **155** and KI (step 3). The electron-transfer step takes place via an outer-sphere (dissociative) pathway, meaning the aryl radical is short-lived. The main differences between the mechanism proposed by Hayashi and Shirakawa[204] and the current one are that the former is not a chain mechanism and the order of the electron-transfer/proton-transfer steps.

**Scheme 139**. Base-promoted HAS: chain mechanism proposed by Studer and Curran[12]

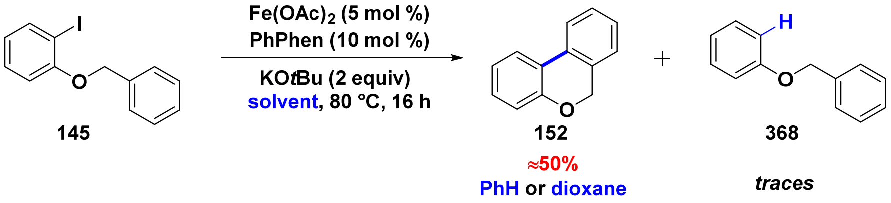


## 5.2 Results and discussion

### 5.2.1 Reaction optimization

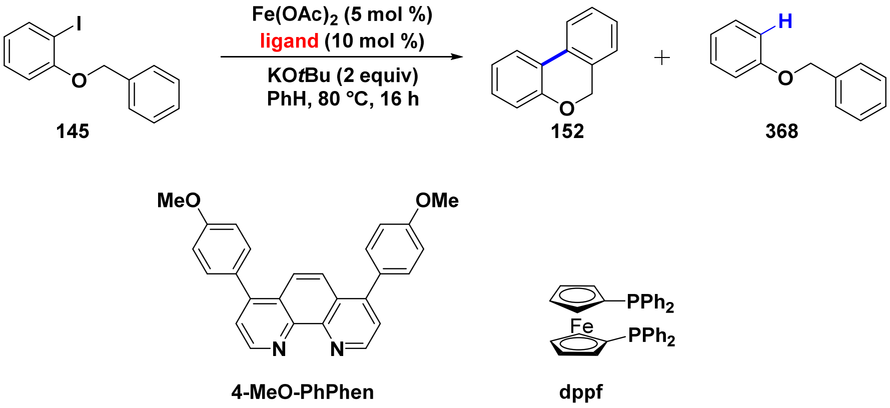
Initially, iodobenzylether **145** was cyclized under the Fe catalysis conditions previously established by our group (**Scheme 140**).[197] Employing either benzene or dioxane as the solvent at 80 °C, benzopyran **152** was observed in about 50% yield, along with traces of dehalogenation **368**.

**Scheme 140**. Initial studies for Fe-catalyzed intramolecular arylation



The optimization of the reaction was pursued on iodobenzylether **145** with a ligand screen (**Table 26**). PhPhen provided the best yield (45%, entry 1), while Phen provided 38% desired product **152** (entry 3). Another Phen-type ligand (4-MeO-PhPhen) containing two EDG substituents afforded an improved yield (53%, entry 4). Other ligands such as bipyridine, ethylenediamine, *cis*-cyclohexane-1,2-diol, ethanolamine provided the product in much lower yields (entries 5-8). DMEDA, Lei's catalyst of choice, resulted in only 6% yield of **152** (entry 9), while TMEDA gave almost no conversion (entry 10). One phosphine, dppf, was also unreactive under the reaction conditions (entry 11). Although 4-MeO-PhPhen gave the best yield, the optimization was continued with PhPhen (or Phen) as these are commercially available.

**Table 26**. Ligand screen for Fe-catalyzed intramolecular arylation



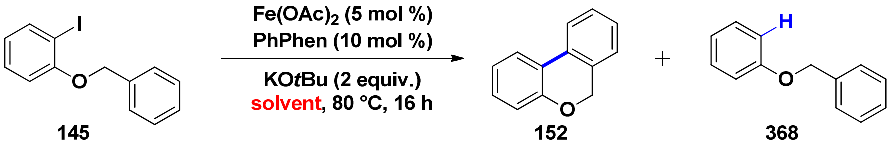
| entry | ligand | yield[a] (%) 145 | 152 | 368 |
|---|---|---|---|---|
| 1 | **PhPhen** | 34 | **45** | 2 |
| 2[b] | PhPhen | 70 | 19 | 1 |
| 3 | Phen | 61 | 35 | 2 |
| 4 | **4-MeO-PhPhen** | 35 | **53** | 3 |
| 5 | bipyridine | 77 | 9 | <2 |
| 6 | ethylenediamine | 75 | 14 | 2 |

| | | | | |
|---|---|---|---|---|
| 7 | *cis*-cyclohexane-1,2-diol | 60 | 28 | <2 |
| 8 | ethanolamine | 56 | 27 | 4 |
| 9 | DMEDA | 85 | 6 | 0 |
| 10 | TMEDA | >95 | <5 | 0 |
| 11 | dppf | >95 | <5 | 0 |

[a] $^{1}$H NMR yield using trimethoxybenzene as internal standard. [b] KO*t*Bu (3 equiv)

Next, the solvent and other parameters were screened (**Table 27**). Dioxane provided the product in only 21% yield (entry 1) versus benzene in 45% yield (entry 2). Increasing the amount of ligand to 30 mol % in the reaction resulted in improved conversion and provided benzopyran **152** in 64% yield (entry 3). The breakthrough came when pyridine was employed as solvent. Iodoarene **145** was completely consumed in the reaction to provide **152** in 80%, along with 9% debrominated ether **368** (entry 4). To our surprise, *similar yields were observed in the absence of the iron catalyst (entry 5).*

**Table 27**. Screen of reaction parameters for the intramolecular cyclization



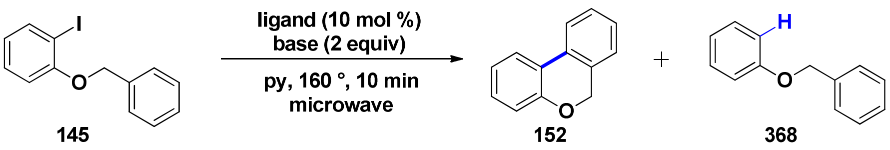
| entry | solvent | yield[a] (%) | | |
|---|---|---|---|---|
| | | **145** | **152** | **368** |
| 1 | dioxane | 67 | 21 | 2 |
| 2 | PhH | 34 | 45 | 2 |
| 3[b] | PhH | 18 | 64 | 8 |
| 4 | pyridine | <1 | **80** | 9 |
| *5*[c] | *pyridine* | *12* | ***79*** | *4* |

[a] $^{1}$H NMR yield using trimethoxybenzene as internal standard. [b] PhPhen 30 mol %. [c] No Fe(OAc)$_2$.

*Having confirmed that the intramolecular cyclization of iodobenzyl ether **145** occurred in the absence of an iron catalyst*, the optimization of the transition metal-free transformation was continued. In order to improve the reaction conditions, the optimization was pursued under microwave irradiation.[206] Use of a microwave enabled the reaction time to be shortened to 10 min, at a temperature of 160 °C. Moreover, the PhPhen ligand could be replaced by the less expensive phenanthroline (**Table 28**, entry 1). Under the new conditions, ***the reaction even occurred in the absence of any ligand/organocatalyst*** (entry 2)! However, the yield dropped to 50%. In the absence of both base and phenanthroline, there was no reaction (entry 3). Other *tert*-butoxide bases tested under the ligand-free conditions provided only unreacted

**145** (entries 4-5). The HMDS bases gave complete conversion, but mostly dehalogenated material **368** (entries 6-7), with the exception of KHMDS, which provided 25% product (entry 8). A weak base, $K_2CO_3$, was completely unreactive (entry 9). It should also be noted that the reaction was performed with KO*t*Bu that was purified via sublimation, and no difference in the yield was observed to the unsublimed version. Both sublimed and unsublimed KO*t*Bu were checked for metal contaminants via ICP-AES analysis, but no metal contaminants were discovered.

**Table 28**. Optimization of the Fe-free arylation under microwave conditions[a]



| | | | yield[a] (%) | | |
|---|---|---|---|---|---|
| entry | organocatalyst | base | **145** | **152** | **368** |
| *1* | *Phen* | *KOtBu* | ***<1*** | *77* | ***4*** |
| *2* | --- | *KOtBu* | ***20*** | ***50*** | ***18*** |
| 3 | --- | --- | >95 | 0 | 0 |
| 4 | --- | LiO*t*Bu | >95 | 0 | 0 |
| 5 | --- | NaO*t*Bu | >95 | 0 | 0 |
| 6 | --- | LiHMDS | <1 | 0 | 81 |
| 7 | --- | NaHMDS | <1 | 0 | 64 |
| 8 | --- | KHMDS | <1 | 25 | 60 |
| 9 | --- | $K_2CO_3$ | >95 | 0 | 0 |

[a] $^1$H NMR yield using trimethoxybenzene as internal standard.

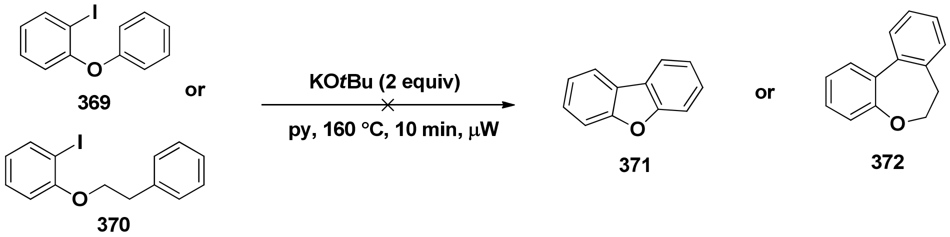
### 5.2.2 Reaction scope

The scope of the reaction was explored with the help of a postdoc in the group, Dr. Yoko Takahashi, who was involved in synthesizing some starting materials, as well as performing some of the cyclizations and helping with the mechanism determination. All the reactions were performed with freshly sublimed KO*t*Bu.

The ring size of the cyclization was evaluated under the metal-free, ligand-free conditions (**Scheme 141**). Unfortunately, no five-membered or seven-membered products **371** or **372** were formed. Instead, iodoarene **369** underwent coupling with pyridine as the major product (dehalogenation was also observed), while iodoarene **370** decomposed to 2-

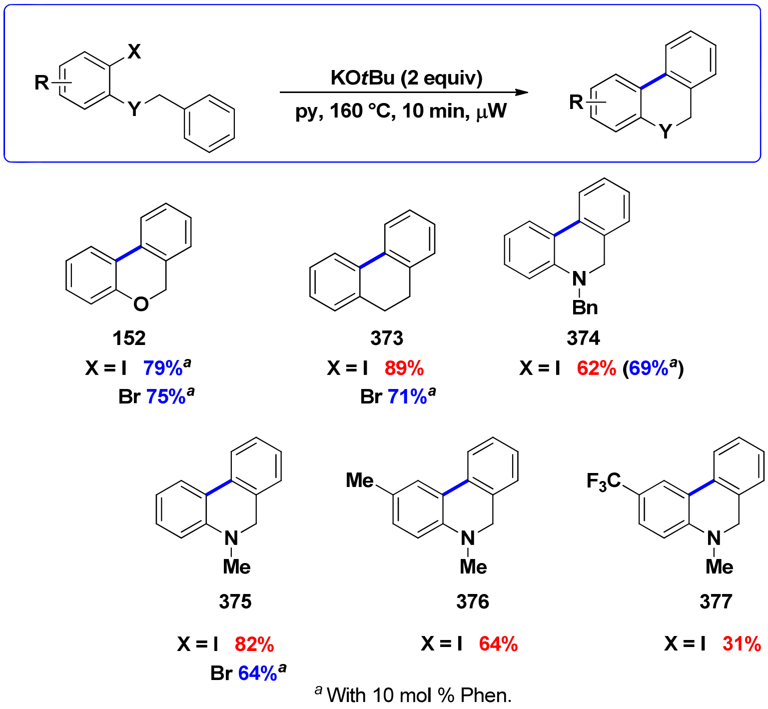
iodophenol. In contrast, similar five-membered or seven-membered rings are accessible via Pd-catalysis.[16,17]

**Scheme 141**. Evaluation of ring size for the intramolecular cyclization



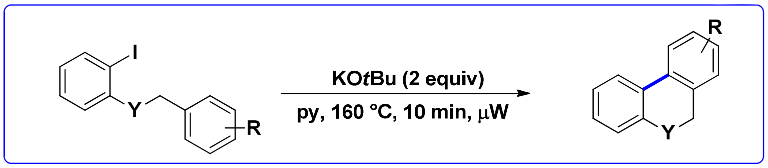
To continue the scope, both iodide and bromide analogues of **145** underwent cyclization to provide **152** in good yields in presence of 10 mol % Phen (**Scheme 142**). Other classes of substrates besides ethers were also tested. An all-carbon tether provided the desired product **373** in 89% yield starting from the iodide, ***in the absence of Phen***. The corresponding bromide could also be cyclized in 71% yield in presence of catalytic Phen (the reaction works in absence of Phen, but in a diminished yield). Incorporation of a nitrogen atom in the tether allowed for the isolation of the corresponding phenanthridine **375** in 82% yield, ***in the absence of Phen***, while the corresponding bromide resulted in 64% yield, with 10 mol % Phen. A benzyl protected iodoaniline also worked in the cyclization, providing **374** in 62% isolated yield, in presence of Phen. Other protecting groups tested, Piv and Cbz, resulted in decomposition in the presence of the strong base KO*t*Bu. Substitution on the aryl halide ring was also possible, a Me group being well tolerated in 64% of **376**, while $CF_3$ gave a poor yield, 31% of **377**. In general, aryl iodides cyclized well ***in the absence of phenanthroline***, with the exception of ether substrates, while the corresponding bromides provided better yields in presence of 10 mol % phen.

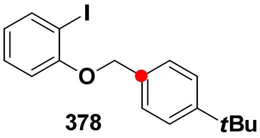
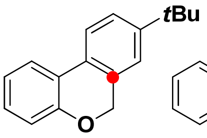
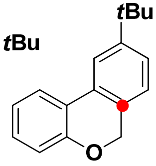
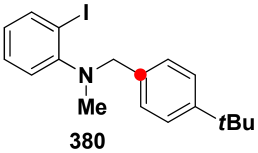
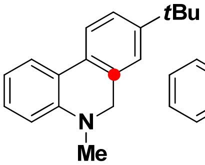
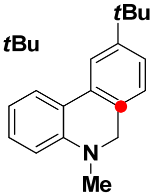
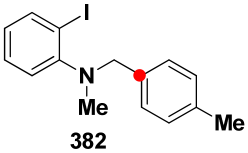
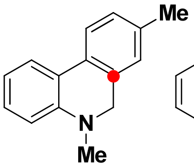
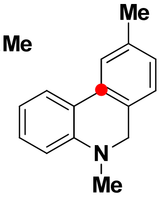
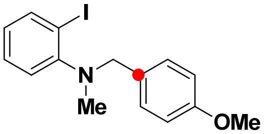
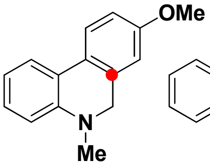
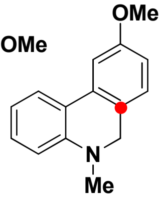
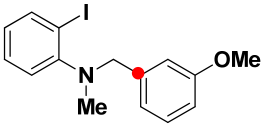
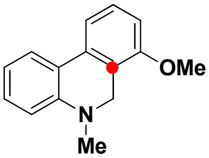
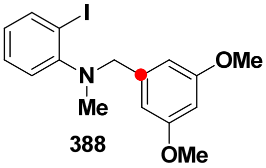
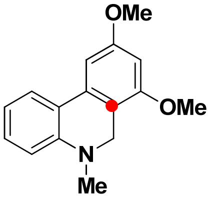
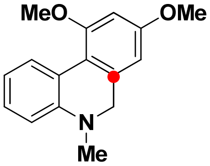
**Scheme 142**. Scope evaluation of the KO*t*Bu-promoted cyclization

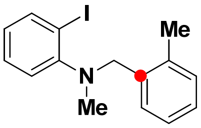
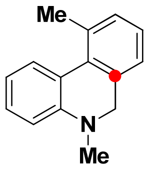
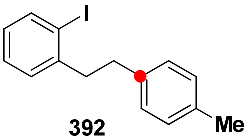
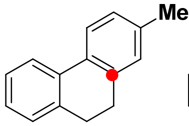
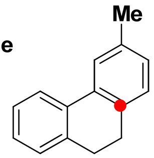


Furthermore, substitution on the benzyl moiety of the aryl system was also explored (**Table 29**). In most cases, a mixture of regioisomeric products was observed (structures were confirmed via 1D nOe). *p-tert*-Butyl-substituted aryl ether **378** cyclized to give a 5:1 mixture of two regioisomers, **379a** and **379b** in 88% yield (entry 1). An analogous *N*-methyl aniline **380** exhibited the same trend, with an even better regioisomeric ratio (10:1, entry 2). *p*-Methyl and *p*-methoxy-substituted aniline derivatives **382** and **384** also provided the corresponding phenanthridines **383a/b** and **385a/b** in good yields and ratios (entries 3 and 4). Substitution in the *meta* position gave rise to major isomer **387a** in 67% yield, along with traces of an unidentified minor isomer (entry 5). Di-methoxy-substituted aniline **388** yielded a 7:1 mixture of products in 62% yield (entry 6). The reaction was sensitive to sterics, as the *ortho*-susbtituted aniline **390** cyclized in only 25% yield (entry 7). Lastly, *p*-Me-substituted carbon analogue **392** reacted in 92% yield to give a 2.3:1 mixture of isomers (entry 8). Interestingly, the major isomer was opposite to what was observed with the other *para*-substituted substrates.

**Table 29**. Scope of the benzyl ether



| entry | arene | products | yield[a] (ratio a:b) |
|---|---|---|---|
| 1 |  **378** |  **379a**  **379b** | 88% (5:1)[b] |
| 2 |  **380** |  **381a**  **381b** | 86% (10:1) |
| 3 |  **382** |  **383a**  **383b** | 82% (>15:1) |
| 4 |  **384** |  **385a**  **385b** | 83% (10:1) |
| 5 |  **386** |  **387a** | 67% |
| 6 |  **388** |  **389a**  **389b** | 62% (7:1) |

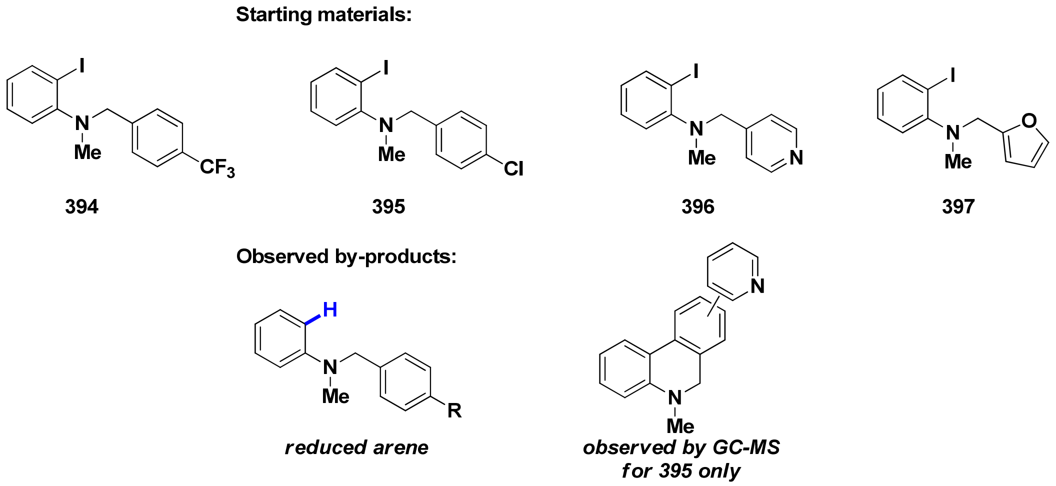
| | | | |
|---|---|---|---|
| 7 |  **390** |  **391a** | 25% |
| 8 |  **392** |  **393a**  **393b** | 92% (1:2.3) |

---

[a] Isolated yields on 0.5 mmol. In certain cases, traces of the reduced arene were observed. [b] With 10 mol % Phen.

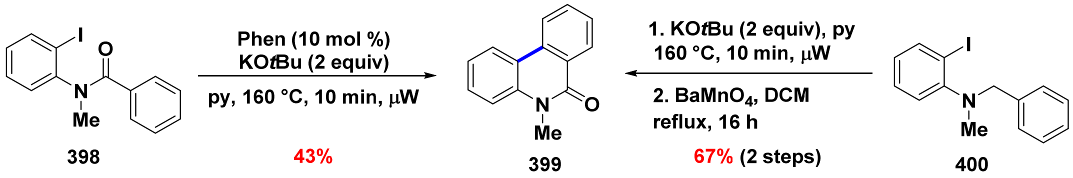
The reaction was found sensitive to substitution by electron withdrawing groups ($CF_3$) or heterocycles (pyridine, furan), as these resulted in decomposition and some reduced arene (20% in case of **396**) (**Scheme 143**). *para*-Chloride **395** provided some decomposition, but also a low yielding (<25%) mixture of product, reduced arene and replacement of the chloride by pyridine in the cyclized product (mass observed by LC-MS).

**Scheme 143**. Substrates that resulted in decomposition/reduced arene



Phenanthridone **399** can also be cyclized from the corresponding amide **398**, albeit in a low yield (43%,**Scheme 144**). An alternative, better yielding, two-step procedure to aceess phenanthridones is the cyclization of aniline **400**, followed by oxidation with barium manganate (67% over two steps).

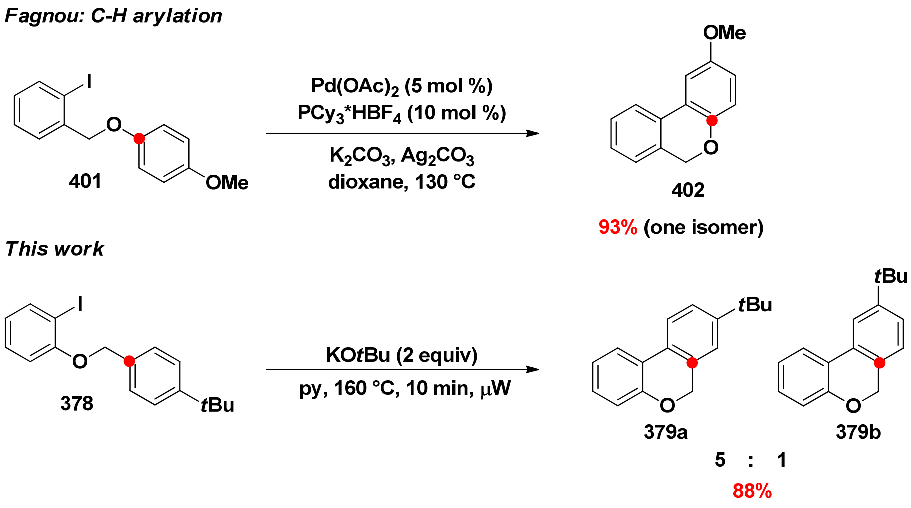
**Scheme 144**. Access to phenanthridone **399** via two routes



## 5.2.3 Mechanistic studies

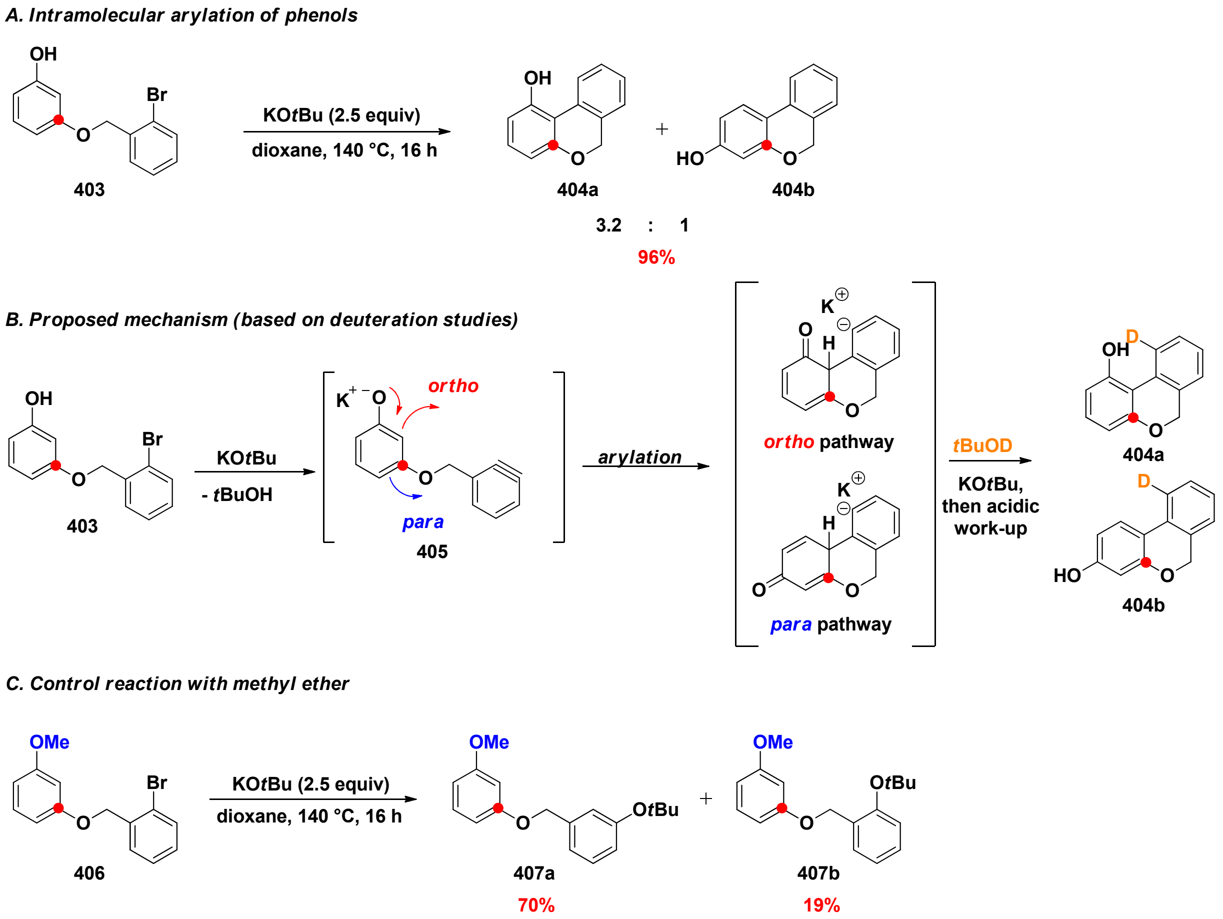
The most surprising discovery during the scope evaluation was the isolation of regioisomeric products when substitution was present on the benzyl moiety (**Table 29**). In their intramolecular C–H arylation studies on similar starting materials, the group of Fagnou isolated only one product, **402** (**Scheme 145**).[17] Furthermore, benzopyran **402** corresponded to the minor product isolated in our work, **379b**. In addition to the aforementioned observation, the absence of a transition metal in our optimized reaction conditions, along with use of a strong base at elevated temperatures, led us to reject a C–H activation pathway.

**Scheme 145**. Comparison of Fagnou's cyclization with the KO*t*Bu-promoted intramolecular arylation



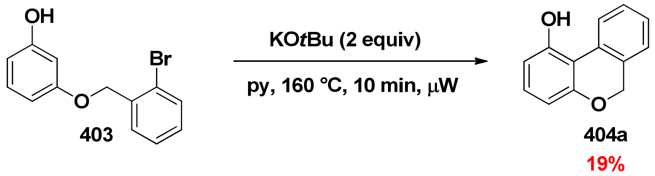
The formation of regioisomeric products in presence of a strong base was perhaps more reminiscent of a benzyne pathway.[207] Bajracharya and Daugulis reported the KO*t*Bu-mediated intramolecular arylation of phenols and proposed a benzyne pathway for the transformation (**Scheme 146**).[208] Employing aryl bromides, a 3.2:1 mixture of regioisomeric products **404a** and **404b** was isolated. It was speculated that the reaction proceeded through the initial formation of a benzyne intermediate **405** in presence of the strong base at 140 °C. Cyclization of intermediate **405** occured either via *ortho* or *para* attack with respect to the potassium phenolate. Subsequent protonation by *t*BuOH and aromatization lead to the formation of products **404a** and **404b**. When deuterated *t*BuOD was added to the reaction, D was incorporated at the C-10 position in both products **404**, thus confirming the benzyne pathway. Moreover, a control reaction employing methyl ether **406** did not produce any cyclization product, only trapping of benzyne by an external nucleophile (*t*BuO$^{-}$) to provide a 3.7:1 mixture of **407a**:**407b** (**Scheme 146C**).

**Scheme 146**. Daugulis' work A. Intramolecular arylation of phenols B. Proposed mechanism C. Control reaction with methyl ether[208]



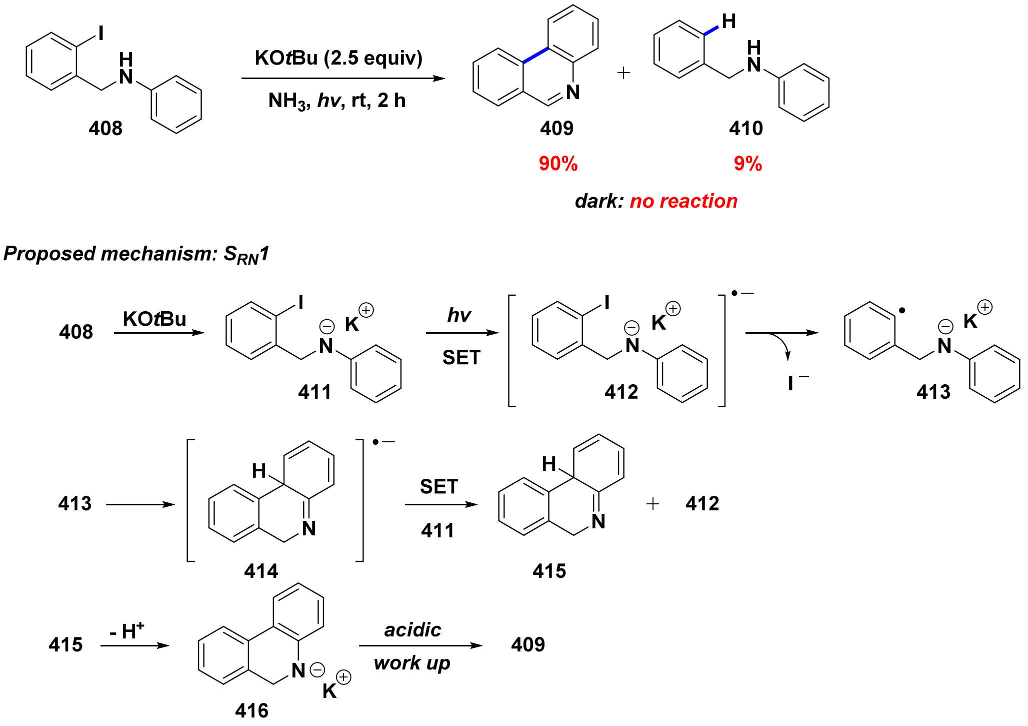
To test if cyclization via a benzyne pathway was occurring in our reaction system, benzyl ether **403** was cyclized under the optimized microwave conditions (**Scheme 147**). Only one isomer, *"ortho"* **404a** was isolated in 19%, along with 45% unreacted **403**, compared to 96% yield reported by Daugulis for the two isomers.[208] Alone, the experiment neither proves nor disproves the existence of a benzyne pathway in our reaction. However, a methoxy-substituted arene **406** did not undergo the cyclization under Daugulis' benzyne conditions (**Scheme 146C**),[208] while several methoxy-substituted arenes were shown to be viable substrates in our case, even in the *meta*-position (**Table 29**). The regioisomeric ratios obtained by Daugulis ranged between 1.1:1 to 5.5:1, while most of the ratios we observed were >5:1. The observations inclined us to believe that the intermediacy of benzyne as a main reaction pathway was less likely in our transformation; however, we cannot discount the involvement of a benzyne activation as initiation in a radical mechanism.[209]

**Scheme 147**. Control experiment for a benzyne mechanism



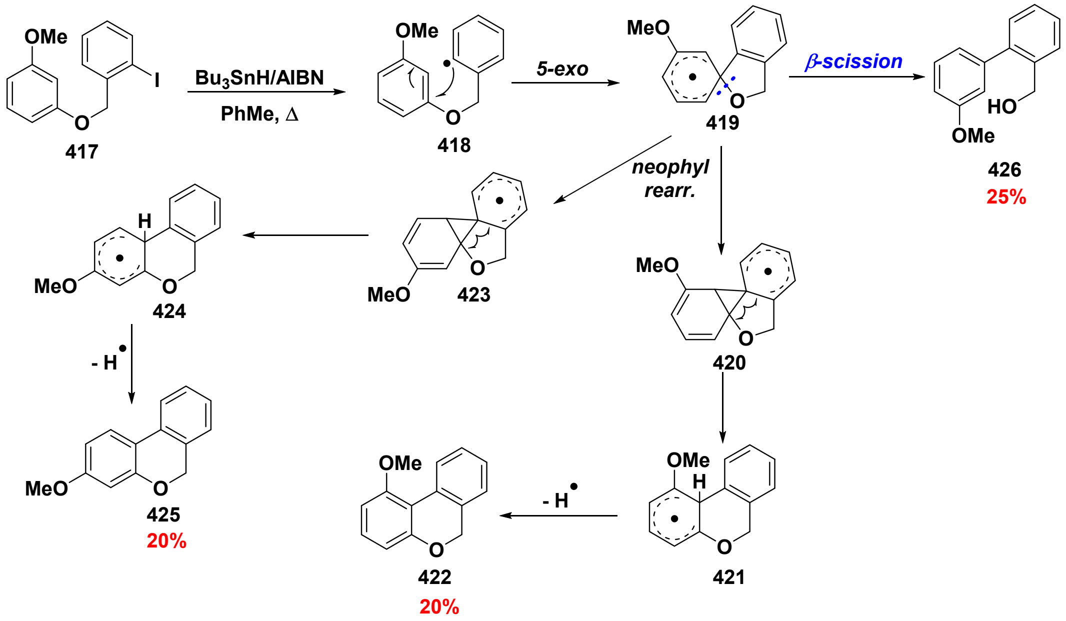
Next, a radical mechanism was considered for our system. Recent publications from the group of Rossi reported the synthesis of phenanthridine via irradiation (photochemical reactor with two 400 W Hg lamps) of iodobenzylamine **408** in presence of KO*t*Bu (**Scheme 148**).[210] No reaction occurred in the dark. An $S_{RN}1$ mechanism was suggested for the reaction (**Scheme 148**). After deprotonation of the aniline by KO*t*Bu to give anion **411**, initiation is proposed to occur via a photoinduced one electron transfer (ET) to give radical anion **412**. Loss of iodide would give rise to another radical anion **413**, capable of intramolecular attack of the other aryl ring to provide conjugated radical **414**. The reaction cycle is propagated by electron transfer from intermediate **414** to anion **411**, which also releases **415**. Under the basic reaction conditions, intermediate **415** is deprotonated to provide **416**. During the acidic work up of the reaction, **416** is protonated and oxidized under air to the desired phenanthridine **409**. Regioisomeric products were never observed when the aniline was substituted, the only by-product isolated being the reduced starting material **410**.[210]

**Scheme 148**. Photoinduced phenanthridine synthesis and mechanism[210]



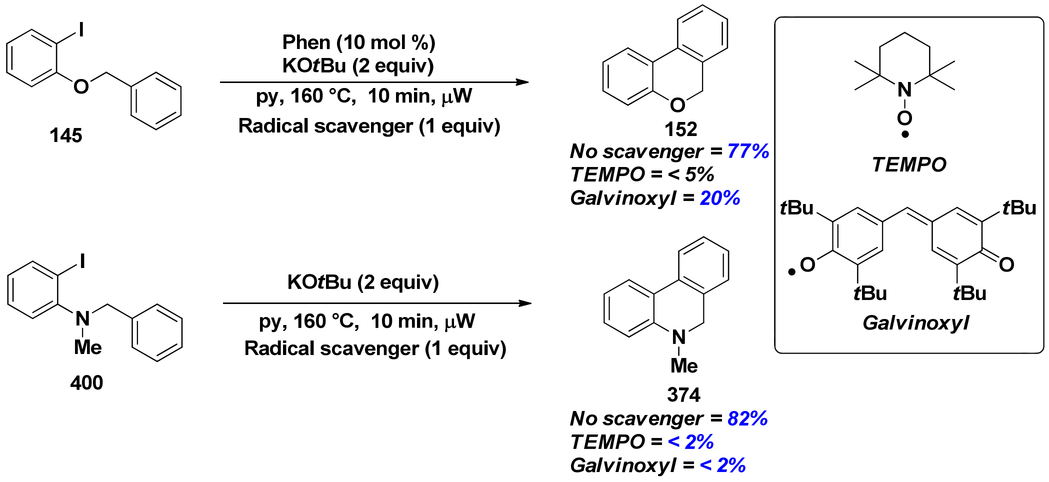
Additionally, iodobenzylether **145** had been previously submitted to refluxing AIBN/Bu$_3$SnH in toluene and the desired benzopyran was obtained in 18% yield, along with other rearranged products from β-scission (**Scheme 51**, *vide supra*). Moreover, when substituents were present in the *meta*-position, a regioisomeric mixture of **422** and **425** was observed by the group of Bowman (**Scheme 149**).[211] The reaction followed a general HAS mechanism, with initiation mediated by AIBN/Bu$_3$SnH and generation of an aryl radical **418**, which underwent a *5-exo-trig* cyclization to produce spiro radical **419**. Then, radical **419** was able to undergo a neophyl (1,2-phenyl) rearrangement and ring expansion in two distinct ways to produce isomers **421** and **424**, which upon rearomatization[211] provided the final products **422** and **425** in 20% yield each. β-Scission of radical **419** also occurred to produce alcohol **426** in 25% yield.

**Scheme 149.** Generation of regioisomeric products via HAS



Back to our microwave reaction, experiments performed in presence of known radical scavengers such as TEMPO or galvinoxyl shut down the reaction (**Scheme 150**), an indication towards a radical pathway. The regioisomeric distributions obtained in our intramolecular cyclization can also be explained through an HAS mechanism, involving *5-exo* or *6-exo/endo-trig*, followed by neophyl rearrangement (**Scheme 151**, *vide infra*).

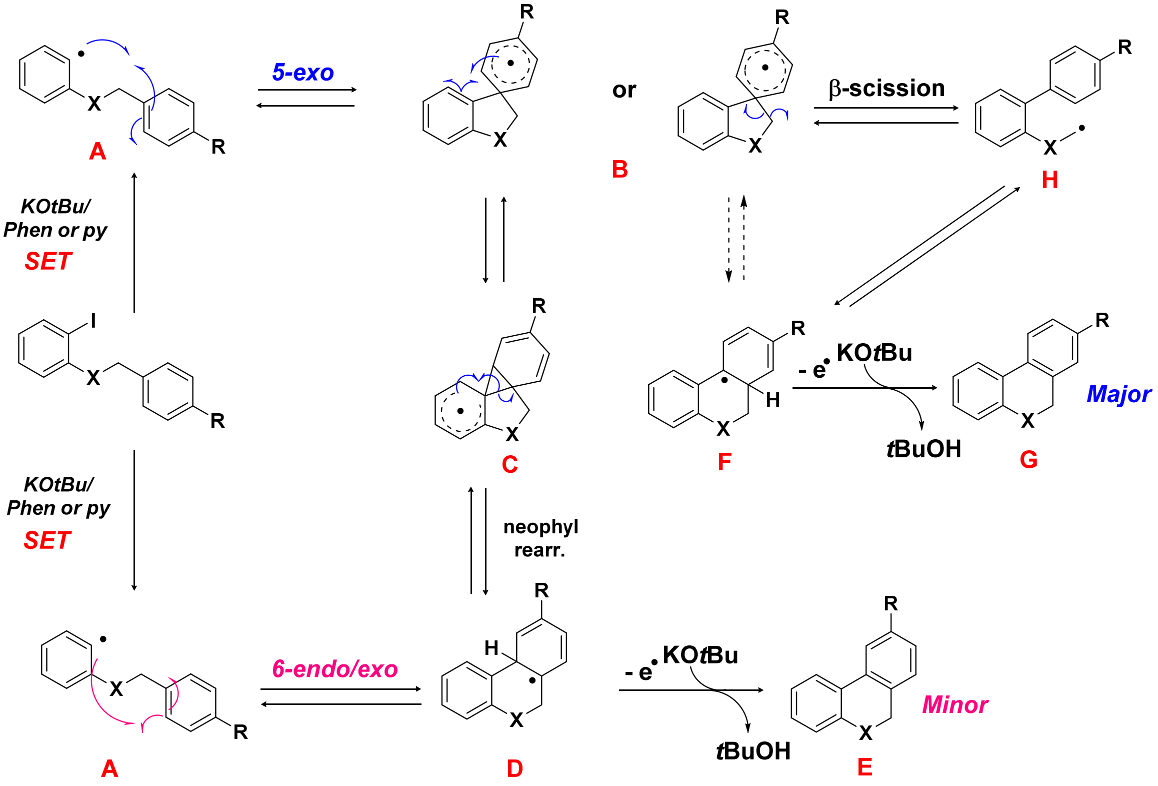
**Scheme 150.** Radical inhibition studies



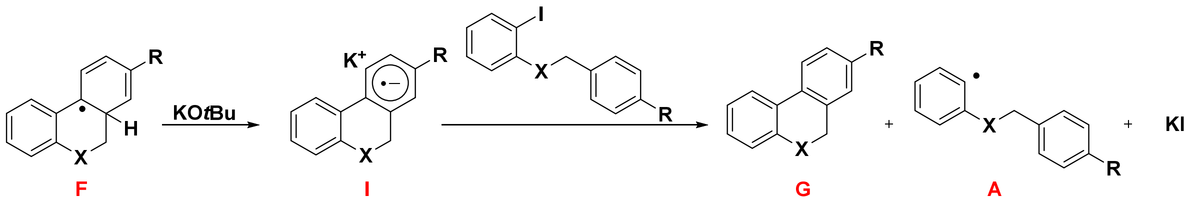
Then, the question arises, what is responsible for the initial single electron transfer? In the examples above, electron transfer occurred from an initiator (e.g. AIBN) or was photoinduced. However, none of the circumstances are valid for our system. Nonetheless, KO*t*Bu is known to function as a single or two-electron donor to certain functional groups.[212] Phenanthroline, and other conjugated derivatives, have a low lying LUMO and can act as an SET acceptor, delocalizing an electron around the ring.[204] The LUMO of Phen would explain why it is suitable for the reaction, while bipyridine, a non-conjugated system, is not. But the majority of the scope for the present transformation was performed in absence of Phen, in the sole presence of two equivalents KO*t*Bu and pyridine as the solvent. Thus, the exact mechanism of the SET to the aryl iodide bond is yet to be fully understood.

Based on our radical scavenging studies, the formation of regioisomeric products and the similarities between HAS and the current transformation, the following mechanism was suggested for a *para*-substituted arene (**Scheme 151**). At high temperature, a favourable interaction between KO*t*Bu and Phen or pyridine is responsible for the initial generation of radical **A** (most likely through generation of a radical anion first, then loss of iodide). A kinetically favoured *5-exo-trig* ipso attack gives rise to spiro radical **B**, which can form a fused cyclic species **C** via *3-exo* closure. Radical **C** can undergo a neophyl rearrangement to give **D**, followed by rearomatization mediated by the base to give rise to the minor product **E**. The major product **G** is produced via a ring expansion of intermediate **B**, followed by loss of a proton and an electron. Alternatively, the minor isomer **E** can arise from a *6-endo/exo* ring cyclization. β-Scission is also a viable alternative for Sn-mediated radical reactions, especially in presence of a heteroatom which can stabilize alkyl radical **H** with its lone pair. No ether product derived from radical **H** was isolated in our system, due to the absence of a quenching H source (such as $Bu_3SnH$ in **Scheme 51**). Thus, alkyl radical **H** is proposed to attack the aryl ring in an *ortho* fashion and provide cyclohexadienyl intermediate **F**. Alternatively, a concerted ring enlargement from **B** to **F** is less likely. The β-scission pathway accounts for the formation of the major product for *para*-, *meta*- and *ortho*-substituted derivatives. In case of iodoarene **392** with an all-carbon tether, the reverse selectivity can be explained by lack of stabilization of the primary alkyl radical in the β-scission step (**Table 29**, entry 8). The rearomatization step may occur as previously described by Studer and Curran[12] (**Scheme 139**, *vide supra*): (i) proton transfer by KO*t*Bu to give rise to a powerful reducing agent **I** which can (ii) transfer an electron to another aryl iodide to provide the product **G** and regenerate aryl radical **A** (**Scheme 152**).

**Scheme 151**. Plausible reaction mechanism



**Scheme 152**. Plausible rearomatization step for the base-promoted HAS

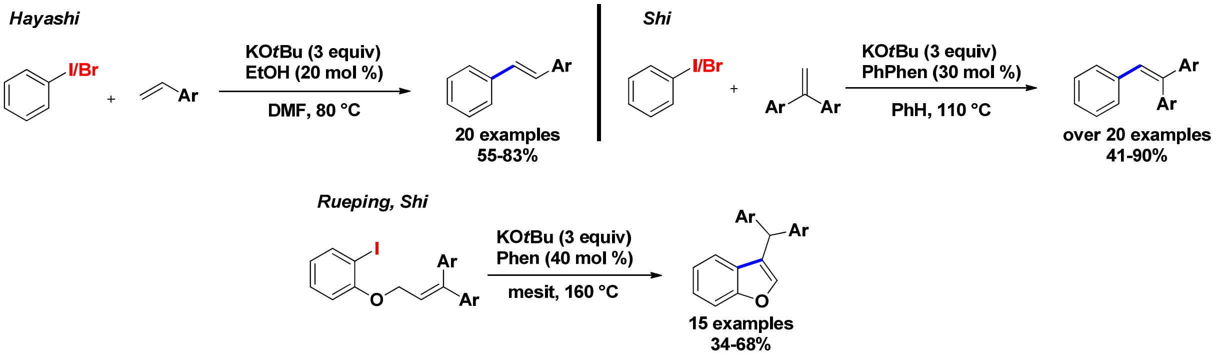


## 5.2.4 Related work

The impact of the transition metal free, KO*t*Bu-mediated reactions is tremenduous. Shortly after our disclosure of the project in 2011, reports appeared on the KO*t*Bu-mediated intermolecular and intramolecular alkenylation reactions from the groups of Hayashi, Shi and

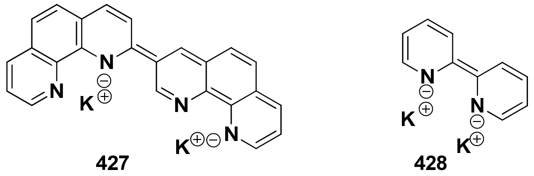
Rueping (**Scheme 153**).[213] In addition, other research groups expanded the scope of the "ligands" or "organocatalysts" for the TM-free arylation to alcohols,[214] diols,[215] proline,[216] porphyrin,[217] a pyridinium carboxylate,[218] a macrocyclic aromatic pyridine,[219] a MOF (metal-organic framework)[220] or, in some cases, no organocatalyst at all.[221]

**Scheme 153**. KO*t*Bu-mediated alkenylation[213]

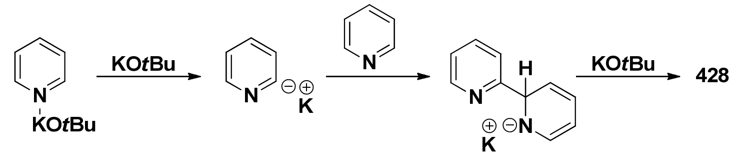


During the preparation of the current thesis, two interesting reports related to the origin of the radical formation appeared in the literature. The first report, from Murphy's group, argued that organic electron donors derived from phenanthroline **427** or pyridine **428** are formed *in situ* by deprotonation from the base and can trigger the reaction (**Scheme 154**).[209] In absence of nitrogen-based additives, a benzyne-pathway was proposed to give rise to an electron-donor species.[209] The second report, from Wilden's group, clearly showed that no additives were necessary for the intermolecular arylation of aryl iodides with unactivated arenes at 160 °C, overall disagreeing with Murphy's electron donor hypothesis.[222] The paper by Wilden *et al* argues that the alkoxide (*tert*-butoxide) can supply electrons to an organic substrate when it is highly dissociated from the cation, thus the degree of dissociation is important (**Scheme 155**).[222] KO*t*Bu is superior to NaO*t*Bu or LiO*t*Bu, due to a longer K–O bond (2.46 Å versus 1.70-2.05 for Li and Na).[223] The publications show that KO*t*Bu-mediated transformations are still a "hot" topic in organic chemistry and the initiation step of the reaction is highly debatable.

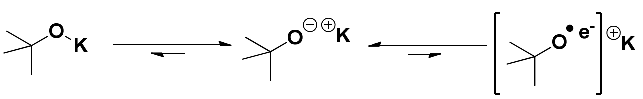
**Scheme 154**. Murphy's hypothesis: "super electron-donors" from Phen (427) and pyr (428)



*Proposed mechanism for the formation of 428*



**Scheme 155**. Wilden's hypothesis: alkoxide dissociation leads to electron transfer



## 5.3 Conclusion

In summary, a transition metal-free intramolecular cyclization of aryl ethers, amides and anilines was developed. The reaction occurred in the sole presence of two equivalents potassium *tert*-butoxide as the base and pyridine as the solvent under microwave conditions, when anilines were used as substrates, or with 10 mol % Phen additive for ethers and amides. The reaction was proved to proceed through homolytic aromatic substitution, where a *5-exo-trig ipso* cyclization was favoured, followed by ring expansion to provide the major product. The resulting phenanthridine and phenanthridinone products are part of many alkaloid natural products. Base-promoted HAS has provided not only a novel way of looking at "C–H functionalization," but also a more environmentally-friendly way to think about radical chemistry.

# Chapter 6: Nickel-catalyzed intramolecular arylation of unactivated alkyl iodides

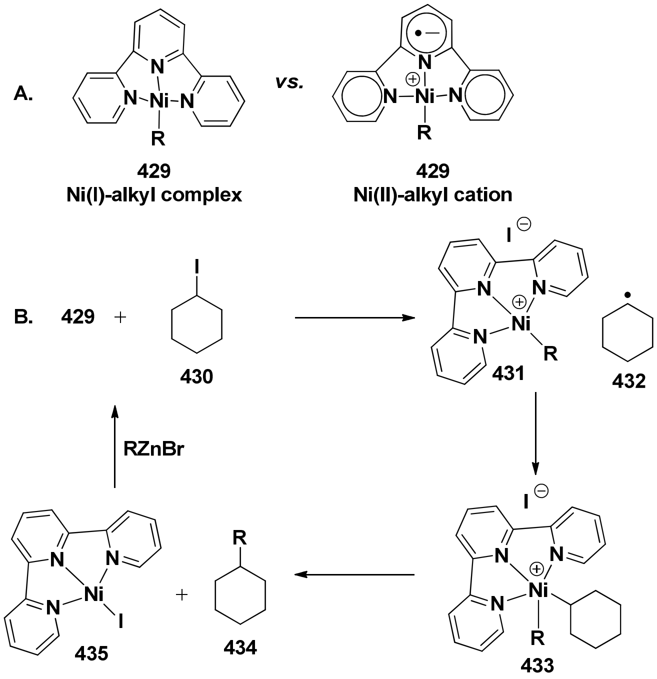
Reference: Beaulieu, L.-P. B.; Sustac Roman, D.; Vallée, F. ; Charette, A. B. *Chem. Commun.* **2012**, *48*, 8249.

## 6.1 Introduction

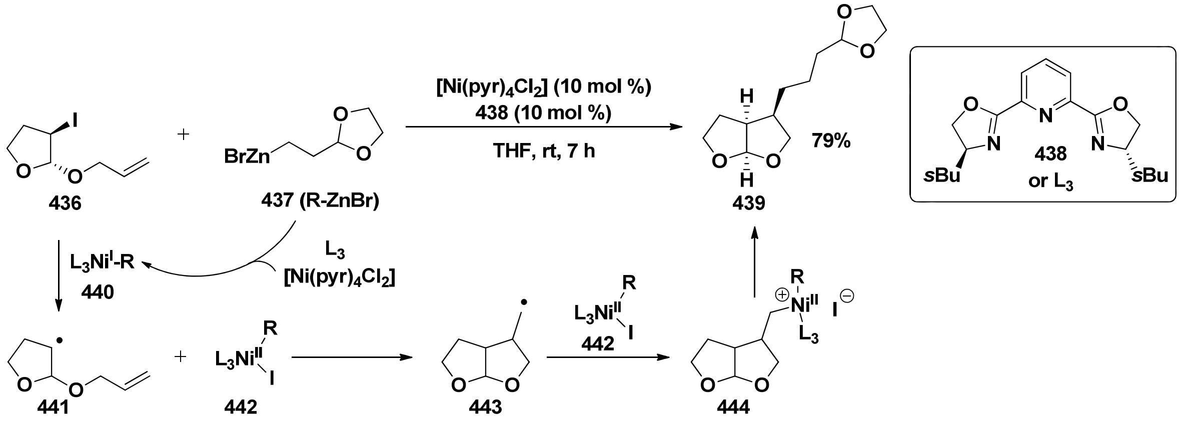
Nickel complexes are versatile catalysts for cross-coupling or direct functionalization reactions.[224] In 1972, Kumada *et al* employed nickel complexes as catalysts for the coupling of aryl or alkenyl halides with Grignard reagents.[225] In 1977, Negishi *et al* reported the cross-coupling of organozinc compounds with aryl halides in presence of $Ni^0$ complexes as catalysts.[226] Later, transformations of organometallic compounds via Ni catalysis were extensively studied by the Knochel[227] and Fu[228] groups. In contrast with Pd-catalyzed reactions, many transformations involving Ni catalysts are proposed to occur through a radical pathway.[229] For example, Vicic and co-workers disclosed a $Ni^I$-terpyridine-alkyl complex **429** involved in alkyl-alkyl Negishi cross-coupling (**Scheme 156**).[230] Extensive studies revealed that complex **429** does not undergo the traditional oxidative addition, transmetalation and reductive elimination pathway to afford the final product. Instead, the best representation for the ground-state of complex **429** is a $Ni^{II}$-methyl cation and a reduced ligand containing an unpaired electron (**Scheme 156A**).[230b] The electron can then be transferred to an alkyl halide **430** to provide an alkyl radical **432** and complex **431** (**Scheme 156B**). Due to the proximity of alkyl radical **432** and complex **431**, an oxidative radical addition occurs next, to provide $Ni^{III}$ complex **433**, followed by a fast reductive elimination to provide complex **435** and the desired product **434**.[230b]

Later, Cárdenas *et al* disclosed a Ni-catalyzed intramolecular cyclization of alkyl halides with olefins, followed by coupling with organozinc reagents (**Scheme 157**).[231] It was found that a pybox-type ligand **438** and $[Ni(pyr)_4Cl_2]$ as the catalyst provided the best yields. Based on their experimental studies, the proposed mechanism involved the following: (i) generation of complex **440**, (ii) capable of SET to the aryl iodide **436** to give alkyl radical **441**; then, (iii) radical **441** undergoes a fast *5-exo-trig* cyclization to provide radical **443**, (iv) which in presence of $Ni^{II}$ complex **442** does an oxidative radical addition to provide complex **444**. Finally, (v) reductive elimination of complex **444** releases the desired product **439** and a $Ni^{I}$ complex, which reacts with organozinc **437** to regenerate catalyst **440**. Both *cis* and *trans* diastereomers of **436** provided the same yield and stereochemistry of the product **439**, indicating a common reaction intermediate for both pathways (presumably **441**).[231]

**Scheme 156**. A. Representations of complex **429**. B. Plausible radical mechanism[230]

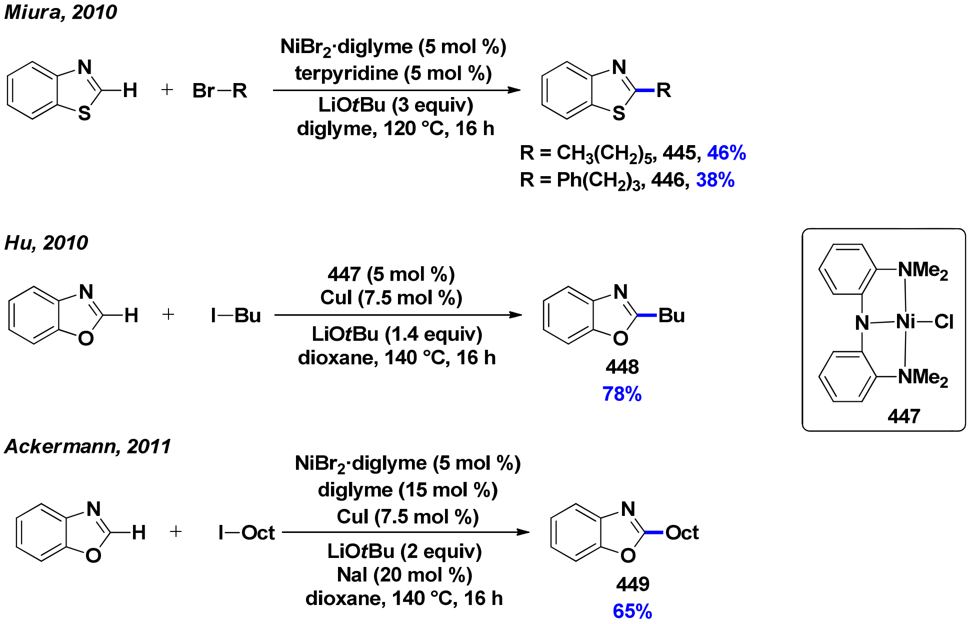


**Scheme 157**. Ni catalyzed cyclization and coupling with organozinc reagents, and proposed mechanism[231]



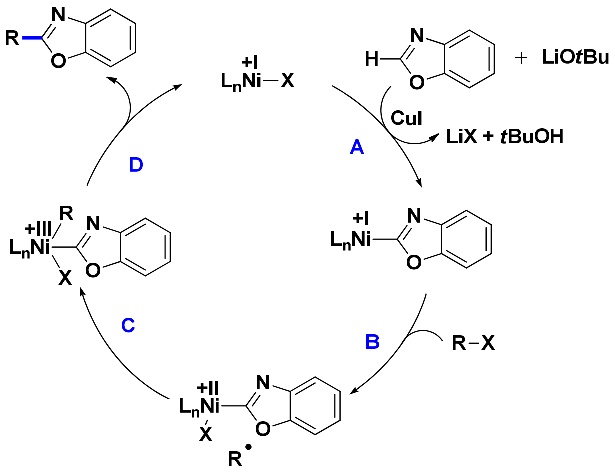
Pd-catalyzed direct alkylation was discussed in Section 1.3.1. In contrast with the use of Pd, examples of direct C–H transformations involving Ni complexes are scarcer in the literature. The direct addition of unactivated alkyl halides to sp centers (Sonogashira-type) in presence of Ni catalysts was first reported by the Hu group.[232] The functionalization of aromatic heterocycles possessing an acidic proton (such as benzoazoles or benzothiazoles, with pKa 24-28, comparable to terminal alkynes) with non-activated alkyl halides has recently been demonstrated by several groups. For example, Miura's group described in 2010 two examples of coupling of benzothiazole with alkyl bromides in presence of $NiBr_2$·diglyme as the catalyst and terpyridine as the ligand (**Scheme 158**).[233] The groups of Hu[234] and Ackermann[235] disclosed the effective alkylation of benzoazoles in presence of Ni complexes (**447** or $NiBr_2$·diglyme) and CuI as catalysts (**Scheme 158**). Although the reaction could occur in the sole presence of the Ni catalyst, improved yields were obtained with the addition of 7.5 mol % CuI.

**Scheme 158**. Coupling of heterocycles with unactivated alkyl halides via Ni catalysis



The working mechanistic hypothesis of Ackermann's reaction involves Cu as a transmetalation mediator from the anionic azole to Ni (**Scheme 159**, step **A**).[235] The next steps are similar to the previous work by Vicic:[230] (**B**) formation of a an alkyl radical, (**C**) oxidative addition of this radical to the $Ni^{II}$ complex and (**D**) reductive elimination to provide the coupled product.[235]

**Scheme 159**. Working mechanistic hypothesis[235]



## 6.1.1 Research goal

We wished to extend the intermolecular and intramolecular direct arylations previously reported by our group (Chapter 5) to an alkyl system. Direct alkylation, as explained in Section 1.3.1, faces two main obstacles: (1) difficult oxidative addition compared to aryl halides, due to the alkyl halides being more electron rich, and (2) high tendency for *β*-hydride elimination. It was hypothesized that an intramolecular alkyl system, with the β-position blocked, would be ideal for the study (**Scheme 160**). A goal of the work was also to avoid the use of an expensive transition metal, such as Pd or Ru, and instead develop a methodology employing Fe, Ni, Cu or no transition metal. Furthermore, we wished to gain more understanding into the mechanism of the reaction, especially the role of the transition metal.

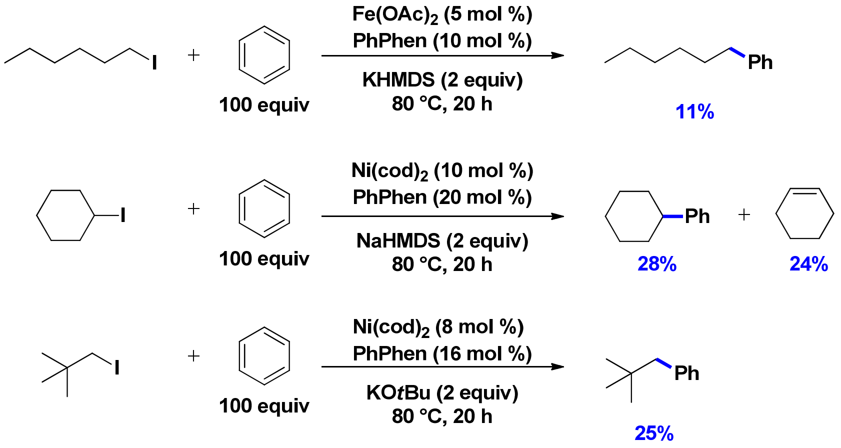
**Scheme 160**. Project goal

## 6.2 Results and discussion

### 6.2.1 Optimization

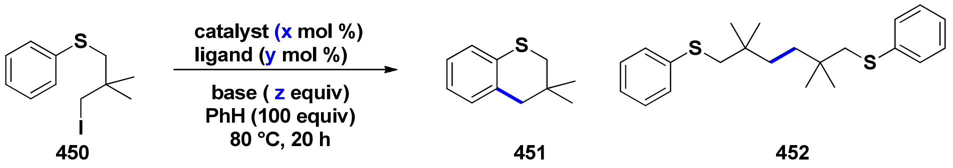
Initial attempts at an intermolecular system were performed by a former MSc student, Frédéric Vallée, and a former PhD student, Dr. Louis-Philippe Bonhomme-Beaulieu.[236] It was found that primary alkyl iodides, such as iodohexane or neopentyl iodide, only provided the desired product in 11% and 25% yields respectively (**Scheme 161**). A secondary alkyl iodide, iodocyclohexane resulted in complete conversion, although only 28% yield of the desired product, along with 24% elimination. Attempts at further optimization of the system were not successful. Perhaps the elimination result is not surprising, in presence of a strong base and at 80 °C for 20 h.

**Scheme 161**. Initial studies for intermolecular direct alkylation



Dr. Beaulieu then focused his efforts on designing an intramolecular system with a quaternary centre in the β-position, thus avoiding any E2 elimination issues. Thioarene **450** containing a *gem*-dimethyl group was chosen as the model substrate for the optimization, due to its straightforward synthesis (**Table 30**). Using our previously published conditions with $Fe(OAc)_2$ (10 mol %), PhPhen (20 mol %) and KO*t*Bu (2 equiv) in PhH at 80 °C,[197] the cyclized product **451** was obtained in 37% yield (entry 1). Changing the base to NaHMDS resulted in no product formation (entry 2). After testing more bases and catalysts (entries 3-5), it was determined that the combination of a $Ni^0$ catalyst, $Ni(PPh_3)_4$, and NaHMDS in the absence of a Phen-type ligand provided 73% yield of product **451** (entry 6). Small amounts of a starting material dimer, **452**, were also observed in the reaction. The catalyst loading could be reduced to 5 mol %, without a major loss of yield (entry 7). Other bases tested in presence of $Ni^0$, resulted in low yields (LiHMDS, entry 8, KO*t*Bu, entry 10), while KHMDS decomposed the starting material (entry 9). The quantity of NaHMDS could be reduced to 1.5 equivalents, to provide product **451** in 75% yield, with only 4% dimer **452**. Control reactions in the absence of the catalyst demonstrated no reactivity at 80 °C or 120 °C (entries 12 and 13). Finally, running the reaction with 5 or 20 mol % catalyst, in the absence of any base, led to only traces of thioarene **451** by GC-MS analysis (entries 14 and 15).

**Table 30**. Optimization of the intramolecular system



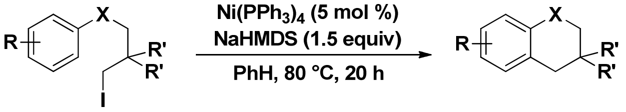
| entry | catalyst (x) | ligand (y) | base (z) | yield[a] (%) | | |
|---|---|---|---|---|---|---|
| | | | | **450** | **451** | **452** |
| 1 | $Fe(OAc)_2$ (10) | PhPhen (20) | KO*t*Bu (2) | 18 | 37 | 0 |
| 2 | $Fe(OAc)_2$ (10) | PhPhen (20) | NaHMDS (2) | 72 | 0 | 0 |
| 3 | $NiCl_2$ (10) | PhPhen (20) | NaHMDS (2) | 37 | 25 | 0 |
| 4 | $Ni(cod)_2$ (10) | PhPhen (20) | NaHMDS (2) | 0 | 47 | 10 |
| 5 | $Ni(PPh_3)_4$ (10) | PhPhen (20) | NaHMDS (2) | 0 | 55 | 13 |
| 6 | $Ni(PPh_3)_4$ (10) | --- | NaHMDS (2) | 0 | 73 | 8 |
| 7 | $Ni(PPh_3)_4$ (5) | --- | NaHMDS (2) | 0 | 68 | 4 |
| 8 | $Ni(PPh_3)_4$ (5) | --- | LiHMDS (2) | 51 | 25 | 5 |
| 9 | $Ni(PPh_3)_4$ (5) | --- | KHMDS (2) | 0 | 0 | 0 |
| 10 | $Ni(PPh_3)_4$ (5) | --- | KO*t*Bu (2) | 59 | 27 | 0 |
| **11** | **$Ni(PPh_3)_4$ (5)** | --- | **NaHMDS (1.5)** | **5** | **75** | **4** |
| 12 | --- | --- | NaHMDS (1.5) | 100 | 0 | 0 |
| 13[b] | --- | --- | NaHMDS (1.5) | 82 | 0 | 0 |
| 14 | $Ni(PPh_3)_4$ (5) | --- | --- | >95 | <5 | 0 |
| 15 | $Ni(PPh_3)_4$ (20) | --- | --- | >95 | <5 | 0 |

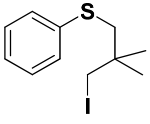
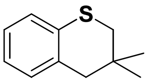
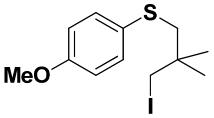
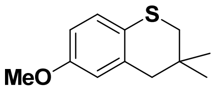
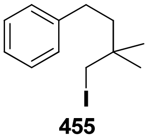
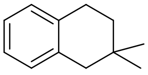
[a] $^1$H NMR yield using trimethoxybenzene as internal standard. [b] Reaction at 120 °C.

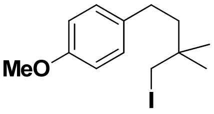
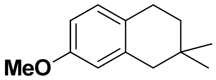
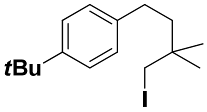
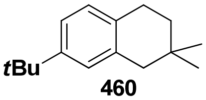
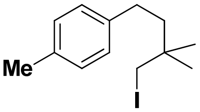
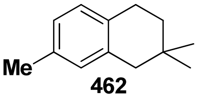
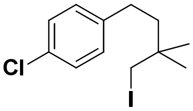
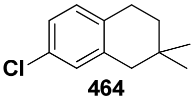
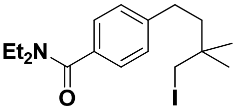
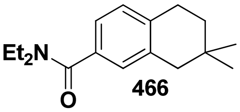
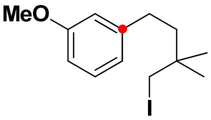
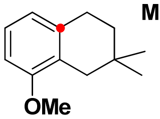
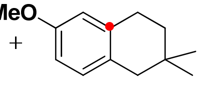
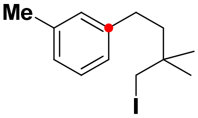
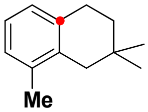
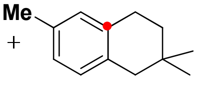
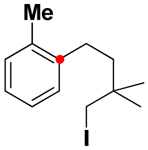
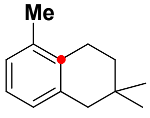
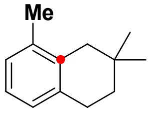
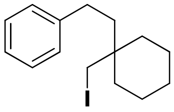
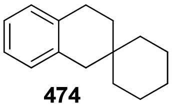
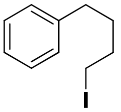
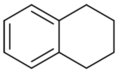
### 6.2.2 Reaction scope

The scope of the transformation was evaluated in collaboration with Dr. Beaulieu (**Table 31**). Substitution on the aryl ring of the thioarene was well tolerated, product **454** being obtained in 88% yield, along with 8% dimer (entry 2). An all-carbon tether could be successfully employed in the reaction (entry 3). The rest of the scope was further evaluated using the carbon tether. Electron donating (methoxy) or electron neutral (methyl, *t*-butyl) at the *para* position provided the desired products **458**, **460**, and **462** in 88%, 85%, and 86% yield, respectively (entries 4-6). A chloride-containing arene **463** could also be cyclized in 74% yield, thus allowing for potential further transformations of **464** via cross-coupling (entry 7).[237] A tertiary amide was also tolerated in the reaction and product **466** was isolated in 70% yield (entry 8). When the starting material contained a *meta*-substitution, a 3:1 mixture of isomers was obtained for both *m*-OMe and *m*-Me (85% and 81% total yield, respectively, entries 9-10). The structures of the regioisomers were determined by 1D nOe experiments. Interestingly, for the major products, **468a** and **470a**, cyclization occurred *ortho* to the substituent, a typical trend observed in HAS. An *ortho*-substituted arene, **471**, gave 71% of the desired product **472a** (entry 11). Upon careful analysis of the $^1$H NMR spectrum of the product, traces of a regioisomer **472b** were observed, and its structure was confirmed by 1D nOe. The *gem*-dimethyl group could be successfully replaced by a cyclohexane, which provided arene **474** in an excellent 94% yield (entry 12). Removing the substituents in the β-position led to traces of the desired product **476**, and mostly elimination product (entry 13). No dimerization was observed in case of the all-carbon tether substrates.

**Table 31**. Scope of the Ni-catalyzed intramolecular alkylation



| entry | starting arene | product(s) | yield[a] (ratio a:b) |
|---|---|---|---|
| 1[b] |  **450** |  **451** | 70% |
| 2[c] |  **453** |  **454** | 88% |
| 3 |  **455** |  **456** | 74% |

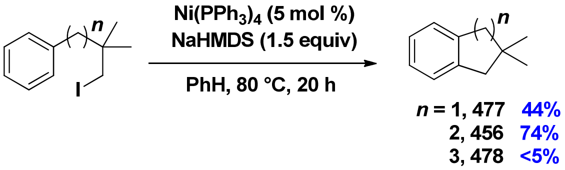
|  |  |  |  |
|---|---|---|---|
| 4 |  **457** |  **458** | 88% |
| 5 |  **459** |  **460** | 85% |
| 6 |  **461** |  **462** | 86% |
| 7 |  **463** |  **464** | 74% |
| 8 |  **465** |  **466** | 70% |
| 9 |  **467** |  **468a** +  **468b** | 85% (3:1) |
| 10 |  **469** |  **470a** +  **470b** | 81% (3:1) |
| 11 |  **471** |  **472a** +  **472b** | 71% (10:1) |
| 12 |  **473** |  **474** | 94% |
| 13[d] |  **475** |  **476** | <5% |

---

[a] Isolated yields on 0.5 mmol. [b] 8% dimer 452 also isolated. [c] 7% corresponding dimer also isolated. [d] The E2 elimination product isolated in 47%.

Next, the ring size of the cyclization was considered (**Scheme 162**). Formation of a five-membered ring **477** was possible in a lower yield (44%), while synthesis of a seven-membered ring **478** led to traces of product and degradation.

**Scheme 162**. Evaluation of the ring size of the cyclization



## 6.2.3 Mechanistic studies

At the onset of the studies, two mechanisms were considered: a Friedel-Crafts pathway or a radical pathway. The control reactions performed in the absence of the base (**Table 30**, entries 14 and 15) led to virtually complete recovery of the starting material, therefore suggesting against the role of the Ni catalyst as a Lewis acid in a potential Friedel-Crafts pathway. As presented in the introductory section of the current chapter, Ni complexes may react via a radical mechanism, and the pathway was further investigated.

### 6.2.3.1 Radical scavenging experiments

The addition of radical scavengers such as TEMPO or galvinoxyl effectively shut down the reaction (**Scheme 163**). In addition, the TEMPO adduct of the starting arene **455** was isolated in 33% yield (**Table 32**, entry 1). In absence of the base, only 5% yield product **479** was isolated, an amount equal to the quantity of catalyst present in the reaction medium (entry 2). The latter result suggests that $Ni(PPh_3)_4$ may act as a radical initiator, while the former result demonstrates the necessity of the base to regenerate the Ni catalyst. In absence of the catalyst, no product **479** was produced, with nearly complete recovery of the starting material (entry 3). Finally, in the absence of both the base and catalyst, only starting material was recovered (entry 4).

**Scheme 163**. Radical scavenging experiments

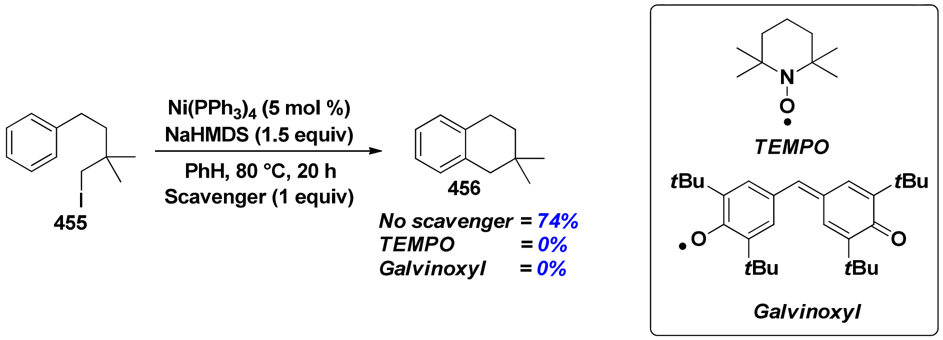
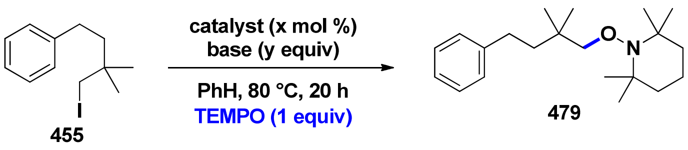


**Table 32**. TEMPO scavenging experiments



| | | | yield[a] (%) | |
|---|---|---|---|---|
| entry | catalyst (x) | base (y) | **455** | **479** |
| 1 | Ni(PPh$_3$)$_4$ (5) | NaHMDS (1.5) | 63 | 33 |
| 2 | Ni(PPh$_3$)$_4$ (5) | --- | 93 | 5 |
| 3 | --- | NaHMDS (1.5) | 93 | 0 |
| 4 | --- | --- | 96 | 0 |

[a] Isolated yields.

### 6.2.3.2 NMR experiments

To obtain more information on the nickel species present the reaction, equimolar amounts of NaHMDS and Ni(PPh$_3$)$_4$ were dissolved in C$_6$D$_6$ in an NMR tube. The $^1$H NMR spectrum showed the following signals: triphenylphosphine aromatic signals, HMDS signal at 0.1 ppm, and one singlet at 0.48 ppm (**Figure 17**). The same signals were observed at room temperature and at 70 °C. It was hypothesized that the unknown singlet may correspond to a possible adduct formation between the Ni catalyst and the base.

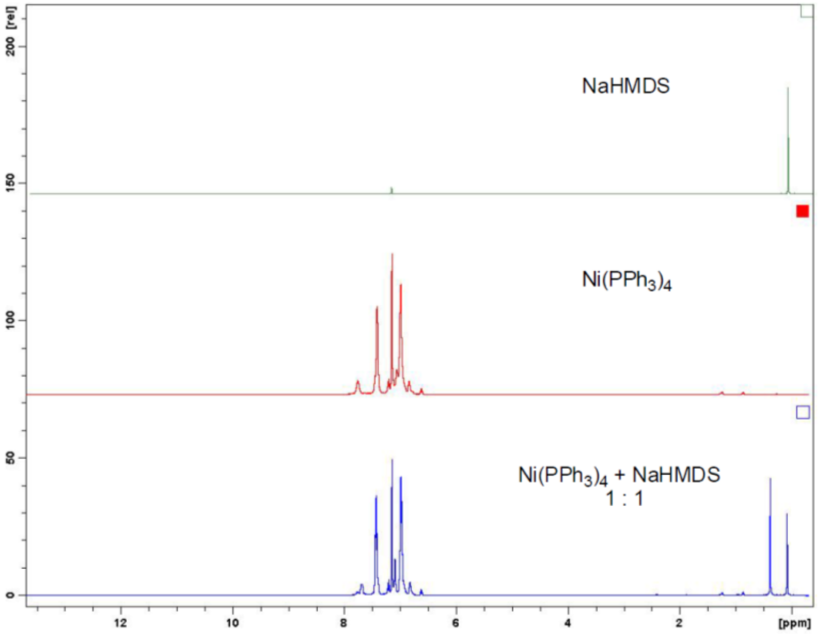


**Figure 17**. $^1$H NMR study in presence of NaHMDS (top), Ni(PPh$_3$)$_4$ (middle), and equimolar amounts of Ni(PPh$_3$)$_4$ and NaHMDS (0.05 mmol each, bottom) at 70 °C in 0.75 mL $C_6D_6$

To further investigate the formation of the presumed adduct, a Diffusion Ordered Spectroscopy (DOSY) experiment was performed with the help of Dr. Cédric Malveau (NMR Department, Université de Montréal). DOSY is a 2D NMR technique measuring the diffusion coefficients ($D$) of molecules in a solution, which are reported on one axis, while the typical chemical shift information is presented on the other.[238] The diffusion coefficient $D$ depends on the molecular weight, size, shape, and charge of the molecule, as well as other parameters such as temperature or aggregation state. $D$ is determined according to the Stokes-Einstein equation (1), where $k_B$ is Boltzmann's constant, $T$ the temperature, $\eta$ the viscosity, and $r$ the hydrodynamic radius of the molecule. In a more simple way, DOSY is able to separate the species in a mixture of compounds spectroscopically; the technique is somewhat reminiscent of a chromatography experiment. The experiment has been previously used to distinguish between mononuclear and dinuclear Pd complexes.[239]

$$D = (k_BT)/6\pi\eta r \tag{1}$$

Upon submitting a 1:1 mixture of Ni(PPh$_3$)$_4$ and NaHMDS to a DOSY experiment, the spectrum in **Figure 18** was obtained. The signal at 0.48 ppm has a similar diffusion coefficient to $Ni(PPh_3)_4$, and is larger than the NaHMDS signal at 0.1 ppm. The experiment confirms the existence of a new species in the solution.

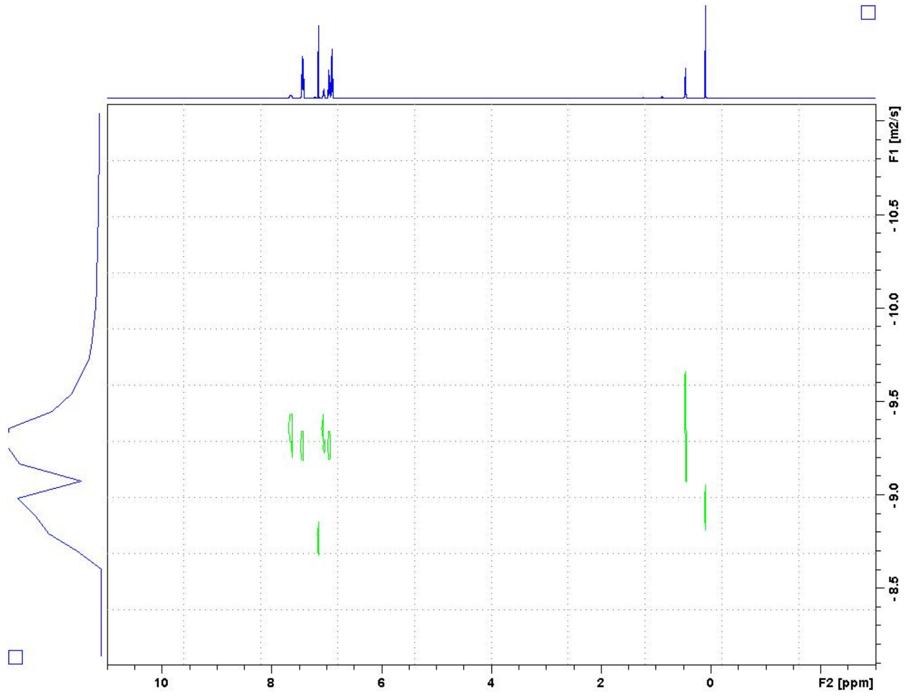


**Figure 18.** DOSY NMR study in presence of equimolar amounts of $Ni(PPh_3)_4$ and NaHMDS (0.05 mmol each) at room temperature in 0.75 mL $C_6D_6$ with a gradient of 48.2 $Gcm^{-1}$ (the peak around 7.2 ppm corresponds to $C_6D_6$)

A more detailed experiment was carried out with $Ni(PPh_3)_4$, **455** and NaHMDS (in a stoichiometric ratio of 1:2:3, respectively) in $C_6D_6$ (**Figure 19**). The $^1H$ NMR spectrum led to the observation of an additional set of signals shifted slightly downfield from those of **455** in addition to the signals for **455**, **456** and for the free and two bound states of NaHMDS.

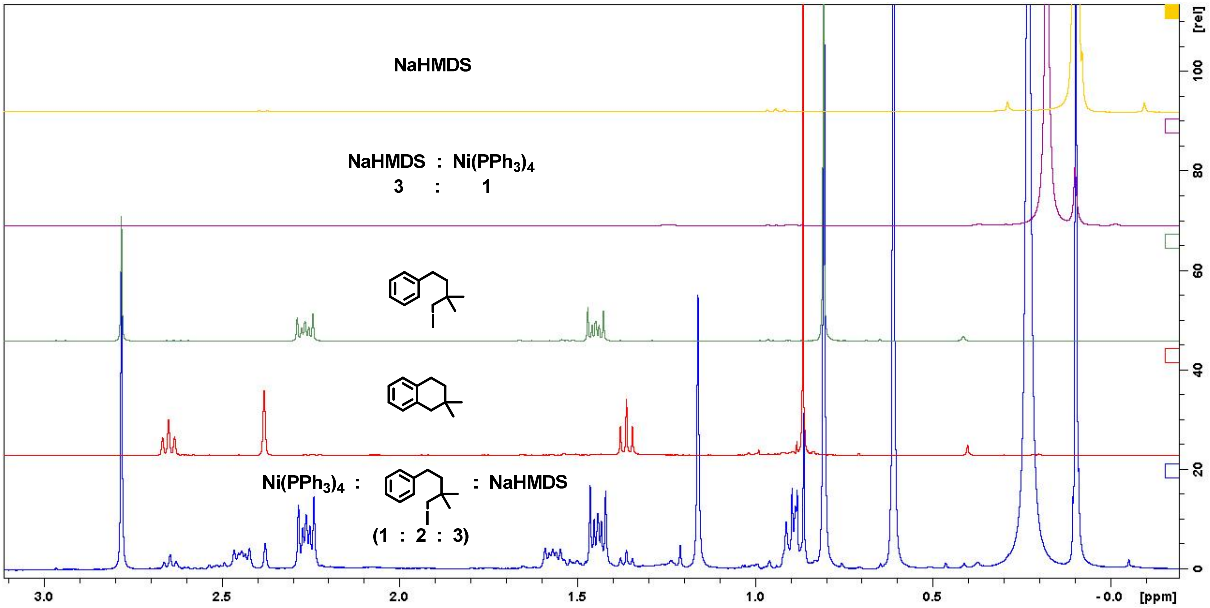


**Figure 19**. Comparison among the aliphatic region of the $^1$H NMR spectra of NaHMDS, NaHMDS : Ni(PPh$_3$)$_4$ (3:1), **455**, **456**, and Ni(PPh$_3$)$_4$ : **455** : NaHMDS (1:2:3) in $C_6D_6$ at 25 °C

A DOSY NMR of the latter mixture was also performed. According to the relative integration values of the singlet at 0.62 ppm (H$^C$) compared to the shifted signals of **455** (H$^D$, H$^E$, and H$^F$), NaHMDS and **455** would associate to Ni(PPh$_3$)$_n$ in a stoichiometric ratio of 1:1:1 (**Figure 20**). Due to the complexity of the DOSY spectrum, the values for the diffusion coefficients of the protons are presented in **Table 33**, with the values for the new Ni(PPh$_3$)$_n$/NaHMDS/**455** adduct **481** highlighted in red (all around 6 units). Moreover, filtration of the mixture over silica and rinsing with hexanes, followed by concentration of the filtrate and analysis by $^1$H NMR, led to the disappearance of the peaks corresponding to **481**, thus supporting the formation of an adduct, and not a reaction by-product.

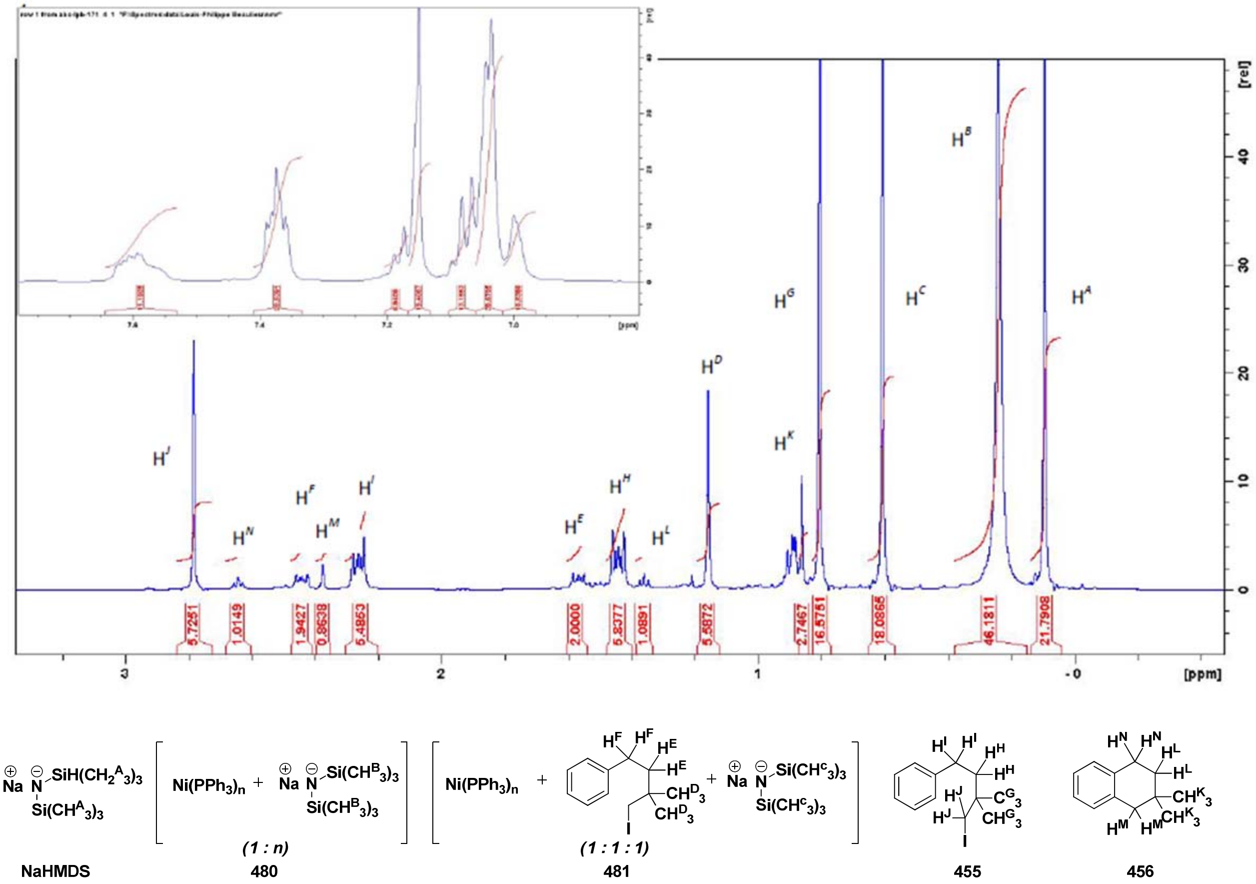


**Figure 20**. Zoom-in of the aliphatic region of the $^{1}$H NMR spectrum of a Ni(PPh$_3$)$_4$ : **455** : NaHMDS (1:2:3) mixture in $C_6D_6$ at 25 °C, with integration and labelling of the protons according to the legend

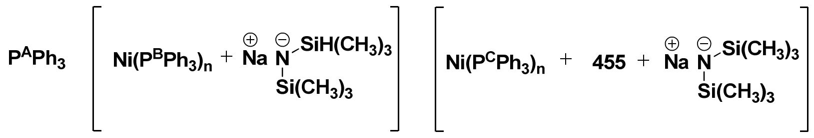
**Table 33**.The diffusion coefficients obtained from a DOSY NMR experiment of a Ni(PPh$_3$)$_4$ : **455** : NaHMDS (1:2:3) mixture in $C_6D_6$ at 25 °C with a gradient of 52.1 Gcm$^{-1}$

| Entry | Proton Label | Chemical Shift (ppm) | Diffusion Constant (E-10 m$^2$s$^{-1}$) |
|---|---|---|---|
| 1 | | 7.65-7.54 | 5.7 |
| 2 | | 7.42-7.33 | 8.9 |
| 3 | | 7.20-7.17 | 10.3 |
| 4 | | 7.17-7.14 | 16.1 |
| 5 | | 7.11-7.02 | 8.2 |
| 6 | | 7.02-6.97 | 6.5 |
| 7 | H$^{J}$ | 2.82-2.75 | 11.0 |
| 8 | H$^{N}$ | 2.67-2.62 | 12.9 |
| 9 | H$^{F}$ | 2.48-2.41 | 6.3 |
| 10 | H$^{M}$ | 2.40-2.36 | 12.6 |

| | | | |
|---|---|---|---|
| 11 | $H^{I}$ | 2.32-2.21 | 11.0 |
| 12 | $H^{E}$ | 1.61-1.55 | 6.2 |
| 13 | $H^{H}$ | 1.48-1.41 | 10.8 |
| 14 | $H^{L}$ | 1.39-1.34 | 11.0 |
| 15 | $H^{D}$ | 1.19-1.13 | 6.0 |
| 16 | $H^{K}$ | 0.87-0.85 | 12.5 |
| 17 | $H^{G}$ | 0.84-0.78 | 10.9 |
| 18 | $H^{C}$ | 0.65-0.57 | 5.9 |
| 19 | $H^{B}$ | 0.33-0.15 | 6.0 |
| 20 | $H^{A}$ | 0.14-0.05 | 13.1 |

Additionally, $^{31}$P NMR analysis of the Ni(PPh$_3$)$_n$/NaHMDS/**455** mixture revealed the presence of free PPh$_3$, suggesting the dissociation of one or more phosphine ligands from the Ni catalyst to allow for the formation of the adduct. $^{31}$P DOSY analysis of the latter mixture revealed two other signals with similar diffusion coefficients, probably corresponding to adducts **480** and **481** (**Table 34**). The $^{31}$P NMR signal for Ni(PPh$_3$)$_4$ was not observed, suggesting the complete consumption of the Ni complex in the formation of the adducts.

**Table 34**. DOSY $^{31}$P NMR experiment involving a Ni(PPh$_3$)$_4$ : **455** : NaHMDS (1:2:3) mixture in 0.75 mL of C$_6$D$_6$, performed at 25 °C with a gradient of 49.8 Gcm$^{-1}$



$P^{A}Ph_3$ $\left[Ni(P^{B}Ph_3)_n + Na^{\oplus}\,{}^{\ominus}N(SiH(CH_3)_3)(Si(CH_3)_3)\right]$ $\left[Ni(P^{C}Ph_3)_n + 455 + Na^{\oplus}\,{}^{\ominus}N(Si(CH_3)_3)_2\right]$

**free PPh$_3$** **480** **481**

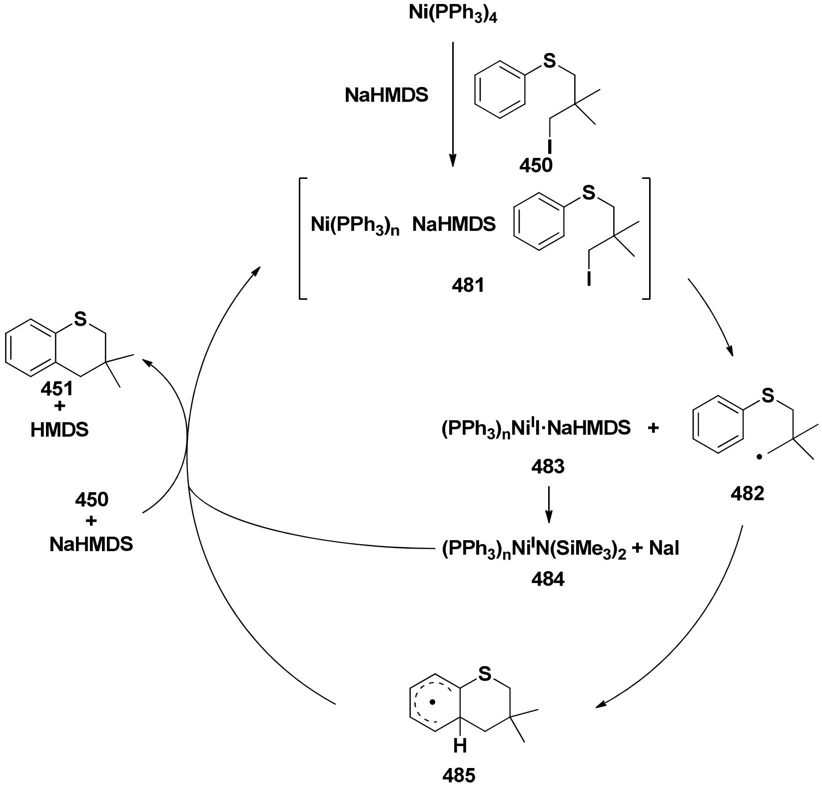
| Entry | Phosphorus Label | Chemical Shift (ppm) | Diffusion Constant (E-10 m$^2$s$^{-1}$) |
|---|---|---|---|
| 1 | $P^{B}$ or $P^{C}$ | 33.78-32.72 | 6.2 |
| 2 | $P^{B}$ or $P^{C}$ | 30.93-29.91 | 5.9 |
| 3 | $P^{A}$ | -4.60- -5.80 | 8.6 |

Taken together, all the NMR experiments suggest the formation of an interaction between the catalyst, the starting material and the base, with the dissociation of PPh$_3$ ligands. Until more evidence about the nature of the species is gathered, we have referred to it with a more general term, adduct (addition of three different molecules to form a single species, in such a way that there is a change in connectivity but no loss of atoms from any components).[240,241] It is also hypothesized that adduct **481** is responsible for single electron transfer during the catalytic cycle.

#### 6.2.3.3 Proposed mechanism

Based on the radical scavenging experiments, as well as the discovery of adduct **481** via DOSY NMR, a plausible cyclization mechanism is shown in **Scheme 164**. Initially, adduct **481** forms among the $Ni^0$ catalyst, NaHMDS and **450**. The adduct is then responsible for a single electron transfer to form alkyl radical **482** and $Ni^I$ species **483**. A similar free radical formation was also proposed by Cárdenas and co-workers.[231] Alkyl radical **482** cyclizes in a *6-endo/exo-trig* fashion to give cyclohexadienyl radical **485**. $Ni^I$ species **483** can also form $Ni^I$ **484** and NaI. Rearomatization of radical **485** regenerates the catalytically active Ni species.

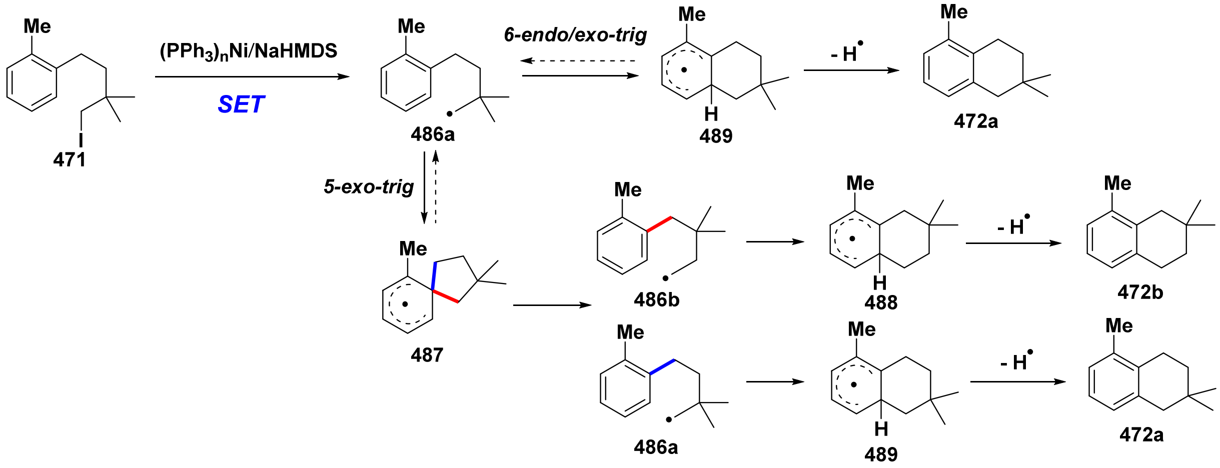
**Scheme 164**. Plausible catalytic cycle



The *6-endo/exo-trig* pathway can also explain the formation of cyclized products in case of the all-carbon tether. For *meta*-substituted alkyl iodides **467** and **469**, the major products **468a** and **470a**, result from cyclization of the *ortho*-position of the substituent, a typical trend observed in radical transformations.[119] In case of *ortho*-substituted compound

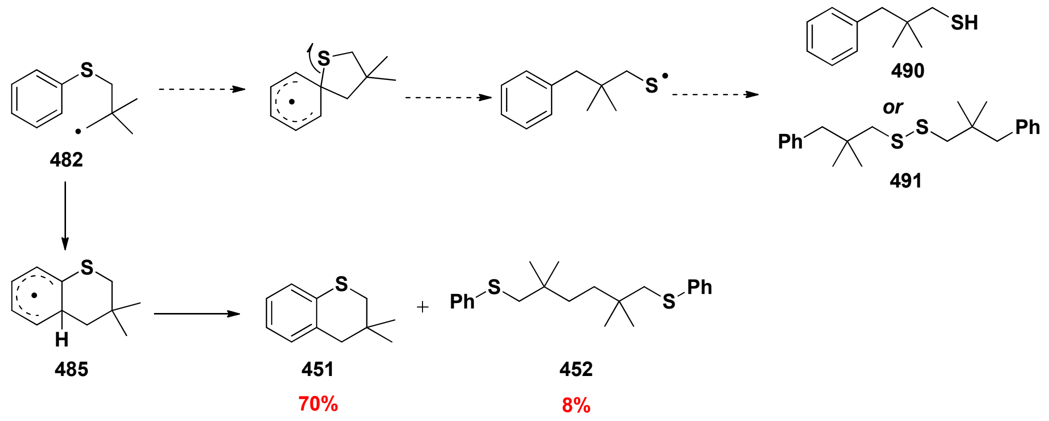
**471**, the major product **472a** can also be formed via the same cyclization. However, minor product **472b** cannot arise via the same mechanism. A spiro cyclization, followed by ring expansion can be invoked to account for the generation of **472b** (**Scheme 165**). After the formation of alkyl radical **486a** via SET from the Ni adduct, a *5-endo-trig spiro* cyclization leads to formation of cyclohexadienyl intermediate **487**. Homolytic cleavage of either the blue or red bond of **487** leads to radicals **486b** and **486a**, respectively. Then, cyclization of alkyl radicals **486b** and **486a** in an *ortho* fashion results in the formation of cyclohexadienyl intermediates **488** and **489**, which, upon rearomatization, form **472b** and **472a**, respectively. The cleavage of the red bond is favoured, as it results in the formation of a stable neopentyl radical **486a**, stabilized through hyperconjugation and inductive effects. As mentioned above, *6-endo/exo-trig* leading to cyclohexadienyl radical **489** can only form major product **472a**.

**Scheme 165**. Spiro pathway for the cyclization of *ortho*-substituted alkyl iodide **471**



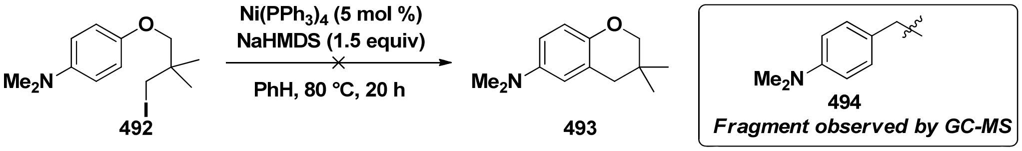
The *ipso* pathway is less likely in case of thioether substrates (**Scheme 166**). No thiol **490** or disulfide product **491** were ever observed in the reaction, only dimer **452** (structure determined by HMBC). The preferred *ortho* pathway for thioethers may be explained through the longer C–S (around 180 pm) versus C–C bond (around 154 pm).

**Scheme 166**. Possible *ipso* pathway for thioethers

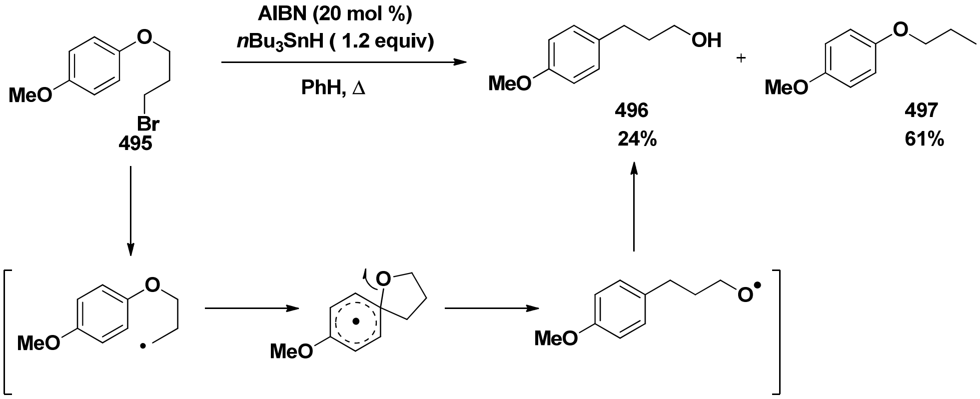


To further investigate the *ipso* cyclization in presence of a heteroatom, ether substrate **492** was submitted to the cyclization conditions (**Scheme 167**). No desired cyclized product **493** was isolated. Instead, fragments of the translocated compounds **494** were observed by GC-MS analysis of the reaction mixture. The result implies formation of a *spiro* intermediate, followed by β-fission. The pathway is well established for AIBN/$Bu_3SnH$ promoted radical reactions for ethers or protected amines.[242] In a typical example, alcohol **496** was obtained in 24% via *ipso* substitution, along with 61% dehalogenated product **497** (**Scheme 168**).[242a] The tendency of alkyl ethers to undergo *ipso* substitution, can also be explained by the shorter C–O bond length (around 143 pm).

**Scheme 167**. Attempts at cyclization of ether **491**



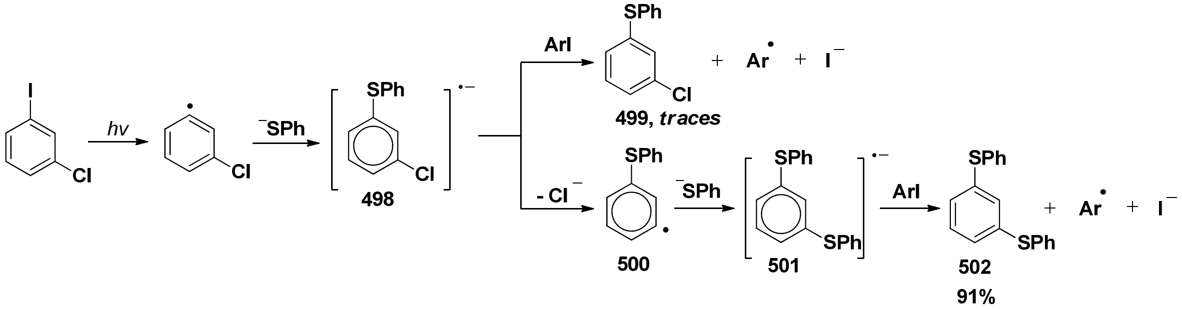
**Scheme 168**. Aryl translocation: oxygen to carbon



### 6.2.3.4 Rearomatization step

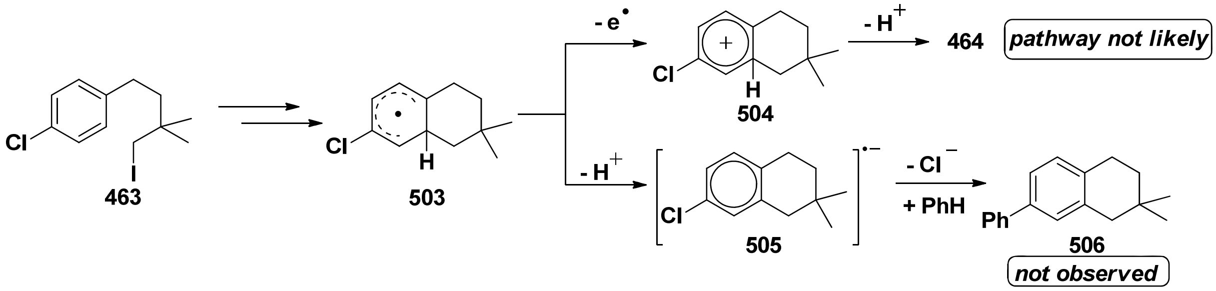
As discussed in Section 1.4, the rearomatization or oxidation step of the cyclohexadienyl radical is highly debatable in HAS chemistry. The step involves the loss of an electron and a proton, possible in either order. Curran and Studer suggested that in presence of a strong base, formation of a cyclohexadienyl cation is unlikely; in contrast, loss of a proton to a strong base such as KO*t*Bu gives rise to a radical anion capable of electron transfer to another aryl halide, therefore propagating the chain.[12] The latter rearomatization mechanism was also suggested for our work in Chapter 5 (**Scheme 152**, *vide supra*). For the current alkyl cyclization, we can also rule out the formation of a cyclohexadienyl cation, due to the presence of the strong base NaHMDS (**Scheme 170**, *vide infra*). The pathway proposed by Curran and Studer is an attractive alternative. In 1974, Bunnett and Creary disclosed the replacement of two halogens in dihalobenzenes without the intermediacy of monosubstituted products.[243] In other words, formation of a radical anion on an aromatic ring where another halogen is present, would lead to loss of the halogen, and disubstitution. When *m*-chloroiodobenzene was irradiated in presence of thiophenoxide anion, the resulting radical anion **498** provided radical **500** via loss of chloride (**Scheme 169**). Radical **500** reacted with another thiophenoxide anion to provide **501**, which could transfer an electron to another aryl iodide and propagate the chain. Disubstituted **502** was obtained in 91% yield, along with traces of **499**. Later, Lei observed diarylation as the major product when dihalobenzenes were employed in his study and suggested the intermediacy of a radical anion in the reaction.[203]

**Scheme 169**. Bunnett and Creary's probe for radical anion formation



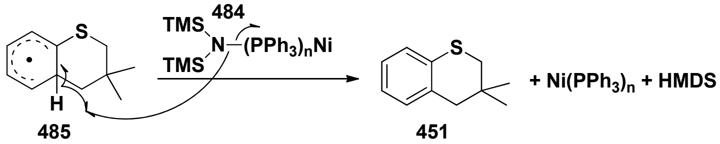
However, in our case, chloride-substituted compound **463** underwent the cyclization to give **464** in 74% yield, with the chloride surviving the reaction (**Table 31**). No coupling with the benzene solvent **506** was observed (**Scheme 170**). The intramolecular fragmentation of the substrate via loss of chloride should be favoured over intermolecular transfer of an electron to another alkyl iodide in a radical chain propagation. In Chapter 5, when a chloride-substituted substrate **395** was submitted to the KO*t*Bu-mediated reaction, traces of coupling of the product with the pyridine solvent via loss of chloride were observed by LC-MS (**Scheme 143**, *vide supra*). Therefore, a radical propagation process as proposed by Curran and Studer[12] for the KO*t*Bu reactions may be ruled out.

**Scheme 170**. Possible rearomatization pathways in the reaction



The more likely pathway is the direct involvement of a Ni species in the rearomatization step. Two different possibilities arise here: (a) the direct abstraction of H atom from **485** by Ni-amide complex **484** or (b) electron transfer from a possible radical anion **505** directly to Ni$^{I}$. The hydrogen atom abstraction (a) would parallel Curran, Bowman and Storey's proposed H-atom abstraction by AIBN (**Scheme 48**, *vide supra*). Additionally, it regenerates the Ni$^{0}$ catalyst and leads to the formation of HMDS as by-product (**Scheme 171**). Ni$^{III}$-imide complexes or Cu$^{II}$-amide complexes have been previously shown to perform hydrogen atom abstraction from an $sp^3$ C–H bond in various amination reactions.[244] The latter possibility (b) cannot be ruled out; moreover, the involvement of traces of oxygen in the reaction for rearomatization also cannot be dismissed.

**Scheme 171**. Proposed hydrogen atom abstraction by complex **484**



## 6.3 Conclusion

In summary, the intramolecular cyclization of alkyl iodides was reported in presence of $Ni(PPh_3)_4$ as the catalyst and NaHMDS as the base. The reaction tolerated a variety of functional groups, but required blocking of the β-position to avoid elimination reactions. The TEMPO adduct of the starting material was isolated, thus clearly demonstrating the involvement of radical species in the process. DOSY NMR studies revealed the existence of an adduct between the catalyst, the base and the starting material. The adduct is presumed to facilitate electron transfer between the $Ni^0$ catalyst and the alkyl iodide. Then, the cyclization proceeded through either *ortho* or *ipso* attack, depending on the nature of the tether (carbon vs. thioether).

# Chapter 7: Conclusion and perspectives

The functionalization of C–H bonds as a means of achieving C–C bond formation was the main theme of my PhD research. On the one hand, part of the work involved the use of transition metal catalysis for accomplishing activation of $sp^2$ and $sp^3$ centers. In particular, the direct functionalization of cyclopropanes is a topic of great significance in our group, and the results presented in the thesis have added to the few other examples in the literature. On the other hand, base-promoted homolytic aromatic substitution is a topic introduced recently in the literature, and the work that we and many others have disclosed has lead to a "renaissance"[245] of radical chemistry in organic synthesis.

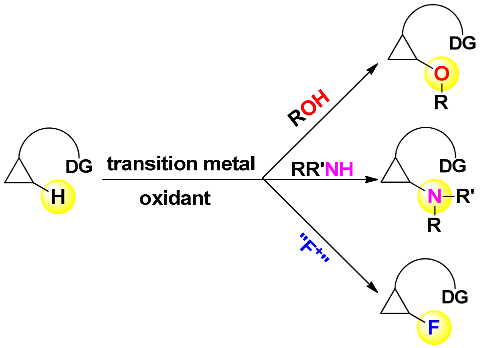
## 7.1 Direct functionalizations of cyclopropanes

Throughout the work, three distinct direct functionalizations of cyclopropanes were described. In an intramolecular system, the formation of 3,3'-cyclopropyloxindoles was found possible via a Pd-catalyzed, Ag-mediated cyclization of 2-bromoanilides. Through epimerization studies, a possible enolate arylation mechanism was ruled out. The calculated kinetic isotope effect suggested C–H bond breaking as the rate-limiting step. A concerted metalation-deprotonation mechanism mediated by either carbonate or phosphate was proposed for the reaction. In addition, a complimentary ring-opening of cyclopropanes was pursued. It was demonstrated that synthetically useful benzazepinone products can be synthesized via activation of a cyclopropane with a Pd catalyst, followed by nitrogen-assisted ring-opening. Key to the reaction was the use of a bulky ligand, $P\textit{t}Bu_3$, which also aided in the ring-opening. Finally, an intermolecular arylation of cyclopropanes was achieved using an *N,N*-bidentate auxiliary. The mechanism proposed involved a $Pd^{II/IV}$ catalytic cycle, where the acetate moiety acted as proton shuttle.

Certainly, one extension to the work would be the pursuit of an enantioselective cyclopropane arylation. Judicious screen of ligands for an intramolecular system could be a start point. For an intermolecular system, unfortunately, use of a tight binding auxiliary such as the picolinamide or aminoquinolinamide prevents the use of an additional ligand for palladium, as was demonstrated during our work. Since acetate or pivalate were proven necessary in the reaction, one possibility is the use of a chiral acid. Yu's group designed novel chiral amino acids to achieve enantioselectivity.[84] An initial screen of a few basic amino acids unfortunately led to no enantioselectivity in our picolinamide system. Nonetheless, the screen could be extended to other classes of acids, such as phosphoric acids. An alternate possibility would be the use of a monodentate chelating group that allows for a chiral ligand at the Pd centre.

Finally, the development of methodologies for the synthesis of cyclopropyl C-heteroatom bonds is attractive (**Scheme 172**). Although initial screenings for the acetoxylation reaction have not been fruitful, there remain many things to be investigated. In addition, transition metal-catalyzed direct fluorination of cyclopropanes with an electrophilic source of fluorine, which can also act as an oxidant, is worth pursuing.

**Scheme 172**. Proposed route to cyclopropyl C-heteroatom bond synthesis

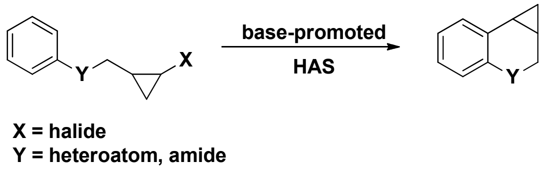


## 7.2 Base-promoted homolytic aromatic substitution

A transition metal-free intramolecular system for the cyclization of aryl ethers, amines and amides was developed. The reaction occurred in the presence of KO*t*Bu as the base and pyridine as the solvent, under microwave conditions. The formation of regioisomers when substitution was present on one of the aryl groups, along with radical scavenging experiments, led us to propose a homolytic aromatic substitution pathway for the transformation. Moreover, the interaction of a $Ni^0$ catalyst and NaHMDS promoted the cyclization of unactivated alkyl iodides at mild temperatures. The latter transformation was also proposed to occur via an HAS-like pathway. DOSY NMR studies determined the formation of an intereaction between the catalyst, base and starting material, presumably responsible for an electron transfer.

An extension of the work, based on our interest in cyclopropane functionalization, may involve addition of a cyclopropyl radical onto an arene in an HAS fashion (**Scheme 173**). Moreover, the design of domino radical cyclizations is also an alluring topic.

**Scheme 173**. HAS with a cyclopropyl radical



## 7.3 Direct functionalization of imidazo[1,5-*a*]azines

Prompted by easy access to a variety of imidazo[1,5-*a*]azines through a $Tf_2O$-promoted cyclization, we investigated the functionalization of the substrates through Ru-catalyzed arylation. Indeed, the fused nitrogen-heterocyle proved to be a good directing group for Ru. A thorough investigation of the influence of the sterics and electronics of the reaction demonstrated a clear preference for electron-withdrawing groups on the starting imidazo[1,5-*a*]pyridine. The proposed mechanism involved formation of a ruthenacycle prior to the oxidative addition step. An extension to the work would be to further arylate the imidazo[1,5-*a*]pyridines at the C-1 position via Pd catalysis, and explore the Ru- and Pd-catalyzed reactions in a one-pot procedure.

# Experimental Part

All non-aqueous reactions were run under argon atmosphere with flame-dried glassware using standard techniques for manipulating air-sensitive compounds.[246] Anhydrous solvents were obtained by filtration through drying columns or by distillation over sodium or calcium hydride. Commercial reagents were used as supplied or purified by standard techniques where necessary. The reported yields represent the yields of products isolated following recrystallization or flash chromatography.

Flash column chromatography was performed using 230-400 mesh silica or performed on an automatic purification system using the indicated solvent system (Teledyne Isco Combiflash® Rf or Sq16x). Pre-packed normal phase silica gel columns were used for separation of products using Teledyne Isco RediSep® Rf High Performance Gold or Silicycle SiliaSepTM High Performance columns (12g or 24g). Analytical thin-layer chromatography (TLC) was performed on pre-coated, glass-backed silica gel plates (Merck 60 F254) and visualized by UV absorbance (254 nm), and/or ceric ammonium molybdate (CAM), and potassium permanganate ($KMnO_4$). Analytical supercritical fluid chromatography was performed with a Berger SFC fashioned with a UV diode detector. SFC results are reported as follows: column type, eluent, retention time (tr).

Nuclear magnetic resonance spectra were recorded on an Avance AV400 MHz, Avance AV300 MHZ, DRX400 MHz, AV500 MHZ, or AV700 MHZ ($^1$H, $^{13}$C, $^{19}$F, 1D NOESY) spectrometer. Chemical shifts for $^1$H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CHCl_3$, $\delta = 7.26$ ppm). The data was reported as follows: chemical shift, multiplicity (s = singlet, s (br) = broad singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublets of doublets, t = triplet, q = quadruplet, m = multiplet), integration and coupling constant in Hz. Chemical shifts for $^{13}$C NMR spectra were recorded in parts per million from tetramethylsilane using the central peak of $CDCl_3$ (77.16 ppm) as the internal standard. All $^{13}$C NMR spectra were obtained with complete proton decoupling.

Infrared spectra were taken on a Bruker Vertex Series FTIR (neat) with the important vibrations reported in reciprocal centimeters ($cm^{-1}$). Melting points were obtained using a Thomas Hoover melting point apparatus and are uncorrected.

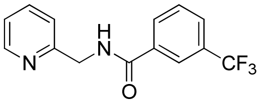
High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal using either ESI, or APPI ionization modes. X-ray structures were obtained though Laboratoire de diffraction des rayons-X de l'Université de Montréal using an Enraf-Nonius CAD-3 or CAD-4 apparatus.

# Experimental section of Chapter 2

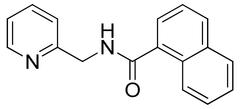
*Synthesis of amides*

**Procedure A**: To a cooled (ice/water bath) solution of 2-picolylamine (10 mmol, 1.0 equiv) in DCM (0.2 *M*) was added the corresponding acyl chloride (11 mmol, 1.1 equiv) and triethylamine (12 mmol, 1.2 equiv) dropwise. The reaction was allowed to warm to room temperature and stirred under an atmosphere of argon until complete (followed by TLC). The reaction was quenched by the addition of saturated *aqueous* $NaHCO_3$ (20 mL) and extracted with DCM (3x25 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified either by flash chromatography (Hex/EtOAc) or hot filtration (EtOAc).

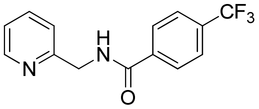
**Procedure B**: The corresponding carboxylic acid (10.5 mmol, 1.05 equiv) was dissolved in DCM (0.2 *M*) in a 100 mL round-bottomed flask. DMF (2-3 drops) was added to the solution, and the reaction was thoroughly purged with argon. Oxalyl chloride (11 mmol, 1.1 equiv) was added dropwise over 30 min. The reaction was stirred for an additional 1-2 h at ambient temperature (or until complete by TLC). The reaction was then concentrated to remove excess oxalyl chloride. The residue was dissolved in DCM (0.2 *M*) and cooled in an ice/water bath. 2-Picolylamine (10 mmol, 1.0 equiv) and triethylamine (12 mmol, 1.2 equiv) were added dropwise. The reaction was allowed to warm up to room temperature and stirred overnight (or until complete by TLC). The reaction was quenched by the addition of saturated *aqueous* $NaHCO_3$ (20 mL) and extracted with DCM (3x25 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified either by flash chromatography (Hex/EtOAc) or hot filtration (EtOAc).



***N*-(pyridin-2-ylmethyl)-3-(trifluoromethyl)benzamide (A1)**: Synthesized according to **Procedure B**, on a 10 mmol scale. After work-up, the residue was flashed in 50-100% EtOAc/Hex to give 2.54 g (9.06 mmol, 91% yield) of a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.50 (dd, 1H, *J* = 4.9, 0.6 Hz), 8.17-8.08 (m, 2H), 8.02 (d, 1H, *J* = 7.8 Hz), 7.73-7.60 (m, 2H), 7.50 (t, 1H, *J* = 7.8 Hz), 7.30 (d, 1H, *J* = 7.9 Hz), 7.22-7.14 (m, 1H), 4.72 (d, 2H, *J* = 5.0 Hz) ppm. $^{19}$F NMR (376 MHz, $CDCl_3$): δ -62.7 ppm.$^{13}$C NMR (75 MHz, $CDCl_3$): δ 166.1, 156.1, 149.0, 137.0, 135.2, 131.3 (q, $J_{C\text{-}F}$ = 32.8 Hz), 130.4 (m), 129.2, 128.1(q, $J_{C\text{-}F}$ = 3.8 Hz), 125.6 (q, $J_{C\text{-}F}$ = 272.3 Hz), 124.4 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.6, 122.3, 44.9 ppm. FTIR (cm$^{-1}$) (neat): 3323, 3069, 1753, 1477, 1330, 1119. HRMS (ESI, Pos): calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$: 281.0896, found 281.0896 *m/z*.



***N*-(pyridin-2-ylmethyl)-1-naphthamide (A2)**: Synthesized according to **Procedure B**, on a 10 mmol scale. After work-up, the resulting solid was purified by hot filtration from EtOAc. A brown solid was obtained (1.34 g, 5.11 mmol, 51%). mp: 105-106 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.54 (dd, 1H, *J* = 4.8, 0.7 Hz), 8.44-8.36 (m, 1H), 7.93 (d, 1H, *J* = 8.2 Hz), 7.91-7.84 (m, 1H), 7.76-7.68 (m, 2H), 7.59-7.45 (m, 3H), 7.39 (d, 1H, *J* = 7.9 Hz), 7.34 (br, s, 1H), 7.25-7.20 (m, 1H), 4.88 (d, 2H, *J* = 5.0 Hz) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.7, 156.2, 149.2, 140.0, 134.4, 133.8, 130.8, 130.4, 128.4, 127.2, 126.5, 125.7, 125.4, 124.9, 122.6, 122.3, 45.0 ppm. FTIR (cm$^{-1}$) (neat): 3244, 3057, 1632, 1545, 1315, 776, 755. HRMS (ESI, Pos): calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1179, found 263.1186 *m/z*.

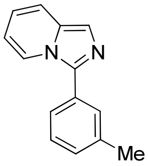


***N*-(pyridin-2-ylmethyl)-4-(trifluoromethyl)benzamide (A3)**: Synthesized according to **Procedure A**, on a 5 mmol scale. After work-up, the residue was flashed in 50-100% EtOAc/Hex to give 1.29 g (4.6 mmol, 92% yield) of a white solid. mp: 102-104 °C. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.57 (dd, 1H, *J* = 4.9, 0.9 Hz), 7.99 (dd, 1H, *J* = 8.1, 0.6 Hz), 7.79 (br. s), 7.76-7.67 (m, 3H), 7.37-7.30 (m, 1H), 7.29-7.20 (m, 1H), 4.77 (d, 2H, *J* = 4.5 Hz) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -62.9 ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 155.8, 149.1, 137.8, 137.1, 133.5 (q, $J_{C\text{-}F}$ = 32.1 Hz), 127.1, 125.7 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.2 (q, $J_{C\text{-}F}$ = 272.1 Hz), 122.7, 122.4, 44.8 ppm. FTIR ($cm^{-1}$) (neat): 3325, 1642, 1550, 1324, 1306, 1109, 1069. HRMS (ESI, Pos): calcd for $C_{14}H_{12}F_3N_2O$ $[M+H]^+$: 281.0896, found 281.0883 *m/z*.

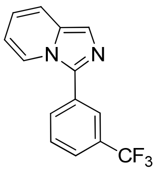
*Synthesis of imidazo[1,5-a]pyridines*

**Procedure C**: Adapted from a literature procedure,[114] in a flame-dried 20 mL microwave vial, the starting amide (3 mmol, 1.0 equiv) was dissolved in 6 mL dry DCM under Ar and the vial was crimped. To this, 2-methoxypyridine (3.3 mmol, 1.1 equiv) was added, and the reaction was cooled in an ice/water bath. Triflic anhydride (freshly distilled over $P_2O_5$) (4.5 mmol, 1.5 equiv) was added dropwise (reaction turned dark red). After the addition was complete, the reaction was stirred at room temperature for 5 min, then at 35 °C o/n. The reaction was cooled to room temperature and quenched by the slow addition of saturated *aqueous* $NaHCO_3$ (8 mL), followed by stirring for 5 min. Then, the two layers were separated and the *aqueous* layer was extracted with DCM (2x15 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated.

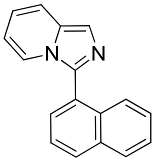
Some of the imidazo[1,5-*a*]azines have been previously reported in the literature.[114,122]



**3-(*m*-tolyl)imidazo[1,5-*a*]pyridine (186)**: Synthesized according to **Procedure C** on a 2.69 mmol scale. After work-up, the residue was flashed in 15-20% EtOAc/Hex to give 469 mg (2.25 mmol, 84%) of a red oil. $^1H$ NMR (300 MHz, $CDCl_3$): δ 8.26 (dq, 1H, *J* = 7.3, 1.0 Hz), 7.63 (ddd, 1H, *J* = 1.5, 1.1, 0.9 Hz), 7.61-7.56 (m, 1H), 7.55 (d, 1H, *J* = 0.9 Hz), 7.48 (dt, 1H, *J* = 9.2, 1.2 Hz), 7.40 (t, 1H, *J* = 7.6 Hz), 7.28-7.22 (m, 1H), 6.72 (ddd, 1H, *J* = 9.2, 6.4, 0.9 Hz), 6.56 (ddd, 1H, *J* = 7.4, 6.3, 1.2 Hz), 2.44 (s, 3H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 139.0, 138.4, 131.6, 130.1, 129.7, 129.0, 128.9, 124.9, 121.7, 120.3, 119.0, 118.9, 113.2, 21.6 ppm. FTIR ($cm^{-1}$) (neat): 2966, 2921, 1633, 1506, 1351, 1033. HRMS (ESI, Pos): calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.1073, found 209.1083 *m/z*.



**3-(3-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine (187)**: Synthesized according to Procedure C on a 3 mmol scale. After work-up, the residue was flashed in 15-20% EtOAc/Hex to give 540 mg (2.06 mmol, 69%) of a dark orange solid. mp: <50 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 8.23 (dd, 1H, *J* = 7.2, 0.8 Hz), 8.09 (s, 1H), 8.00 (d, 1H, *J* = 7.4 Hz), 7.71-7.61 (m, 2H), 7.59 (s, 1H), 7.52 (d, 1H, *J* = 9.2 Hz), 6.79 (ddd, 1H, *J* = 9.2, 6.4, 0.6 Hz), 6.64 (dd, 1H, *J* = 7.4, 6.2, 1.2 Hz) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -64.2 ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 136.7, 132.2, 131.9 (q, $J_{C\text{-}F}$ = 32.5 Hz), 131.3, 130.9 (m), 129.7, 125.8 (q, $J_{C\text{-}F}$ = 272.5 Hz), 125.2 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.8 (q, $J_{C\text{-}F}$ = 3.9 Hz), 121.2, 121.1, 119.4, 119.1, 114.0 ppm. FTIR (cm$^{-1}$) (neat): 3066, 2936, 1320, 1308, 1164, 1107. HRMS (ESI, Pos): calcd for $C_{14}H_{10}F_3N_2$ [M+H]$^+$: 263.0791, found 263.0790 *m/z*.

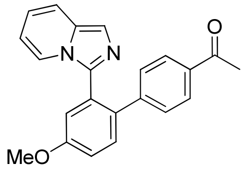


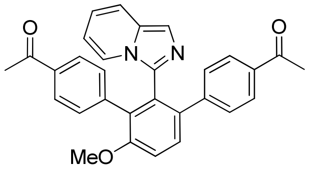
**3-(naphthalen-1-yl)imidazo[1,5-*a*]pyridine (192)**: Synthesized according to Procedure C on a 3 mmol scale. After work-up, the residue was flashed in 15-20% EtOAc/Hex to give 622 mg (2.55 mmol, 85%) of a brown solid. mp: 121-123 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, 1H, *J* = 8.2 Hz), 7.94 (d, 1H, *J* = 8.1 Hz), 7.78-7.64 (m, 4H), 7.60 (t, 1H, *J* = 7.7 Hz), 7.57-7.49 (m, 1H), 6.75 (dd, 1H, *J* = 9.1, 6.4 Hz), 6.47 (t, 1H, *J* = 6.8 Hz) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 137.0, 134.1, 132.0, 131.2, 129.9, 128.7, 127.4, 127.1, 126.4, 125.7, 125.4, 121.9, 120.3, 119.0, 118.7, 112.8 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2865, 1353, 1055, 1033, 902. HRMS (ESI, Pos): calcd for $C_{14}H_{12}N_2$ [M+H]$^+$: 245.1073, found 245.1065 *m/z*.

*Ruthenium-catalyzed direct arylation*

**Procedure D**: To a microwave vial (previously kept in an oven and cooled under argon) fit with a stir bar, the corresponding imidazo[1,5-*a*]azine (if solid, 0.4 mmol, 1.0 equiv), 2,4,6-trimethylbenzoic acid (0.12 mmol, 0.3 equiv) and the aryl bromide (0.48 mmol, 1.2 equiv), if solid, were added. The vial was then placed in a glove box where dichloro(p-cymene)ruthenium dimer (0.02 mmol, 0.05 equiv) and potassium carbonate (0.8 mmol, 2.0 equiv) were added. The vial was crimped and taken out of the glove box. The aryl bromide (0.48 mmol, 1.2 equiv), if liquid, was added via syringe, followed by dry toluene (2 mL); or, if the imidazo[1,5-*a*]azine was an oil, it was added at this point as a solution in 2 mL toluene (0.2 *M* solution). The reaction was stirred at 130 °C for 15 h. Then, the reaction was allowed to cool to rt, and filtered over a pad of silica and celite, rinsing with EtOAc (15-20 mL). The organic layer was washed with a solution of saturated *aqueous* $K_2CO_3$ (15 mL), water (15 mL). The *aqueous* layer was extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography.

**Procedure E**: To a microwave vial (previously kept in an oven and cooled under argon) fit with a stir bar, the corresponding imidazo[1,5-*a*]azine (if solid, 0.4 mmol, 2.0 equiv), 2,4,6-trimethylbenzoic acid (0.06 mmol, 0.3 equiv) and the aryl bromide (0.2 mmol, 1.0 equiv), if solid, were added. The vial was then placed in a glove box where dichloro(p-cymene)ruthenium dimer (0.01 mmol, 0.05 equiv) and potassium carbonate (0.4 mmol, 2.0 equiv) were added. The vial was crimped and taken out of the glove box. The aryl bromide (0.2 mmol, 1.0 equiv), if liquid, was added via syringe, followed by dry toluene (2 mL); or, if the imidazo[1,5-*a*]azine was an oil, it was added at this point as a solution in 2 mL toluene (0.2 *M* solution). The reaction was stirred at 130 °C for 15 h. Then, the reaction was allowed to cool to rt, and filtered over a pad of silica and celite, rinsing with EtOAc (15-20 mL). The organic layer was washed with a solution of saturated *aqueous* $K_2CO_3$ (15 mL), water (15 mL). The *aqueous* layer was extracted with EtOAc (2x10 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography.





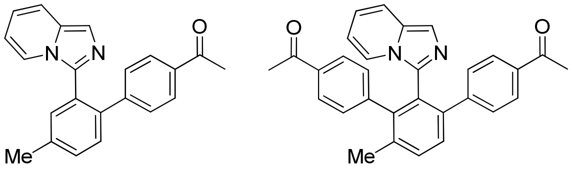
**1-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-methoxy-[1,1'-biphenyl]-4-yl)ethanone (182a)** and **1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-methoxy-[1,1':3',1''-terphenyl]-4,4''-**

**diyl)diethanone (182b)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (25-80% EtOAc/Hex) to give **182a** (70 mg, 0.204 mmol, 51%) as a yellow oil and **182b** (40 mg, 0.087 mmol, 22%) as a dark oil.

Synthesized according to **Procedure E**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80% EtOAc/Hex) to give **182a** (63.5 mg, 0.186 mmol, 93%) and unreacted **182** (19 mg, 0.0847 mmol, 21%).

**182a**: $^1$H NMR (300 MHz, $CDCl_3$): δ δ 7.72-7.64 (m, 2H), 7.54-7.45 (m, 2H), 7.37-7.31 (m, 1H), 7.23 (d, 1H, $J$ = 2.8 Hz), 7.19 (dd, 1H, $J$ = 7.2, 0.9 Hz), 7.13 (dd, 1H, $J$ =8.6, 2.8 Hz), 7.12-7.06 (m, 2H), 6.52 (ddd, 1H, $J$ = 9.1, 6.4, 0.7 Hz), 6.15 (td, 1H, $J$ = 6.8, 1.1 Hz), 3.89 (s, 3H), 2.48 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 159.9, 145.2, 137.4, 135.3, 132.9, 131.5, 130.8, 130.0, 128.5, 128.1, 120.9, 120.2, 118.8, 118.2, 116.7, 116.6, 112.4, 55.7, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2865, 1678, 1602, 1264, 1177, 1051. HRMS (ESI, Pos): calcd for $C_{22}H_{19}N_2O_2$ [M+H]$^+$: 343.1441, found 343.1424 *m/z*.

**182b**: $^1$H NMR (400 MHz, $CDCl_3$): δ 7.71-7.63 (m, 4H), 7.56 (d, 1H, $J$ = 8.6 Hz), 7.28-7.15 (m, 4H), 7.06 (d, 2H, $J$ = 8.3 Hz), 6.47 (dd, 1H, $J$ = 9.0, 6.4 Hz), 6.22 (t, 1H, $J$ = 6.4 Hz), 3.83 (s, 3H), 2.48 (d, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 198.0, 197.9, 156.9, 145.2, 141.2, 135.5, 135.4, 135.3, 134.9, 132.5, 131.0, 130.1, 129.5, 129.4, 128.5, 128.2, 127.6, 120.3, 119.8, 118.3, 118.2, 112.8, 112.6, 56.2, 26.7 (2) ppm. FTIR (cm$^{-1}$) (neat): 2938, 2865, 1677, 1355, 1264, 1056, 1006. HRMS (ESI, Pos): calcd for $C_{30}H_{25}N_2O_3$ [M+H]$^+$: 461.1860, found 461.1861 *m/z*.

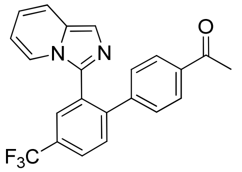


**1-(2'-(imidazo[1,5-a]pyridin-3-yl)-4'-methyl-[1,1'-biphenyl]-4-yl)ethanone (186a) and 1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-methyl-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (186b)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (25-80% EtOAc/Hex) to give **186a** (113 mg, 0.356 mmol, 87%) as a thick yellow oil and **186b** (8 mg, 0.017 mmol, 4%) as a thick yellow oil.

Synthesized according to **Procedure E**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80% EtOAc/Hex) to give **186a** (64 mg, 0.196 mmol, 98%) and unreacted **186** (21 mg, 0.10 mmol, 25%). The dimer **188** was also isolated (14 mg, 0.0338 mmol, 17%).

**186a**: $^1$H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, 2H, *J* = 8.5 Hz), 7.56-7.48 (m, 2H), 7.48-7.43 (m, 1H), 7.41-7.36 (m, 1H), 7.32 (d, 1H, *J* = 9.2 Hz), 7.18 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.12 (d, 2H, *J* = 8.4 Hz), 6.50 (ddd, 1H, *J* = 9.1, 6.4, 0.8 Hz), 6.13 (td, 1H, *J* = 6.8, 1.1 Hz), 2.47 (s, 3H), 2.45 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.7, 145.4, 138.8, 137.6 (2), 135.4, 133.0, 130.7, 130.6, 130.1, 128.5, 128.4, 128.2, 120.8, 120.1, 118.6, 118.1, 112.2, 26.6, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1678, 1603, 1354, 1265, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{22}H_{19}N_2O$ $[M+H]^+$: 327.1492, found 327.1507 *m/z*.

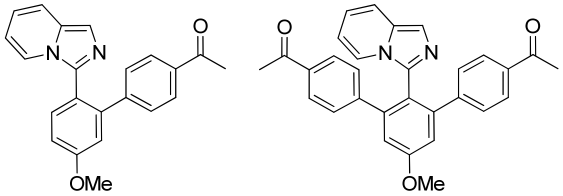
**186b**: $^1$H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, 2H, *J* = 8.5 Hz), 7.60-7.54 (m, 2H), 7.52 (d, 1H, *J* = 7.9 Hz), 7.46-7.39 (m, 3H), 7.28-7.23 (m, 2H), 7.05 (d, 2H, *J* = 8.5 Hz), 6.89 (d, 1H, *J* = 1.7 Hz), 6.62 (dd, 1H, *J* = 8.9, 6.4 Hz), 6.24 (t, 1H, *J* = 6.7 Hz), 2.62 (s, 3H), 2.47 (s, 3H), 1.99 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 203.0, 197.9, 145.6, 143.4, 140.0, 139.0, 138.0, 137.8, 137.3, 136.3, 133.1, 131.0, 130.1, 130.0, 129.0, 128.8, 128.6, 127.7, 121.1, 120.3, 118.8, 118.2, 112.3, 30.3, 27.0, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2972, 1682, 1346, 1056, 1032, 1013. HRMS (ESI, Pos): calcd for $C_{30}H_{25}N_2O_2$ $[M+H]^+$: 445.1910, found 445.1904 *m/z*.



**1-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethanone (187a)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified in flash chromatography (10-80% EtOAc/Hex) to give **187a** (108 mg, 0.284 mmol, 71%) and a mixture of **187b**, **187a** and $MesCO_2H$ (13 mg).

Synthesized according to **Procedure E**, employing 4’-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80% EtOAc/Hex) to give **187a** (74 mg, 0.195 mmol, 98%) and unreacted **187** (18 mg, 0.069 mmol, 17%).

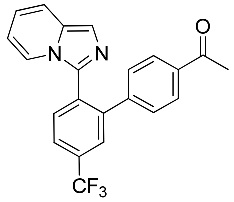
**187a**: $^1$H NMR (300 MHz, $CDCl_3$): δ 8.01 (d, 1H, *J* = 1.2 Hz), 7.83 (dd, 1H, *J* = 8.2, 1.3 Hz), 7.77-7.65 (m, 3H), 7.54 (s, 1H), 7.37 (d, 1H, *J* = 9.2 Hz), 7.20-7.12 (m, 3H), 6.57 (ddd, 1H, *J* = 9.1, 6.4, 0.6 Hz), 6.25-6.17 (m, 1H), 2.49 (s, 3H) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -64.04 ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.6, 143.9, 143.8 (m), 136.3, 135.8, 133.2 (q, $J_{C\text{-}F}$ = 33.0 Hz), 131.0, 130.8, 129.6, 129.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 128.7, 128.3, 126.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 125.7 (q, $J_{C\text{-}F}$ = 272.6 Hz), 120.7, 120.5, 119.2, 118.4, 112.9, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1681, 1321, 1261, 1056, 1005. HRMS (ESI, Pos): calcd for $C_{22}H_{16}F_3N_2O$ $[M+H]^+$: 381.1209, found 381.1208 *m/z*.

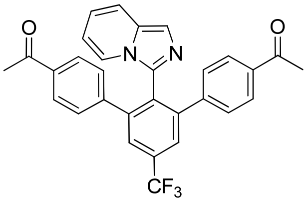


**1-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-5'-methoxy-[1,1'-biphenyl]-4-yl)ethanone (165a) and 1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-5'-methoxy-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (165b)**: Synthesized according to **Procedure D**, employing *4’-chloroacetophenone* as the coupling partner. After work-up, the residue was purified by flash chromatography (20-80% EtOAc/Hex) to give **165a** (67 mg, 0.196 mmol, 49%) as a yellow solid and **165b** (36 mg, 0.078 mmol, 20%) as an off-white solid.

**165a**: mp = 122-126 °C. $^1$H NMR (500 MHz, acetone-$d_6$): δ 7.73 (d, 2H, *J* = 8.5 Hz), 7.61-7.54 (m, 1H), 7.45-7.39 (m, 2H), 7.37 (dd, 1H, *J* = 7.2, 0.9 Hz), 7.23 (d, 2H, *J* = 8.5 Hz), 7.19-7.14 (m, 2H), 6.57 (ddd, 1H, *J* = 9.1, 6.3, 0.8 Hz), 6.31-6.24 (m, 1H), 3.95 (s, 3H), 2.47 (s, 3H) ppm. $^{13}$C NMR (125 MHz, acetone-$d_6$): δ 197.5, 161.8, 146.2, 143.2, 138.1, 136.8, 134.5, 131.5, 129.3, 129.0, 122.4, 122.0, 120.7, 119.3, 118.9, 116.3, 115.0, 112.9, 56.1, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2950, 2865, 1678, 1600, 1356, 1056, 1013. HRMS (ESI, Pos): calcd for $C_{22}H_{19}N_2O_2$ $[M+H]^+$: 343.1441, found 343.1454 *m/z*.

**165b**: mp = 229-231 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 4H, *J* = 8.4 Hz), 7.26 (d, 1H, *J* = 0.6 Hz), 7.24-7.17 (m, 2H), 7.14-7.10 (m, 4H), 7.10 (s, 2H), 6.48 (ddd, 1H, *J* = 9.1, 6.4, 0.7 Hz), 6.21 (td, 1H, *J* = 7.3, 1.1 Hz), 3.95 (s, 3H), 2.49 (s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 160.6, 145.4, 145.1, 135.8, 135.0, 129.7, 128.6, 128.1, 120.2, 119.8, 119.7, 118.3, 118.2, 115.4, 112.6, 55.8, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2939, 2865, 1670, 1594, 1345, 1266, 1209, 1055, 1013. HRMS (ESI, Pos): calcd for $C_{30}H_{25}N_2O_3$ $[M+H]^+$: 461.1860, found 461.1865 *m/z*.

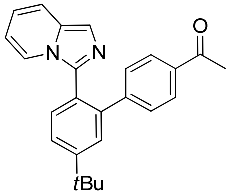


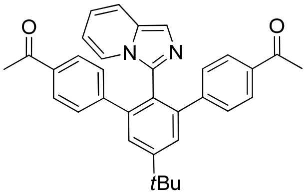


**1-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-5'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethanone (166a) and 1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-5'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (166b)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified by flash chromatography (15-50% EtOAc/Hex) to give **166a** (92 mg, 0.242 mmol, 60%) as a thick yellow oil and **166b** (63 mg, 0.126 mmol, 32%) as a brown solid.

**166a**: $^1$H NMR (300 MHz, $CDCl_3$): δ 7.90-7.68 (m, 5H), 7.55 (d, 1H, *J* = 0.7 Hz), 7.37 (d, 1H, *J* = 9.2 Hz), 7.22-7.12 (m, 3H), 6.58 (ddd, 1H, *J* = 9.2, 6.4, 0.7 Hz), 6.25-6.15 (m, 1H), 2.50 (s, 3H) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -62.6 ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 197.6, 144.0, 141.0, 136.2, 135.9, 133.0, 132.4, 132.1 (q, $J_{C\text{-}F}$ = 32.7 Hz), 131.2, 128.7, 128.3, 127.2 (m), 125.7 (q, $J_{C\text{-}F}$ = 272.6 Hz), 125.4 (m), 120.9, 120.6, 119.2, 118.4, 112.9, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2950, 2844, 1681, 1332, 1122, 1056, 1013. HRMS (ESI, Pos): calcd for $C_{22}H_{16}F_3N_2O$ $[M+H]^+$: 381.1209, found 381.1223 *m/z*.

**166b**: mp = 229-231 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, 2H, *J* = 0.4 Hz), 7.76-7.70 (m, 4H), 7.33-7.25 (m, 2H), 7.18 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.15-7.09 (m, 4H), 6.54 (ddd, 1H, *J* = 9.1, 6.4, 0.7 Hz), 6.27 (td, 1H, *J* = 7.4, 1.1 Hz), 2.51 (s, 6H) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -62.7 ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.6, 144.5, 144.0, 136.2, 133.6, 132.6 (q, $J_{C\text{-}F}$ = 33.0 Hz), 130.9, 130.1, 128.6, 128.4, 126.7 (m), 124.8 (q, $J_{C\text{-}F}$ = 273.1 Hz), 120.5, 119.9, 118.9, 118.4, 113.3, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 1938, 2823, 1682, 1357, 1263, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{30}H_{22}F_3N_2O_2$ [M+H]$^+$: 499.1628, found 499.1609 *m/z*.

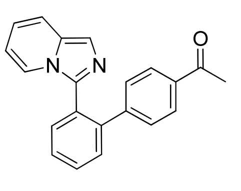


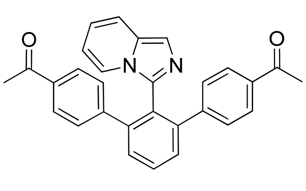


**1-(5'-(tert-butyl)-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1'-biphenyl]-4-yl)ethanone (167a) and 1,1'-(5'-(tert-butyl)-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (167b)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone as the coupling partner. After work-up, the residue was purified by flash chromatography (20-80% EtOAc/Hex) to give **167a** (81 mg, 0.220 mmol, 55%) as a thick brown oil and **167b** (42 mg, 0.086 mmol, 22%) as an off-white solid.

**167a**: $^1$H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H, *J* = 8.2 Hz), 7.66-7.63 (m, 1H), 7.60-7.52 (m, 2H), 7.49 (s, 1H), 7.32 (d, 1H, *J* = 9.2 Hz), 7.28-7.23 (m, 1H), 7.16 (d, 2H, *J* = 8.2 Hz), 6.51 (dd, 1H, *J* = 9.1, 6.4 Hz), 6.15 (t, 1H, *J* = 6.8 Hz), 2.49 (s, 3H), 1.41 (s, 9H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 197.8, 153.2, 146.1, 140.2, 137.5, 135.6, 132.0, 130.6, 128.4 (2), 127.2, 125.9, 125.8, 121.0, 120.0, 118.6, 118.2, 112.2, 35.1, 31.4, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2844, 1680, 1603, 1455, 1355, 1056, 1014. HRMS (ESI, Pos): calcd for $C_{25}H_{25}N_2O$ [M+H]$^+$: 369.1961, found 369.1959 *m/z*.

**167b**: mp = 212-214 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, 4H, *J* = 8.7 Hz), 7.57 (s, 2H), 7.28 (d, 1H, *J* = 0.7 Hz), 7.26-7.20 (m, 2H), 7.15-7.09 (m, 4H), 6.51-6.46 (m, 1H), 6.20 (ddd, 1H, *J* = 7.3, 6.4, 0.9 Hz), 2.50 (s, 6H), 1.45 (s, 9H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.9, 153.6, 146.1, 143.2, 135.6, 135.3, 129.7, 128.7, 128.2, 127.3, 124.5, 120.4, 120.0, 118.4, 118.2, 112.6, 35.2, 31.4, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2939, 2865, 1678, 1454, 1266, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{33}H_{31}N_2O_2$ [M+H]$^+$: 487.2380, found 487.2390 *m/z*.





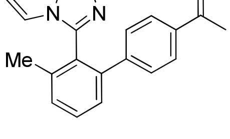
**1-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1'-biphenyl]-4-yl)ethanone (164a)** and **1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (164b)**: Synthesized according to **Procedure D**, employing the corresponding 4-haloacetophenone as the coupling partner. After work-up, the residue was purified by flash chromatography (20-100% EtOAc/Hex, RediSep Gold column 12 g) to give **164a** as a thick yellow oil and **164b** as a brown solid.

*4'-bromoacetophenone*: **164a** (51 mg, 0.163 mmol, 41%) and **164b** (39 mg, 0.091 mmol, 23%); *4'-chloroacetophenone*: **164a** (62 mg, 0.199 mmol, 50%) and **164b** (46 mg, 0.107 mmol, 27%); *4'-iodoacetophenone*: **164a** (39 mg, 0.125 mmol, 31%) and **164b** (34 mg, 0.079 mmol, 20%); *4'-bromoacetophenone* (*3 equiv*): **164a** (133 mg, 0.309 mmol, 77%) and **164b** (none observed)

**164a**: $^1$H NMR (400 MHz, CDCl$_3$): δ 7.75-7.66 (m, 3H), 7.63-7.52 (m, 2H), 7.51 (s, 1H), 7.34 (d, 1H, *J* = 9.2 Hz), 7.22 (dd, 1H, *J* = 7.2, 0.9 Hz), 7.18-7.10 (m, 2H), 6.53 (ddd, 1H, *J* = 9.1, 6.4, 0.7 Hz), 6.17 (td, 1H, *J* = 8.8, 1.1 Hz), 2.49 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 197.8, 145.4, 140.6, 137.4, 135.7, 132.4, 130.7, 130.2, 130.0, 128.8 (2), 128.5, 128.3, 120.8, 118.7, 118.2, 112.4, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2844, 1679, 1356, 1265, 1055, 1006.

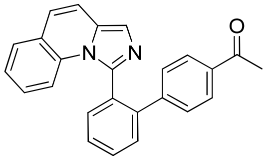
HRMS (ESI, Pos): calcd for $C_{21}H_{17}N_2O$ [M+H]$^+$: 313.1335, found 313.1340 *m/z*.

**164b**: mp = 92-94 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.74-7.66 (m, 5H), 7.61-7.56 (m, 2H), 7.29 (s, 1H), 7.27-7.23 (m, 1H), 7.19 (dd, 1H, *J* = 7.1, 0.8 Hz), 7.11-7.09 (m, 4H), 6.50 (ddd, 1H, *J* = 9.2, 6.4, 0.6 Hz), 6.22 (td, 1H, *J* = 7.3, 1.2 Hz), 2.50 (s, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 197.8, 145.4, 143.6, 135.7, 135.1, 130.4, 130.1, 129.8, 128.6, 128.2, 127.3, 120.2, 120.0, 118.5, 118.3, 112.8, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2949, 2844, 1674, 1356, 1265, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{29}H_{23}N_2O_2$ [M+H]$^+$: 431.1754, found 431.1772 *m/z*.

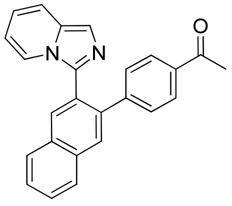


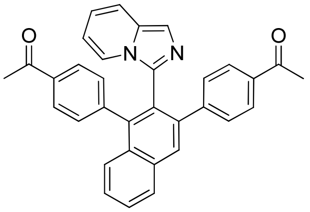
**1-(2'-(imidazo[1,5-a]pyridin-3-yl)-3'-methyl-[1,1'-biphenyl]-4-yl)ethanone (189a)**: Synthesized according to **Procedure D**, employing 4'-bromoacetophenone (1.5 equiv) as the coupling partner. After work-up, the residue was purified by flash chromatography (20-50%

$Et_2O$/Hex) to give **189a** (82 mg, 0.251 mmol, 63%) as a brown solid and unreacted **189** (3 mg, <4%). mp = 119-122 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.65 (d, 2H, *J* = 8.6 Hz), 7.51-7.45 (m, 2H), 7.42-7.37 (m, 1H), 7.37-7.30 (m, 2H), 7.15 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.10 (d, 2H, *J* = 8.5 Hz), 6.54 (ddd, 1H, *J* = 9.1, 6.3, 0.8 Hz), 6.25 (ddd, 1H, *J* = 7.2, 6.3, 1.1 Hz), 2.46 (s, 3H), 2.17 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): 197.0, 145.8, 142.5, 140.6, 136.0, 135.4, 130.4, 130.0 (2), 128.5, 128.1, 127.6, 125.6, 120.7, 119.7, 118.4, 118.3, 112.5, 26.7, 20.1 ppm. FTIR (cm$^{-1}$) (neat): 2939, 2826, 1679, 1604, 1355, 1266, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{22}H_{19}N_2O$ $[M+H]^+$: 327.1492, found 327.1505 *m/z*.



**1-(2'-(imidazo[1,5-*a*]quinolin-1-yl)-[1,1'-biphenyl]-4-yl)ethanone (190a)**: Synthesized according to **Procedure D**, employing 4’-bromoacetophenone as the coupling partner. After work-up, the residue was purified in flash chromatography (20-80% EtOAc/Hex) to give **190a** (96 mg, 0.264 mmol, 66%) as a brown solid. mp = 156-158 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, 1H, *J* = 7.4 Hz), 7.67 (td, 1H, *J* = 7.5, 1.2 Hz), 7.64-7.57 (m, 1H), 7.56-7.51 (m, 3H), 7.50 (s, 1H), 7.44 (d, 1H, *J* = 7.5 Hz), 7.27-7.17 (m, 3H), 7.14-7.06 (m, 1H), 6.98 (d, 2H, *J* = 8.3 Hz), 6.85 (d, 1H, *J* = 9.4 Hz), 2.41 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 197.8, 144.9, 141.5, 140.7, 135.4, 132.5, 131.9, 131.4, 130.4, 130.2, 130.0, 128.9 (2), 128.5, 127.8, 127.5, 125.3, 125.2, 121.7, 121.5, 116.9, 116.5, 26.6 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1681, 1605, 1372, 1266, 1055, 1013. HRMS (ESI, Pos): calcd for $C_{25}H_{19}N_2O$ $[M+H]^+$: 363.1492, found 363.1458 *m/z*.





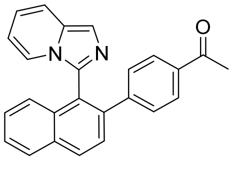
**1,1'-(2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-(trifluoromethyl)-[1,1':3',1''-terphenyl]-4,4''-diyl)diethanone (191a)** and **1,1'-((2-(imidazo[1,5-*a*]pyridin-3-yl)naphthalene-1,3-diyl)bis(4,1-phenylene))diethanone (191b)**: Synthesized according to **Procedure D**, employing 4’-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (20-80% EtOAc/Hex) to give **191a** (46 mg, 0.127 mmol, 32%) as a thick brown oil and **191b** (38 mg, 0.079 mmol, 20%) as a thick brown oil.

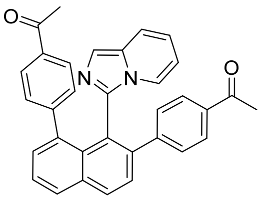
Synthesized according to **Procedure E**, employing 4’-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80% EtOAc/Hex) to give **191a** (30 mg, 0.083 mmol, 41%) and unreacted **191** (10 mg, 0.041 mmol, 10%).

**191a**: $^{1}$H NMR (300 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.01 (s, 1H), 7.92 (t, 2H, *J* = 8.3 Hz), 7.71 (d, 2H, *J* = 8.0 Hz), 7.61-7.49 (m, 3H), 7.33 (d, 1H, *J* = 9.2 Hz), 7.29-7.18 (m, 3H), 6.52 (dd, 1H, *J* = 8.1, 7.2 Hz), 6.16 (t, 1H, *J* = 6.5 Hz), 2.48 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.8, 145.4, 138.0, 135.7, 133.8, 132.9, 132.4, 129.7, 128.5 (2), 128.3, 128.2, 127.6, 127.3, 126.7, 120.8, 120.2, 118.8, 118.3, 112.5, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2865, 1677, 1603, 1403, 1264, 1055, 1010. HRMS (ESI, Pos): calcd for $C_{25}H_{19}N_2O$ $[M+H]^+$: 363.1492, found 363.1509 *m/z*.

**191b**: $^{1}$H NMR (300 MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.05 (d, 1H, *J* = 8.0 Hz), 7.90 (d, 1H, *J* = 8.0 Hz), 7.77-7.70 (m, 3H), 7.70-7.60 (m, 2H), 7.59-7.47 (m, 2H), 7.32-7.17 (m, 5H), 7.08 (d, 1H, *J* = 7.7 Hz), 6.51 (t, 1H, *J* = 7.5 Hz), 6.32-6.21 (m, 1H), 2.57 (s, 3H), 2.52 (s, 3H) ppm.

$^{13}$C NMR (125 MHz, $CDCl_3$): δ 197.9 (2), 145.3, 143.2, 142.6, 139.5, 136.0, 135.7, 135.2, 134.1, 131.7, 131.4, 129.6, 129.5, 129.1, 128.8, 128.6, 128.1, 127.8, 127.6, 127.4, 126.7, 120.2, 119.7, 118.4, 118.3, 112.7, 26.7 (2) ppm. FTIR (cm$^{-1}$) (neat): 2938, 2843, 1681, 1604, 1455, 1357, 1266, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{33}H_{25}N_2O_2$ $[M+H]^+$: 481.1910, found 481.1933 *m/z*.

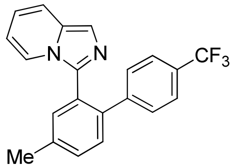




**1-(4-(1-(imidazo[1,5-a]pyridin-3-yl)naphthalen-2-yl)phenyl)ethanone (192a)** and **1-(4-(1-(1-(4-acetylphenyl)imidazo[1,5-a]pyridin-3-yl)naphthalen-2-yl)phenyl)ethanone (192b)**: Synthesized according to **Procedure D**, employing 4’-bromoacetophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (20-80% EtOAc/Hex) to give **192a** (83 mg, 0.228 mmol, 57%) as a green solid and **192b** (36 mg, 0.075 mmol, 19%) as a thick brown oil. Structure of **192b** was confirmed by HMBC, COSY and NOESY experiments on a 700 MHz spectrometer.

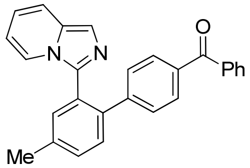
**192a**: mp = 171-174 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, 1H, *J* = 8.4 Hz), 7.96 (d, 1H, *J* = 7.9 Hz), 7.71 (d, 2H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.6 Hz), 7.64 (s, 1H), 7.61 (d, 1H, *J* = 8.4 Hz), 7.55 (t, 1H, *J* = 7.4 Hz), 7.46 (t, 1H, *J* = 7.4 Hz), 7.40 (d, 1H, *J* = 9.2 Hz), 7.21 (d, 2H, *J* = 8.2 Hz), 7.12 (d, 1H, *J* = 7.1 Hz), 6.57 (dd, 1H, *J* = 9.0, 6.4 Hz), 6.20 (t, 1H, *J* = 6.8 Hz), 2.49 (s, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 197.8, 145.7, 139.9, 135.6, 135.0, 133.7, 133.4, 130.6, 130.4, 128.8, 128.2 (2), 127.6, 127.4, 126.9, 126.3, 125.4, 120.9, 120.2, 118.7, 118.3, 112.5, 26.7 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1678, 1601, 1357, 1261, 1054, 1013. HRMS (ESI, Pos): calcd for $C_{25}H_{19}N_2O$ [M+H]$^+$: 363.1492, found 363.1496 *m/z*.

**192b**: $^1$H NMR (700 MHz, CDCl$_3$): δ 8.16 (d, 1H, *J* = 8.5 Hz), 8.02 (dd, 1H, *J* = 8.2, 1.2 Hz), 7.65-7.61 (m, 3H), 7.58 (dd, 1H, *J* = 8.1, 7.2 Hz), 7.55 (dd, 1H, *J* = 8.0, 1.9 Hz), 7.32 (dd, 1H, *J* = 7.0, 1.2 Hz), 7.12 (dd, 1H, *J* = 8.0, 1.7 Hz), 7.08 (dd, 1H, *J* = 8.0, 1.9 Hz), 7.03 (dd, 1H, *J* = 7.0, 1.0 Hz), 6.95 (d, 2H, *J* = 8.3 Hz), 6.93-6.91 (m, 2H), 6.71 (dd, 1H, *J* = 8.0, 1.8 Hz), 6.45 (dd, 1H, *J* = 9.1, 6.3 Hz), 6.34-6.28 (m, 1H) 2.46 (s, 3H), 2.40 (s, 3H) ppm. $^{13}$C NMR (175 MHz, CDCl$_3$): δ 197.8, 197.7, 146.1, 145.9, 142.9, 139.5, 135.3, 135.2, 134.6, 134.1, 131.7, 131.5, 131.3, 129.5, 129.1 (2), 128.5, 127.9 (2), 126.8, 126.1, 126.0, 125.5, 124.7, 120.5, 120.0, 118.3, 117.8, 112.8, 26.7, 26.6 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2865, 1675, 1601, 1356, 1264, 1056, 1014. HRMS (ESI, Pos): calcd for $C_{33}H_{25}N_2O_2$ [M+H]$^+$: 481.1910 *m/z*, found 481.1916 *m/z*.

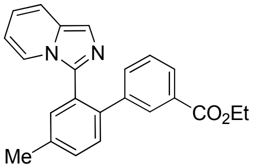


**3-(4-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (186d)**: Synthesized according to **Procedure D**, employing 4-trifluoromethylbromebenzene as the coupling partner. After work-up, the residue was purified via flash chromatography (10-80% EtOAc/Hex) to give **186d** (84 mg, 0.238 mmol, 60%) as an off-white solid. Traces of a dimer

**188** were observed by LC-MS analysis. mp = 120-122 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.54 (dd, 1H, *J* = 1.2, 0.6 Hz), 7.51 (d, 1H, *J* = 0.8 Hz), 7.47-7.43 (m, 1H), 7.42-7.38 (m, 1H), 7.38-7.31 (m, 3H), 7.18 (dq, 1H, *J* = 7.2, 1.0 Hz), 7.14 (d, 2H, *J* 8.0 Hz), 6.53 (ddd, 1H, *J* = 9.2, 6.4, 0.9 Hz), 6.16 (ddd, 1H, *J* = 7.3, 6.3, 1.2 Hz), 2.46 (s, 3H) ppm. $^{19}$F NMR (282 MHz, CDCl$_3$): δ -62.6 ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 144.2, 138.9, 137.5, 137.4, 133.0, 130.8, 130.7, 130.2, 129.2 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.6, 128.4, 125.3 (q, $J_{C\text{-}F}$ = 3.6 Hz), 123.1 (q, $J_{C\text{-}F}$ = 272.0 Hz), 120.8, 120.2, 118.6, 118.2, 112.3, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2939, 2865, 1323, 1164, 1121, 1056, 1015, 851. HRMS (ESI, Pos): calcd for $C_{21}H_{16}F_3N_2$ [M+H]$^+$: 353.1261, found 353.1269 *m/z*.

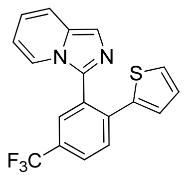


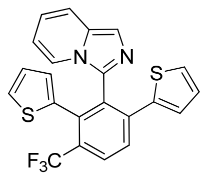
**(2'-(imidazo[1,5-a]pyridin-3-yl)-4'-methyl-[1,1'-biphenyl]-4-yl)(phenyl)methanone (186f)**: Synthesized according to **Procedure D**, employing 4'-bromobenzophenone as the coupling partner. After work-up, the residue was purified via flash chromatography (10-80% EtOAc/Hex) to give **186f** (57.5 mg, 0.148 mmol, 37%) as a brown oil, a mixture of **186f** and **186g** (23 mg, 4:1, 10% **186f**) and **188** (15 mg, 18%). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.66-7.59 (m, 2H), 7.59-7.48 (m, 6H), 7.42 (d, 3H, *J* = 6.3 Hz), 7.36 (d, 1H, *J* = 8.9 Hz), 7.19 (d, 1H, *J* = 6.8 Hz), 7.13 (d, 2H, *J* = 8.3 Hz), 6.55 (t, 1H, *J* = 8.1 Hz), 6.16 (t, 1H, *J* = 7.1 Hz), 2.47 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 196.4, 144.7, 138.9, 137.7, 137.6, 135.8, 133.0, 132.4, 130.8, 130.7, 130.2, 130.0, 128.6, 128.3, 127.9, 121.0, 120.2, 118.6, 118.2, 112.2, 21.2 ppm. FTIR (cm$^{-1}$) (neat): 2972, 1654, 1602, 1276, 1056, 1014. HRMS (ESI, Pos): calcd for $C_{27}H_{12}N_2O$ [M+H]$^+$: 389.1648, found 389.1657 *m/z*.



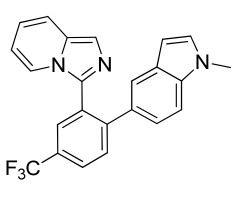
**ethyl 2'-(imidazo[1,5-*a*]pyridin-3-yl)-4'-methyl-[1,1'-biphenyl]-3-carboxylate (186h)**: Synthesized according to **Procedure D**, employing ethyl-3-bromobenzoate as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80%

EtOAc/Hex) to give **186h** (68 mg, 0.191 mmol, 48%, containing traces of $MesCO_2H$) as a thick yellow oil and dimer **188** (17 mg, 0.041 mmol, 20%). Compound **186h** was further washed with saturated *aqueous* $K_2CO_3$ to remove traces of $MesCO_2H$. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, 1H, *J* = 1.6 Hz), 7.76 (dt, 1H, *J* = 7.1, 1.6 Hz), 7.56-7.45 (m, 3H), 7.38 (d, 1H, 7.9 Hz), 7.30 (d, 1H, *J* = 9.1 Hz), 7.15 (d, 1H, *J* = 7.1 Hz), 7.11-7.01 (m, 2H), 6.48 (dd, 1H, *J* = 9.1, 6.3 Hz), 6.11 (td, 1H, *J* = 7.2, 1.0 Hz), 4.29 (q, 2H, *J* = 7.1 Hz), 2.44 (s, 3H), 1.33 (t, 3H, *J* = 7.1 Hz) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 166.4, 140.7, 138.4, 137.7 (2), 133.0, 132.3, 130.8 (2), 130.6, 130.1, 129.1, 128.5, 128.3, 128.2, 121.0, 120.1, 118.5, 118.1, 112.2, 61.0, 21.1, 14.4 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2844, 1714, 1354, 1233, 1055, 1014, 730. HRMS (ESI, Pos): calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$: 357.1598, found 357.1609 *m/z*.

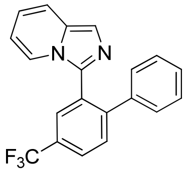




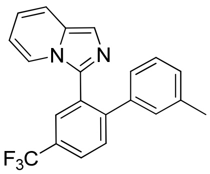
**3-(2-(thiophen-2-yl)-5-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine (187c)**: Synthesized according to Procedure D, employing 2-bromothiophene as the coupling partner. After work-up, the residue was purified via flash chromatography (10-80% EtOAc/Hex) to give **187c** (76 mg, 0.221 mmol, 55%) as a thick yellow oil and a mixture of **187c** and **187d** (40 mg, containing 22% **187c** and 6% **187d**). However, compound **187d** could not be separated and thus not characterized. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.84-7.72 (m, 2H), 7.62 (s, 1H), 7.44 (d, 1H, *J* = 9.2 Hz), 7.21 (dd, 1H, *J* = 7.2, 0.7 Hz), 7.16 (dd, 1H, *J* = 5.1, 1.1 Hz), 6.79 (dd, 1H, *J* = 5.1, 3.7 Hz), 6.69-6.58 (m, 2H), 6.29 (td, 1H, *J* = 7.5, 1.0 Hz) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -64.02 ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 140.1, 138.0 (m), 137.7, 131.2, 130.3 (q, $J_{C\text{-}F}$ = 33.0 Hz), 130.2, 130.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 128.8, 127.8, 127.6, 126.9, 126.6 (q, $J_{C\text{-}F}$ = 3.6 Hz), 125.7 (q, $J_{C\text{-}F}$ = 272.4 Hz), 120.9, 120.5, 119.2, 118.3, 112.9 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1321, 1119, 1056, 1004, 696. HRMS (ESI, Pos): calcd for $C_{18}H_{12}F_3N_2S$ $[M+H]^+$: 345.0668, found 345.0668 *m/z*.



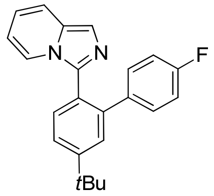
**3-(2-(1-methyl-1H-indol-5-yl)-5-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine (187e)**: Synthesized according to **Procedure D**, employing 5-bromo-1-methyl-1*H*-indole as the coupling partner. After work-up, the residue was purified via flash chromatography (10-80% EtOAc/Hex) to give **187e** (127 mg, 0.324 mmol, 81%) as an off-white solid. Traces of the corresponding diarylated imidazopyridine **187f** were also observed by LC-MS. mp = 142-144 °C. $^{1}$H NMR (400 MHz, CDCl$_3$): δ 8.00 (s, 1H), 7.79 (dd, 1H, *J* = 8.2, 1.3 Hz), 7.73 (d, 1H, *J* = 8.1 Hz), 7.57 (s, 1H), 7.50 (d, 1H, *J* = 1.0 Hz), 7.30 (dd, 1H, *J* = 9.1, 1.0 Hz), 7.15 (dd, 1H, *J* = 7.2, 0.9 Hz), 7.01 (d, 1H, *J* = 8.6 Hz), 6.97 (d, 1H, *J* = 3.1 Hz), 6.82 (dd, 1H, *J* = 8.6, 1.6 Hz), 6.44 (ddd, 1H, *J* = 9.1, 6.4, 0.8 Hz), 6.37 (dd, 1H, *J* = 3.1, 0.7 Hz), 6.03 (td, 1H, *J* = 6.8, 1.0 Hz), 3.66 (s, 3H) ppm. $^{19}$F NMR (376 MHz, CDCl$_3$): δ -62.3 ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 146.2, 137.2, 136.3, 131.3, 130.8, 130.4, 129.7 (q, $J_{C\text{-}F}$ = 3.8 Hz), 129.6, 129.5, 129.4 (q, $J_{C\text{-}F}$ = 33.0 Hz), 128.8, 126.2 (q, $J_{C\text{-}F}$ = 3.2 Hz), 125.6 (q, $J_{C\text{-}F}$ = 272.3 Hz), 121.6, 121.1, 120.7, 120.4, 118.7, 117.9, 112.1, 109.4, 101.5, 32.9 ppm. FTIR (cm$^{-1}$) (neat): 2967, 2865, 1321, 1168, 1056, 1006. HRMS (ESI, Pos): calcd for $C_{23}H_{16}F_3N_3$ [M+H]$^+$: 392.1369, found 392.1383 *m/z*.

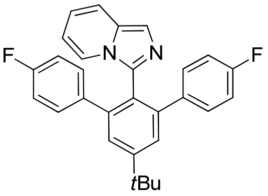


**3-(4-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (187g)**: Synthesized according to **Procedure D**, employing bromobenzene as the coupling partner. After work-up, the residue was purified via flash chromatography (10-50% EtOAc/Hex) to give **187g** (120 mg, 0.355 mmol, 89%) as a thick brown oil. The corresponding diarylated imidazopyridine **187h** was not observed. $^{1}$H NMR (400 MHz, CDCl$_3$): δ 8.01 (s, 1H), 7.80 (d, 1H, *J* = 8.1 Hz), 7.67 (d, 1H, *J* = 8.1 Hz), 7.55 (s, 1H), 7.33 (d, 1H, *J* = 9.1 Hz), 7.18-6.98 (m, 6H), 6.53 (dd, 1H, *J* = 8.3, 7.2 Hz), 6.19-6.05 (m, 1H) ppm. $^{19}$F NMR (376 MHz, CDCl$_3$): δ -62.4 ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 144.8, 139.1, 136.4, 130.9, 130.8, 130.4 (q, $J_{C\text{-}F}$ = 32.9 Hz), 129.6, 129.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 128.7, 128.1, 127.9, 126.4 (q, $J_{C\text{-}F}$ = 3.8 Hz), 125.4 (q, $J_{C\text{-}F}$ = 272.1 Hz), 120.8, 120.6, 118.8, 118.0, 112.3 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1356, 1121, 1055, 1005, 729. HRMS (ESI, Pos): calcd for $C_{20}H_{14}F_3N_2$ [M+H]$^+$: 339.1104, found 339.1096 *m/z*.



**3-(3'-methyl-4-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (187i)**: Synthesized according to **Procedure D**, employing 3-chlorotoluene as the coupling partner. After work-up, the residue was purified via flash chromatography (10-50% EtOAc/Hex) to give **187i** (108 mg, 0.306 mmol, 77%) as a thick brown oil. The corresponding diarylated imidazopyridine was not observed, but traces of an imidazopyridine dimer were observed by LC-MS. $^{1}$H NMR (400 MHz, CDCl$_3$): δ 8.01 (s, 1H), 7.79 (d, 1H, *J* = 9.1 Hz), 7.67 (d, 1H, *J* = 8.2 Hz), 7.55 (s, 1H), 7.34 (d, 1H, *J* = 9.2 Hz), 7.16 (d, 1H, *J* = 7.2 Hz), 7.13-7.07 (m, 2H), 7.05-6.92 (m, 2H), 6.54 (dd, 1H, *J* = 8.8, 6.7 Hz), 6.14 (t, 1H, *J* = 6.8 Hz), 2.14 (s, 3H) ppm. $^{19}$F NMR (376 MHz, CDCl$_3$): δ -40.4 ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 144.9, 139.0, 138.4, 136.6, 130.9, 130.7, 130.2 (q, $J_{C\text{-}F}$ = 33.1 Hz), 129.6, 129.5 (q, $J_{C\text{-}F}$ = 3.8 Hz), 128.8, 128.6, 128.5, 126.3 (q, $J_{C\text{-}F}$ = 3.9 Hz), 125.4 (q, $J_{C\text{-}F}$ = 272.4 Hz), 125.0, 120.9, 120.5, 118.8, 118.0, 112.2, 21.3 ppm. FTIR (cm$^{-1}$) (neat): 2972, 2865, 1321, 1121, 1056, 1005. HRMS (ESI, Pos): calcd for $C_{21}H_{15}F_3N_2$ [M+H]$^+$: 353.1260, found 353.1274 *m/z*.



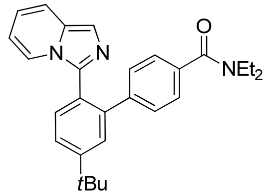


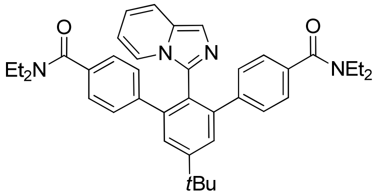
**3-(5-(tert-butyl)-4'-fluoro-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (167c)** and **3-(5'-(tert-butyl)-4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)imidazo[1,5-*a*]pyridine (167d)**: Synthesized according to **Procedure D**, employing 4-bromofluorobenzene as the coupling partner. After work-up, the residue was purified by flash chromatography (20-80% EtOAc/Hex) to give **167c** (65 mg, 0.189 mmol, 47%) as an off-white solid and **167d** (37 mg, 0.0844 mmol, 21%) as a green solid.

**167c**: mp = 194-197 °C. $^{1}$H NMR (500 MHz, CDCl$_3$): δ 7.61 (d, 1H, *J* = 8.0 Hz), 7.55-7.49 (m, 3H), 7.36-7.31 (m, 1H), 7.21 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.06-7.00 (m, 2H), 6.85-6.78 (m, 2H), 6.53 (ddd, 1H, *J* = 9.2, 6.4, 0.7 Hz), 6.16 (td, 1H, *J* = 6.8, 1.1 Hz), 1.41 (s, 9H) ppm. $^{19}$F

NMR (376 MHz, CDCl$_3$): δ -115.4 (m) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.1 (d, $J_{C\text{-}F}$ = 246.6 Hz), 153.1, 140.3, 137.9, 137.2 (d, $J_{C\text{-}F}$ = 3.3 Hz), 132.0, 130.5, 129.8 (d, $J_{C\text{-}F}$ = 8.3 Hz), 127.2, 125.9, 125.2, 121.2, 120.1, 118.5, 118.1, 115.4 (d, $J_{C\text{-}F}$ = 21.4 Hz), 112.0, 35.0, 31.4 ppm. FTIR (cm$^{-1}$) (neat): 2951, 2865, 1438, 1159, 1055, 838. HRMS (ESI, Pos): calcd for $C_{23}H_{22}FN_2$ [M+H]$^+$: 345.1716, found 345.1760 *m/z*.

**167d**: Mp = 156-158 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.50 (s, 2H), 7.33-7.31 (m, 1H), 7.28-7.23 (m, 1H), 7.21 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.03-6.96 (m, 4H), 6.83-6.75 (m, 4H), 6.55-6.49 (m, 1H), 6.26-6.20 (m, 1H), 1.44 (s, 9H) ppm. $^{19}$F NMR (376 MHz, CDCl$_3$): δ -115.7- -115.6 (m) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.1 (d, $J_{C\text{-}F}$ = 246.5 Hz), 153.5, 143.2, 137.1 (d, $J_{C\text{-}F}$ = 3.0 Hz), 135.7, 130.1 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.5, 126.8, 124.1, 120.6, 119.2, 118.5, 118.2, 115.2 (d, $J_{C\text{-}F}$ = 21.3 Hz), 112.6, 35.2, 31.5 ppm. FTIR (cm$^{-1}$) (neat): 2965, 2843, 1505, 1222, 1055, 836. HRMS (ESI, Pos): calcd for $C_{29}H_{25}F_2N_2$ [M+H]$^+$: 439.1980, found 439.1998 *m/z*.



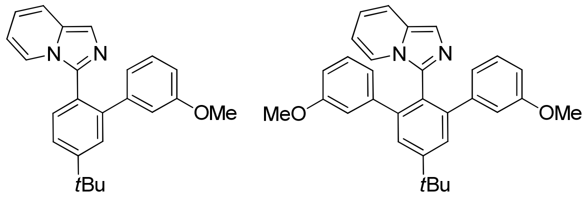


**5'-(tert-butyl)-N,N-diethyl-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1'-biphenyl]-4-carboxamide (167e)** and **5'-(tert-butyl)-N4,N4,N4'',N4''-tetraethyl-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxamide (167f)**: Synthesized according to **Procedure D**, employing 4-bromo-*N,N*-diethylbenzamide as the coupling partner. After work-up, the residue was purified in flash chromatography (25-80% EtOAc/Hex) to give **167e** (117 mg, 0.275 mmol, 69%) as an off-white solid and **167f** (22 mg, 0.0367 mmol, 9%) as an off-white solid.

**167e**: mp = 144-146 °C. $^1$H NMR (500 MHz, CDCl$_3$): δ 7.67-7.61 (m, 1H), 7.55 (dq, 2H, *J* = 4.3, 2.1 Hz), 7.51 (s, 1H), 7.31 (dt, 1H, *J* = 9.2, 1.1 Hz), 7.16 (dq, 1H, *J* = 7.2, 1.0 Hz), 7.13-7.05 (m, 4H), 6.47 (ddd, 1H, *J* = 9.1, 6.3, 0.8 Hz), 6.10 (td, 1H, *J* = 6.8, 1.1 Hz), 3.46 (br. s, 2H), 2.99 (br. s, 2H), 1.41 (s, 9H), 1.17 (br. s, 3H), 0.97 (br. s, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$): δ 171.0, 153.1, 142.0, 140.4, 137.9, 135.9, 132.0, 130.5, 128.1, 127.0, 126.4, 125.9, 125.5, 121.4, 120.1, 118.2, 118.1, 111.7, 43.2, 39.3, 35.0, 31.4, 14.2, 13.0 ppm. FTIR (cm$^{-1}$)

(neat): 2938, 2866, 1628, 1357, 1056, 1014, 751. HRMS (ESI, Pos): calcd for $C_{28}H_{32}N_3O$ $[M+H]^+$: 426.254, found 426.2554 *m/z*.

**167f**: mp = 80-84 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.27-7.24 (m, 1H), 7.24-7.18 (m, 2H), 7.13-7.02 (m, 8H), 6.44 (dd, 1H, *J* = 9.7, 6.4 Hz), 6.21-6.12 (m, 1H), 3.44 (br. s, 4H), 3.05 (br. s, 4H), 1.45 (s, 9H), 1.18 (br. s, 6H), 0.99 (br. s, 6H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 171.2, 153.4, 143.5, 142.1, 135.8, 135.7, 129.5, 128.5, 126.8, 126.0, 124.4, 120.8, 119.6, 118.0 (2), 112.0, 43.2, 39.4, 35.2, 31.5, 14.3, 13.0 ppm. FTIR (cm$^{-1}$) (neat) 2938, 2866, 1624, 1426, 1056, 1014, 749. HRMS (ESI, Pos): calcd for $C_{39}H_{45}N_4O_2$ $[M+H]^+$: 601.3537, found 601.3533 *m/z*.

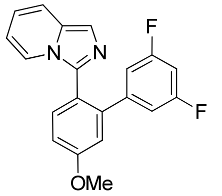


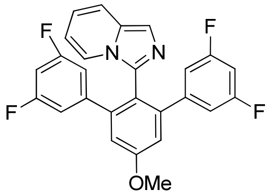
**3-(5-(tert-butyl)-3'-methoxy-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (167g)** and **3-(5'-(tert-butyl)-3,3''-dimethoxy-[1,1':3',1''-terphenyl]-2'-yl)imidazo[1,5-*a*]pyridine (167h)**: Synthesized according to **Procedure D**, employing 3-bromoanisole as the coupling partner. After work-up, the residue was purified by flash chromatography (20-80% EtOAc/Hex) to give a mix of **167g** and **167h** (101 mg) consisting of **167g** (0.190 mmol, 47%) and **167h** (0.0722 mmol, 18%). **167h** could not be separated from **167g** and could not be characterized.

Synthesized according to **Procedure E**, employing 3-bromoanisole (0.206 mmol) as the coupling partner. After work-up, the residue was purified via flash chromatography (15-80% EtOAc/Hex) to give **167g** (71 mg, 0.199 mmol, 97%) and unreacted **167** (25 mg, 0.0501 mmol, 25%). Traces of the imidazopyridine dimer were also observed by LC-MS.

**167g**: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, 1H, *J* = 8.1 Hz), 7.60-7.51 (m, 3H), 7.32 (d, 1H, *J* = 9.2 Hz), 7.21 (d, 1H, *J* = 7.2 Hz), 7.08 (t, 1H, *J* = 8.0 Hz), 6.78 (d, 1H, *J* = 7.5 Hz), 6.66 (dd, 1H, *J* = 8.3, 2.5 Hz), 6.56-6.47 (m, 2H), 6.12 (t, 1H, *J* = 6.7 Hz), 3.49 (s, 3H), 1.42 (s, 9H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 159.4, 153.0, 142.5, 141.0, 138.2, 132.0, 130.5, 129.5, 127.1, 125.9, 125.2, 121.4, 120.6, 119.8, 118.5, 117.9, 113.7, 112.8, 111.8, 55.2, 35.0, 31.4

ppm. FTIR ($cm^{-1}$) (neat): 2966, 2844, 1356, 1179, 1054, 730. HRMS (ESI, Pos): calcd for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1961, found 357.1969 *m/z*.

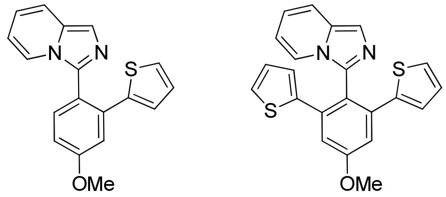




**3-(3',5'-difluoro-5-methoxy-[1,1'-biphenyl]-2-yl)imidazo[1,5-a]pyridine (165c)** and **3-(3,3'',5,5''-tetrafluoro-5'-methoxy-[1,1':3',1''-terphenyl]-2'-yl)imidazo[1,5-a]pyridine (165d)**: Synthesized according to **Procedure D**, employing 1-bromo-3,5-difluorobenzene as the coupling partner. After work-up, the residue was purified in flash chromatography (5-80% EtOAc/Hex) to give **165c** (22 mg, 0.025 mmol, 16%) as a yellow oil and **165d** (72 mg, 0.161 mmol, 40%) as a white solid.

**165c:** $^1$H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, 1H, *J* = 8.5 Hz), 7.50 (d, 1H, *J* = 0.7 Hz), 7.36 (dt, 1H, *J* = 9.2, 1.1 Hz), 7.25-7.21 (m, 1H), 7.08 (dd, 1H, *J* = 8.5, 2.7 Hz), 7.04 (d, 1H, *J* = 2.6 Hz), 6.61-6.53 (m, 4H), 6.25 (ddd, 1H, *J* = 7.3, 6.3, 1.2 Hz), 3.92 (s, 3H) ppm. $^{19}$F NMR (470 MHz, $CDCl_3$): δ -109.7 (d). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 163.7 (d, $J_{C-F}$ = 13.0 Hz), 161.7 (d, $J_{C-F}$ = 13.0 Hz), 160.8, 143.7 (t, $J_{C-F}$ = 9.8 Hz), 141.0 (d, $J_{C-F}$ = 2.4 Hz), 136.8, 133.8, 130.6, 121.1, 120.8, 120.1, 118.5, 118.4, 112.4, 111.2 (d, $J_{C-F}$ = 26.1 Hz), 111.1 (d, $J_{C-F}$ = 13.5 Hz), 102.9 (t, $J_{C-F}$ = 25.2 Hz), 55.7 ppm. FTIR ($cm^{-1}$) (neat): 2922, 1748, 1622, 1592, 1433, 1356, 1056. HRMS (ESI, Pos): calcd for $C_{20}H_{15}F_2N_2O$ $[M+H]^+$: 337.1147, found 337.1150 *m/z*.

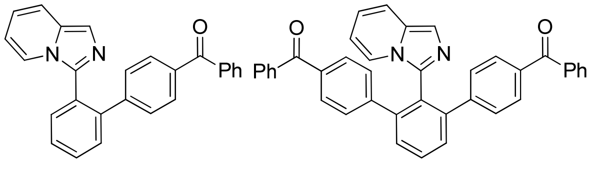
**165d**: mp = 203-204 °C. $^1$H NMR (400 MHz, acetone-d$_6$): δ 7.49-7.37 (m, 2H), 7.32 (d, 1H, *J* = 0.7 Hz), 7.25 (s, 2H), 6.85-6.70 (m, 6H), 6.61 (ddd, 1H, *J* = 9.1, 6.4, 0.8 Hz), 6.47-6.36 (m, 1H), 4.04 (s, 3H) ppm. $^{19}$F NMR (282 MHz, acetone-d$_6$): δ 65.7 (m) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 164.7 (d, $J_{C-F}$ = 13.4 Hz), 161.6 (d, $J_{C-F}$ = 13.2 Hz), 161.4, 144.9 (t, $J_{C-F}$ = 10.0 Hz), 144.7 (t, $J_{C-F}$ = 2.3 Hz), 135.1, 131.0, 121.6, 120.5, 120.2, 119.4, 118.7, 116.4, 113.4, 112.7 (d, $J_{C-F}$ = 25.8 Hz), 112.6 (d, $J_{C-F}$ = 9.3 Hz), 103.2 (t, $J_{C-F}$ = 25.8 Hz), 56.2 ppm. FTIR ($cm^{-1}$) (neat): 2939, 1618, 1455, 1116, 1055, 1032, 1013. HRMS (ESI, Pos): calcd for $C_{26}H_{17}F_4N_2O$ $[M+H]^+$: 449.1272, found 449.1284 *m/z*.



**3-(4-methoxy-2-(thiophen-2-yl)phenyl)imidazo[1,5-*a*]pyridine (165e)** and **3-(4-methoxy-2,6-di(thiophen-2-yl)phenyl)imidazo[1,5-*a*]pyridine (165f)**: Synthesized according to **Procedure D**, employing 2-bromothiophene as the coupling partner. After work-up, the residue was purified in flash chromatography (20-100% EtOAc/Hex, RediSep Gold column 12 g) to give **165e** (12 mg, 0.039 mmol, 10%) as a yellow oil and **165f** (34 mg, 0.084 mmol, 22%) as a green solid.

**165e**: $^1$H NMR (300 MHz, CDCl$_3$): δ 7.59-7.51 (m, 2H), 7.40 (dt, 1H, *J* = 9.2, 1.1 Hz), 7.28-7.23 (m, 1H), 7.20 (d, 1H, *J* = 5.3 Hz), 7.10 (dd, 1H, *J* = 5.1, 1.2 Hz), 7.01 (dd, 1H, *J* = 8.5, 2.7 Hz), 6.76 (dd, 1H, *J* = 5.1, 3.6 Hz), 6.63-6.53 (m, 2H), 6.23 (td, 1H, *J* = 6.8, 1.2 Hz), 3.92 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 160.7, 141.7, 137.2, 136.1, 134.1, 130.7, 127.5, 126.3, 125.9, 121.3, 120.8, 119.8, 118.6, 118.2, 115.0, 113.8, 112.2, 55.7 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2844, 1456, 1346, 1055, 1013. HRMS (ESI, Pos): calcd for $C_{18}H_{15}N_2OS$ [M+H]$^+$: 307.0900, found 307.0910 *m/z*.

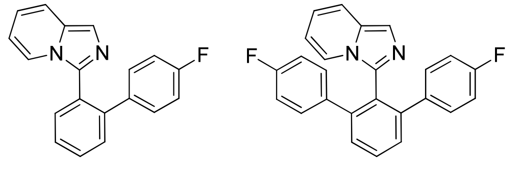
**165f**: mp = 171-172 °C. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.51 (s, 1H), 7.39 (d, 1H, *J* = 9.2 Hz), 7.28-7.23 (m, 1H), 7.07 (dd, 2H, *J* = 5.1, 0.6 Hz), 6.77 (dd, 2H, *J* = 4.9, 3.8 Hz), 6.65 (dd, 2H, *J* = 3.6, 0.6 Hz), 659 (dd, 1H, *J* = 9.1, 6.4 Hz), 6.34-6.24 (m, 1H), 3.95 (s, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$): δ 160.5, 141.6, 139.0, 134.6, 130.4, 127.1, 126.4 (2), 121.0, 119.8, 118.8, 118.6, 118.2, 114.9, 112.5, 55.7 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2865, 1455, 1347, 1055, 1014. HRMS (ESI, Pos): calcd for $C_{22}H_{16}N_2OS_2$ [M+H]$^+$: 389.0777, found 389.0769 *m/z*.



**(2'-(imidazo[1,5-a]pyridin-3-yl)-[1,1'-biphenyl]-4-yl)(phenyl)methanone (164c)** and **(2'-(imidazo[1,5-a]pyridin-3-yl)-[1,1':3',1''-terphenyl]-4,4''-diyl)bis(phenylmethanone) (164d)**: Synthesized according to **Procedure D**, employing 4-bromobenzophenone (3 equiv) as the coupling partner. After work-up, the residue was purified by flash chromatography (15-100% EtOAc/Hex) to give **164d** (148 mg) as a thick brown oil, **164c** (10 mg) as a thick dark oil and a mix of **164c** and **164d** (40 mg, 1:6), to a total of **164c** (0.0374 mmol, 9%) and **164d** (0.332 mmol, 83%).

**164c**: $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, 1H, *J* = 7.0 Hz), 7.68-7.61 (m, 4 H), 7.61-7.53 (m, 4H), 7.47-7.35 (m, 3H), 7.29-7.25 (m, 1H), 7.22 (d, 1H, *J* = 6.4 Hz), 7.16 (d, 2H, *J* = 8.1 Hz), 6.57 (dd, 1H, *J* = 9.1, 6.3 Hz), 6.19 (t, 1H, *J* = 6.4 Hz) ppm. $^{13}$C NMR (175 MHz, CDCl3): δ 196.4, 144.7, 140.6, 137.7, 137.5, 136.1, 132.5 (2), 130.7, 130.3, 130.2, 130.1, 130.0, 129.0, 128.8, 128.4, 128.0, 121.0, 120.4, 118.6, 118.2, 112.3 ppm. FTIR (cm$^{-1}$) (neat): 2865, 2844, 1656, 1602, 1277, 1055, 1013, 739, 701. HRMS (ESI, Pos): calcd for $C_{26}H_{16}N_2O$ $[M+H]^+$: 375.1492, found 375.1481 *m/z*.

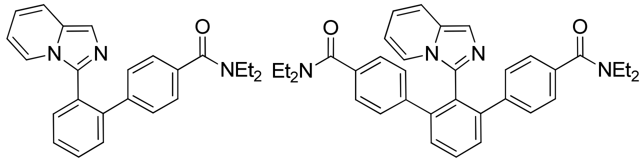
**164d**: $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.74-7.69 (m, 1H), 7.68-7.62 (m, 6H), 7.59-7.50 (m, 6H), 7.47-7.38 (m, 4H), 7.33 (s, 1H), 7.28 (d, 1H, *J* = 9.3 Hz), 7.23 (d, 1H, *J* = 7.2 Hz), 7.13 (d, 4H, *J* = 8.2 Hz), 6.52 (dd, 1H, *J* = 8.8, 6.4 Hz), 6.24 (td, 1H, *J* = 7.2, 0.9 Hz) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 196.3, 144.8, 143.6, 137.7, 136.0, 135.1, 132.4, 130.4, 130.0 (2), 129.9, 129.8, 128.3 (2), 127.4, 120.3, 120.1, 118.4, 118.2, 112.6 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2844, 1652, 1600, 1273, 1056, 696. HRMS (ESI, Pos): calcd for $C_{39}H_{27}N_2O_2$ $[M+H]^+$: 555.2067, found 555.2063 *m/z*.



**3-(4'-fluoro-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (164e)** and **3-(4,4''-difluoro-[1,1':3',1''-terphenyl]-2'-yl)imidazo[1,5-*a*]pyridine (164f)**: Synthesized according to **Procedure D**, employing 4-bromofluorobenzene (3 equiv) as the coupling partner. After work-up, the residue was purified by flash chromatography (20-80% EtOAc/Hex) to give **164e** (19 mg, 0.0659 mmol, 16%) as a thick brown oil and **164f** (85 mg, 0.220 mmol, 55%) as an off-white solid.

**164e**: $^{1}$H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.60-7.48 (m, 4H), 7.35 (dt, 1H, *J* = 9.2, 1.1 Hz), 7.18 (dd, 1H, *J* = 7.2, 1.0 Hz), 7.06-7.00 (m, 2H), 6.84-6.76 (m, 2H), 6.55 (ddd, 1H, *J* = 9.1, 6.4, 0.9 Hz), 6.17 (ddd, 1H, *J* = 7.3, 6.3, 1.2 Hz) ppm. $^{19}$F NMR (470 MHz, $CDCl_3$): δ – 115.1 (m) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 163.2, 161.2, 140.7, 137.7, 136.5 (d, $J_{C\text{-}F}$ = 3.2 Hz), 132.4, 130.6, 130.2, 129.9, 129.8 (d, $J_{C\text{-}F}$ = 8.1 Hz), 128.8, 128.1, 121.0, 118.6, 118.2, 115.4 (d, $J_{C\text{-}F}$ = 21.4 Hz), 112.2 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2865, 1506, 1357, 1223, 1055, 1013, 762. HRMS (ESI, Pos): calcd for $C_{19}H_{14}FN_2$ $[M+H]^+$: 289.1136, found 289.1129 *m/z*.

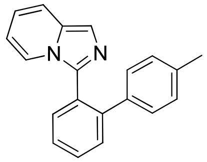
**164f**: Mp = 171-172 °C. $^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.67-7.57 (m, 1H), 7.52 (s, 1H), 7.49 (d, 1H, *J* = 1.0 Hz), 7.31 (s, 1H), 7.28-7.21 (m, 1H), 7.16 (dd, 1H, *J* = 7.2, 0.9 Hz), 7.03-6.92 (m, 4H), 6.83-6.72 (m, 4H), 6.50 (ddd, 1H, *J* = 9.1, 6.4, 0.8 Hz), 6.21 (td, 1H, *J* = 7.3, 1.1 Hz) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ – 115.4 (m) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 163.7, 143.6, 136.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 135.6, 130.1, 130.0 (d, $J_{C\text{-}F}$ = 7.9 Hz), 129.6 (2), 127.4, 120.3, 119.8, 118.3, 118.2, 115.0 (d, $J_{C\text{-}F}$ = 21.4 Hz), 112.4 ppm. FTIR (cm$^{-1}$) (neat): 2938, 28651346, 1223, 1055, 1013, 739. HRMS (ESI, Pos): calcd for $C_{25}H_{17}F_2N_2$ $[M+H]^+$: 383.1354, found: 383.1350 *m/z*.

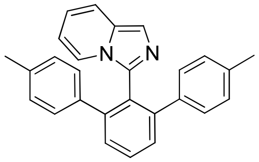


***N,N*-diethyl-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1'-biphenyl]-4-carboxamide (164g)** and ***N$^4$,N$^4$,N$^{4''}$,N$^{4''}$*-tetraethyl-2'-(imidazo[1,5-*a*]pyridin-3-yl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxamide (164h)**: Synthesized according to **Procedure D**, employing 4-bromo-*N,N*-diethylbenzamide (3 equiv) as the coupling partner. After work-up, the residue was purified by flash chromatography (15-100% EtOAc/Hex) to give **164g** (15 mg, 0.041 mmol, 10%) as a thick brown oil and **164h** (93 mg, 0.171 mmol, 43%) as a thick green-brown oil.

**164g**: $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, 1H, *J* = 7.0 Hz), 7.60-7.51 (m, 4H), 7.33 (d, 1H, *J* = 9.2 Hz), 7.17-7.04 (m, 5H), 6.49 (dd, 1H, *J* = 9.1, 6.3 Hz), 6.15-6.07 (m, 1H), 3.47 (br s, 2H), 2.98 (br s, 2H), 1.18 (br s, 3H), 0.94 (br s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): δ 171.0, 141.4, 140.9, 137.8, 136.1, 132.4, 130.6, 130.0 (2), 128.9, 128.4, 128.1, 126.4, 121.2, 120.3, 118.4, 118.1, 111.8, 43.2, 39.3, 14.2, 13.0 ppm. FTIR (cm$^{-1}$) (neat): 2937, 2866, 1627, 1427, 1055, 1012. HRMS (ESI, Pos): calcd for $C_{24}H_{23}N_3NaO$ $[M+Na]^+$: 392.1733, found 392.1749 *m/z*.

**164h**: $^1$H NMR (400 MHz, $CDCl_3$): δ 7.69-7.62 (m, 1H), 7.59-7.50 (m, 2H), 7.23-7.14 (m, 1H), 7.12-7.06 (m, 4H), 7.06-7.00 (m, 4H), 6.46-6.42 (m, 1H), 6.22-6.14 (m, 1H), 3.46 (br s, 4H), 3.01 (br 2, 4H), 1.17 (br s, 6H), 0.96 (br s, 6H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 171.0, 143.8, 141.4, 135.8, 135.5, 130.2, 129.6, 129.5, 128.4, 127.3, 126.0, 120.6, 119.7, 118.0 (2), 112.1, 43.2, 39.4, 14.2, 13.0 ppm. FTIR (cm$^{-1}$) (neat): 2938, 2844, 1620, 1425, 1287, 1055, 1016. HRMS (ESI, Pos): calcd for $C_{35}H_{36}N_4NaO_2$ $[M+Na]^+$: 567.2730, found 567.2727 *m/z*.

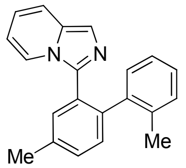


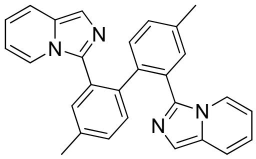


**3-(4'-methyl-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (164i)** and **3-(4,4''-dimethyl-[1,1':3',1''-terphenyl]-2'-yl)imidazo[1,5-*a*]pyridine (164j)**: Synthesized according to **Procedure D**, employing 4-chlorotoluene (3 equiv) as the coupling partner. After work-up, the residue was purified by flash chromatography (10-60% EtOAc/Hex) to give **164i** (36 mg, 0.127 mmol, 32%) as a thick yellow oil and **164j** (60 mg, 0.160 mmol, 40%) as an off-white solid.

**164i**: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.67 (dt, 1H, $J$ = 7.5, 1.0 Hz), 7.57-7.53 (m, 2H), 7.52 (d, 1H, $J$ = 0.7 Hz), 7.51-7.43 (m, 1H), 7.33 (dt, 1H, $J$ = 9.1, 1.1 Hz), 7.22-7.12 (m, 1H), 6.97-6.89 (m, 4H), 6.52 (ddd, 1H, $J$ = 9.1, 6.3, 0.9 Hz), 6.41 (ddd, 1H, $J$ =7.3, 6.3, 1.2 Hz), 2.21 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 141.7, 138.2, 137.6, 137.0, 132.4, 130.6, 130.2, 129.8, 129.2, 128.7, 127.9, 127.7, 121.3, 120.0, 118.4, 118.0, 111.9, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2949, 2844, 1507, 1356, 1055, 1009, 724. HRMS (ESI, Pos): calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1386, found 285.1400 *m/z*.

**164j**: p = 158-159 °C. $^1$H NMR (300 MHz, $CDCl_3$): δ 7.64-7.56 (m, 1H), 7.52 (s, 1H), 7.49 (d, 1H, $J$ = 1.3 Hz), 7.32 (s, 1H), 7.27-7.18 (m, 2H), 6.91 (s, 8H), 6.52-6.42 (m, 1H), 6.19 (td, 1H, $J$ = 7.0, 1.1 Hz), 2.21 (s, 6H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): δ 144.5, 137.9, 136.6, 136.3, 129.9, 129.4, 129.3, 128.7, 128.2, 127.1, 120.8, 119.5, 118.0, 117.9, 112.0, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2949, 2844, 1356, 1056, 1014, 792, 740. HRMS (ESI, Pos): calcd for $C_{27}H_{23}N_2$ [M+H]$^+$: 375.1856, found 375.1868 *m/z*.





**3-(2',4-dimethyl-[1,1'-biphenyl]-2-yl)imidazo[1,5-*a*]pyridine (186c)** and **3,3'-(4,4'-dimethyl-[1,1'-biphenyl]-2,2'-diyl)diimidazo[1,5-*a*]pyridine (188):** Synthesized according to **Procedure D**, employing 2-bromotoluene (1.24 equiv) as the coupling partner, except on a 0.2 mmol scale. After work-up, the residue was purified by flash chromatography (15-100% EtOAc/Hex) to give **186c** (16 mg, 0.054 mmol, 27%) as a dark oil and **188** (19 mg, 0.046 mmol, 46%) as an off-white solid.

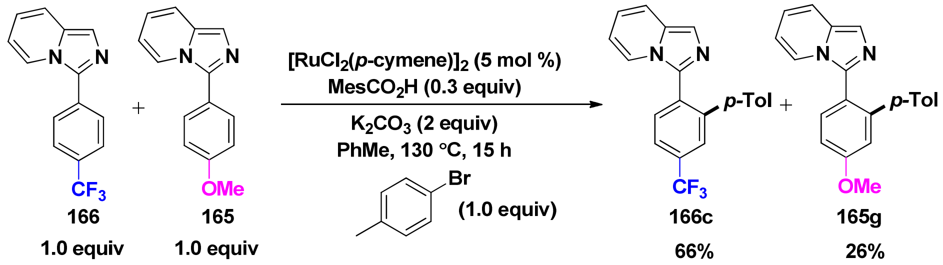
**186c**: $^1$H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, 1H, *J* = 1.2, 0.6 Hz), 7.43 (d, 1H, *J* = 0.8 Hz), 7.37-7.33 (m, 2H), 7.33-7.30 (m, 1H), 7.28 (dt, 1H, *J* = 9.1, 1.2 Hz), 7.04-6.99 (m, 2H), 6.99-6.90 (m, 2H), 6.52 (ddd, 1H, *J* = 9.1, 6.4, 0.9 Hz), 6.18 (ddd, 1H, *J* = 7.3, 6.3, 1.2 Hz), 2.46 (s, 3H), 2.05 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 140.1, 138.9, 138.2, 137.6, 135.6, 132.4, 131.1, 130.5, 130.3, 130.0, 129.9, 129.7, 127.3, 125.5, 121.4, 120.0, 118.3, 118.1, 111.6, 21.2, 20.2 ppm. FTIR (cm$^{-1}$) (neat): 2922, 2865, 1352, 1055, 1013, 725, 698. HRMS (ESI, Pos): calcd for $C_{21}H_{18}N_2$ [M+H]$^+$: 299.1543, found 299.1544 *m/z*.

**188**: mp = 230-233 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.86-7.76 (m, 1H), 7.29 (s, 1H), 7.28-7.24 (m, 2H), 7.10-7.03 (m, 1H), 6.99 (d, 1H, *J* = 7.7 Hz), 6.55 (dd, 1H, *J* = 8.9, 6.4 Hz), 6.23 (t, 1H, *J* = 6.6 Hz), 2.32 (s, 3H) ppm. $^{13}$C NMR (125 MHz, $CDCl_3$): δ 138.3, 137.6, 137.1, 131.2, 131.0, 130.6, 130.0, 128.6, 122.0, 120.1, 118.5, 118.0, 112.0, 21.1 ppm. FTIR (cm$^{-1}$) (neat): 2939, 2865, 1354, 1055, 1032, 1012, 748. HRMS (ESI, Pos): calcd for $C_{28}H_{22}N_4Na$ [M+Na]$^+$: 437.1737, found 437.1758 *m/z*.

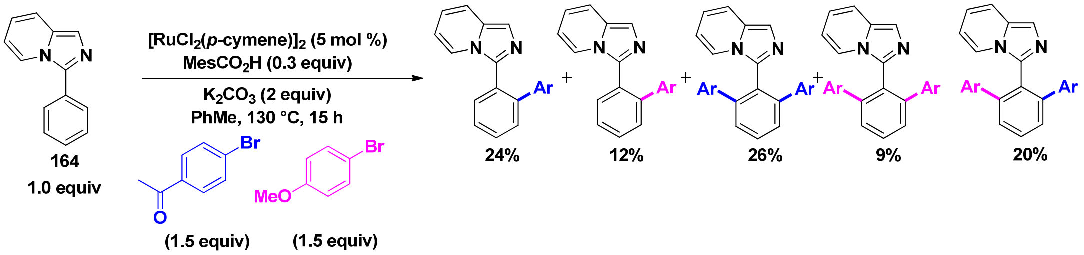
*Deuterium exchange experiments*

To a microwave vial (previously kept in an oven and cooled under argon) fit with a stir bar, the corresponding imidazopyridine (if solid, 0.2 mmol, 1.0 equiv) and 2,4,6-trimethylbenzoic acid (0.06 mmol, 0.3 equiv) were added. The vial was then placed in a glove box where dichloro(*p*-cymene)ruthenium dimer (0.01 mmol, 0.05 equiv) and potassium carbonate (0.4 mmol, 2.0 equiv) were added. The vial was crimped and taken out of the glove box. Toluene (dry, 0.9 mL) and deuterium oxide (0.1 mL) were added via syringe. The reaction was stirred at 130 °C for 15 h. Then, the reaction was allowed to cool to rt, and filtered over a pad of silica and celite, rinsing with EtOAc (15-20 mL). The reaction was flashed in 20% EtOAc/Hex on a small column. The product was analyzed by $^1$H NMR. The results are summarized in Schemes 68 and 69 (Chapter 2).

*Competition experiments*



To a microwave vial (previously kept in an oven and cooled under argon) fit with a stir bar, the corresponding imidazopyridines, 3-(4-methoxyphenyl)imidazo[1,5-*a*]pyridine **165** and 3-(4-(trifluoromethyl)phenyl)imidazo[1,5-*a*]pyridine **166** (0.2 mmol, 1.0 equiv each), and 2,4,6-trimethylbenzoic acid (0.06 mmol, 0.3 equiv) were added. The vial was then placed in a glove box where dichloro(*p*-cymene)ruthenium dimer (0.01 mmol, 0.05 equiv) and potassium carbonate (0.4 mmol, 2.0 equiv) were added. The vial was crimped and taken out of the glove box. 4-Bromotoluene (0.2 mmol, 1.0 equiv), was added via syringe, followed by dry toluene (1 mL). The reaction was stirred at 130 °C for 15 h. Then, the reaction was allowed to cool to rt, and filtered over a pad of silica and celite, rinsing with EtOAc (15-20 mL). The organic layer was washed with a solution of saturated *aqueous* $K_2CO_3$ (15 mL), water (15 mL). The *aqueous* layer was extracted with EtOAc (2* 10 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography in 15-100% EtOAc/Hex to provide 51 mg of a mixture of **166** and **166c** (0.14:1) and 40 mg of a mixture of **165** and **165g** (2:1). The estimated yields based on $^1$H NMR ratios of product versus starting material were: **166c** 66% and **165g** 26%.



To a microwave vial (previously kept in an oven and cooled under argon) fit with a stir bar, 3-phenylimidazo[1,5-*a*]pyridine **164** (0.4 mmol, 1.0 equiv), 4-bromoacetophenone (0.6 mmol, 1.5 equiv), and 2,4,6-trimethylbenzoic acid (0.12 mmol, 0.3 equiv) were added. The vial was then placed in a glove box where dichloro(*p*-cymene)ruthenium dimer (0.02 mmol, 0.05 equiv) and potassium carbonate (0.8 mmol, 2.0 equiv) were added. The vial was crimped and taken out of the glove box. 4-Bromoanisole (0.6 mmol, 1.5 equiv), was added via syringe, followed by dry toluene (2 mL). The reaction was stirred at 130 °C for 15 h. Then, the reaction was allowed to cool to rt, and filtered over a pad of silica and celite, rinsing with EtOAc (15-20 mL). The organic layer was washed with a solution of saturated *aqueous* $K_2CO_3$ (15 mL), water (15 mL). The *aqueous* layer was extracted with EtOAc (2*10 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$) and concentrated *in vacuo*. The resulting residue was purified by flash chromatography in 15-100% EtOAc/Hex to provide a mixture of mono- and diarylated products. The estimated yields based on $^1$H NMR ratios are shown in the equation above.

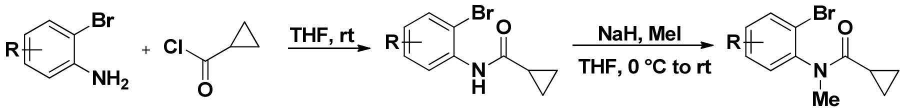
# Experimental section of Chapter 3

## Part 1

*Synthesis of 2-bromoanilines*

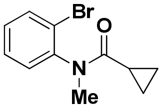
The following 2-bromoanilines were obtained via bromination from their corresponding anilines according to literature procedure: 2-bromo-4-methylaniline,[247] 4-amino-3-bromobenzaldehyde,[247] 2-bromo-4-(trifluoromethyl)aniline,[248] 4-amino-3-bromobenzonitrile,[248] 2-bromo-4-chloroaniline,[249] ethyl 4-amino-3-bromobenzoate,249 2-bromo-3,4-dimethoxyaniline,[250] and 2-bromo-4-methoxyaniline.[250]

*Synthesis of 2-bromoanilides*

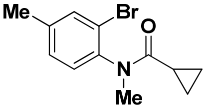


**Procedure F**: To a 0.1 *M* solution of the corresponding 2-bromoaniline (1.0 equiv) in THF, was added cyclopropanecarbonyl chloride (1.1 equiv) dropwise, forming a cloudy off-white solution. The mixture was stirred overnight (16 h) at ambient temperature. EtOAc (40 mL) was added and the solution was washed with saturated *aqueous* $NaHCO_3$ (3x40 mL), and brine (2x40 mL). The combined organics were then dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give a white solid, which was used crude in the subsequent methylation step.

The crude intermediate was dissolved in THF (0.1 *M*), cooled to 0 °C, where NaH (1.5 equiv) was added, forming a grey solution. After 15 minutes, MeI (7.0 equiv) was added dropwise. The reaction was allowed to warm up to rt and stirred overnight (16 h). The reaction was quenched with water (40 mL), and EtOAc (40 mL) was added. The layers were separated, and the *aqueous* layer was extracted with EtOAc (3x50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give the desired product. The crude was then purified via column chromatography in the given solvent.

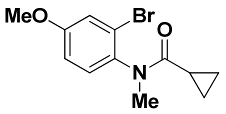


***N*-(2-bromophenyl)-*N*-methylcyclopropanecarboxamide (219b)**: Synthesized according to **Procedure F** on a 14.4 mmol scale. The product was obtained as a brown oil in 90% yield (3.3 g, 13.0 mmol). The observed characterization data was consistent with that previously reported in the literature.[251]

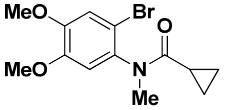


***N*-(2-bromo-4-methylphenyl)-*N*-methylcyclopropanecarboxamide (B1):** Synthesized according to **Procedure F** on a 7.07 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a brown oil in 65% yield (1.23 g, 4.60 mmol). $^1$H NMR ($CDCl_3$, 400

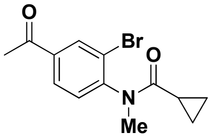
MHz): δ 7.53 (s, 1H), 7.27 (d, 1H, *J* = 7.9 Hz), 7.23-7.21 (m, 1H), 3.20 (s, 3H), 2.40 (s, 3H), 1.27-1.19 (m, 1H), 1.05-0.96 (m, 2H), 0.65-0.56 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 173.1, 139.8, 139.6, 133.7, 129.3, 123.0, 35.6, 20.5, 11.8, 8.1, 7.6 ppm. FTIR (cm$^{-1}$) (neat): 3011, 1655, 1493, 1390, 1283, 1058, 823, 577. HRMS (ESI, Pos) calcd for $C_{12}H_{14}BrNNaO$ $[M+Na]^+$: 290.0151, found 290.0144 *m/z.*



***N*-(2-bromo-4-methoxyphenyl)-*N*-methylcyclopropanecarboxamide (B2)**: Synthesized according to **Procedure F** on a 7.46 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a dark purple oil in 70% yield (1.49 g, 5.25 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.282-7.279 (m, 1H), 7.23 (d, 1H, *J* = 2.8 Hz), 6.92 (dd, 1H, *J* = 8.7, 2.8 Hz), 3.85 (s, 3H), 3.20 (s, 3H), 1.24-1.18 (m, 1H), 1.08-0.95 (m, 2H), 0.69-0.55 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 173.7, 159.4, 135.5, 130.3, 124.0, 118.5, 114.5, 55.7, 36.1, 12.0, 8.4, 7.9 ppm. FTIR (cm$^{-1}$) (neat): 3009, 1653, 1493, 1390, 1031, 890, 605. HRMS (APPI, Pos) calcd for $C_{12}H_{15}BrNO_2$ $[M+H]^+$: 284.0281, found 284.0272 *m/z.*

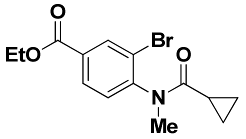


***N*-(2-bromo-4,5-dimethoxyphenyl)-*N*-methylcyclopropanecarboxamide (B3)**: Synthesized according to **Procedure F** on a 3.13 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a dark purple solid in 80% yield (0.782 g, 2.49 mmol). mp: 75-78 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.06 (s, 1H), 6.81 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.14 (s, 3H), 1.22-1.14 (m, 1H), 1.00-0.89 (m, 2H), 0.62-0.52 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 173.7, 149.2, 149.1, 135.2, 115.3, 113.6, 112.2, 56.23, 56.19, 35.9, 12.0, 8.4, 7.9 ppm. FTIR (cm$^{-1}$) (neat): 2937, 1648, 1525, 1382, 1070, 898, 875, 637; HRMS (ESI, Pos) calcd for $C_{13}H_{16}BrNNaO_3$ $[M+Na]^+$: 336.0206, found 336.0207 *m/z.*

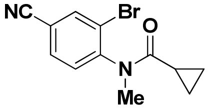


***N*-(4-acetyl-2-bromophenyl)-*N*-methylcyclopropanecarboxamide (B4)**: Synthesized according to **Procedure F** on a 5.18 mmol scale and then purified via column chromatography

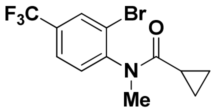
(5% EtOAc/Hex) to give an orange oil in 65% yield (1.04 g, 3.39 mmol). $^1$H NMR (CDCl$_3$, 300 MHz): δ 8.27 (d, 1H, *J* = 1.9 Hz), 7.97 (dd, 1H, *J* = 8.1, 1.9 Hz), 7.47 (d, 1H, *J* = 8.1 Hz), 3.22 (s, 3H), 2.63 (s, 3H), 1.13-0.98 (m, 3H), 0.68-0.58 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 195.6, 173.0, 146.9, 137.9, 133.8, 130.4, 128.7, 124.4, 35.9, 26.7, 12.6, 8.8, 8.4 ppm. FTIR (cm$^{-1}$) (neat): 3010, 1768, 1687, 1655, 1424, 1264, 1127, 1085, 604. HRMS (ESI, Pos) calcd for $C_{13}H_{14}BrNNaO_2$ [M+Na]$^+$: 318.0100, found 318.0099 *m/z.*



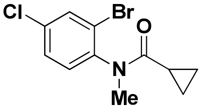
**Ethyl 3-bromo-4-(*N*-methylcyclopropanecarboxamido)benzoate (B4)**: Synthesized according to **Procedure F** on a 4.07 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a light yellow solid in 66% yield (0.88 g, 2.70 mmol). mp: 68-72°C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.29 (d, 1H, *J* = 1.9 Hz), 8.00 (dd, 1H, *J* = 8.1, 1.9 Hz), 7.39 (d, 1H, *J* = 8.1 Hz), 4.34 (q, 2H, *J* = 7.1 Hz), 3.15 (s, 3H), 1.34 (dd, 3H, *J* = 9.2, 5.1 Hz), 1.06-0.89 (m, 3H), 0.61-0.50 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.0, 163.4, 145.7, 133.9, 130.7, 129.11, 128.97, 122.9, 60.6, 34.9, 13.3, 11.5, 7.7, 7.3 ppm. FTIR (cm$^{-1}$) (neat): 3013, 1715, 1649, 1592, 1471, 1280, 1121, 753. HRMS (ESI, Pos) calcd for $C_{14}H_{16}BrNNaO_3$ [M+Na]$^+$: 348.0206, found 348.0206 *m/z.*



***N*-(2-bromo-4-cyanophenyl)-*N*-methylcyclopropanecarboxamide (B5)**: Synthesized according to **Procedure F** on a 4.10 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 84% yield (0.949 g, 3.40 mmol). mp: 210-213°C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.99 (s, 1H), 7.69 (dd, 1H, *J* = 8.1, 1.6 Hz), 7.48 (d, 1H, *J* = 8.1 Hz), 3.18 (s, 3H), 1.07-0.93 (m, 3H), 0.70-0.56 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.9, 147.3, 137.3, 132.6, 131.1, 124.8, 116.6, 113.6, 36.0, 12.7, 9.0, 8.6 ppm. FTIR (cm$^{-1}$) (neat): 2927, 2229, 1660, 1481, 1425, 1143, 610. HRMS (ESI, Pos) calcd for $C_{12}H_{11}BrN_2NaO$ [M+Na]$^+$: 300.9950, found 300.9944 *m/z.*

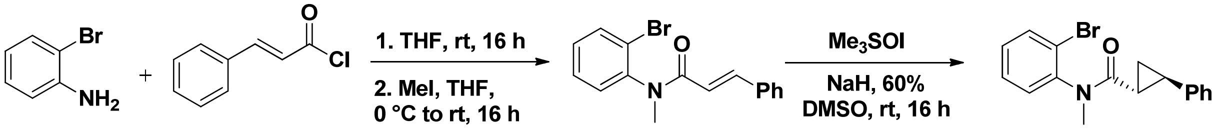


***N*-(2-bromo-4-(trifluoromethyl)phenyl)-*N*-methylcyclopropanecarboxamide (B6)**: Synthesized according to **Procedure F** on a 0.92 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a white solid in 72% yield (0.214 g, 0.663 mmol). mp: 49-52°C. $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 7.95 (s, 1H), 7.66-7.64 (m, 2H), 7.49 (d, 1H, $J$ = 8.0 Hz), 3.19 (s, 3H), 1.08-0.96 (m, 3H), 0.67-0.57 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 173.1, 146.3, 131.7 (q, $J_{C\text{-}F}$ = 33.5 Hz), 131.1 (q, $J_{C\text{-}F}$ = 3.9 Hz), 130.7, 126.0 (q, $J_{C\text{-}F}$ = 3.5 Hz), 122.8 (q, $J_{C\text{-}F}$ = 273 Hz), 35.9, 12.6, 8.9, 8.4 ppm. $^{19}$F NMR (282 MHz, CDCl$_3$): δ - 62.7. FTIR (cm$^{-1}$) (neat): 2935, 1783, 1657, 1428, 1157, 935, 680, 648. HRMS (ESI, Pos) calcd for $C_{12}H_{11}BrF_3NNaO$ [M+Na]$^+$: 343.9868, found 343.9868 *m/z.*



***N*-(2-bromo-4-chlorophenyl)-*N*-methylcyclopropanecarboxamide (B7)**: Synthesized according to **Procedure F** on a 6.55 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAC/Hex to give a light pink solid in 63% yield (1.18 g, 4.08 mmol). mp: 61-63°C. $^{1}$H NMR (CDCl$_3$, 300 MHz): δ 7.70 (d, 1H, $J$ = 2.3 Hz), 7.37 (dd, 1H, $J$ = 8.4, 2.3 Hz), 7.30 (d, 1H, $J$ = 8.4 Hz), 3.18 (s, 3H), 1.15-0.95 (m, 3H), 0.68-0.57 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 173.5, 141.8, 134.8, 133.6, 131.0, 129.3, 124.6, 36.1, 12.5, 8.9, 8.4 ppm. FTIR (cm$^{-1}$) (neat): 2932, 1655, 1556, 1285, 1034, 894, 579. HRMS (APPI, Pos) calcd for $C_{11}H_{12}BrClNO$ [M+H]$^+$: 287.9785, found 287.9776 *m/z.*

*Synthesis of **trans-rac-N-(2-bromophenyl)-N-methyl-2-phenylcyclopropanecarboxamide (250)***

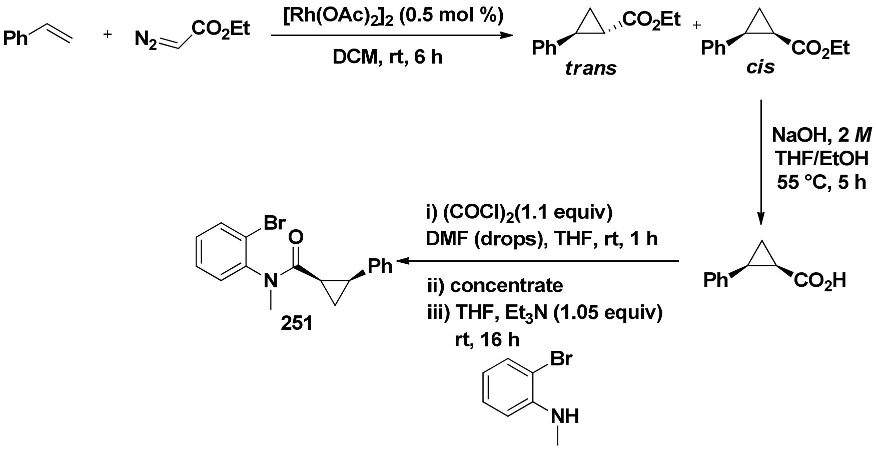


To a solution of 2-bromoaniline (11.6 mmol, 1 equiv) in THF (25 mL) was added cinnamyl chloride (11.9 mmol, 1.1 equiv) under Ar. The reaction was stirred at room temperature for 16 h. Then, EtOAc (50 mL) was added and the organic phase was washed with saturated *aqueous* NaHCO$_3$ solution (2x30 mL) and brine (15 mL). The organic phase was dried over anhydrous Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The resulting solid was dried on a vacuum pump, then dissolved in 25 mL of THF, purged with argon, and cooled down in an ice bath. NaH (15.9 mmol, 1.37 equiv) was added to the solution portionwise over a few minutes. The reaction was stirred for an additional 10 min at 0 °C, then MeI (17.4 mmol, 1.5 equiv) was added to the reaction. The reaction was allowed to warm up to room temperature, and stirred overnight. The reaction was quenched with water (15 mL), and extracted with EtOAc (3x25 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was flashed in 5-30% EtOAc/Hex to give 77% (2.8 g) of *N*-(2-bromophenyl)-*N*-methylcinnamamide as an off-white solid to be used in the subsequent step.

To a solution of trimethylsulfoxonium iodide (2 equiv) in DMSO (100 mL) was added NaH (2 equiv) portionwise over 15 min. The reaction was allowed to stir for 30 min at room temperature, then a solution of *N*-(2-bromophenyl)-*N*-methylcinnamamide in 5 mL of DMSO was added dropwise. The reaction was allowed to stir for 16 h. Then, the reaction was neutralized with 2.0 *M* HCl, and extracted with EtOAc (2x25 mL). The combined organic layer was washed with brine (2x30 mL), dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography in 5-10% EtOAc/Hex, affording the title compound as a clear oil in 75% yield and as the *trans*-racemic product.

**250**: reported as a 1:1 mixture of rotamers. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.57 (br d, 1H), 7.39-7.36 (m, 1H), 7.28-7.25 (m, 1H), 7.19-7.11 (m, 4H), 6.97 (d, 1H, *J* = 7.7 Hz), 6.90 (d, 1H, *J* = 7.7 Hz), 3.25 (s, 3H), 2.62-2.49 (m, 1H), 1.70-1.57 (m, 1H), 1.43-1.37 (m, 1H), 1.14-1.02 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 172.3, 172.2, 142.7, 142.6, 140.8, 140.7, 134.0, 133.9, 130.4, 130.2, 129.8 (2C), 129.0 (2C), 128.4, 128.3, 126.9, 126.4, 126.2, 124.0, 123.7, 36.3, 36.2, 26.6, 26.2, 23.8, 23.3, 17.4, 16.4 ppm. FTIR (cm$^{-1}$) (neat): 3002, 1647, 1583, 1457, 1423, 1358, 1312, 749, 728, 697. HRMS (ESI, Pos) calcd for C17H16BrNNaO $[M+Na]^+$: 352.0307, found 352.0304 *m/z*.

*Synthesis of* **cis-*rac*-N-(2-bromophenyl)-N-methyl-2-phenylcyclopropanecarboxamide (251)**

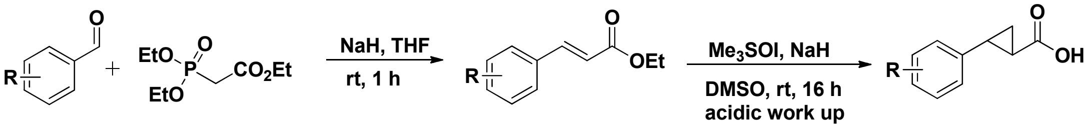


To a 250-mL round-bottom flask (flame-dried and cooled under Ar) was added $[Rh(OAc)_2]_2$ (70 mg, 0.324 mmol, 0.5 mol %) and DCM (100 mL). Styrene (11.0 mL, 97 mmol, 3 equiv) was added via syringe, and the reaction was cooled to 0 ºC. Ethyl diazoacetate (3.7 g, 32.4 mmol, 1.0 equiv) was then added over 60 min via a syringe pump. The reaction was stirred for another 3 h, then filtered through a silica-cotton plug and concentrated *in vacuo*. The racemic mixture was then flashed in 5-10% EtOAc/Hex and the *cis*-product isolated in 28 % yield (1.7 g, 8.9 mmol).

1.7 g (8.9 mmol) of the *cis*-racemic cyclopropane ester was then placed in a 100-mL round-bottom flask containing 15 mL of THF and 10 mL of MeOH. 2.0 *M* NaOH (19 mL, 37.4 mmol, 5.0 equiv) was then added and the mixture was heated to 55 ºC for 5 hours. The reaction was then cooled to ambient temperature, acidified with 30 mL of 10% HCl. This was transferred to a 250-mL separatory funnel and extracted with benzene (3x25 mL). The combined organics were then washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated *in vacuo* to give the desired *cis-rac*-cyclopropanecarboxylic acid.

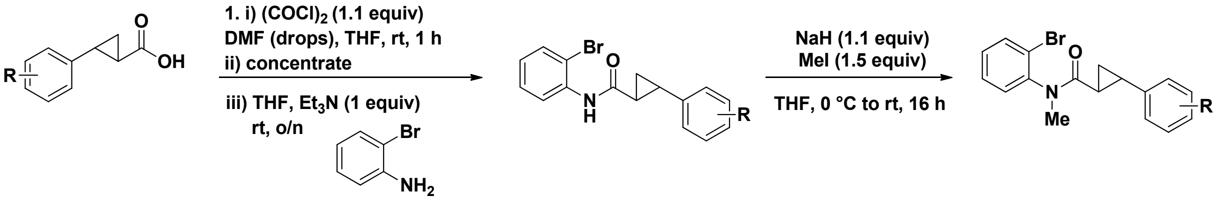
**251** was then synthesized according to **Procedure H** (*vide infra*) on a 1.9 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), affording the *cis-racemic* product **251** as a clear oil in 79% yield (494 mg, 1.50 mmol). Reported as a 3:1 mixture of rotamers. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.67 (two d, 1H, $J$ = 8.0, 1.3 Hz), 7.41-7.15 (m, 7H), 6.87 (dd, 1H, $J$ = 7.8, 1.6 Hz), 3.07 & 3.01 (s, 3H), 2.30 & 2.06 (q, 1H, $J$ =8.4 Hz), 1.90-1.86 & 1.81-1.77 (m, 1H), 1.73-1.66 (m, 1H), 1.21-1.14 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 169.5, 168.4, 143.0, 142.4, 137.2, 136.6, 133.8, 133.6, 130.6, 130.2, 129.7, 129.6, 129.5, 128.8, 128.6, 128.2, 127.8, 127.4, 126.2, 126.1, 123.7, 123.2, 35.9, 35.8, 26.5, 25.5, 24.4, 21.0, 12.2, 11.2 ppm. FTIR (cm$^{-1}$) (neat): 3059, 3008, 1655, 1497, 1476, 1458, 1329, 1068, 1026, 728, 696, 664. HRMS (ESI, Pos) calcd for $C_{17}H_{16}BrNNaO$ [M+Na]$^+$: 352.0308, found 352.0305 *m/z*.

*Synthesis of trans-rac-2-arylcyclopropanecarboxylic acids*

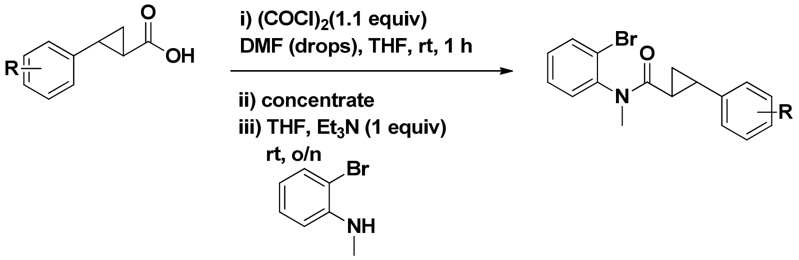


The ethyl-(*E*)-3-arylacrylates were synthesized according to the literature procedure.[252] The Corey-Chaykovsky cyclopropanation was performed as outlined in the literature,[253] except an acidic work up was added to isolate the carboxylic acid. All the intermediates have been previously synthesized and match reported literature data.

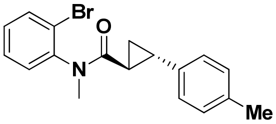
*Synthesis of 2-bromoanilides using trans-rac-2-arylcyclopropanecarboxylic acids*



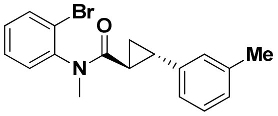
**Procedure G**: To a THF (0.3 *M*) solution of the corresponding cyclopropanecarboxylic acid (1.0 equiv) under Ar, was added catalytic DMF (2-3 drops). Oxalyl chloride (1.1 equiv) was then added dropwise over 30 min. The reaction was stirred for an additional 30 min at ambient temperature (or until complete by TLC) and then concentrated *in vacuo* to remove excess oxalyl chloride. The residue was re-dissolved in THF (10 mL). 2-Bromoaniline (0.95 equiv), then $Et_3N$ (1.0 equiv) were both added dropwise. The reaction was stirred at ambient temperature for a further 16 h. It was then quenched with water (10 mL), and the *aqueous* layer was extracted with EtOAc (2x25 mL). The combined organic layers were washed with saturated *aqueous* $NaHCO_3$ solution (20 mL), brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude was then dissolved in THF (10 mL) in a 25-mL round-bottomed flask under argon and cooled in an ice bath. NaH (1.1 equiv) was added portionwise. The reaction was stirred for an additional 10 min, then MeI (1.5 equiv) was added. The reaction was allowed to warm up to ambient temperature and stirred for 16 h. Then, the reaction was quenched with water (10 mL) and extracted with EtOAc (3x20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography. As indicated, the desired products were *trans*-racemic.



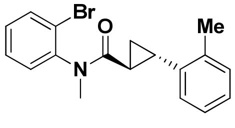
**Procedure H**: To a THF (0.3 *M*) solution of the corresponding cyclopropanecarboxylic acid (1.0 equiv) under Ar, was added catalytic DMF (2-3 drops). Oxalyl chloride (1.1 equiv) was then added dropwise over 30 min. The reaction was stirred for an additional 30 min at ambient temperature (or until complete by TLC). The reaction was then concentrated *in vacuo* to remove excess oxalyl chloride, and the residue was re-dissolved in THF (10 mL). 2-bromo-*N*-methylaniline[254] (0.95 equiv), then $Et_3N$ (1.0 equiv) were both added dropwise. The reaction was stirred at ambient temperature for a further 16 h. It was then quenched with water (10 mL), and the aqueous layer was extracted with EtOAc (2x25 mL). The combined organic layers were washed with saturated *aqueous* $NaHCO_3$ solution (20 mL) and brine (10 mL), and dried over anhydrous $Na_2SO_4$. After filtration and concentrating *in vacuo*, the residue was purified by flash chromatography or re-crystallization to give *trans*-racemic products.



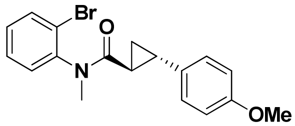
***trans-rac-N*-(2-bromophenyl)-*N*-methyl-2-(p-tolyl)cyclopropanecarboxamide (B8)**: Synthesized according to **Procedure H** on a 2.85 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give an off-white solid in 77% yield (769 mg, 2.30 mmol). Reported as a 1:1 mixture of rotamers. mp: 98-99 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.69-7.59 (two d, 1H), 7.38-7.36 (m, 1H), 7.28-7.26 (m, 1H), 7.22-7.17 (m, 1H), 7.00-6.97 (m, 2H), 6.89 (dd, 1H, $J$ = 8.0, 1.5 Hz), 6.80 (dd, 1H, $J$ = 8.0, 1.5 Hz), 3.25 (s, 3H), 2.60-2.47 (m, 1H), 2.26 (s, 3H), 1.67-1.54 (m, 1H), 1.41-1.34 (m, 1H), 1.11-0.99 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.4, 172.2, 142.7, 142.6, 137.6 (2), 135.7 (2), 133.9 (2), 130.4, 130.1, 129.8, 129.7, 129.0 (2), 128.9, 126.8 (2C, 126.3, 124.0, 123.7, 36.2 (2), 26.2, 25.9, 23.5, 23.0, 21.1 (2), 17.2, 16.3 ppm. FTIR (cm$^{-1}$) (neat): 3082, 3024, 1644, 1581, 1475, 1423, 963, 871, 671. HRMS (ESI, Pos) calcd for $C_{18}H_{19}BrNO$ [M+H]$^+$: 344.0646, found 344.0649 *m/z*.



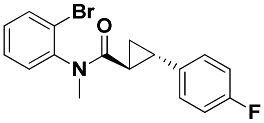
***trans-rac-N*-(2-bromophenyl)-*N*-methyl-2-(*m*-tolyl)cyclopropanecarboxamide (B9)**: Synthesized according to **Procedure G** on a 3.0 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give an off-white solid in 74% yield (764 mg, 2.22 mmol). Reported as a 1:1 mixture of rotamers. mp: 87-88 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.72-7.62 (two br d, 1H, $J$ = 7.3 Hz), 7.41-7.40 (m, 1H), 7.32-7.27 (m, 1H), 7.24-7.21 (m, 1H), 7.10-7.07 (m, 1H), 6.97-6.96 (d, 1H, $J$ = 7.2 Hz), 6.86-6.71 (m, 2H), 3.28 (s, 3H), 2.63-2.50 (m, 1H), 2.27 (s, 3H), 1.72-1.59 (m, 1H), 1.47-1.41 (m, 1H), 1.15-1.04 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.2, 172.1, 142.7, 142.6, 140.6, 140.5, 137.8, 137.7, 133.9 (2), 130.4, 130.1, 129.7 (2), 129.0, 128.9, 128.2, 128.1, 127.9, 127.3, 126.9, 124.0, 123.8, 123.7, 123.3, 36.2, 36.1, 26.4, 26.1, 23.6, 23.0, 21.4, 17.2, 16.2 ppm. FTIR (cm$^{-1}$) (neat): 2922, 1650, 1607, 1427, 1363, 1252, 1031, 930, 730, 697, 673. HRMS (ESI, Pos) calcd for $C_{18}H_{19}BrNO$ [M+H]$^+$: 344.0644, found 344.0647 *m/z*.



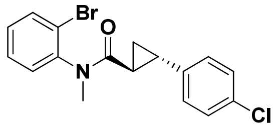
***trans-rac-N*-(2-bromophenyl)-*N*-methyl-2-(o-tolyl)cyclopropanecarboxamide (B10)**: Synthesized according to **Procedure H** on a 1.9 mmol scale, then purified by flash chromatography (5-20% EtOAc/Hex), to give a clear oil in 94% yield (618 mg, 1.80 mmol). Reported as a 1:1 mixture of rotamers. mp: 91-93 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71-7.66 (m, 1H), 7.40-7.37 (m, 2H), 7.27-7.21 (m, 1H), 7.12-7.06 (m, 2H), 7.02-6.97 (m, 1H), 6.74-6.66 (m, 1H), 3.29 (s, 3H), 2.70-2.56 (m, 1H), 2.39 (d, 3H, $J$ = 9.0 Hz), 1.69-1.53 (m 1H), 1.46-1.41 (m, 1H), 1.12-0.99 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.5, 172.4, 142.7, 142.6, 138.4 (2C), 138.3, 137.9, 134.0 (2), 130.3, 130.1, 129.8, 129.7, 129.0 (2), 126.4, 126.1, 126.0, 125.5, 123.9, 36.2, 36.1, 24.5, 24.4, 21.4, 19.8, 19.7, 16.3, 15.8 ppm. FTIR ($cm^{-1}$) (neat): 2939, 1644, 1580, 1477, 1358, 1270, 1059, 1029, 767, 752, 723. HRMS (ESI, Pos) calcd for $C_{18}H_{19}BrNO$ $[M+H]^+$: 344.0644, found 344.0644 *m/z*.



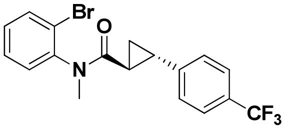
***trans*-*rac*-*N*-(2-bromophenyl)-2-(4-methoxyphenyl)-*N*-methylcyclopropanecarboxamide (B11)**: Synthesized according to **Procedure G** on a 2.37 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give a clear oil in 74% yield (632 mg, 1.75 mmol). Reported as a 1:1 mixture of rotamers. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.71-7.61 (two br d, 1H), 7.42-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.23-7.19 (m, 1H), 6.94 (d, 1H, *J* = 8.4 Hz), 6.86 (d, 1H, *J* = 8.5 Hz), 6.73 (dd, 2H, *J* = 8.8, 2.5 Hz), 3.75 (s, 3H), 3.27 (s, 3H), 2.60-2.47 (m, 1H), 1.68-1.55 (m, 1H), 1.39-1.32 (m, 1H), 1.10-0.99 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 172.4, 172.3, 158.1 (2C), 142.7, 142.6, 133.9 (2), 132.7, 132.6, 130.4, 130.2, 129.8, 129.7, 129.0, 128.9, 128.0, 127.5 (2), 124.0, 123.7, 113.8, 55.3 (2), 36.2, 36.1, 25.9, 25.6, 23.5, 23.0, 17.0, 16.1 ppm. FTIR ($cm^{-1}$) (neat): 28344, 1651, 1611, 1583, 1514, 1475, 1245, 1119, 1034, 823, 671. HRMS (ESI, Pos) calcd for $C_{18}H_{18}BrNNaO_2$ $[M+Na]^+$: 382.0413, found 382.0407 *m/z*.



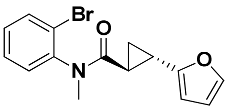
***trans*-*rac*-*N*-(2-bromophenyl)-2-(4-fluorophenyl)-*N*-methylcyclopropanecarboxamide (B12)**: Synthesized according to **Procedure H** on a 3.5 mmol scale. The residue was purified by re-crystallization from EtOAc/Hex, to give a white solid in 78% yield (931 mg, 2.68 mmol). Reported as a 1:1 mixture of rotamers. mp: 99-100 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.67-7.55 (two br d, 1H), 7.37-7.36 (m, 1H), 7.26-7.25 (m, 1H), 7.19-7.15 (m, 1H), 6.93-6.89 (m, 1H), 6.84-6.80 (m 3H), 3.23 (s, 3H), 2.57-2.45 (m, 1H), 1.68-1.57 (m 1H), 1.38-1.32 (m, 1H), 1.07-0.97 (m, 1H) ppm. $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 171.8, 171.7, 162.4, 160.0, 142.4 (2), 136.2 (d, $J_{C\text{-}F}$ = 3 Hz), 136.1 (d, $J_{C\text{-}F}$ = 3 Hz), 133.8, 133.7, 130.1, 130.0, 129.7 (2), 128.9, 128.8, 128.1, 128.0, 127.6, 127.7, 123.8, 123.5, 115.1, 115.0, 114.9, 114.8, 36.0 (2), 25.6, 25.2, 23.6, 23.1, 16.9, 16.0 ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -116.6 (m) ppm. FTIR ($cm^{-1}$) (neat): 2966, 1650, 1528, 1510, 1475, 1419, 1320, 1211, 1083, 864, 746, 671, 572. HRMS (ESI, Pos) calcd for $C_{17}H_{16}BrFNO$ $[M+H]^+$: 348.0394, found 348.0392 *m/z*.



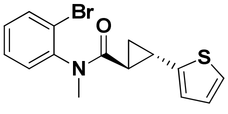
***trans-rac-N*-(2-bromophenyl)-2-(4-chlorophenyl)-*N*-methylcyclopropanecarboxamide (B13)**: Synthesized according to **Procedure H** on a 1.9 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give a white solid in 77% yield (533 mg, 1.46 mmol). Reported as a 1:1 mixture of rotamers. mp: 80-82 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.57 (two br d, 1H, *J* = 8.3 Hz), 7.41-7.37 (m, 1H), 7.27-7.25 (m, 1H), 7.13-7.11 (m, 2H), 6.98 (d, 1H, *J* = 8.1 Hz), 6.82 (d, 1H, *J* = 8.1 Hz), 3.25 (s, 3H), 2.56-2.46 (m, 1H), 1.72-1.61 (m, 1H), 1.40-1.33 (m, 1H), 1.11-1.00 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 171.8, 171.7, 142.5, 142.4, 139.2 (2), 133.9, 133.8, 131.8 (2), 130.2, 130.0, 129.8 (2), 129.0, 128.9, 128.4 (2), 128.3, 128.0, 127.7, 123.9, 123.6, 36.2, 36.14, 25.8, 25.4, 23.9, 23.5, 17.2, 16.3 ppm. FTIR ($cm^{-1}$) (neat): 2922, 2866, 1657, 1492, 1477, 1358, 1056, 1012. HRMS (ESI, Pos) calcd for $C_{17}H_{16}BrClNO$ $[M+H]^+$: 364.0098, found 364.0097 *m/z*.



***trans-rac-N*-(2-bromophenyl)-N-methyl-2-(4-(trifluoromethyl)phenyl)cyclopropanecarboxamide (B14)**: Synthesized according to **Procedure H** on a 1.36 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give a yellow solid in 66% yield (356 mg, 0.894 mmol). Reported as a 1:1 mixture of rotamers. mp: 74-75 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.71-7.57 (two br d, 1H), 7.43-7.39 (m, 3H), 7.27-7.26 (m, 1H), 7.23-7.19 (m, 1H), 7.09 (d, 1H, *J* = 7.9 Hz), 6.99 (d, 1H, *J* = 7.9 Hz), 3.26 (s, 3H), 2.69-2.59 (m, 1H), 1.77-1.66 (m 1H), 1.49-1.42 (m, 1H), 1.18-1.06 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 171.6, 171.5, 145.0 (2), 142.5, 142.4, 134.0 (2), 130.2, 130.1, 129.9 (2), 129.1, 129.0, 126.8, 126.4, 125.3-125.2 (m), 123.9, 123.7, 36.2 (2), 26.1, 25.7, 24.3, 23.8, 17.6, 16.6 ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -62.3 (d, $J$ = 9.7 Hz) ppm. FTIR (cm$^{-1}$) (neat): 2931, 1655, 1618, 1476, 1423, 1323, 162, 1116, 1067, 826, 727, 711. HRMS (ESI, Pos) calcd for $C_{18}H_{16}BrF_3NO$ [M+H]$^+$: 398.0362, found 398.0355 *m/z*.



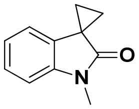
***trans-rac-N*-(2-bromophenyl)-2-(furan-2-yl)-*N*-methylcyclopropanecarboxamide (B15)**: Synthesized according to **Procedure H** on a 2.85 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give a yellow oil in 77% yield (707 mg, 2.21 mmol). Reported as a 1:1 mixture of rotamers. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.66-7.59 (two br d, 1H, $J$ = 8.0 Hz), 7.39-7.29 (m, 2H), 7.21-7.16 (m, 1H), 7.10-7.08 (m, 1H), 6.15-6.13 (m, 1H), 5.96-5.82 (br d, 1H, $J$ = 12.7, 2.6 Hz), 3.21 (s, 3H), 2.54-2.44 (m, 1H), 1.59-1.46 (m, 2H), 1.16-1.06 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 171.5, 171.4, 154.0 (3), 142.4, 142.3, 140.8, 140.7, 133.8, 130.2, 130.0, 129.7 (2), 128.9 (2), 123.9, 123.5, 110.2, 105.0, 104.8, 36.1 (2), 32.2, 21.4, 19.5, 19.1, 15.0, 14.4 ppm. FTIR (cm$^{-1}$) (neat): 3008, 2923, 1650, 1583, 1507, 1422, 1315, 1131, 1119, 1013, 764, 727. HRMS (ESI, Pos) calcd for $C_{15}H_{14}BrNNaO_2$ [M+Na]$^+$: 342.0100, found 342.0099 *m/z*.



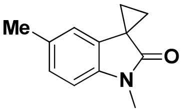
***trans-rac-N*-(2-bromophenyl)-*N*-methyl-2-(thiophen-2-yl)cyclopropanecarboxamide (B16)**: Synthesized according to **Procedure G** on a 2.76 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), to give an off-white solid in 67% yield (622 mg, 1.85 mmol). Reported as a 1:1 mixture of rotamers. mp: 119-121 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.69-7.64 (m, 1H), 7.41-7.31 (m, 2H), 7.24-7.20 (m, 1H), 7.00 (t, 1H, $J$ = 4.5 Hz), 6.81-6.79 (m, 1H), 6.66-6.59 (two d, 1H, $J$ = 3.2 Hz), 3.25 (s, 3H), 2.72-2.53 (m, 1H), 1.73-1.62 (m 1H), 1.48-1.43 (m, 1H), 1.15-1.04 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ171.6, 171.5, 144.9, 144.8, 142.6, 142.5, 134.0 (2), 130.4, 130.1, 129.9, 129.8, 129.1, 129.0, 126.7, 126.6, 124.2, 124.1, 123.7, 123.6, 123.3, 123.1, 36.2 (2), 24.4, 24.0, 21.5, 21.3, 17.9, 17.1 ppm. FTIR (cm$^{-1}$) (neat): 2923, 1643, 1582, 1476, 1426, 1203, 1056, 923, 761, 700. HRMS (ESI, Pos) calcd for $C_{15}H_{15}BrNO$ [M+H]$^+$: 336.0052, found 336.0050 *m/z*.

*Synthesis of spiro 3,3'-cyclopropyl oxindoles*

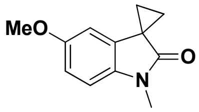
**Procedure I**: To a 5 mL microwave vial in a glovebox was added in the following order: $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), $PCy_3$ (7.0 mg, 0.025 mmol), $K_2CO_3$ (104 mg, 0.75 mmol) and $Ag_3PO_4$ (0.17 mmol, 69.1 mg). The vial was crimped shut. The corresponding 2-bromoanilide (0.50 mmol) was weighed into a vial, dissolved in 0.4 mL of toluene and added to the reaction vial. The vial containing 2-bromoanilide was rinsed with 3x0.2 mL of toluene for a total volume of 1.0 mL. The yellowish-orange solution was then heated to 130 °C in an oil bath for 3 h as indicated by TLC. The reaction turned black within five minutes. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, rinsing with 15 mL EtOAc, and concentrated *in vacuo* to give the crude product. The crude was purified via column chromatography over silica gel using the given solvent gradient.



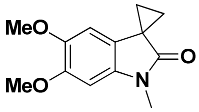
**1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (220)**: Synthesized according to **Procedure I** on a 0.464 mmol scale to give an orange solid in 90% yield (72. 4 mg, 0.418 mmol). The observed characterization data was consistent with that previously reported in the literature.[92]



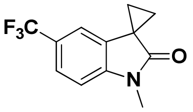
**1',5'-dimethylspiro[cyclopropane-1,3'-indolin]-2'-one (227)**: Synthesized according to **Procedure I** on a 0.508 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a light pink solid in 81% yield (77.2 mg, 0.412 mmol). mp: 75-78°C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.06-7.04 (m, 1H), 6.81-6.78 (m, 1H), 6.66 (dd, 1H, $J$ = 1.0, 0.4 Hz), 3.28 (s, 3H), 2.35 (s, 3H), 1.74-1.69 (m, 2H), 1.50-1.46 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 177.2, 141.3, 131.6, 131.0, 130.3, 127.1, 119.2, 107.8, 27.1, 26.7, 21.2, 19.1 ppm. FTIR (cm$^{-1}$) (neat): 2918, 1691, 1493, 1392, 1230, 890, 700, 554. HRMS (ESI, Pos) calcd for $C_{12}H_{13}NNaO$ $[M+Na]^+$: 210.0889, found 210.0881 *m/z.*



**5'-methoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (228)**: Synthesized according to **Procedure I** on a 0.506 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a cream-coloured solid in 67% yield (69.4 mg, 0.342 mmol). mp: 72-75°C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.80 (d, 2H, *J* = 2.1 Hz), 6.47 (t, 1H, *J* = 0.9 Hz), 3.80 (s, 3H), 3.29 (s, 3H), 1.75 (m, 2H), 1.49 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 176.8, 155.9, 137.3, 132.4, 111.0, 108.3, 106.1, 56.0, 27.5, 26.7, 19.3 ppm. FTIR (cm$^{-1}$) (neat): 2930, 1694, 1370, 1210, 793. HRMS (APPI, Pos) calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$: 204.1019, found 204.1027 *m/z.*

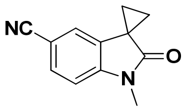


**5',6'-dimethoxy-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (229)**: Synthesized according to **Procedure I** on a 0.5 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a cream-coloured solid in 74% yield (86.3 mg, 0.37 mmol). mp: 148-150°C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.55 (s, 1H), 6.45 (s, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 3.27 (s, 3H), 1.69-1.66 (m, 2H), 1.45-1.42 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 177.5, 148.9, 145.1, 137.3, 121.6, 104.3, 94.8, 57.1, 56.7, 27.3, 26.7, 18.7 ppm. FTIR (cm$^{-1}$) (neat): 2932, 1687, 1508, 1285, 1150, 901, 777. HRMS (ESI, Pos) calcd for $C_{13}H_{15}NNaO_3$ $[M+Na]^+$: 256.0944, found 256.0942 *m/z.*

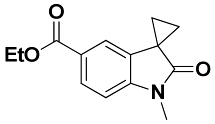


**1'-methyl-5'-(trifluoromethyl)spiro[cyclopropane-1,3'-indolin]-2'-one (230)**: Synthesized according to **Procedure I** on a 0.485 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 85% yield (99.4 mg, 0.412 mmol). mp: 132-134°C. $^1$H NMR ($CDCl_3$, 400

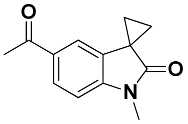
MHz): δ 7.53 (d, 1H, $J$ = 8.2 Hz), 7.05 (dd, 1H, $J$ = 1.2, 0.5 Hz), 6.96 (d, 1H, $J$ = 8.2 Hz), 3.32 (s, 3H), 1.82-1.79 (m, 2H), 1.59-1.61 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): 177.1, 146.5, 131.6, 124.6 (q, $J_{C\text{-}F}$ = 271 Hz), 124.6 (q, $J_{C\text{-}F}$ = 4.1 Hz), 124.5 (q, $J_{C\text{-}F}$ = 32.7 Hz), 119.2, 115.5 (q, $J_{C\text{-}F}$ = 3.6 Hz), 114.4, 27.2, 26.9, 19.8 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): -61.3 ppm. FTIR (cm$^{-1}$) (neat): 2925, 1708, 1624, 1460, 1163, 954, 520; HRMS (ESI, Pos) calcd for $C_{12}H_{10}F_3NNaO$ [M+Na]$^+$: 264.0606, found 264.0603 *m/z.*



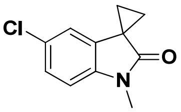
**1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-5'-carbonitrile (231)**: Synthesized according to **Procedure I** on a 0.524 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 78% yield (80.9 mg, 0.409 mmol). mp: 124-127°C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.58 (dd, 1H, $J$ = 8.1, 1.5 Hz), 7.07 (d, 1H, $J$ = 1.3 Hz), 6.95 (d, 1H, $J$ = 8.1 Hz), 3.32 (s, 3H), 1.82 (m, 2H), 1.60 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 176.8, 147.4, 132.16, 132.12, 121.7, 119.5, 108.4, 105.2, 27.0, 26.9, 20.2 ppm. FTIR (cm$^{-1}$) (neat): 3053, 2919, 2220, 1711, 1618, 1591, 1253, 829. HRMS (ESI, Pos) calcd for $C_{12}H_{10}N_2NaO$ [M+Na]$^+$: 221.0685, found 221.0681 *m/z.*



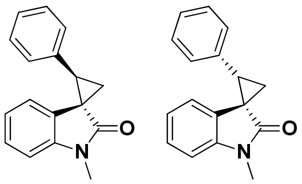
**Ethyl 1'-methyl-2'-oxospiro[cyclopropane-1,3'-indoline]-5'-carboxylate (232)**: Synthesized according to **Procedure I** on a 0.432 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 99% yield (105 mg, 0.426 mmol). mp: 124-126°C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.00 (d, 1H, $J$ = 8.1 Hz), 7.50 (s, 1H), 6.91 (d, 1H, $J$ = 8.1 Hz), 4.35 (q, 2H, $J$ = 7.0 Hz), 3.32 (s, 3H), 1.77 (m, 2H), 1.61-1.60 (m, 2H), 1.38 (t, 3H, $J$ = 7.0 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 177.4, 166.6, 147.6, 130.9, 129.5, 124.4, 119.6, 107.5, 61.0, 27.1, 26.9, 19.6, 14.5 ppm. FTIR (cm$^{-1}$) (neat): 2961, 1701, 1615, 1298, 1104, 1025, 772. HRMS (ESI, Pos) calcd for $C_{14}H_{15}NNaO_3$ [M+Na]$^+$: 268.0944, found 268.0940 *m/z.*



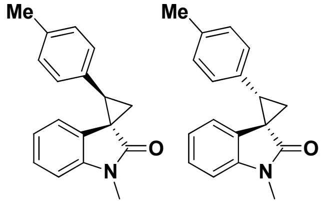
**5'-acetyl-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (233)**: Synthesized according to **Procedure I** on a 0.412 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a cream-coloured solid in 62% yield (54.9 mg, 0.255 mmol). mp: 165-167 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.93-7.90 (m, 1H), 7.49 (d, 1H, *J* = 1.3 Hz), 6.93 (dd, 1H, *J* = 8.1, 3.3 Hz), 3.33 (s, 3H), 2.58 (s, 3H), 1.80-1.76 (m, 2H), 1.63-1.61 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 197.1, 177.5, 147.9, 131.8, 131.3, 129.0, 118.2, 107.3, 27.1, 26.9, 26.5, 19.8 ppm. FTIR (cm$^{-1}$) (neat): 2920, 2851, 1711, 1659, 1616, 1424, 1259, 826, 618, 535. HRMS (ESI, Pos) calcd for $C_{13}H_{13}NNaO_2$ [M+Na]$^+$: 238.0838, found 238.0833 *m/z.*



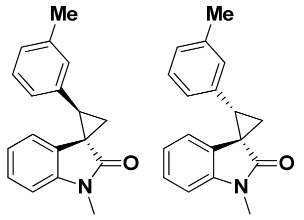
**5'-chloro-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (234)**: Synthesized according to **Procedure I** on a 0.491 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a pink-colored solid in 89% yield (90.4 mg, 0.437 mmol). mp: 130-132°C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.23 (d, 1H, *J* = 8.3 Hz), 6.83-6.81 (m, 2H), 3.29 (s, 3H), 1.78-1.77 (m, 2H), 1.54 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 176.6, 142.2, 132.8, 127.5, 126.7, 118.9, 108.9, 27.3, 26.8, 19.6 ppm. FTIR (cm$^{-1}$) (neat): 3058, 2924, 1697, 1612, 1587, 1388, 1085, 802, 666, 545, 458. HRMS (APPI, Pos) calcd for $C_{11}H_{11}ClNO$ [M+H]$^+$: 208.0525, found 208.0524 *m/z.*



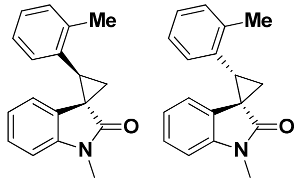
**(1*S*,2*R*)-1'-methyl-2-phenylspiro[cyclopropane-1,3'-indolin]-2'-one (235a) and (1R,2*R*)-1'-methyl-2-phenylspiro[cyclopropane-1,3'-indolin]-2'-one (235b)**: Synthesized according to **Procedure I**, *except the reaction was run for 15 h*, from *trans-racemic* **235** on a 0.5 mmol scale and then purified via column chromatography over silica gel in 5-20% EtOAc/Hex to give a yellow oil in 90% yield (112 mg, 0.449 mmol) as an inseparable mixture of major and minor diastereomers (6:1 dr). From *cis-racemic* **235** on a 0.4 mmol scale: 93% yield, (93 mg, 0.37 mmol) in 1:5 dr. Diastereomeric ratios were determined via $^1$H NMR. $^1$H NMR (CDCl$_3$, 400 MHz): Major **235a**: δ 7.33-7.26 (m, 4H), 7.21-7.14 (m, 3H), 6.99 (d, 1H, *J* = 7.9 Hz), 6.70 (t, 1H, *J* = 7.5 Hz), 5.98 (d, 1H, *J* = 7.6 Hz), 3.34 (s, 3H), 3.38-3.34 (m, 1H), 2.20 (dd, 1H, *J* = 9.1, 4.5 Hz), 2.0 (dd, 1H, *J* = 8.0, 4.4 Hz), Minor **235b**: δ 7.35-6.87 (m, 9H), 3.16 (s, 3H), 3.18-3.15 (m, 1H), 2.41 (dd, *J* = 8.6, 4.9 Hz), 2.07 (dd, 1H, *J* = 8.9, 4.6 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): mixture: δ 176.5 (2), 143.9, 135.2, 134.4, 130.9, 130.0, 129.3, 128.7, 128.0, 127.6, 127.4, 127.3, 126.9, 126.6, 125.8, 121.9, 121.5, 120.7, 118.1, 107.9, 107.8, 38.2, 35.9, 33.9, 33.4, 26.7, 26.5, 22.6, 22.5 ppm. FTIR (cm$^{-1}$) (neat): 3056, 3028, 1699, 1614, 1468, 1345, 1128, 747, 696. HRMS (ESI, Pos): calcd for $C_{17}H_{16}NO$ [M+H]$^+$: 250.1226, found 250.1224 *m/z*.



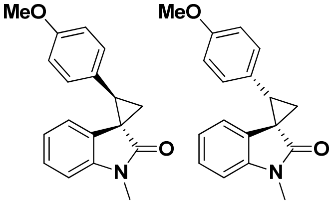
**(1*S*,2*R*)-1'-methyl-2-(*p*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (236a) and (1*R*,2*R*)-1'-methyl-2-(*p*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (236b)**: Synthesized according to **Procedure I** on a 0.496 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 93% yield (121 mg, 0.459 mmol) as an inseparable mixture of major and minor diastereomers (8:1 dr). *Reaction was also run for 15 h* to give 89% yield (118 mg, 6:1 dr). Diastereomeric ratios were determined via $^1$H NMR. $^1$H NMR (CDCl$_3$, 400 MHz): Major **236a**: δ 7.34-7.07 (m, 5H), 6.90-6.86 (m, 1H), 6.72 (t, 1H, *J* = 7.5 Hz), 6.03 (d, 1H, *J* = 7.5 Hz), 3.33 (s, 3H), 3.36-3.32 (m, 1H), 2.34 (s, 3H), 2.18 (dd, 1H, *J* = 8.9, 4.5 Hz), 1.99 (dd, 1H, *J* = 7.8, 4.5 Hz), Minor 2**36b**: δ 7.37-6.86 (m, 8H), 3.19 (s, 3H), 3.16-3.13 (m, 1H), 2.42-2.38 (m, 1H), 2.34 (s, 3H), 2.06 (dd, 1H, *J* = 9.0, 4.7 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): Major **236a**: δ 176.6, 143.8, 137.0, 132.1, 129.8, 129.1, 127.7, 126.5, 121.5, 120.8, 107.8, 35.7, 33.4, 26.7, 22.6, 21.2, Minor **236b**: δ 176.6, 149.3, 136.8, 131.3, 129.4, 126.8, 125.8, 121.9, 118.7, 118.1, 107.8, 36.1, 33.9, 26.5, 22.6, 21.3 ppm. FTIR (cm$^{-1}$) (neat): 3001, 2922, 1701, 1614, 1517, 1378, 1215, 1158, 748, 585. HRMS (ESI, Pos) calcd for $C_{18}H_{17}NNaO$ $[M+Na]^+$: 286.1202, found 286.1199 *m/z*.



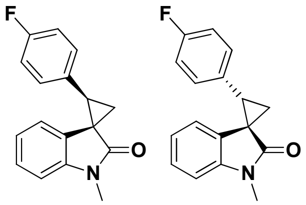
**(1*S*,2*R*)-1'-methyl-2-(*m*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (237a) and (1*R*,2*R*)-1'-methyl-2-(*m*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (237b)**: Synthesized according to **Procedure I** on a 0.485 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 98% yield (126 mg, 0.477 mmol) as an inseparable mixture of major and minor diastereomers (11:1 dr). *Reaction was also run for 15 h* to give 98% (129 mg, 7:1 dr). Diastereomeric ratios were determined via $^1$H NMR. $^1$H NMR ($CDCl_3$, 400 MHz): Major **237a**: δ 7.18-7.14 (m, 2H), 7.08-7.06 (m, 1H), 7.03 (br s, 1H), 6.98 (d, 1H, *J* = 7.6 Hz), 6.88 (d, 1H, *J* = 7.8 Hz), 6.71 (td, 1H, *J* = 7.6, 1.0 Hz), 6.03 (dt, 1H, *J* = 7.5, 0.5 Hz), 3.34 (s, 3H), 3.35-3.30 (m, 1H), 2.31 (s, 3H), 2.18 (dd, 1H, *J* = 9.1, 4.5 Hz), 2.00 (dd, 1H, *J* = 8.0, 4.5 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): mixture: δ 176.5, 143.9, 138.1, 137.4, 135.1, 134.3, 131.0, 130.7, 130.2, 128.2 (2C), 128.1, 127.8, 127.7, 126.9, 126.8, 126.6, 126.3, 121.9, 121.5, 120.8, 118.1, 107.8 (2C), 38.2, 35.9, 33.9, 33.4, 26.7, 26.5, 22.6, 21.5, 21.4 ppm. FTIR (cm$^{-1}$) (neat): 2922, 1702, 1650, 1613, 1492, 1346, 1128, 730, 672. HRMS (ESI, Pos) calcd for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1383, found 264.1380 *m/z*.



**(1*S*,2*R*)-1'-methyl-2-(*o*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (238a) and (1*R*,2*R*)-1'-methyl-2-(*o*-tolyl)spiro[cyclopropane-1,3'-indolin]-2'-one (238b)**: Synthesized according to **Procedure I** on a 0.471 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 94% yield (90.4 mg, 0.437 mmol) as an inseparable mixture of major and minor diastereomers (14:1 dr). *Reaction was also run for 15 h* to give 80% yield (108 mg, 7:1 dr). Diastereomeric ratios were determined via $^1$H NMR. $^1$H NMR ($CDCl_3$, 400 MHz): Major **238a**: δ 7.40 (d, 1H, *J* = 7.4 Hz), 7.28-7.15 (m, 3H), 7.06-7.05 (m, 1H), 6.89 (d, 1H, *J* = 7.8 Hz), 6.69-6.65 (m, 1H), 5.88 (d, 1H, *J* = 7.5 Hz), 3.37 (s, 3H), 3.39-3.31 (m, 1H), 2.27 (dd, 1H, *J* = 9.0, 4.5 Hz), 2.06 (dd, 1H, *J* = 8.0, 4.5 Hz), 1.78 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): mixture: δ 176.6, 173.9, 143.7, 143.5, 139.3, 138.0, 133.7, 130.7, 130.1, 130.0, 129.7, 129.1, 128.7, 127.7, 127.6, 127.5, 126.7, 125.9, 125.7, 122.0, 121.6, 119.9, 118.2, 107.9, 107.8, 36.8, 35.1, 33.3, 33.1, 26.8, 26.6, 22.6, 22.5, 19.5, 19.2 ppm. FTIR (cm$^{-1}$) (neat): 2938, 1701, 1646, 1493, 1380, 1344, 1133, 748, 728. HRMS (ESI, Pos): calcd for $C_{18}H_{18}NO$ $[M+H]^+$: 264.1382, found 264.1379 *m/z*.

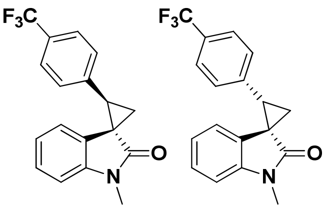


**(1*S*,2*R*)-2-(4-methoxyphenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (239a) and (1*R*,2*R*)-2-(4-methoxyphenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (239b)**: Synthesized according to **Procedure I** on a 0.496 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an off-white in 92% yield (127 mg, 0.456 mmol) as an inseparable mixture of major and minor diastereomers (10:1 dr). *Reaction was also run for 15 h* to give 91% (127 mg, 6:1 dr). Diastereomeric ratios were determined via $^1$H NMR. mp: 76-74°C. $^1$H NMR ($CDCl_3$, 400 MHz): Major **239a**: δ 7.16 (td, 1H, *J* = 7.8, 1.1 Hz), 7.10 (d, 2H, *J* = 8.3 Hz), 6.88-6.81 (m, 3H), 6.71 (td, 1H, *J* = 7.7, 0.6 Hz), 6.00 (dd, 1H, *J* = 7.5, 0.6 Hz), 3.79 (s, 3H), 3.32 (s, 3H), 3.32-3.29 (m, 1H), 2.17 (dd, 1H, *J* = 9.2, 4.5 Hz), 1.95 (dd, 1H, *J* = 7.9, 4.5 Hz), Minor **239b**: δ 7.37-6.80 (m, 8H), 3.78 (s, 3H), 3.18 (s, 3H), 3.15-3.12 (m, 1H), 2.37 (dd, 1H, *J* = 8.6, 4.8 Hz), 2.05 (dd, 1H, *J* = 8.6, 4.8 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): Major **239a**: δ 176.5, 158.8, 143.8, 131.0, 127.7, 127.2, 126.5, 121.5, 120.8, 113.8, 107.8, 55.3, 35.3, 33.4, 26.6, 22.8, Minor **239b**: δ 174.0, 158.7, 143.4, 130.3, 128.3, 127.0, 126.7, 122.6, 121.9, 118.0, 113.4, 55.2, 37.8, 33.9, 26.5, 22.7 ppm. FTIR (cm$^{-1}$) (neat): 2933, 1704, 1613, 1515, 1494, 1346, 1249, 974, 696. HRMS (ESI, Pos) calcd for $C_{18}H_{17}NNaO_2$ $[M+Na]^+$: 302.1152, found 302.1147 *m/z*.



**(1*S*,2*R*)-2-(4-fluorophenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (240a) and (1*R*,2*R*)-2-(4-fluorophenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (240b)**: Synthesized according to **Procedure I** on a 0.498 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a white solid in 99% yield (132 mg, 0.494 mmol) as a separable mixture of major and minor diastereomers (8:1 dr). Diastereomeric ratios were determined via $^{1}$H NMR. *Reaction was also run for 15 h* to give 87% (116 mg) of a white solid **240a** and 12% (16 mg) of a white solid **240b**. Major **240a**: mp: 69-70 °C. $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.19-7.13 (m, 3H), 7.01-6.96 (m, 2H), 6.89-6.87 (m, 1H), 6.72 (td, 1H, *J* = 7.6, 1.0 Hz), 5.94 (d, 1H, J = 7.8 Hz), 3.33 (s, 3H), 3.32-3.29 (m, 1H), 2.19 (dd, 1H, *J* = 9.2, 4.6 Hz), 1.93 (dd, 1H, *J* = 7.9, 4.3 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 176.3, 162.0 9 (d, $J_{C\text{-}F}$ = 245.0 Hz), 143.9, 131.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 130.6 (d, $J_{C\text{-}F}$ = 3.2 Hz), 127.3, 126.8, 121.6, 120.7, 115.3 (d, $J_{C\text{-}F}$ = 22.0 Hz), 107.9, 34.9, 33.2, 26.7, 22.7 ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -114.6 (m) ppm. FTIR ($cm^{-1}$) (neat): 2938, 2844, 1696, 1612, 1510, 1379, 1245, 1090, 1015, 841, 750. HRMS (ESI, Pos) calcd for $C_{17}H_{15}FNO$ $[M+H]^+$: 268.1132, found 268.1128 *m/z*.

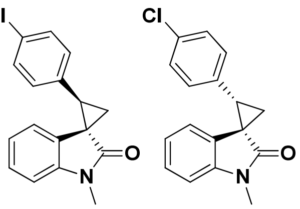
Minor **240b**: mp: 111-114 °C. $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.31-7.27 (m, 3H), 7.08 (td, 1H, *J* = 7.5, 0.9 Hz), 7.01-6.96 (m, 3H), 6.90 (d, 1H, *J* = 7.8 Hz), 3.19 (s, 3H), 3.15-3.12 (m, 1H), 2.36 (dd, 1H, *J* = 8.6, 5.0 Hz), 2.07 (dd, 1H, *J* = 9.1, 5.0 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 173.9, 162.0 (d, $J_{C\text{-}F}$ = 245 Hz), 143.6, 130.9 (d, $J_{C\text{-}F}$ = 8.1 Hz), 130.7, 130.1 (d, $J_{C\text{-}F}$ = 3.1 Hz), 127.0, 122.1, 118.2, 114.9 (d, $J_{C\text{-}F}$ = 21.5 Hz), 108.0, 37.3, 33.9, 26.6, 22.8 ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -115.2 (m) ppm. FTIR ($cm^{-1}$) (neat): 2922, 1704, 1615, 1512, 1469, 1315, 1252, 1230, 1196, 1131, 1102, 908, 730. HRMS (ESI, Pos) calcd for $C_{17}H_{15}FNO$ $[M+H]^+$: 268.1132, found 268.1130 *m/z*.



**(1*S*,2*R*)-1'-methyl-2-(4-(trifluoromethyl)phenyl)spiro[cyclopropane-1,3'-indolin]-2'-one (241a) and (1*R*,2*R*)-1'-methyl-2-(4-(trifluoromethyl)phenyl)spiro[cyclopropane-1,3'-indolin]-2'-one (241b)**: Synthesized according to **Procedure I** on a 0.30 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 85% yield (80.7 mg, 0.254 mmol) as a separable mixture of major and minor diastereomers (5:1 dr). Diastereomeric ratios were determined via $^1$H NMR. *Reaction was also run for 15 h* to give 71% (113 mg) of an orange solid **241a** and 19% (31 mg) of an off-white solid **241b**.

Major **241a**: mp: 123-125 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.55 (d, 2H, *J* = 8.2 Hz), 7.31 (d, 2H, *J* = 8.2 Hz), 7.18 (td, 1H, *J* = 7.7, 0.9 Hz), 6.89 (d, 1H, *J* = 7.9 Hz), 6.72 (td, 1H, *J* = 7.6, 0.9 Hz), 5.95 (d, 1H, J = 7.3 Hz), 3.34 (s, 3H), 3.35-3.31 (m, 1H), 2.13 (dd, 1H, *J* = 9.1, 4.7 Hz), 2.00 (dd, 1H, *J* = 8.0, 4.7 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.0, 143.9 139.4, 130.3, 130.0 (q, $J_{C\text{-}F}$ = 32.0 Hz), 128.2-120.0 (q, $J_{C\text{-}F}$ = 272.0 Hz), 127.0, 126.8, 125.3 (q, $J_{C\text{-}F}$ = 3.9 Hz), 121.7, 120.5, 108.0, 35.1, 32.3, 26.7, 22.2 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -62.4 (s) ppm. FTIR (cm$^{-1}$) (neat): 2934, 1695, 1615, 1496, 1322, 1160, 1112, 1066, 977, 852, 751. HRMS (ESI, Pos) calcd for $C_{18}H_{15}F_3NO$ [M+H]$^+$: 318.1100, found 318.1097 *m/z*.

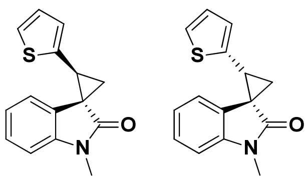
Minor **241b**: mp: 138-139 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.56 (d, 2H, *J* = 8.2 Hz), 7.44 (d, 2H, *J* = 8.2 Hz), 7.31 (td, 1H, *J* = 7.6, 1.2 Hz), 7.10 (td, 1H, *J* = 7.5, 0.9 Hz), 6.99 (dd, 1H, *J* = 7.5, 0.9), 6.91 (d, 1H, *J* = 7.8 Hz), 3.19 (s, 3H), 3.20-3.16 (m, 1H), 2.41(dd, 1H, *J* = 8.5, 5.0 Hz), 2.12 (dd, 1H, *J* = 9.0, 5.0 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 173.7, 143.7, 138.5, 130.4, 129.7, 129.5 (q, $J_{C\text{-}F}$ = 32.0 Hz), 124.4 (q, $J_{C\text{-}F}$ = 272.0 Hz), 127.5, 125.0 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.2, 118.3, 108.2, 37.3, 34.2, 26.6, 22.6 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -62.4 (s) ppm. FTIR (cm$^{-1}$) (neat): 2930, 1699, 1615, 1493, 1379, 12544, 1193, 1121, 1069, 744. HRMS (ESI, Pos) calcd for $C_{18}H_{15}F_3NO$ [M+H]$^+$: 318.1100, found 318.1097 *m/z*.



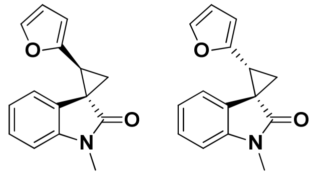
**(1*S*,2*R*)-2-(4-chlorophenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (242a) and (1*R*,2*R*)-2-(4-chlorophenyl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (242b)**: Synthesized according to **Procedure I** on a 0.348 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give an orange solid in 95% yield (93.8 mg, 0.331 mmol) as a separable mixture of major and minor diastereomers (5:1 dr). Diastereomeric ratios were determined via $^1$H NMR. *Reaction was also run for 15 h* to give 73% (103 mg) of an orange solid **242a** and 15% (21 mg) of an off-white solid **242b**.

Major **242a**: mp: 126-128 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.25 (m, 2H), 7.19 (td, 1H, $J$ = 7.7, 1.1 Hz), 7.12 (d, 2H, $J$ = 8.7 Hz), 6.89 (d, 1H, $J$ = 8.0 Hz), 6.75 (td, 1H, $J$ = 7.7, 0.9 Hz) 5.98 (d, 1H, J = 7.5 Hz), 3.34 (s, 3H), 3.31-3.27 (m, 1H), 2.19 (dd, 1H, $J$ = 9.0, 4.5 Hz), 1.94 (dd, 1H, $J$ = 7.9, 4.5 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 176.2, 143.9, 133.8, 133.2, 131.3, 128.6, 127.1, 126.4, 121.7, 120.7, 108.0, 35.0, 33.2, 26.7, 22.4 ppm. FTIR (cm$^{-1}$) (neat): 2927, 1686, 1610, 1491, 1465, 1292, 1085, 1016, 785, 548. HRMS (ESI, Pos) calcd for $C_{17}H_{15}ClNO$ [M+H]$^+$: 284.0837, found 284.0834 *m/z*.

Minor **242b**: mp: 110-111 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.56 (td, 1H, $J$ = 7.8, 1.2 Hz), 7.27-7.24 (m, 4H), 7.08 (td, 1H, $J$ = 7.5, 0.9 Hz), 6.97 (dd, 1H, $J$ = 7.5, 0.9 Hz), 6.90 (d, 1H, $J$ = 7.8, 0.9 Hz), 3.19 (s, 3H), 3.14-3.10 (m, 1H), 2.35 (dd, 1H, $J$ = 8.6, 5.0 Hz), 2.07 (dd, 1H, $J$ = 8.8, 4.9 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 173.8, 143.6, 133.1, 133.0, 130.7, 130.6, 128.2, 127.1, 122.1, 118.2, 108.0, 37.3, 34.0, 26.6, 22.6 ppm. FTIR (cm$^{-1}$) (neat): 2923, 1697, 1614, 1492, 1469, 1345, 1315, 1195, 1109, 975, 746, 530. HRMS (ESI, Pos) calcd for $C_{17}H_{15}ClNO$ [M+H]$^+$: 284.0837, found 284.0837 *m/z*.



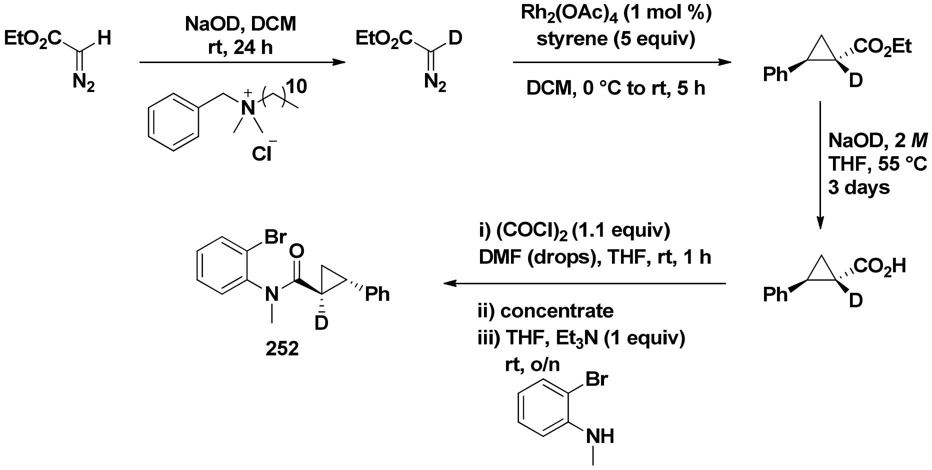
**(1*S*,2*S*)-1'-methyl-2-(thiophen-2-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (243a) and (1*R*,2*S*)-1'-methyl-2-(thiophen-2-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (243b)**: Synthesized according to **Procedure I** on a 0.496 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 92% yield (127 mg, 0.456 mmol) as an inseparable mixture of major and minor diastereomers (10:1 dr). *Reaction was also run for 15 h* to give 67% (86 mg, 10:1 dr). Diastereomeric ratios were determined via $^{1}$H NMR. $^{1}$H NMR (CDCl$_3$, 400 MHz): Major **243a**: δ 7.22-7.18 (m, 2H), 6.97-6.96 (m, 1H), 6.91-6.87 (m, 2H), 6.78 t(d, 1H, *J* = 7.6, 0.8 Hz), 6.24 (d, 1H, *J* = 7.5 Hz), 3.32 (s, 3H), 3.32-3.28 (m, 1H), 2.25 (dd, 1H, *J* = 9.0, 4.5 Hz), 2.02 (dd, 1H, *J* = 7.6, 4.5 Hz); Minor **243b**: δ 7.41-6.85 (m, 7H), 3.21 (s, 3H), 3.20-3.18 (m, 1H), 2.35 (dd, 1H, *J* = 8.5, 5.0 Hz), 2.14 (dd, 1H, *J* = 8.9, 4.6 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): Major **243a**: δ 175.9, 143.9, 139.1, 127.5, 127.0, 126.8, 125.4, 121.8, 120.4, 108.0, 34.2, 30.1, 28.6, 26.7, 23.8; Minor **243b**: δ 176.1, 143.5, 137.9, 127.1, 126.9, 126.7, 125.9, 124.7, 122.0, 118.2, 34.3, 32.7, 26.5, 24.0 ppm. FTIR (cm$^{-1}$ ) (neat): 2937, 1699, 1649, 1613, 1493, 1423, 1380, 1028, 749, 696. HRMS (ESI, Pos): calcd for C$_{15}$H$_{14}$NOS [M+H]$^+$: 256.0791, found 256.0787 *m/z*.



**(1*S*,2*S*)-2-(furan-2-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (244a) and (1*R*,2*S*)-2-(furan-2-yl)-1'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (244b)**: Synthesized according to **Procedure I** on a 0.494 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 79% yield (92.2 mg, 0.388 mmol) as an inseparable mixture of major and minor diastereomers (9:1 dr). *Reaction was also run for 15 h* to give 40% (37 mg, >10:1 dr). Diastereomeric ratios were determined via $^{1}$H NMR. Major **244a**: $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 7.32-7.31 (m, 1H), 7.20 (t, 1H, *J* = 7.7 Hz), 6.87 (d, 1H, *J* = 7.7 Hz), 6.83 (t, 1H, *J* = 7.6 Hz), 6.48 (d, 1H, *J* = 7.4 Hz), 3.31 (s, 3H), 3.14-3.11 (m, 1H), 2.18 (dd, 1H, *J* = 9.2, 4.5 Hz), 2.12 (dd, 1H, *J* = 7.5, 4.5 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 175.7, 150.4, 144.0, 142.2, 127.3, 127.1, 122.0, 120.2, 110.7, 109.4, 108.1, 33.9, 28.7, 26.7, 21.3 ppm. FTIR (cm$^{-1}$)

(neat): 2937, 1699, 1613, 1494, 1421, 1375, 1342, 1329, 1128, 1011, 735, 547. HRMS (ESI, Pos) calcd for $C_{15}H_{14}NO_2$ $[M+H]^+$: 240.1019, found 240.1016 *m/z*.

*Synthesis of d-labeled trans-rac-N-(2-bromophenyl)-N-methyl-2-phenylcyclopropanecarboxamide **252***



Deuterated ethyl diazoacetate was synthesized according to the literature procedure[255] and then used in the Rh-catalyzed cyclopropanation of styrene as described in the synthesis of ***cis*-250**.

The resulting *trans*-cyclopropane (410 mg, 2.15 mmol) was dissolved in 6 mL of THF and transferred to a 25 mL round-bottom flask. To this was added NaOD (2.0 M, 3.2 mL, 6.45 mmol, 3.0 equiv) and the reaction was heated to 55 ºC for 3 days. It was then acidified with 10 mL of 2.0 *M* HCl and extracted with EtOAc (3x10 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give a yellow solid in quantitative yield which was used crude in the amide synthesis by **Procedure H**. The deuterated *trans-racemic* product was obtained as a white solid in 70% yield (500 mg, 1.51 mmol) and confirmed by $^1$H NMR.

*Kinetic Isotope Effect Studies*

Two parallel reactions using *trans-rac-N*-(2-bromophenyl)-*N*-methyl-2-phenylcyclopropanecarboxamide **250** and *d*-labeled *trans-rac-N*-(2-bromophenyl)-*N*-methyl-

2-phenylcyclopropanecarboxamide **252** were performed on a 0.5 mmol scale in accordance with **Procedure I**. A known amount of internal standard (1,3,6-trimethoxybenzene) was added to each reaction and the formation of the major product was monitored over time using $^{1}$H NMR. The product concentration for the major product was then plotted vs. time to determine the rate of reaction ($k_H$ and $k_D$) for both reactions.

| entry | [P] deuterated | [P] non-deuterated | time (min) |
|---|---|---|---|
| 1 | 0.028 | 0.056 | 30 |
| 2 | 0.033 | 0.0714 | 45 |
| 3 | 0.039 | 0.11 | 60 |
| 4 | 0.053 | 0.1792 | 90 |
| 5 | 0.07 | 0.21 | 120 |

**Linear equation for *d*-labeled substrate: y = 4.6897E-04x + 1.2241E-02**

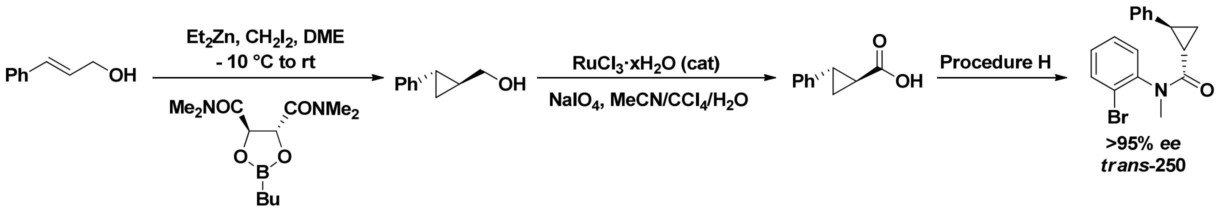
**Linear equation for normal substrate (1sa): y = 1.8363E-03x - 1.3862E-03**

**$k_H/k_D$ = 3.9**

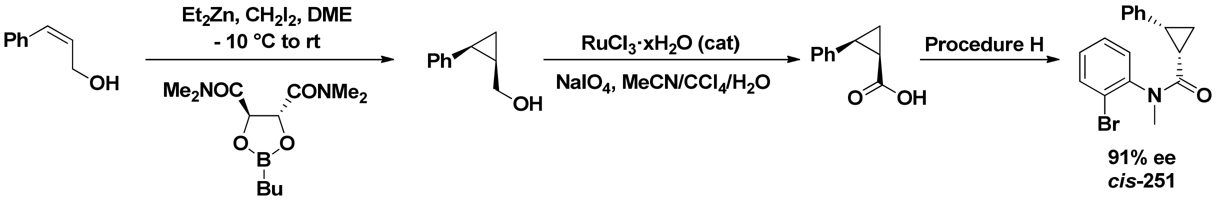
*Isomerization studies*

The studies were performed according to **Procedure I** and as stated in Scheme 94, and the results were analyzed by $^{1}$H NMR only, employing trimethoxybenzene as internal standard.

*Preparation of enantioenriched* **250**

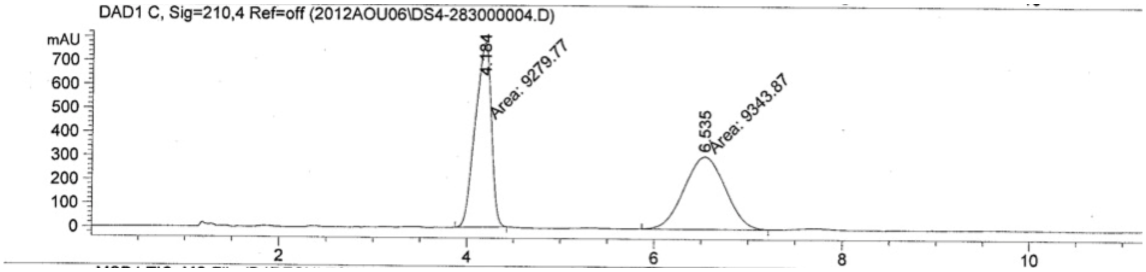


*Preparation of enantioenriched* **251**



91% ee
*cis*-**251**

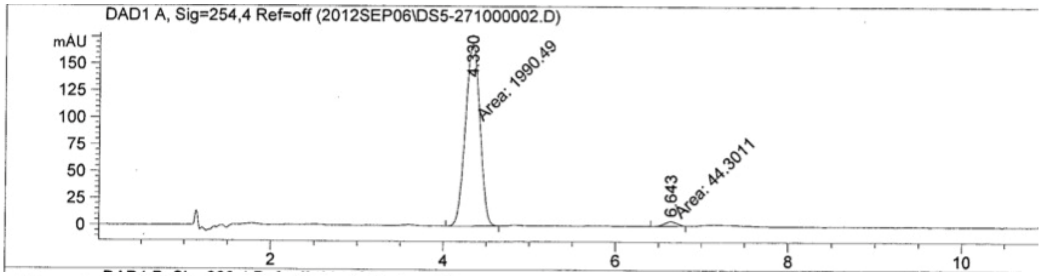
Enantioenriched samples of both *trans*- and *cis*- *N*-(2-bromophenyl)-*N*-methyl-2-phenylcyclopropanecarboxamide **250** and **251** were synthesized as shown above, starting from either *trans*- or *cis*- cinnamyl alcohol via an asymmetric Simmons-Smith cyclopropanation according to the literature procedure.[256] The enantioenriched *trans*- or *cis*-cyclopropanes were then oxidized to the corresponding carboxylic acid[257] and then converted to their amide analogues via **Procedure H**. The enantiomeric excess for both substrates were determined by SFC analysis on a chiral stationary phase. Enantioenriched **251** could not be separated by SFC; % ee was determined using the *cis*-carboxylic acid. For **250**: (Ad-H 25 cm, 5% MeOH, 5mL/min, 35ºC, 150 bar, 254 nm, tr (major) 4.3 min, tr (minor) 6.6 min). **SFC trace:**



```
Signal 2: DAD1 B, Sig=220,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.184 MM     0.1992 7392.40381  618.37195  50.1068
   2   6.535 MM     0.5082 7360.90088  241.39609  49.8932

Totals :                   1.47533e4   859.76804
```

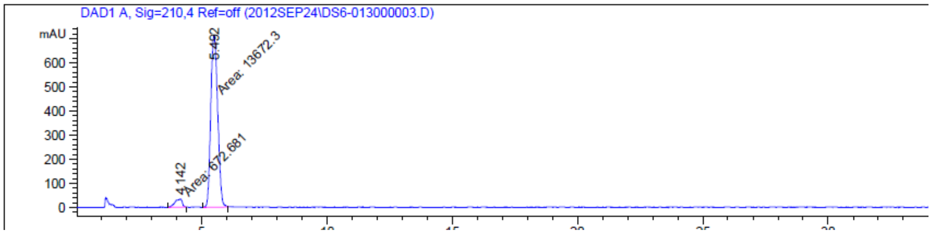


```
Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.330 MM    0.1959 1990.48682  169.32448  97.8228
   2   6.643 MM    0.1718   44.30108    4.29743   2.1772

Totals :                  2034.78790  173.62191
```

For **251**: (Ad-H 25 cm, 5% MeOH, 5mL/min, 35ºC, 150 bar, 254 nm, tr (major) 5.49 min, tr (minor) 3.98 min). **SFC trace:**



```
Signal 1: DAD1 A, Sig=210,4 Ref=off

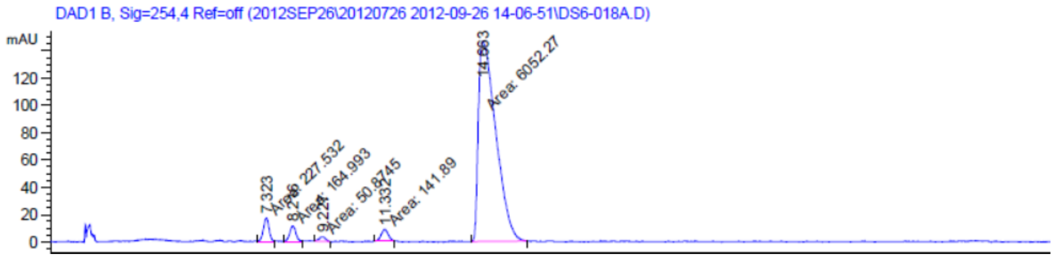
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   4.142 MM    0.3360  672.68127   33.36401   4.6893
   2   5.492 MM    0.3206 1.36723e4  710.66248  95.3107

Totals :                  1.43450e4  744.02648
```

*Epimerization Studies*

Two sets of reactions were set up and carried out in parallel using **Procedure I** on a 0.4 mmol scale (with enantioenriched **250** and **251**). Samples were taken out of the reactions after 3 h and 21 h and analyzed by $^1$H NMR (diastereomeric ratio) and SFC. The SFC traces at 3 h are presented below.

For **235a** from **250**: (Ad-H 25 cm, 5% MeOH, 5mL/min, 35ºC, 150 bar, 254 nm, tr (major) 14.6, 11.3 min, tr (minor) 7.32, 8.22, 9.23 min).

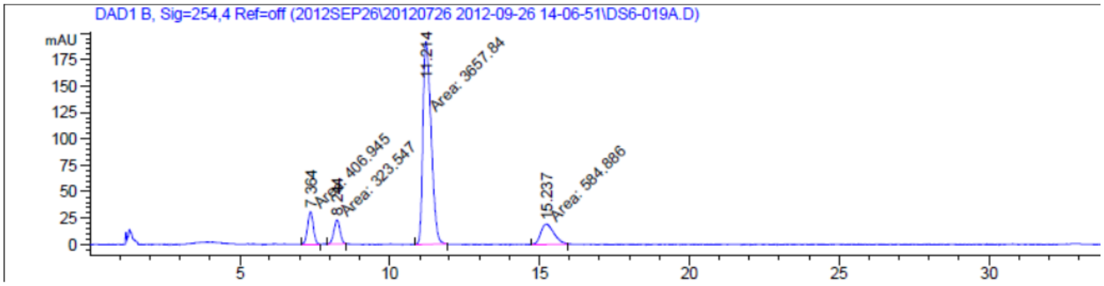


```
Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.323 MM    0.2207  227.53218   17.18419   3.4280
   2   8.216 MM    0.2407  164.99333   11.42589   2.4858
   3   9.227 MM    0.2461   50.87452    3.44530   0.7665
   4  11.332 MM    0.2778  141.88979    8.51239   2.1377
   5  14.663 MM    0.6853 6052.26660  147.18364  91.1821

Totals :                  6637.55642  187.75142
```

For **235b** from **251**:(Ad-H 25 cm, 5% MeOH, 5mL/min, 35ºC, 150 bar, 254 nm, tr (major) 11.2, 15.2 min, tr (minor) 7.36, 8.24 min).

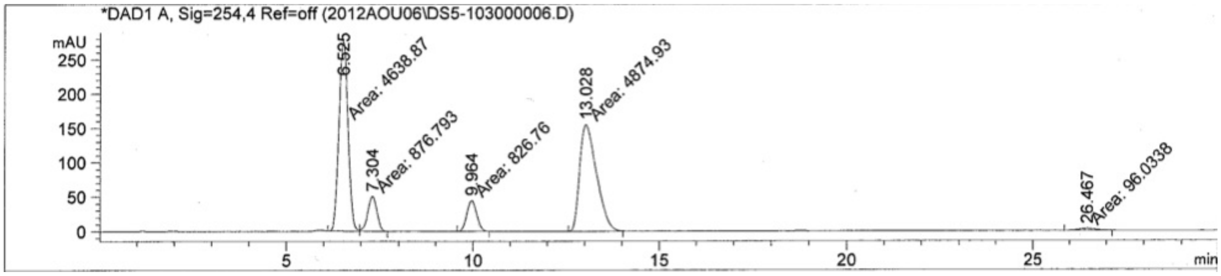


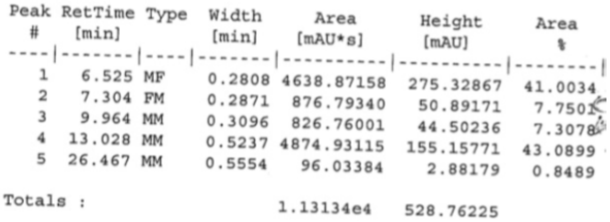
```
Signal 2: DAD1 B, Sig=254,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   7.364 MM    0.2212  406.94470   30.65820   8.1827
   2   8.244 MM    0.2373  323.54654   22.72843   6.5058
   3  11.214 MM    0.3180 3657.83862  191.71494  73.5508
   4  15.237 MM    0.5116  584.88580   19.05581  11.7607

Totals :                  4973.21567  264.15737
```

Racemic trace **235a** and **235b**:





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Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
  1   6.525 MF    0.2808 4638.87158  275.32867  41.0034
  2   7.304 FM    0.2871  876.79340   50.89171   7.7501
  3   9.964 MM    0.3096  826.76001   44.50236   7.3078
  4  13.028 MM    0.5237 4874.93115  155.15771  43.0899
  5  26.467 MM    0.5554   96.03384    2.88179   0.8489

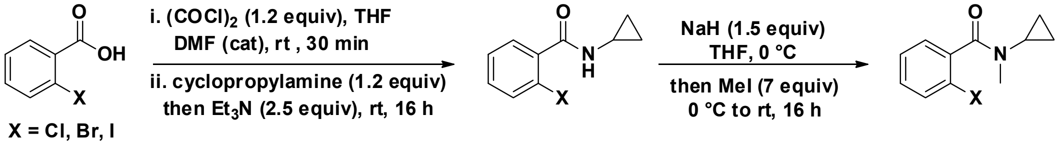
Totals :                 1.13134e4  528.76225
```

## Part 2

*Synthesis of 2-bromobenzoic acids*

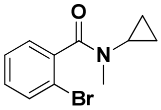
2-Bromo-3,4,5-trimethoxybenzoic acid[258] and 2-bromo-3,5-dimethylbenzoic acid[259] were synthesized according to literature procedures.

*Synthesis of 2-halobenzamides*

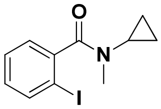


**Procedure J**: To a solution of the corresponding 2-halobenzoic acid (1.0 equiv) in THF (0.2 *M*), was added 2-3 drops DMF. Oxalyl chloride (1.2 equiv) was slowly added over 15 minutes, causing bubbling and the formation of a bright yellow solution. The reaction was stirred for 30 min or until complete by TLC. Then, cyclopropylamine (1.2 equiv) was added dropwise. After 10 min, $Et_3N$ (2.5 equiv)) was added slowly, forming a faint yellow precipitate. The reaction was stirred overnight (16 h) at ambient temperature. The reaction was quenched with 10% HCl (50 mL), dissolving the white precipitate, and then transferred to a 250 mL separatory funnel. The layers were separated, and the *aqueous* layer was extracted with DCM (3x50 mL). The combined organics were then washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give the desired product as an off-white solid. The crude intermediate was dissolved in 50 mL THF, cooled to 0 °C, and NaH was added (1.5 equiv) forming a grey solution. After 15 min, MeI (7.0 equiv) was added dropwise. The reaction was allowed to warm up to ambient temperature and stirred overnight

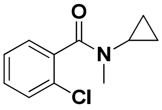
(16 h). The reaction was quenched with water (50 mL), EtOAc (50 mL), and transferred to a 250 mL separatory funnel. The layers were separated, and the *aqueous* layer was extracted with EtOAc (3x50 mL). The combined organics were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo*. The crude was purified via column chromatography over silica gel to provide the desired product.



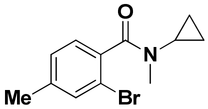
**2-Bromo-*N*-cyclopropyl-*N*-methylbenzamide (258)**: Synthesized according to **Procedure J** on a 8.25 mmol scale and then purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to give a yellow oil in 100% yield (2.09 g, 8.25 mmol). Mixture of rotamers. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.49-7.44 (m, 1H), 7.29-7.23 (m, 1H), 7.18-7.11 (m, 2H), 3.05 (s, 2.38H), 2.85-2.73 (m, 0.24H), 2.69 (s, 0.63H), 2.67-2.59 (m, 0.80H), 0.84-0.74 (m, 0.86H), 0.41-0.39 (m, 2.93H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 171.1, 170.6, 139.9, 138.9, 132.63, 132.50, 130.1, 129.8, 127.85, 127.71, 127.61, 127.2, 118.98, 118.92, 36.3, 34.0, 31.9, 29.9, 9.3 (br), 7.68 (br), 6.7 (br) ppm. FTIR (cm$^{-1}$) (neat): 3012, 1637, 1455, 1362, 1076, 766. HRMS (APPI, Pos): calc. for $C_{11}H_{13}BrNO$ $[M+H]^+$: 254.0182, found 254.0175 *m/z*.



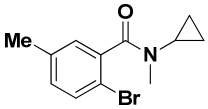
**2-Iodo-*N*-cyclopropyl-*N*-methylbenzamide (258a)**: Synthesized according to **Procedure J** on a 12.4 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a brown oil in 85% yield (3.17 g, 10.5 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.80-7.76 (m, 1H), 7.37-7.32 (m, 1H), 7.19-7.16 (m, 1H), 7.06-7.00 (m, 1H), 3.10 (s, 2.32H), 2.87-2.84 (m, 0.26H), 2.74 (s, 0.76H), 2.69-2.66 (m, 0.79H), 0.87-0.84 (br m, 1.02H), 0.53-0.45 (br m, 3.12H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 171.6, 171.2, 143.2, 142.2, 138.24, 138.12, 129.5, 129.1, 127.8, 127.2, 126.75, 126.58, 126.3, 92.0, 91.7, 77.6, 77.2, 76.7, 36.0, 33.5, 31.6, 29.3, 8.2 (br), 6.0 (br) ppm. FTIR (cm$^{-1}$) (neat): 3050, 1634, 1381, 1210, 930. HRMS (APPI, Pos): calc. for $C_{11}H_{13}INO$ $[M+H]^+$: 302.0042, found 302.0036 *m/z*.



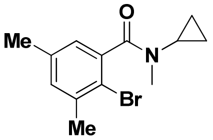
**2-Chloro-*N*-cyclopropyl-*N*-methylbenzamide (258b)**: Synthesized according to **Procedure J** on a 12 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a yellow oil in 91% yield (2.06 g, 9.82 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.35-7.22 (m, 4H), 3.07 (s, 2.35 H), 2.8-2.83 (m, 0.20 H), 2.73 (s, 0.58 H), 2.70-2.63 (m, 0.79H), 0.81-0.75 (br m, 0.85H), 0.44-0.42 (br m, 3.17H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 169.3, 168.9, 137.1, 136.1, 129.3, 129.09, 128.98, 128.63, 128.50, 127.04, 126.86, 126.5, 126.0, 35.2, 33.1, 30.9, 29.0, 7.6 (br), 5.9 (br) ppm. FTIR (cm$^{-1}$) (neat): 3060, 1637, 1482, 1433, 1319, 859 ppm. HRMS (APPI, Pos): calc. for $C_{11}H_{13}ClNO$ [M+H]$^+$: 210.0688, found 210.0680 *m/z.*



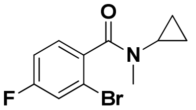
**2-Bromo-*N*-cyclopropyl-*N*,4-dimethylbenzamide (C1)**: Synthesized according to **Procedure J** on a 2.3 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a yellow solid in 79% yield (0.49 g, 1.82 mmol). mp: 53 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.40 (dd, 1H, *J* = 8.0, 5.1 Hz), 7.05-7.00 (m, 2H), 3.10 (s, 2.17H), 2.90-2.86 (m, 0.29H), 2.77 (s, 0.75H), 2.74-2.69 (m, 0.72H), 2.28 (s,3H), 0.91-0.80 (br m, 1.03H), 0.49-0.47 (m, 2.9H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz ): δ 171.3, 170.8, 139.7, 138.7, 137.8, 137.2, 132.3, 131.0, 128.2, 115.58, 115.48, 36.3, 32.0, 29.8, 20.8, 9.5 (br), 7.5 (br), 6.8 (br) ppm. FTIR (cm$^{-1}$) (neat): 3002, 1635, 1508, 1020, 815, 630, 591. HRMS (APPI, Pos): calc. for $C_{12}H_{15}BrNO$ [M+H]$^+$: 268.0340, found 268.0332 *m/z.*



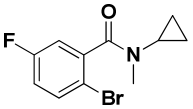
**2-Bromo-*N*-cyclopropyl-*N*,5-dimethylbenzamide (C2)**: Synthesized according to **Procedure J** on a 10.0 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a brown oil in 21% yield (0.55 g, 2.05 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.38 (m, 1H), 7.13 (m, 2H), 3.10 (s, 2.33H), 2.89-2.87 (m, 0.29H), 2.77 (s, 0.68H), 2.72-2.69 (m, 0.79H), 2.34 (s, 3H), 0.90-0.81 (br m, 1H), 0.50-0.47 (br m, 2.96H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 170.9, 170.5, 140.1, 139.7, 136.7, 135.7, 132.60, 132.49, 128.2, 127.6, 127.3, 127.1, 118.43, 118.36, 36.0, 33.7, 31.6, 29.6, 20.6, 8.2 (br), 6.3 (br), 5.90 (br) ppm. FTIR ($cm^{-1}$) (neat): 2922, 1640, 1380, 1287, 1028, 821, 576. HRMS (APPI, Pos): calc. for $C_{12}H_{15}BrNO$ $[M+H]^+$: 268.0340, found 268.0332 *m/z.*



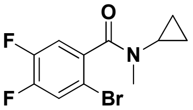
**2-Bromo-*N*-cyclopropyl-*N*, 3,5-trimethylbenzamide (C3)**: Synthesized according to **Procedure J** on a 8.1 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a yellow oil in 83% yield (1.89 g, 6.69 mmol). $^1H$ NMR ($CDCl_3$, 400 MHz): 7.07-6.85 (m, 2H), 3.08 (s, 1.14H), 3.04 (s, 0.70H), 2.91-2.83 (m, 0.26H), 2.74 (s, 0.53H), 2.73-2.64 (m, 0.46H), 2.37-2.26 (m, 6H), 0.88-0.81 (m, 1.26H), 0.65-0.55 (br m, 1.31H), 0.54-0.39 (br m, 2.21H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ 172.1, 171.5, 140.4, 139.4, 138.6, 138.3, 137.1, 131.8, 131.6, 131.2, 126.0, 125.6, 125.1, 118.1, 36.4, 34.1, 32.1, 30.0, 23.2, 23.2, 21.4, 20.9, 9.7 (br), 7.4 (br), 6.7 (br) ppm. FTIR ($cm^{-1}$) (neat): 3275, 2921, 1672, 1602, 1417, 1113, 963, 835, 63. HRMS (APPI, Pos): calc. for $C_{13}H_{17}BrNO$ $[M+H]^+$: 282.0481, found 282.0488 *m/z.*



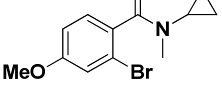
**2-Bromo-*N*-cyclopropyl-4-fluoro-*N*-methylbenzamide (C4)**: Synthesized according to **Procedure J** on a 10.0 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give an off-white solid in 87% yield (2.36 g, 8. 66 mmol). mp: 54 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.32-7.28 (m, 1H), 7.26-7.20 (m, 1H), 7.05 (td, 1H, $J$ = 8.0, 3.0 Hz), 3.09 (s, 2.44H), 2.85 (dt, 0.21H, $J$ = 12.0, 6.0 Hz), 2.76 (s, 0.64H), 2.68 (dt, 0.82 H, $J$ = 11.5, 5.5 Hz), 0.90-0.79 (br m, 0.88H), 0.51-0.48 (br m, 3.12H) ppm. $^{13}C$ NMR ($CDCl_3$, 75MHz): δ 170.1, 169.6, 161.9 (d, $J_{C\text{-}F}$ = 252.0 Hz), 161.7 (d, $J_{C\text{-}F}$ = 252.0 Hz), 136.1 (d, $J_{C\text{-}F}$ = 4.0 Hz) 135.1 (d, $J_{C\text{-}F}$ = 4.0 Hz), 129.0 (d, $J_{C\text{-}F}$ = 9.0 Hz), 128.8, 119.8 (d, $J_{C\text{-}F}$ = 25.0 Hz), 119.6 (d, $J_{C\text{-}F}$ = 25.0 Hz), 119.3 (d, $J_{C\text{-}F}$ = 9.0 Hz), 119.3 (d, $J_{C\text{-}F}$ = 9.0 Hz), 115.0 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 36.1, 33.9, 31.7, 29.7, 8.5 (br), 6.5 (br) ppm. $^{19}F$ NMR ($CDCl_3$, 282 MHz): δ -109.9 (m), -110.4 (m) ppm. FTIR ($cm^{-1}$) (neat): 3016, 1637, 1418, 931, 826. HRMS (APPI, Pos): calc. for $C_{11}H_{12}BrFNO$ $[M+H]^+$: 272.0087, found 272.0081 *m/z.*



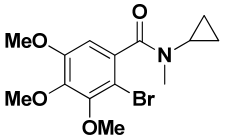
**2-Bromo-*N*-cyclopropyl-5-fluoro-*N*-methylbenzamide (C5)**: Synthesized according to **Procedure J** on a 2.0 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a light pink solid in 32% yield (0.17 g, 0.63 mmol). mp: 52 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.51-7.48 (m, 1H), 6.98-6.93 (m, 2H), 3.10 (m, 2.35 H), 2.87-2.85 (m, 0.24H), 2.77 (s, 0.59H), 2.72-2.67 (m, 0.79H), 0.90-0.80 (br m, 0.90H), 0.64-0.45 (br m, 3.21H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 170.0, 162.1 (d, $J_{C\text{-}F}$ = 249.0 Hz), 161.8 (d, $J_{C\text{-}F}$ = 249.0 Hz), 141.7 (d, $J_{C\text{-}F}$ = 7.0 Hz), 140.6 (d, $J_{C\text{-}F}$ = 7.0 Hz), 134.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 134.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 117.6 (d, $J_{C\text{-}F}$ = 23.0 Hz), 117.4 (d, $J_{C\text{-}F}$ = 23.0 Hz), 115.4 (d, $J_{C\text{-}F}$ = 24.0 Hz), 115.3 (d, $J_{C\text{-}F}$ = 24.0 Hz), 113.6, 36.4, 34.3, 32.0, 30.14, 30.14, 6.94 (br). $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -113.4 (ddd, $J_{C\text{-}F}$ = 8.0, 5.0, 5.0 Hz),-114.2 (ddd, $J_{C\text{-}F}$ = 8.0, 5.0, 5.0 Hz) ppm. FTIR (cm$^{-1}$) (neat): 2923, 1638, 1433, 1361, 1026, 893, 815, 588. HRMS (APPI, Pos): calc. for $C_{11}H_{12}BrFNO$ [M+H]$^+$: 272.0087, found 272.0081 *m/z.*



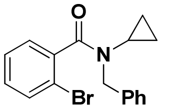
**2-Bromo-*N*-cyclopropyl-4,5-difluoro-*N*-methylbenzamide (C6)**: Synthesized according to **Procedure J** on a 7.8 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a light orange solid in 68% yield (1.55 g, 5.34 mmol). mp: 61 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.38 (m, 1H), 7.13-7.07 (m, 1H), 3.08 (s, 2.42H), 2.86-2.85 (m, 0.29H), 2.79 (s, 0.66H), 2.72-2.68 (m, 0.82H), 0.93-0.77 (br m, 0.90H), 0.55-0.50 (m, 2.91H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 150.2 (dd, $J_{C\text{-}F}$ = 255.0, 14.0 Hz), 149.7 (dd, $J_{C\text{-}F}$ = 252.0, 13.0 Hz), 136.8 (t, $J_{C\text{-}F}$ = 5.0 Hz),122.1 (dd, $J_{C\text{-}F}$ = 20.0 Hz), 117.0 (dd, $J_{C\text{-}F}$ = 20.0 Hz), 113.3 (dd, $J_{C\text{-}F}$ = 7.0, 4.0 Hz), 36.5, 34.4, 32.0, 30.2, 9.0 (br) ppm. $^{19}$F NMR (282 MHz, $CDCl_3$): δ -133.5 (m), -134.0 (m), -136.8 (m), -137.6 (m) ppm. FTIR (cm$^{-1}$) (neat): 2924, 1638, 1430, 1293, 887, 797, 594. HRMS (APPI, Pos): calc. for $C_{11}H_{11}BrF_2NO$ [M+H]$^+$: 289.9990, found 289.9987 *m/z.*



**2-Bromo-*N*-cyclopropyl-4-methoxy-*N*-methylbenzamide (C7)**: Synthesized according to **Procedure J** on a 12.5 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a yellow oil in 90% yield (3.20 g, 11.3 mmol). $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.45-7.40 (m, 1H), 6.79-6.76 (m, 2H), 3.80 (s, 3.83H), 3.11 (s, 3H), 2.91-2.86 (m, 0.51H), 2.80 (s, 1.22H), 2.76-2.73 (m, 1.11H), 0.96-0.81 (m, 3.58H), 0.53-0.50 (m, 2.88H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 170.6, 170.2, 158.9, 158.5, 140.4, 139.4, 133.2, 133.1, 116.2, 115.7, 113.1, 112.6, 109.1, 108.9, 55.4, 36.0, 33.8, 31.7, 29.7, 9.1 (br), 7.6 (br), 6.5 (br) ppm. FTIR (cm$^{-1}$) (neat): 3009, 1638, 1462, 1304, 12355, 1014, 815, 597. HRMS (APPI, Pos): calc. for $C_{12}H_{15}BrNO_2$ $[M+H]^+$: 284.0287, found 284.0281 *m/z.*



**2-Bromo-*N*-cyclopropyl-3,4,5-trimethoxy-*N*-methylbenzamide (C8)**: Synthesized according to **Procedure J** on a 10.0 mmol scale and then purified via column chromatography (5% EtOAc/Hex) to give a pink solid in 50% yield (1.70 g, 4.95 mmol). mp: 52 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.58 (s, 1H), 3.86-3.82 (m, 6 H), 3.82-3.81 (m, 3H), 3.07 (s, 2.17H), 2.89-2.82 (m, 3.29H), 2.76 (s, 0.82H), 2.73-2.68 (m, 0.72H), 0.90-0.75 (m, 1.24H), 0.63-0.56 (m, 0.72H), 0.56-0.48 (m, 2.31H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 171.0, 170.5, 153.6, 153.2, 151.17, 151.06, 143.48, 143.34, 135.5, 134.5, 106.9, 106.4, 105.9, 61.3, 61.3, 56.4, 56.4 36.4, 34.2, 32.0, 30.1, 7.2 (br), 6.5 (br) ppm. FTIR (cm$^{-1}$) (neat): 3263, 3006, 1643, 1421, 1193, 1053, 752, 532 ppm. HRMS (APPI, Pos): calc. for $C_{14}H_{19}BrNO_4$ $[M+H]^+$: 344.0503, found 344.0492 *m/z.*



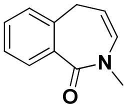
***N*-Benzyl-2-bromo-*N*-cyclopropylbenzamide (263)**:

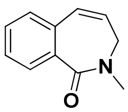
Following the first part of **Procedure J**, the intermediate 2-bromo-*N*-cyclopropylbenzamide was benyzlated as follows:

The intermediate (0.50 g, 2.08 mmol) was dissolved in DMF (10 mL) in a 50-mL round-bottom flask. $Cs_2CO_3$ (1.35 g, 4.16 mmol, 2.0 equiv) was then added, followed by tetrabutylammonium iodide (TBAI) (77.0 mg, 0.02 mmol, 0.1 equiv). After stirring for 10 min, benzyl bromide (0.27 mL, 2.29 mmol, 2.0 equiv) was added to the cloudy cream-colored solution. The reaction was stirred for 16 h at ambient temperature, then quenched with 25 mL water and transferred to a 125-mL separatory funnel. The *aqueous* layer was extracted with EtOAc (3x25mL). The combined organic layers were washed with 5% LiCl solution (25 mL) to remove any trace DMF, and with brine (25 mL); then, dried over anhydrous $Na_2SO_4$, filtered and concentrated *in vacuo* to give a brown oil. The crude product was purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 5-50% EtOAc/Hex. The desired product **263** was isolated as a yellow oil (0.44 g, 1.49 mmol, 72% yield). $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.47-7.06 (m, 9H), 4.73-4.61 (br m, 1.16H), 4.63 (s, 0.97H), 4.21 (d, $J$ = 9.5 Hz, 0.30H), 3.18 (br m, 0.43H) 2.62-2.54 (m, 0.14H), 2.48-2.40 (m, 0.60H), 0.90-0.30 (m, 3.22H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 171.36, 171.17, 141.1, 139.8, 138.4, 137.6, 136.9, 132.87, 132.84, 132.80, 130.5, 130.0, 128.75, 128.65, 128.62, 128.58, 128.00, 127.80, 127.67, 127.62, 127.48, 127.35, 127.25, 127.06, 119.5, 119.2, 65.4, 53.2, 50.2, 30.7, 28.6, 9.8 (br), 8.7 (br), 7.0 (br) ppm. FTIR ($cm^{-1}$) (neat): 3435, 2923, 1639, 1454, 1046, 768, 697, 505. HRMS (APPI, Pos): calc. for $C_{17}H_{17}BrNO$ $[M+H]^+$: 330.0493, found 330.0488 *m/z*.

*Synthesis of Benzo[c]azepin-1-ones*

**Procedure K**: To a 5 mL microwave vial in a glovebox was added in the following order: $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), P*t*$Bu_3$•$HBF_4$ (7.2 mg, 0.025 mmol), $K_2CO_3$ (76 mg, 0.55 mmol) and $Ag_3PO_4$ (69.1 mg, 0.16 mmol). The vial was crimped shut and taken out of the glovebox. The corresponding cyclopropylbenzamide (0.50 mmol) was weighed into a vial, dissolved in 0.5 mL of toluene and added to the reaction vial. The vial was rinsed with 4x0.5 mL of toluene for a total volume of 2.5 mL. The solution was then heated to 125 °C in an oil bath for 16 h. The reaction turned black within five minutes. The reaction was cooled to ambient temperature, filtered over a cotton-Celite® plug, and rinsed with EtOAc (25 mL). It was then concentrated *in vacuo* to give the crude product, which was purified via column chromatography over silica gel (RediSep® Rf Gold 24g) in 10-50% EtOAc/Hex to provide the cyclized products.



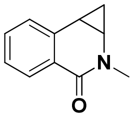


**2-methyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (259) and**

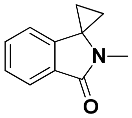
**2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (260)**: Synthesized according to **Procedure K** to give **259** as an orange oil in 66% yield (58 mg, 0.34 mmol) and **260** as an orange oil in 26% yield (23 mg, 0.13 mmol).

**259**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.87-7.84 (m, 1H), 7.37 (td, 1H, *J* = 7.4, 1.4 Hz), 7.30-7.25 (m, 2H), 7.06 (d, 1H, *J* = 7.6 Hz), 5.96 (d, 1H, *J* = 7.5 Hz), 5.62 (q, 1H, *J* = 7.3 Hz), 3.28 (s, 3H), 3.21 (d, 2H, *J* = 7.2 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 75MHz): δ 169.5, 143.4, 134.0, 131.6, 131.3, 130.7, 126.6, 126.2, 117.8, 36.4, 31.4 ppm. FTIR (cm$^{-1}$) (neat): 2924, 1656, 1364, 1285, 735, 609. HRMS (APPI, Pos): calc. for $C_{11}H_{12}NO$ [M+H]$^+$: 174.0914, found 174.0913 *m/z.*

**260**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.03-8.01 (m, 1H), 7.46-7.36 (m, 2H), 7.22-7.20 (m, 1H), 6.81 (d, 1H, *J* = 9.9 Hz), 6.41-6.35 (m, 1H), 3.62 (d, 2H, *J* = 6.8 Hz), 3.22 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.8, 135.6, 134.7, 131.2, 130.3, 129.8, 128.5, 127.8, 106.2, 46.3, 36.5 ppm. FTIR (cm$^{-1}$) (neat): 2923, 1688, 1428, 756, 708, 595. HRMS (APPI, Pos): calc. for $C_{11}H_{12}NO$ [M+H]$^+$: 174.0914, found 174.0913 *m/z.*

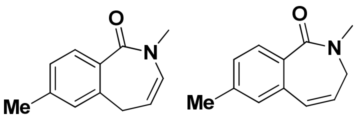


**2-methyl-1a,2-dihydro-1*H*-cyclopropa[*c*]isoquinolin-3(7b*H*)-one (261)**: Synthesized according to **Procedure K**, *using PCy$_3$ instead of PtBu$_3$•HBF$_4$ as a ligand at 135 °C*, to give an orange oil in 39% yield (34 mg, 0.20 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.15 (d, 1H, *J* = 7.6 Hz), 7.44-7.36 (m, 2H), 7.31-7.27 (m, 1H), 3.25 (s, 3H), 3.14 (ddd, 1H, *J* = 8.2, 6.5, 3.9 Hz), 2.30 (ddd, 1H, *J* = 9.6, 8.3, 5.8 Hz), 1.34 (ddd, 1H, *J* = 9.8, 6.4, 5.2 Hz), 0.28-0.24 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 161.5, 139.2, 131.8, 129.0, 128.2, 126.6, 125.5, 36.3, 34.9, 15.0, 13.7 ppm. FTIR (cm$^{-1}$) (neat): 2928, 1621, 1333, 903, 724, 649. HRMS (APPI, Pos): calc. for $C_{11}H_{12}NO$ [M+H]$^+$: 174.0914, found 174.0913 *m/z.*



**2'-methylspiro[cyclopropane-1,1'-isoindolin]-3'-one (262)**: Synthesized according to **Procedure K**, *using PCy$_3$ instead of PtBu$_3$•HBF$_4$ as a ligand at 135 °C*, to give an orange oil in 15% yield (13 mg, 0.075 mmol). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.88 (d, 1H, *J* = 7.6 Hz), 7.52-7.48 (m, 1H), 7.42 (td, 1H, *J* = 7.4, 0.7 Hz), 7.05 (d, 1H, *J* = 7.6 Hz), 2.87 (s, 3H), 1.59-

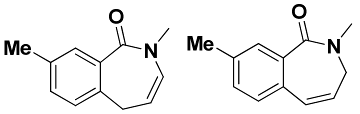
1.56 (m, 2H), 1.36-1.33 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.1, 147.2, 131.8, 131.4, 127.4, 123.6, 117.7, 45.1, 24.0, 10.3 ppm. FTIR (cm$^{-1}$) (neat): 3502, 2926, 1722, 1591, 1472, 765, 690. HRMS (APPI, Pos): calc. for $C_{11}H_{12}NO$ [M+H]$^+$: 174.0914, found 174.0913 *m/z.*



**2,7-dimethyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (268) and 2,7-dimethyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (269)**: Synthesized according to **Procedure K** to give **268** as a yellow oil in 71% yield (65 mg, 0.35 mmol) and **269** as a yellow oil in 27% yield (25 mg, 0.13 mmol).

**268**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.68 (s, 1H), 7.17 (d, 1H, *J* = 8.0 Hz), 6.95 (dd, 1H, *J* = 7.7, 2.7 Hz), 5.94 (dd, 1H, *J* = 8.0, 3.0 Hz), 5.62 (qd, 1H, *J* = 7.0, 3.0 Hz), 3.27 (s, 3H), 3.17 (dd, 2H, *J* = 7.0, 3.0 Hz), 2.33 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 169.7, 140.6, 136.3, 133.7, 132.4, 131.6, 130.5, 126.1, 118.1, 36.5, 30.9, 21.0 ppm. FTIR (cm$^{-1}$) (neat): 3325, 2952, 1626, 1602, 1405, 1098, 752, 681. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO$ [M+H]$^+$: 188.1079, found 188.1070 *m/z.*

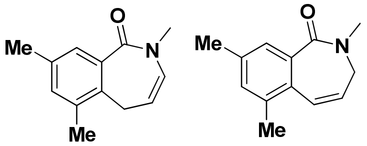
**269**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.82 (s, 1H), 7.23 (s, 1H), 7.11-7.09 (m, 1H), 6.78 (d, 1H, *J* = 9.8 Hz), 6.34-6.28 (m, 1H), 3.60 (d, 2H, *J* = 6.8 Hz), 3.21 (s, 3H), 2.40 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.8, 137.7, 135.2, 134.5, 132.0, 131.28, 131.21, 128.6, 128.4, 46.3, 36.3, 21.2 ppm. FTIR (cm$^{-1}$) (neat): 3339, 2921, 1626, 1603, 1391, 835, 713. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO$ (M+H)$^+$: 188.1077, found 188.1070 *m/z.*



**2,8-dimethyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (270) and 2,8-dimethyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (271)**: Synthesized according to **Procedure K** to give **270** as an orange oil in 62% yield (57 mg, 0.31 mmol) and **271** as an orange oil in 30% yield (28 mg, 0.15 mmol).

**270**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.76 (d, 1H, *J* = 7.9 Hz), 7.09 (d, 1H, *J* = 7.9 Hz), 6.87 (s, 1H), 5.95 (d, 1H, *J* = 7.6 Hz), 5.63-5.57 (m, 1H), 3.27 (s, 3H), 3.17 (d, 2H, *J* = 7.2 Hz), 2.34 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 169.4, 143.2, 142.0, 131.29, 131.11, 130.7, 127.4, 126.8, 117.5, 36.4, 31.3, 21.3 ppm. FTIR (cm$^{-1}$) (neat): 3332.42, 2921, 1608, 1389, 1282, 1151, 764. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO$ [M+H]$^+$: 188.1077, found 188.1070 *m/z.*

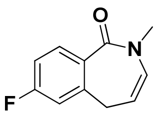
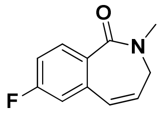
**271**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.91 (d, 1H, *J* = 8.0 Hz), 7.19 (d, 1H, *J* = 8.0), 7.01 (s, 1H), 6.76 (d, 1H, *J* = 10 Hz), 6.37-6.31 (m, 1H), 3.61 (d, 2H, *J* = 7.0 Hz,), 3.19 (s, 3H), 2.36 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 169.0, 140.6, 134.78, 134.71, 132.8, 131.2, 129.5, 128.91, 128.81, 46.4, 36.4, 21.4 ppm. FTIR (cm$^{-1}$) (neat): 3305, 2922, 1621, 1605, 1394, 1064, 832, 755. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO$ [M+H]$^+$: 188.1077, found 188.1070 *m/z.*



**2,6,8-trimethyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (272) and 2,6,8-Trimethyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (273)**: Synthesized according to **Procedure K** to give **272** as an orange oil in 81% yield (72 mg, 0.36 mmol) and **273** as an orange oil in 13% yield (12 mg, 0.59 mmol).

**272**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.48 (d, 1H, *J* = 1.0 Hz), 7.07 (d, 1H, *J* = 1.0 Hz), 5.98 (d, 1H, *J* = 7.0 Hz), 5.62 (dt, 1H, *J* = 15.0, 7.0 Hz), 3.28 (s, 3H), 3.17 (d, 2H, *J* = 8.0 Hz), 2.33 (s, 3H), 2.29 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 170.4, 139.2, 135.6, 134.5, 134.1, 132.3, 130.9, 129.3, 117.6, 36.3, 26.0, 20.9, 19.9. FTIR (cm$^{-1}$) (neat): 3350, 2920, 1625, 1600, 1385, 1119, 1042, 774, 722. HRMS (APPI, Pos): calc. for $C_{13}H_{16}NO$ [M+H]$^+$: 202.1236, found 202.1236 *m/z.*

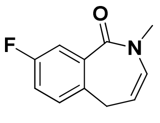
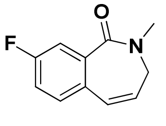
**273**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.60 (td, 1H, *J* = 0.7, 0.4 Hz), 7.08 (ddd, 1H, *J* = 1.1, 0.8, 0.5 Hz), 6.83-6.80 (m, 1H), 6.37-6.31 (m, 1H), 3.56 (d, 2H, *J* = 7.0 Hz), 3.18 (s, 3H), 2.33 (s, 3H), 2.29 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 169.2, 141.9, 137.6, 136.9, 133.0, 131.7, 128.9, 128.4, 123.0, 46.32, 46.30, 29.8, 21.2, 20.3 ppm. FTIR (cm$^{-1}$) (neat): 3276, 2920, 1629, 1601, 1094, 1035, 814. HRMS (APPI, Pos): calc. for $C_{13}H_{16}NO$ [M+H]$^+$: 202.1236, found 202.1226 *m/z.*

**7-fluoro-2-methyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (274) and 7-fluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (275)**: Synthesized according to **Procedure K** to give **274** as a yellow oil in 54% yield (51 mg, 0.27 mmol) and **275** as a yellow oil in 31% yield (29 mg, 0.15 mmol).

**274**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.86 (dd, 1H, $J$ = 9.0, 6.0 Hz), 6.99-6.96 (m, 1H), 6.78-6.75 (m, 1H), 5.98 (dt, 1H, $J$ = 8.0, 1.0 Hz), 5.61-5.59 (m, 1H), 3.27 (s, 3H), 3.19 (d, 2H, $J$ = 7.0Hz) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.3, 164.5 (d, $J_{C\text{-}F}$ = 252.1 Hz), 145.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 133.7 (d, $J_{C\text{-}F}$ = 9.3 Hz), 131.0, 130.1 (d, $J_{C\text{-}F}$ = 3.0 Hz) 116.9, 113.6 (d, $J_{C\text{-}F}$ = 21.3 Hz), 113.0 (d, $J_{C\text{-}F}$ = 21.8 Hz) 36.3, 31.2 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -109.0 (ddd, $J$ = 2 3.0, 8.0, 6.0 Hz) ppm. FTIR (cm$^{-1}$) (neat): 2922, 1621, 1604, 1276, 1060, 900, 742. HRMS (APPI, Pos): calc. for $C_{11}H_{11}FNO$ [M+H]$^+$: 192.0828, found: 192.0819 *m/z.*

**275**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.03 (ddd, 1H, $J$ = 9.0, 6.0, 0.3 Hz), 7.07 (td, 1H, $J$ = 8.4, 3.0 Hz), 6.88 (dd, 1H, $J$ = 9.0, 3.0 Hz), 6.75 (d, 1H, $J$ = 10.0 Hz), 6.44-6.40 (m, 1H), 3.63 (d, 2H, $J$ = 7.0 Hz), 3.20 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.0, 163.5 (d, $J_{C\text{-}F}$ = 251.0 Hz), 137.1 (d, $J_{C\text{-}F}$ = 8.4 Hz), 133.4, 133.9 (d, $J_{C\text{-}F}$ = 2.0 Hz), 133.8, 131.9 (d, $J_{C\text{-}F}$ = 2.8 Hz), 130.9, 115.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 114.5 (d, $J_{C\text{-}F}$ = 21.6 Hz), 46.2, 36.5 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -110.3 (dd, $J$ = 14.6, 8.2 Hz) ppm. FTIR (cm$^{-1}$) (neat): 2925, 1619, 1600, 1478, 1432, 1237, 936, 799, 760, 572, 432. HRMS (APPI, Pos): calc. for $C_{11}H_{11}FNO$ [M+H]$^+$: 192.0817, found 192.0819 *m/z.*

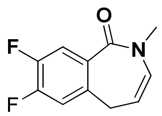



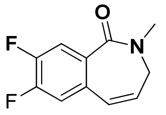
**8-fluoro-2-methyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (276) and 8-fluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (277)**: Synthesized according to **Procedure K** to give **276** as a yellow oil in 64% yield (59 mg, 0.31 mmol) and **277** as a yellow oil in 24% yield (22 mg, 0.12 mmol).

**276**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.58 (dd, 1H, $J$ = 10.0, 3.0 Hz), 7.10-7.04 (m, 2H), 5.97 (d, 1H, $J$ = 7.6 Hz), 5.69-5.63 (m, 1H), 3.30 (s, 3H), 3.20 (d, 2H, $J$ = 7.0 Hz) ppm. δ $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 168.2, 161.4 (d, $J_{C\text{-}F}$ = 244.0 Hz), 139.3 (d, $J_{C\text{-}F}$ = 4.0 Hz), 135.6 (d, $J$=

7.0 Hz), 130.5, 127.8 (d, $J_{C\text{-}F}$ = 8.0 Hz), 118.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 118.0 117.9 (d, $J_{C\text{-}F}$ = 24.0 Hz), 36.5, 30.5 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -116.5 (m) ppm. FTIR (cm$^{-1}$) (neat): 3345, 2926, 1625, 1582, 1489, 1321, 719, 545. HRMS (APPI, Pos): calc. for $C_{11}H_{11}FNO$ [M+H]$^+$: 192.0828, found 192.0819 *m/z.*

**277**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.72-7.70 (m, 1H), 7.22-7.11 (m, 2H), 6.77 (d, 1H, *J* = 10.0 Hz), 6.36-6.33 (m, 1H), 3.62 (d, 2H, *J* = 7.0 Hz), 3.20 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 167.5, 161.9 (d, $J_{C\text{-}F}$ = 249.0 Hz), 137.7 (d, $J_{C\text{-}F}$ = 7.0 Hz), 133.8, 131.10 (d, $J_{C\text{-}F}$ = 3.0 Hz), 130.7 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.2, 118.0 (d, $J_{C\text{-}F}$ = 22.0 Hz), 117.7 (d, $J_{C\text{-}F}$ = 23.0 Hz), 46.3, 36.5 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -113.0 (m) ppm. FTIR (cm$^{-1}$) (neat): 3271, 2923, 1627, 1606, 1484, 1393, 1026, 756, 557. HRMS (APPI, Pos): calc. for $C_{11}H_{11}FNO$ ([M+H]$^+$: 192.0828, found 192.0819 *m/z.*

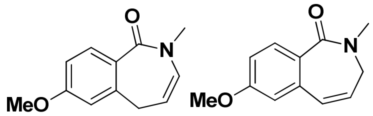




**7,8-difluoro-2-methyl-2,5-dihydro-1H-benzo[c]azepin-1-one (278) and 7,8-difluoro-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (279)**: Synthesized according to **Procedure K** to give **278** as an orange oil in 69% yield (69 mg, 0.33 mmol) and **279** as an orange oil in 15% yield (15 mg, 0.73 mmol).

**278**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.70 (dd, 1H, *J* = 11.1, 8.2 Hz), 6.88 (dd, 1H, *J* = 10.2, 7.4 Hz), 5.98 (dt, 1H, *J* = 7.6, 0.9 Hz), 5.65-5.59 (m, 1H), 3.27 (s, 3H), 3.17 (d, 2H, *J* = 7.2 Hz, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75MHz): δ 167.3, 152.2 (dd, $J_{C\text{-}F}$ = 227.0, 13.0 Hz), 148.9 (dd, $J_{C\text{-}F}$ = 220.0, 13.0 Hz), 140.3 (dd, $J_{C\text{-}F}$ = 6.0, 4.0 Hz), 131.0, 130.6 (dd, $J_{C\text{-}F}$ = 5.0, 3.5 Hz), 122.0 (d, $J_{C\text{-}F}$ = 20.0 Hz), 120.5 (dd, $J_{C\text{-}F}$ = 19.0, 1.5 Hz), 117.2, 117.0 (d, $J_{C\text{-}F}$ = 20.0 Hz), 115.0 (d, $J_{C\text{-}F}$ = 18.0 Hz), 36.6, 30.6 ppm. $^{19}$F NMR (CDCl$_3$, 282 MHz): δ -133.3 (m), -140.8 (m) ppm. FTIR (cm$^{-1}$) (neat): 3280, 2920, 1658, 1615, 1508, 1439, 1387, 1157, 957, 758, 548. HRMS (APPI, Pos): calc. for $C_{11}H_{10}F_2NO$ [M+H]$^+$ : 210.0724, found 210.0725 *m/z.*

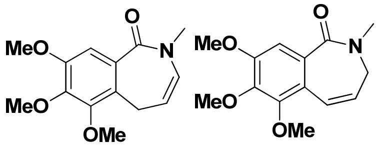
**279**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.85 (dd, 1H, *J* = 11.2, 8.2 Hz), 7.00 (dd, 1H, *J* = 10.7, 7.6 Hz), 6.70 (d, 1H, *J* = 9.9 Hz), 6.42-6.36 (m, 1H), 3.63 (d, 1H, *J* = 6.9 Hz), 3.19 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 166.7, 151.3 (dd, $J_{C\text{-}F}$ = 254.0, 13.0 Hz), 149.6 (dd, $J_{C\text{-}F}$ = 252.0, 13.0 Hz), 132.9 (d, $J_{C\text{-}F}$ = 1.0 Hz), 132.6 (dd, $J_{C\text{-}F}$ = 5.0, 3.0 Hz), 132.1 (dd, $J_{C\text{-}F}$ = 7.0, 4.0 Hz), 130.3 (d, $J_{C\text{-}F}$ = 2.0 Hz), 120.3 (dd, $J_{C\text{-}F}$ = 19.0, 2.0 Hz), 116.7 (d, $J_{C\text{-}F}$ = 17.0 Hz), 46.1, 36.5 ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -134.1 (m), -137.2 (m) ppm. FTIR (cm$^{-1}$) (neat): 3047, 2923, 1626, 1613, 1479, 1278, 886, 818, 754, 606. HRMS (APPI, Pos): calc. for $C_{11}H_{10}F_2NO$ [M+H]$^+$ : 210.0733, found 210.0725 *m/z.*



**7-methoxy-2-methyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (280) and 7-methoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (281)**: Synthesized according to **Procedure K** to give **280** as an orange oil in 51% yield (51 mg, 0.25 mmol), and **281** as an orange oil in 43% yield (43 mg, 0.21 mmol).

**280**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.41 (d, 1H, *J* = 2.0 Hz), 6.98-6.91 (m, 2H), 5.93 (d, 1H, *J* = 8.0 Hz), 5.67-5.61 (dt, 1H, *J* = 15.0, 7.0 Hz), 3.81 (s, 3H), 3.28 (s, 3H), 3.15 (d, 2H, *J* = 7.2 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 169.4, 158.3, 136.0, 134.7, 130.34, 130.29, 127.4, 118.60, 118.44, 115.0, 55.6, 36.6, 30.4 ppm. FTIR (cm$^{-1}$) (neat): 3328, 1626, 1601, 1282, 1032, 750. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO_2$ [M+H]$^+$: 204.1027, found 204.1019 *m/z.*

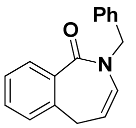
**281**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.51 (t, 1H, *J* = 2.5 Hz), 7.12 (dd, 1H, *J* = 8.7, 2.4 Hz), 7.01-6.98 (m, 1H), 6.76-6.73 (m, 1H), 6.27-6.21 (m, 1H), 3.86, 3.60 (d, 2H, *J* = 6.8 Hz), 3.20 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 168.5, 158.9, 136.7, 134.3, 130.2, 128.0, 127.4, 118.2, 114.2, 55.6, 46.5, 36.4 ppm. FTIR (cm$^{-1}$) (neat): 3356, 2928, 1626, 1601, 1481, 1233, 1030, 789. HRMS (APPI, Pos): calc. for $C_{12}H_{14}NO_2$ [M+H]$^+$: 204.1028, found 204.1019 *m/z.*

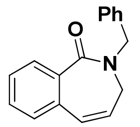


**6,7,8-trimethoxy-2-methyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (282) and 6,7,8-trimethoxy-2-methyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (283)**: Synthesized according to **Procedure K** to give **282** as an orange oil in 17% yield (22 mg, 0.08 mmol), and **283** as an orange oil in 10% yield (12.8 mg, 0.05 mmol).

**282**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.23 (s, 1H), 5.97 (d, 1H, *J* = 8.0 Hz), 5.61 (dt, 1H, *J* = 15.0, 8.0 Hz), 3.90, (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H), 3.28 (s, 3H), 3.23 (d, 2H, *J* = 7.3 Hz) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 169.1, 151.6, 148.2, 145.2, 131.1, 130.4, 129.5, 118.1, 109.9, 61.0, 56.1, 36.6, 22.2 ppm. FTIR ($cm^{-1}$) (neat): 2937, 1656, 1485, 1209, 1166, 1009, 907, 760, 708. HRMS (APPI, Pos): calc. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1238, found 264.1230 *m/z.*

**283**: $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.38 (s, 1H), 7.02-6.99 (m, 1H), 6.36-6.30 (m, 1H), 3.96-3.94 (m, 6H), 3.88 (s, 3H), 3.65-3.63 (m, 2H), 3.23 (s, 3H) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): 169.2, 147.2, 143.0, 136.5, 136.4, 128.5, 128.4, 127.1, 108.9, 60.8, 60.5, 55.6, 46.0, 38.4 ppm. FTIR ($cm^{-1}$) (neat): 2933, 1626, 1195, 1019, 972, 701. HRMS (APPI, Pos): calc. for $C_{14}H_{18}NO_4$ $[M+H]^+$: 264.1239, found 264.1230 *m/z.*





**2-benzyl-2,5-dihydro-1*H*-benzo[*c*]azepin-1-one (265) and 2-benzyl-2,3-dihydro-1*H*-benzo[*c*]azepin-1-one (266)**: Synthesized according to **Procedure K** to give **265** as an orange oil in 59% yield (71.9 mg, 0.29 mmol), and **266** as an orange oil in 37% yield (45.5 g, 0.18 mmol).

**265**: $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.92 (dd, 1H, *J* = 7.7, 1.1 Hz), 7.41-7.26 (m, 7H), 7.07 (d, 1H, *J* = 7.4 Hz), 5.99 (d, 1H, *J* = 7.6 Hz), 5.67 (q, 1H, *J* = 7.4 Hz), 4.95 (s, 2H), 3.20 (d, 2H, *J* = 7.2 Hz) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 169.3, 143.5, 137.6, 133.9, 131.7, 131.4, 129.6, 128.8, 128.0, 127.6, 126.7, 126.2, 119.0, 51.8, 31.6 ppm. FTIR ($cm^{-1}$) (neat): 3060, 3030, 2922, 1619, 1569, 1446, 1311, 724, 698, 463. HRMS (APPI, Pos): calc. for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1231, found 250.1226 *m/z.*

**266**: $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.13-8.11 (m, 1H), 7.50-7.30 (m, 7H), 7.24 (d, 1H, *J* = 7.5 Hz), 6.78 (d, 1H, *J* = 9.9 Hz), 6.16-6.12 (m, 1H), 4.85 (s, 2H), 3.60 (d, 2H, *J* = 6.8 Hz) ppm. $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 171.7, 138.0, 134.3, 131.5, 130.5, 129.1, 128.8, 128.7, 128.6, 128.3, 127.9, 127.7, 106.9, 51.9, 43.8 ppm. FTIR ($cm^{-1}$) (neat): 3064, 3033, 2957, 1629, 1495, 1421, 1277, 797, 700, 474. HRMS (APPI, Pos): calc. for $C_{17}H_{16}NO$ $[M+H]^+$: 250.1232, found 250.1226 *m/z.*

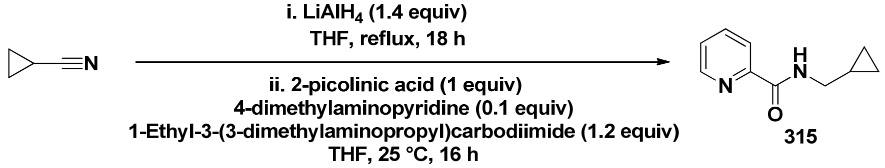
*Hydrogenation of benzazepinones*

Pd on carbon (0.022 mmol) was placed in a 5 mL microwave vial, followed by 1.0 mL EtOH. After purging with $H_2$ gas, benzazepinones **259** and **260** (0.22 mmol) were added as a solution in 1.5 mL EtOH. The reaction was stirred for 16 h under an $H_2$ balloon (1 atm). It was then filtered over a celite/cotton plug, and concentrated *in vacuo* to give a pale yellow solid[260] (35.6 mg, 93%).

## Experimental section of Chapter 4

Auxiliaries **319-321** (obtained via **Procedure A** and/or methylation with MeI) match reported literature data.[195]

*Synthesis of* ***N-(cyclopropylmethyl)picolinamide (315)***



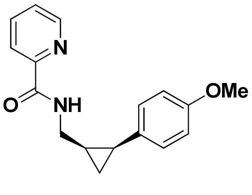
To a 250 mL round-bottom flask fitted with a stir bar (previously flame dried and cooled under Ar) was added $LiAlH_4$ powder (1.06 g, 28 mmol, 1.4 equiv) and the flask was placed in an ice/water bath. Dry THF (100 mL) was added under Ar, and the mixture was stirred for 5 min. Cyclopropanecarbonitrile (1.47 mL, 20 mmol, 1.0 equiv) was added dropwise. The reaction was stirred for 30 min at 0 °C, then fitted with a reflux condenser and refluxed for 18 h under Ar. The reaction was allowed to cool down to room temperature, then cooled in an ice/water bath. Sodium sulfate decahydrate was added to the reaction, slowly at first. Extra THF was also added to the reaction. Enough sodium sulfate decahydrate was added to the heterogeneous reaction to quench all the $LiAlH_4$ and the reaction was stirred at room temperature for another 2 h (until the gray solids turned white). Then, the mixture was filtered over a pad of anhydrous sodium sulfate directly into a 500 mL round-bottom flask, rinsing with about 150 mL dry THF. To the filtrate was directly added 4-dimethylaminopyridine (DMAP) (244 mg, 2 mmol, 0.1 equiv), 2-picolinic acid (2.46 g, 20 mmol, 1 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (3.72 g, 24 mmol, 1.2 equiv). The reaction turned red and was stirred at room temperature for 16 h. The reaction was quenched with a solution of citric acid (approx 0.8 *M*), then transferred to a separatory funnel where

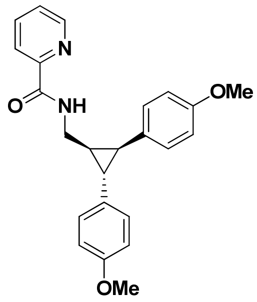
EtOAc (100 mL) was added and the layers were separated. The organic layers was washed two more times with citric acid (15 mL), then saturated *aqueous* $NaHCO_3$ (15 mL), and brine (10 mL). The organic layer was dried ($Na_2SO_4$), filtered and concentrated. The residue was flashed in 20% EtOAc/Hex. 2 g (57%) of a white solid were obtained. mp: <40 °C, decomposition. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.56 (ddd, 1H, *J* = 4.8, 1.6, 0.9 Hz), 8.21 (dt, 1H, *J* = 7.9, 1.1 Hz), 8.12 (br s, 1H), 7.83 (td, 1H, *J* = 7.7, 1.7 Hz), 7.40 (ddd, 1H, *J* = 7.6, 4.8, 1.3 Hz), 3.33 (dd, 2H, *J* = 7.1, 5.9 Hz), 1.11-1.02 (m, 1H), 0.57-0.51 (m, 2H), 0.31-0.25 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 164.2, 150.2, 148.1, 137.4, 126.1, 122.3, 44.3, 10.9, 3.6 ppm. FTIR ($cm^{-1}$) (neat): 3335, 3008, 2935, 1658, 1588, 1567, 1519, 1463, 1333, 1163. HRMS (ESI, Pos) calcd for $C_{10}H_{13}N_2O$ $[M+H]^+$: 177.1022, found 177.1022 *m/z*.

*Palladium-catalyzed arylation of cyclopropanes*

**Procedure L** (or **Condition A** in Scheme 120): To a microwave vial (previously kept in an oven and cooled to room temperature under a stream of Ar) was added *N*-(pyridin-2-ylmethyl)cyclopropanecarboxamide **315** (88.1 mg, 0.5 mmol, 1 equiv) and the corresponding iodoarene (if a solid, 0.75 mmol, 1.5 equiv). The vial was placed in a glove-box, where $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.05 equiv), $Na_2CO_3$ (15.9 mg, 0.15 mmol, 0.3 equiv), and $Ag_3PO_4$ (104.6 mg, 0.25 mmol, 0.5 equiv) were added. The vial was crimped and taken out of the glove-box. Then, the iodoarene (if a liquid, 0.75 mmol, 1.5 equiv) was added via syringe, followed by 2.5 mL (0.2 *M*) dry toluene (via syringe). The reaction was placed in an oil bath and stirred at 130 °C for 15 h. The reaction was allowed to cool to room temperature and filtered over a pad of silica and celite, rinsing with EtOAc (10 mL) and MeOH (5 mL). The filtrate was concentrated, then trimethoxybenzene was added and the $^1$H NMR yield calculated. The residue was purified via flash chromatography.

**Procedure M** (or **Condition B** in Scheme 120): To a microwave vial (previously kept in an oven and cooled to room temperature under a stream of Ar) was added *N*-(pyridin-2-ylmethyl)cyclopropanecarboxamide (88.1 mg, 0.5 mmol, 1 equiv), trimethylacetic acid (15.3 mg, 0.15 mmol, 0.3 equiv), and the corresponding iodoarene (if a solid, 0.75 mmol, 1.5 equiv). The vial was placed in a glove-box, where $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.05 equiv), and $K_2CO_3$ (138.2 mg, 1.0 mmol, 2 equiv) were added. The vial was crimped and taken out of the glove-box. Then, the iodoarene (if a liquid, 0.75 mmol, 1.5 equiv) was added via syringe, followed by 2.5 mL (0.2 *M*) dry toluene (via syringe). The reaction was placed in an oil bath and stirred at 130 °C for 15 h. The reaction was allowed to cool to room temperature and filtered over a pad of silica and celite, rinsing with EtOAc (10 mL) and MeOH (5 mL). The filtrate was concentrated, then trimethoxybenzene was added and the $^1$H NMR yield calculated. The residue was purified via flash chromatography.





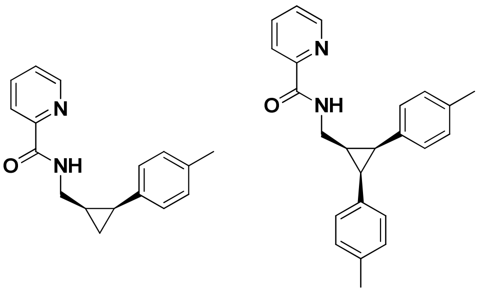
***N*-(((1R,2S)-2-(4-methoxyphenyl)cyclopropyl)methyl)picolinamide (316) and *N*-(((2R,3R)-2,3-bis(4-methoxyphenyl)cyclopropyl)methyl)picolinamide (317):** The reaction was performed according to **Procedure L** on a 0.5 mmol scale using 4-iodoanisole as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **316** (78%), **317** (10%) and unreacted **315** (8%). The reaction was then purified via column chromatography over silica gel (RediSep® Rf Gold 12g) in 15-30% EtOAc/Hex to give **316** (100 mg, 71%), **317** (16 mg, 9%), along with recovered **315** (7 mg, 8%). The diarylated *trans* product **317** contained small traces (<5%) of the corresponding *cis* dimer.

The reaction was performed according to **Procedure M** on a 0.5 mmol scale using 4-iodoanisole as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **316** (66%), **317** (16%) and unreacted **315** (6%). The reaction was then purified via column chromatography over silica gel (RediSep® Rf Gold 12g) in 15-30% EtOAc/Hex to give **316** (102 mg, 72%), **317** (29 mg, 12%), along with recovered **315** (5 mg, 5%). The diarylated *trans* product **317** contained small traces (<5%) of the corresponding *cis* dimer.

**316**: white solid. mp: 61-62 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.53-8.52 (m, 1H), 8.14 (d, 1H, *J* = 7.9 Hz), 7.96 (br s, 1H), 7.80 (td, 1H, *J* = 7.7, 1.8 Hz), 7.38 (ddd, 1H, *J* = 7.5, 4.8, 1.1 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 6.84 (d, 2H, *J* = 8.4 Hz), 3.76 (s, 3H), 3.31-3.25 (m, 1H), 3.08-3.05 (m, 1H), 2.23-2.20 (m, 1H), 1.45-1.43 (m, 1H), 1.04 (td, 1H, *J* = 8.4, 5.4 Hz), 0.88-0.84

(m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.1, 158.2, 150.1, 148.1, 137.3, 130.2, 130.1, 126.0, 122.2, 113.8, 55.3, 39.7, 20.0, 18.0, 8.6 ppm. FTIR (cm$^{-1}$) (neat): 3393, 3004, 1671, 1512, 1464, 1434, 1245, 1178, 1033. HRMS (ESI, Pos) calcd for $C_{17}H_{18}N_2O_2$ [M+H]$^+$: 283.1441, found 283.1430 *m/z*.

**317**: yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 8.53-8.51 (m, 1H), 8.16 (d, 1H, *J* = 7.9 Hz), 8.04 (br s, 1H), 7.82 (td, 1H, *J* = 7.8, 1.7 Hz), 7.40 (ddd, 1H, *J* = 7.6, 4.7, 1.2 Hz), 7.29 (d, 2H, *J* = 8.4 Hz), 7.24 (d, 2H, *J* = 8.6 Hz), 6.89-6.83 (m, 4H), 3.81 (s, 3H), 3.79 (s, 3H), 3.49 (ddd, 1H, *J* = 14.0, 7.2, 7.1 Hz), 3.25 (ddd, 1H, *J* = 14.0, 7.2, 5.4 Hz), 2.50 (dd, 1H, *J* = 9.0, 5.7 Hz), 2.41-2.37 (m 1H), 1.81-1.77 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.3, 158.4, 158.1, 150.1, 148.2, 137.4, 133.8, 130.1, 130.0, 127.7, 126.1, 122.3, 114.0, 113.4, 55.5, 55.4, 39.4, 30.4, 28.1, 26.8 ppm. FTIR (cm$^{-1}$) (neat): 3383, 2932, 2834, 1670, 1610, 1509, 1463, 1433, 1031. HRMS (ESI, Pos) calcd for $C_{24}H_{25}N_2O_3$ [M+H]$^+$: 389.1860, found 389.1860 *m/z.*



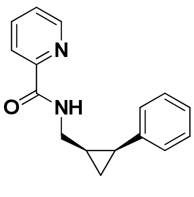
***N*-(((1R,2S)-2-(p-tolyl)cyclopropyl)methyl)picolinamide (323a) and *N*-(((1s,2R,3S)-2,3-di-p-tolylcyclopropyl)methyl)picolinamide (323b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale using 4-iodotoluene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **323a** (73%), **323b** (4%) and unreacted **315** (10%). The reaction was then purified via column chromatography over silica gel in 15-30% EtOAc/Hex to give an inseparable mixture of **323a**, **323b** along with **315** (128 mg, 1:0.05:0.15 ratio determined by $^1$H NMR). Isolated yields calculated based on $^1$H NMR ratio: **323a** (82%), **323b** (4%, *cis:trans*, >10:1), **315** (6%).

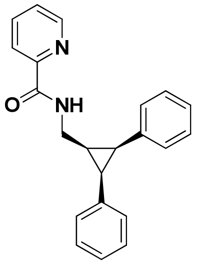
The reaction was performed according to **Procedure M** on a 0.5 mmol scale using 4-iodotoluene as the coupling partner, *except the reaction was run for 45 h.* After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **323a** (64%), **323b** (21%) and unreacted **315** (<2%). The reaction was then purified via column chromatography over silica gel in 15-30% EtOAc/Hex to give an inseparable mixture of **323a** and **323b** (131 mg, 1:

0.41 ratio determined by $^1$H NMR). Isolated yields calculated based on $^1$H NMR ratio: **323a** (64%), **323b** (20%, *cis:trans*, 7:1).

**323a**: yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.53 (d, 1H, $J$ = 4.0 Hz), 8.15 (d, 1H, $J$ = 7.9 Hz), 7.96 (br. s, 1H), 7.80 (td, 1H, $J$ = 7.7, 1.6 Hz), 7.41-7.37 (m, 1H), 7.19-7.17 (m, 2H), 7.11-7.09 (m, 2H), 3.35-3.28 (m, 1H), 3.08-3.02 (m, 1H), 2.31 (s, 3H), 2.29-2.23 (m, 1H), 1.48-1.44 (m, 1H), 1.05 (td, 1H, $J$ = 8.3, 5.5 Hz), 0.99-0.85 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.1, 150.2, 148.1, 137.3, 135.8, 135.0, 129.0, 126.4, 126.0, 122.2, 39.6, 21.1, 20.4, 18.1, 8.4 ppm. FTIR (cm$^{-1}$) (neat): 3393, 2922, 2866, 1672, 1590, 1569, 1516, 1464, 1155. HRMS (ESI, Pos) calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$: 267.1492, found 267.1495 *m/z*.

**323b**: HRMS (ESI, Pos) calcd for $C_{24}H_{25}N_2O$ $[M+H]^+$: 357.1961, found 357.1967 *m/z*.





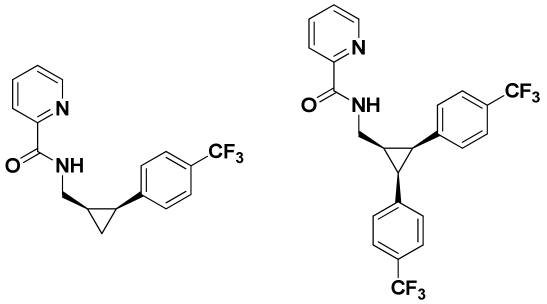
***N*-(((1R,2S)-2-phenylcyclopropyl)methyl)picolinamide (324a) and *N*-(((1S,2R,3S)-2,3-diphenylcyclopropyl)methyl)picolinamide (324b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale using iodobenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **324a** (73%), **324b** (6%) and unreacted **315** (5%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give an inseparable mixture of **324a**, **324b** along with **315** (116 mg, 1: 0.15 : 0.15 ratio determined by $^1$H NMR). Yields calculated based on $^1$H NMR ratio: **324a** (79%), **324b** (6%, *cis:trans*, >10:1), **315** (6%).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using iodobenzene as the coupling partner, *except the reaction was run for 45 h*. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **324a** (74%), **324b** (21%) and unreacted **315** (<2%). The reaction was then purified via column chromatography over silica gel (RediSep® Rf Gold 12g) in 15-30% EtOAc/Hex to give an inseparable mixture of

**324a** and **324b** (107 mg, 1:0.3 ratio determined by $^{1}$H NMR). Yields calculated based on $^{1}$H NMR ratio: **324a** (61%), **324b** (18%, *cis:trans*, 1:1.5). <1% **315** was observed in this case.

**324a**: yellow oil. $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 8.55-8.53 (m, 1H), 8.15 (dt, 1H, *J* = 7.8, 1.2 Hz), 7.94 (br. s, 1H), 7.82 (td, 1H, *J* = 7.7, 1.6 Hz), 7.40 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 7.31-7.28 (m, 4H), 7.21-7.20 (m, 1H), 3.32 (dt, 1H, *J* = 14.1, 7.0 Hz), 3.10-3.07 (m, 1H), 2.32-2.28 (m, 1H), 1.53-1.50 (m, 1H), 1.09 (td, 1H, *J* = 8.3, 5.3 Hz), 1.00-0.87 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 183.8, 150.2, 138.2, 137.4, 129.2, 128.4, 126.4, 126.1, 122.3, 39.7, 20.9, 18.4, 8.6 ppm. FTIR (cm$^{-1}$) (neat): 3391, 2981, 2844, 1671, 1590, 1568, 1464, 1155. HRMS (ESI, Pos) calcd for $C_{16}H_{17}N_2O$ [M+H]$^+$: 253.1335, found 253.1339 *m/z*.

**324b**: HRMS (ESI, Pos) calcd for $C_{22}H_{21}N_2O$ [M+H]$^+$: 329.1648, found 329.1652 *m/z*.

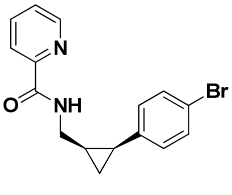


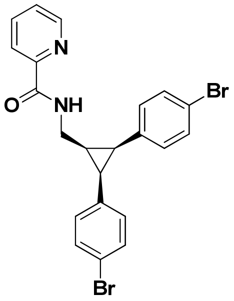
***N*-(((1R,2S)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)methyl)picolinamide** (**325a**) **and *N*-*(((*1s,2R,3S)-2,3-bis(4-(trifluoromethyl)phenyl)cyclopropyl)methyl)picolinamide** (**325b**): The reaction was performed according to **Procedure L** on a 0.5 mmol scale using 4-iodobenzotrifluoride as the coupling partner. After work-up, trimethoxybenzene was added and the $^{1}$H NMR yield determined: **325a** (73%), **325b** (4%) and unreacted **315** (18%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **325a** (108 mg, 67%), **325b** (12 mg, 5%, *cis*), along with recovered **315** (15 mg, 17%).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale using 4-iodobenzotrifluoride as the coupling partner. After work-up, trimethoxybenzene was added and the $^{1}$H NMR yield determined: **325a** (68%), **325b** (8%) and unreacted **315** (18%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex (Silicycle 12 g) to give **325a** (96 mg, 60%), **325b** (17 mg, 7%, *cis*), along with recovered **315** (25 mg, 28%).

**325a**: white solid. mp: 71-72 °C. $^1$H NMR (CDCl$_3$, 700 MHz): δ 8.53 (ddd, 1H, *J* = 4.7, 1.6, 0.9 Hz), 8.14 (dd, 1H, *J* = 7.8, 1.1 Hz), 7.93 (br s, 1H), 7.82 (td, 1H, *J* = 7.7, 1.7 Hz), 7.55 (d, 2H, *J* = 8.1 Hz), 7.44-7.37 (m, 3H), 3.28 (ddd, 1H, *J* = 14.2, 7.6, 6.4 Hz), 3.15-3.06 (m, 1H), 2.38-2.30 (m, 1H), 1.63-1.54 (m, 1H), 1.20-1.12 (m, 1H), 1.06-1.00 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 175 MHz): δ 164.3, 150.0, 148.2, 142.7, 137.5, 129.4, 128.6 (q, $J_{C\text{-}F}$ = 32 Hz), 126.2, 125.3 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.3(q, $J_{C\text{-}F}$ = 270 Hz), 122.3, 39.4, 20.9, 18.9, 9.2 ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz): δ - 62.3 ppm. FTIR (cm$^{-1}$) (neat): 3297, 2924, 1670, 1615, 1568, 1434, 1325, 1246, 1156. HRMS (ESI, Pos) calcd for $C_{17}H_{16}F_3N_2O$ [M+H]$^+$: 321.1209, found 321.1210 *m/z*.

**325b**: thick yellow oil**.** $^1$H NMR (CDCl$_3$, 700 MHz): δ 8.42 (d, 1H, *J* = 4.3 Hz), 8.12 (d, 1H, *J* = 7.8 Hz), 7.81 (td, 1H, *J* = 7.7, 1.5 Hz), 7.76 (br s, 1H), 7.49 (d, 4H, *J* = 8.2 Hz), 7.38 (ddd, 1H, *J* = 7.5, 4.8, 1.1 Hz), 7.11 (d, 4H, *J* = 8.1 Hz), 3.73 (dd, 2H, *J* = 7.7, 5.7 Hz), 2.80 (d, 2H, *J* = 9.2 Hz), 2.21-2.11 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 175 MHz): δ 164.4, 149.6, 148.2, 139.9, 137.4, 130.6, 128.8 (q, $J_{C\text{-}F}$ = 32.1 Hz), 126.3, 125.4 (q, $J_{C\text{-}F}$ = 4.0 Hz), 124.3 (q, $J_{C\text{-}F}$ = 272.0 Hz), 122.2, 35.7, 26.4, 23.8 ppm. $^{19}$F NMR (CDCl$_3$, 376 MHz): δ -62.5 ppm. FTIR (cm$^{-1}$) (neat): 3383, 2924, 1673, 1618, 1519, 1465, 1321, 1161, 1108. HRMS (ESI, Pos) calcd for $C_{24}H_{19}F_6N_2O$ [M+H]$^+$: 465.1396, found 465.1391 *m/z*.



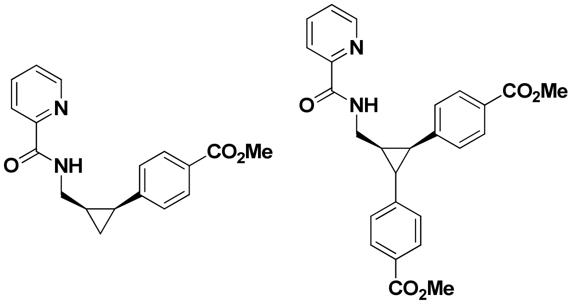


***N*-(((1R,2S)-2-(4-bromophenyl)cyclopropyl)methyl)picolinamide (326a) and *N*-(((1S,2R)-2,3-bis(4-bromophenyl)cyclopropyl)methyl)picolinamide (326b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale using 1-bromo-4-iodobenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **326a** (68%), **326b** (10%) and unreacted **315** (6%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **326a** (96 mg, 68%), **326b** (29 mg, 11%, *cis* containing approx. 15% **326a**), along with recovered **315** (18 mg, 10%).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale using 1-bromo-4-iodobenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **326a** (60%), **326b** (9%) and unreacted **315** (13%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **326a** (96 mg, 58%), **326b** (34 mg, 11%, *cis* containing 23% **326a**), along with recovered **315** (24 mg containing 45% **326a**). **326b** was further purified by preparatory High Pressure Liquid Chromatography (prep-HPLC), in 1-2% *i*PrOH/Hex on a Zorbax RX silica column to obtain a pure sample.

**326a**: white solid. mp: 86 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.53 (d, 1H, *J* = 4.6 Hz), 8.14 (d, 1H, *J* = 7.9 Hz), 7.81 (td, 1H, *J* = 7.7, 1.6 Hz), 7.42-7.38 (m, 3H), 7.15 (d, 2H, *J* = 8.4 Hz), 3.28 (dt, 1H, *J* = 14.2, 7.0 Hz), 3.09-3.02 (m, 1H), 2.25-2.20 (m, 1H), 1.54-1.49 (m, 1H), 1.09 (td, 1H, *J* = 8.3, 5.5 Hz), 0.96-0.86 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 164.2, 150.0, 148.1, 131.5, 130.9, 126.2, 122.2, 120.2, 39.5, 20.4, 18.4, 8.9 ppm. FTIR (cm$^{-1}$) (neat): 3290, 2921, 2866, 1657, 1587, 1567, 1490, 1460, 1332, 1286, 1154. HRMS (ESI, Pos) calcd for $C_{16}H_{16}BrN_2O$ [M+H]$^+$: 331.0440, found 331.0444 *m/z*.

**326b**: thick yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 8.46 (d, 1H, *J* = 4.6 Hz), 8.13 (d, 1H, *J* = 7.8 Hz), 7.81 (t, 1H, *J* = 7.8 Hz), 7.41-7.35 (m, 5H), 6.87 (d, 4H, *J* = 8.4 Hz), 3.72-3.66 (m, 2H), 2.64 (d, 2H, *J* = 9.2 Hz), 2.08-1.96 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.4, 149.8, 148.2, 137.4, 134.8, 132.1, 131.5, 126.2, 122.2, 120.5, 35.7, 25.7, 23.3 ppm. FTIR (cm$^{-1}$) (neat): 3382, 2867, 1669, 1590, 1568, 1518, 1487, 1241, 1197, 1163. HRMS (ESI, Pos) calcd for $C_{22}H_{19}Br_2N_2O$ [M+H]$^+$: 484.9859, found 484.9850 *m/z*.



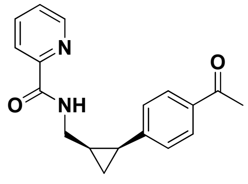
**methyl 4-((1S,2R)-2-(picolinamidomethyl)cyclopropyl)benzoate (327a) and dimethyl 4,4'-((1R,3S)-3-(picolinamidomethyl)cyclopropane-1,2-diyl)dibenzoate (327b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using methyl 4-iodobenzoate as the coupling partner, *except 0.4 equiv $Ag_3PO_4$ were used*. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **327a** (71%), **327b** (8%) and unreacted **315** (14%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **327a** (113 mg, 73%), **327b** (19 mg, 9%, *cis : trans*, 1:0.6), along with recovered **315** (11 mg, 12%).

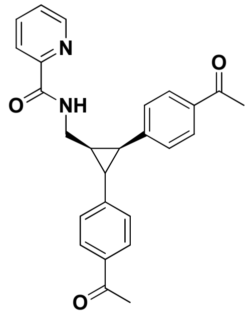
The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using methyl 4-iodobenzoate as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **327a** (66%), **327b** (5%) and unreacted **315** (25%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **327a** (94 mg, 61%), **327b** (11 mg, 5% *trans* and 13 mg, 6% *cis*, for a total of 11%), along with recovered **315** (19 mg, 22%).

**327a**: white solid. mp: 88 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, 1H, *J* = 4.8 Hz), 8.13 (d, 1H, *J* = 7.9 Hz), 7.97 (d, 2H, *J* = 8.2 Hz), 7.91 (br s, 1H), 7.81 (td, 1H, *J* = 7.7, 1.6 Hz), 7.39 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 7.35 (d, 2H, *J* = 8.2 Hz), 3.9 (s, 3H), 3.34 (dt, 1H, *J* = 14.2, 7.1 Hz), 3.07-3.00 (m, 1H), 2.36-2.30 (m, 1H), 1.62-1.56 (m, 1H), 1.15 (td, 1H, *J* = 8.3, 5.6 Hz), 1.08-0.99 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 167.1, 164.2, 150.0, 148.2, 144.0, 137.4, 129.7, 129.0, 128.3, 126.2, 122.2, 52.1, 39.4, 21.1, 19.2, 9.2 ppm. FTIR (cm$^{-1}$) (neat): 3379, 2950, 1717, 1657, 1611, 1587, 1523, 1437, 1276, 1165. HRMS (ESI, Pos) calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$: 311.1390, found 311.1392 *m/z*.
**327b**: *Cis*; yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.42 (ddd, 1H, *J* = 4.7, 1.6, 0.9 Hz), 8.12 (d, 1H, *J* = 7.8 Hz), 7.89 (d, 4H, *J* = 8.4 Hz), 7.83-7.75 (m, 1H), 7.36 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 7.06 (d, 4H, *J* = 8.4 Hz), 3.89 (s, 6H), 3.76 (dd, 2H, *J* = 7.7, 5.8 Hz), 2.80 (d, 2H, *J* = 9.1 Hz), 2.23-2.09 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 167.1, 164.4, 149.7, 148.2, 141.4, 137.4, 130.3, 129.6, 129.4, 128.9, 128.4, 126.2, 122.2, 106.2, 52.2, 35.8, 26.8, 24.2 ppm. FTIR (cm$^{-1}$) (neat): 3385, 2951, 1714, 1672, 1608, 1569, 1519, 1463, 1274, 1185.

*Trans;* yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.51 (d, 1H, *J* = 4.3 Hz), 8.14 (d, 1H, *J* = 7.8 Hz), 8.03 (d, 2H, *J* = 8.3 Hz), 7.96 (d, 2H, *J* = 8.4 Hz), 7.82 (d, 1H, *J* = 7.7, 1.6 Hz), 7.44 (d, 2H, *J* = 8.3 Hz), 7.43-7.37 (m, 1H), 7.26 (d, 1H, *J* = 8.3 Hz), 3.92 (s, 3H), 3.90 (s, 3H), 3.57 (dt, 1H, *J* = 14.3, 7.1 Hz), 3.24 (ddd, 1H, *J* = 14.2, 7.2, 5.5 Hz), 2.72 (dd, 1H, *J* = 9.3, 5.6 Hz), 2.64 (t, 1H, *J* = 5.4 Hz), 2.10-1.98 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 167.0

(2), 164.4, 149.8, 148.2, 146.7, 142.6, 137.5, 130.0 (2), 129.0, 128.9, 126.3, 122.3, 52.3, 52.2, 38.9, 32.3, 30.0, 27.8 ppm. FTIR (cm$^{-1}$) (neat): 3385, 2951, 1714, 1669, 1607, 1570, 1519, 1463, 1273. HRMS (ESI, Pos) calcd for $C_{26}H_{25}N_2O_5$ [M+H]$^+$: 445.1758, found 445.1752 *m/z*.





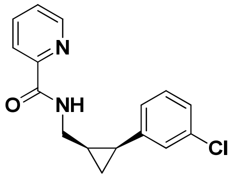
***N*-(((1R,2S)-2-(4-acetylphenyl)cyclopropyl)methyl)picolinamide (328a) and *N*-(((1S,2R)-2,3-bis(4-acetylphenyl)cyclopropyl)methyl)picolinamide (328b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 4-iodoacetophenone as the coupling partner. After work-up, the reaction was purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **328a** (111 mg, 75%), **328b** (29 mg, 14%, *cis:trans*, 1.7:1), along with recovered **315** (11 mg, 12%).

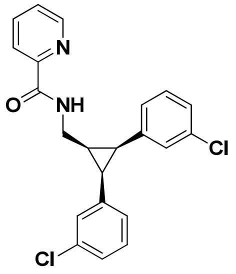
The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 4-iodoacetophenone as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **328a** (65%), **328b** (5%) and unreacted **315** (25%). and then purified via column chromatography over silica gel (RediSep® Rf Gold 12g) in 20-100% EtOAc/Hex to give **328a** (79 mg, 54%), **328b** (19 mg, 9%, *cis:trans*, 1:1), along with recovered **315** (24 mg, 27%).

**328a**: white solid. mp: 100-101 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.52 (d, 1H, *J* = 4.8 Hz), 8.13 (d, 1H, *J* = 7.9 Hz), 7.90-7.88 (m, 3H), 7.81 (td, 1H, *J* = 7.7, 1.6 Hz), 7.42-7.36 (m, 3H), 3.33 (td, 1H, *J* = 14.1, 7.0 Hz), 3.09-3.08 (m, 1H), 2.58 (s, 3H), 2.36-2.31 (m, 1H), 1.64-1.57 (m, 1H), 1.19-1.16 (m, 1H), 1.08-1.04 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 197.9, 164.2, 150.0, 148.1, 144.3, 137.4, 135.4, 129.2, 128.5, 126.2, 122.3, 39.4, 26.7, 21.1, 19.2, 9.3 ppm. FTIR (cm$^{-1}$) (neat): 3376, 2972, 2865, 2844, 1656, 1603, 1566, 1523, 1455, 1266, 1166.

HRMS (ESI, Pos) calcd for $C_{18}H_{19}N_2O_2$ [M+H]$^+$: 295.1441, found 295.1443 *m/z*.

**328b**: Characterized as approx. a 1:1 mixture of *cis*:*trans*. Thick yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.52-8.51 (m, 1H), 8.43 (d, 1H, *J* = 4.8 Hz), 8.14 (dd, 2H, *J* = 12.6, 7.8 Hz), 7.95 (d, 2H, *J* = 8.2 Hz), 7.90 (d, 2H, *J* = 8.2 Hz), 7.85-7.78 (m, 6H), 7.48 (d, 2H, *J* = 8.2 Hz), 7.43-7.40 (m, 2H), 7.29 (d, 2H, *J* = 8.4 Hz), 7.09 (d, 4H, *J* = 8.4 Hz), 3.77 (dd, 2H, *J* = 7.8, 5.8 Hz), 3.58-3.53 (m, 1H), 3.29-3.24 (m, 1H), 2.82 (d, 2H, *J* = 9.2 Hz), 2.75-2.71 (m, 1H), 2.69-2.65 (m, 1H), 2.61 (s, 3H), 2.58 (s, 3H), 2.57 (s, 6H), 2.22-2.14 (m, 1H), 2.10-2.04 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 197.9, 197.8, 197.7, 164.4 (2), 149.7, 149.6, 148.2 (2), 147.0, 141.7, 137.5, 137.4, 135.9, 135.4 (2), 130.5, 129.1, 128.8 (2), 128.4, 128.2, 126.4 (2), 126.3, 122.3, 122.2, 38.9, 32.4, 31.1, 30.1, 27.9, 26.9, 26.7, 26.6, 24.2 ppm. FTIR (cm$^{-1}$) (neat): 3382, 2972, 2866, 2844, 1673, 1603, 1568, 1519, 1464, 1357, 1266. HRMS (ESI, Pos) calcd for $C_{26}H_{25}N_2O_3$ [M+H]$^+$: 413.1860, found 413.1866 *m/z*.





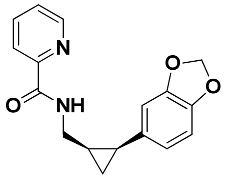
**$N$-(((1R,2S)-2-(3-chlorophenyl)cyclopropyl)methyl)picolinamide (329a) and $N$-(((1S,2R)-2,3-bis(3-chlorophenyl)cyclopropyl)methyl)picolinamide (329b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 1-chloro-3-iodobenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **329a** (76%), **329b** (3%) and unreacted **315** (9%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **329a** (96 mg, 67%), **329b** (15 mg, 8%, *cis* containing 50% **329a**), along with recovered **315** (11 mg, 12%).

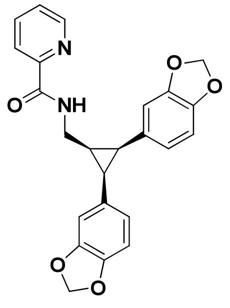
The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 1-chloro-3-iodobenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **329a** (61%), **329b** (8%) and unreacted **315** (13%).The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give

**329a** (64 mg, 43%), **329b** (34 mg, 10%, *cis* containing 40% **329a**), along with recovered **315** (29 mg, containing with 50% **329a**).

**329a**: white solid. mp: 47-48 °C. $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 8.56 (dt, 1H, *J* = 4.7, 0.8 Hz), 8.15 (d, 1H, *J* = 7.8 Hz), 7.86-7.79 (m, 1H), 7.41 (ddd, 1H, *J* = 7.5, 4.8, 1.2 Hz), 7.30 (s, 1H), 7.25-7.14 (m, 3H), 3.33 (dt, 1H, *J* = 14.0, 7.0 Hz), 3.12-3.00 (m, 1H), 2.33-2.21 (m, 1H), 1.58-1.48 (m, 1H), 1.15-1.06 (m, 1H), 1.02-0.95 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.2, 150.0, 148.2, 140.5, 137.4, 129.6, 129.5, 127.2, 126.6, 122.2, 39.6, 20.6, 18.5, 8.9 ppm. FTIR (cm$^{-1}$) (neat): 3680, 3309, 2939, 2865, 2844, 1651, 1595, 1567, 1462, 1393, 1153. HRMS (ESI, Pos) calcd for $C_{16}H_{16}ClN_2O$ [M+H]$^{+}$: 287.0946, found 287.0948 *m/z*.

**329b**: yellow oil. $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 8.47-8.46 (m, 1H), 8.13 (d, 1H, *J* = 7.9 Hz), 7.80 (m, 1H), 7.76 (br. S, 1H), 7.39-7.37 (m, 1H), 7.22-7.17 (m, 6H), 6.81 (d, 2H, *J* = 7.5 Hz), 3.72 (dd, 2H, *J* = 7.6, 6.0 Hz), 2.68 (d, 2H, *J* = 9.2 Hz), 2.11-1.98 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.4, 149.8, 148.2, 137.9, 137.4, 134.2, 130.7, 129.6, 128.2, 126.2, 122.2, 35.8, 26.0, 23.4 ppm. FTIR (cm$^{-1}$) (neat): 3382, 1671, 1593, 1567, 1517, 1433, 1163. HRMS (ESI, Pos) calcd for $C_{22}H_{19}Cl_2N_2O$ [M+H]$^{+}$: 397.0869, found 397.0870 *m/z*.



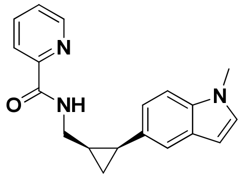


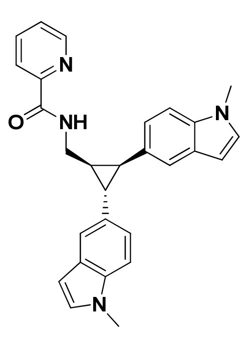
***N*-(((1R,2S)-2-(benzo[d][1,3]dioxol-5-yl)cyclopropyl)methyl)picolinamide (330a) and *N*-(((1S,2R)-2,3-bis(benzo[d][1,3]dioxol-5-yl)cyclopropyl)methyl)picolinamide (330b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 1-iodo-3,4-methylenedioxybenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^{1}$H NMR yield determined: **330a** (69%), **330b** (4%) and unreacted **315** (5%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **330a** (112 mg, 76%), **330b** (17 mg, 8%, *cis:trans*, 1:5), along with recovered **315** (7 mg, 8%).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 1-iodo-3,4-methylenedioxybenzene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **330a** (69%), **330b** (4%) and unreacted **315** (9%). The reaction was then purified via column chromatography over silica gel (RediSep® Rf Gold 12g) in 20-100% EtOAc/Hex to give **330a** (97 mg, 65%), **330b** (12 mg, 6%, *trans*), along with recovered **315** (22 mg, 23%).

**330a**: yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.54 (ddd, 1H, *J* = 4.7, 1.7, 0.9 Hz), 8.17-8.14 (m, 1H), 7.98 (br. s, 1H), 7.82 (td, 1H, *J* = 7.7, 1.7 Hz), 7.40 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 6.79-6.74 (m, 3H), 5.93 (s, 2H), 3.35-3.25 (m, 1H), 3.13-3.04 (m, 1H), 2.22 (td, 1H, *J* = 8.5, 6.2 Hz), 1.48-1.40 (m, 1H), 1.04 (td, 1H, *J* = 8.4, 5.4 Hz), 0.89-0.78 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 164.2, 150.1, 148.1, 147.7, 146.2, 137.4, 132.0, 126.1, 122.2 (2), 109.8, 108.2, 101.0, 39.7, 20.6, 18.1, 8.9 ppm. FTIR (cm$^{-1}$) (neat): 3383, 2981, 2844, 1667, 1590, 1569, 1520, 1502, 1347, 1288, 1232, 1213, 1174. HRMS (ESI, Pos) calcd for $C_{17}H_{17}N_2O_3$ [M+H]$^+$: 297.1234, found 297.1237 *m/z*.

**330b**: yellow oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 8.46 (ddd, 1H, *J* = 4.8, 1.6, 0.9 Hz), 8.14 (dt, 1H, *J* = 7.8, 1.0 Hz), 7.80 (td, 2H, *J* = 7.7, 1.7 Hz), 7.37 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 6.70 (d, 2H, *J* = 8.0 Hz), 6.57-6.51 (m, 4H), 5.91 (s, 4H), 3.74-3.70 (m, 2H), 2.57 (d, 2H, *J* = 9.2 Hz), 1.94-1.86 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 164.3, 150.0, 148.1, 147.5, 146.0, 137.4, 129.7, 126.1, 123.6, 122.3, 110.7, 108.2, 100.2, 36.1, 25.9, 22.8 ppm. FTIR (cm$^{-1}$) (neat): 3382, 2922, 2845, 1672, 1590, 1569, 1520, 1503, 1346, 1285. HRMS (ESI, Pos) calcd for $C_{24}H_{21}N_2O_5$ [M+H]$^+$: 417.1445, found 417.1446 *m/z*.



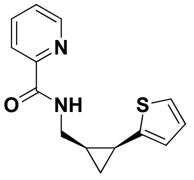


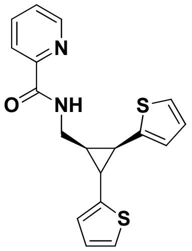
***N*-(((1R,2S)-2-(1-methyl-1H-indol-5-yl)cyclopropyl)methyl)picolinamide (331a) and *N*-(((1s,2R,3S)-2,3-bis(1-methyl-1H-indol-5-yl)cyclopropyl)methyl)picolinamide (331b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 5-iodo-1-methyl-1*H*-indole as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **331a** (77%), **331b** (4%) and unreacted **315** (5%). The reaction was then purified via column chromatography over silica gel in 20-50% EtOAc/Hex to give **331a** (106 mg, 69%), **331b** (30 mg, 14%, *trans*), along with recovered **315** (5 mg, 6%).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 5-iodo-1-methyl-1*H*-indole as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **331a** (29%), **331b** (18%, *cis:trans*, 1:2) and unreacted **315** (28%).

**331a**: Red oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.54 (d, 1H, *J* = 4.2), 8.15 (d, 1H, *J* = 7.9 Hz), 8.00 (br. s, 1H), 7.81-7.78 (m, 1H), 7.53 (s, 1H), 7.38 (dd, 1H, *J* = 6.5, 5.0 Hz), 7.28-7.22 (m, 1H), 7.03 (d, 1H, *J* = 3.0), 6.43 (d, 1H), *J* = 3.0 Hz), 3.77 (s, 3H), 3.35 (dt, 1H, *J* = 14.0, 7.0 Hz), 3.08-3.03 (m, 1H), 2.46-2.40 (m, 1H), 1.54-1.45 (m, 1H), 1.09 (td, 1H, *J* = 8.3, 5.3 Hz), 1.03-0.94 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.1, 150.3, 148.1, 137.3, 135.8, 129.1, 128.8, 128.7, 126.0, 123.5, 122.2, 121.0, 109.1, 100.7, 39.8, 20.9, 18.1, 8.5 ppm. FTIR (cm$^{-1}$) (neat): 3384, 2934, 2844, 1667, 1590, 1569, 1515, 1493, 1368, 1337, 1279, 1244. HRMS (ESI, Pos) calcd for $C_{19}H_{20}N_3O$ $[M+H]^+$: 306.1601, found 306.1602 *m/z*.

**331b**: red oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.52 (ddd, 1H, *J* = 4.5, 1.7, 0.9 Hz), 8.16 (dt, 1H, *J* = 7.8, 1.0 Hz), 7.80 (td, 1H, *J* = 7.7, 1.7 Hz), 7.68 (s, 1H), 7.55 (s, 1H), 7.38 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz), 7.33-7.27 (m, 2H), 7.18 (dd, 1H, *J* = 8.5, 1.7 Hz), 7.04 (dd, 2H, *J* = 10.0, 3.1 Hz), 6.46 (d, 1H, *J* = 3.0 Hz), 6.42 (d, 1H, *J* = 3.0 Hz), 3.80 (s, 3H), 3.77 (s, 3H), 3.57-3.51 (m, 1H), 3.35-3.30 (m, 1H), 2.78 (dd, 1H, *J* = 9.0, 5.7 Hz), 2.67 (t, 1H, *J* = 5.3 Hz), 1.96-1.92 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.2, 150.2, 148.1, 137.4, 135.9, 135.6, 132.9, 129.3, 129.2, 128.8 (2), 128.7, 126.0, 123.5, 122.3, 121.2, 121.1, 118.5, 109.3, 109.2, 100.8, 100.6, 39.8, 33.0 (2), 31.6, 28.0, 27.7 ppm. FTIR (cm$^{-1}$) (neat): 3385, 2972, 2844, 1667, 1568, 1513, 1490, 1432, 1338. HRMS (ESI, Pos) calcd for $C_{28}H_{27}N_4O$ $[M+H]^+$: 435.21794, found 435.2180 *m/z*.



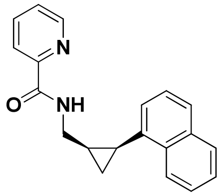


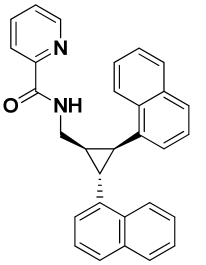
***N*-(((1R,2S)-2-(thiophen-2-yl)cyclopropyl)methyl)picolinamide (332a) and *N*-(((1S,2S)-2,3-di(thiophen-2-yl)cyclopropyl)methyl)picolinamide (332b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 2-iodothiophene as the coupling partner, *except 10 mol % Pd(OAc)$_2$ was used for the reaction*. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **332a** (55%), **332b** (<5%) and unreacted **315** (10%). The reaction was then purified via column chromatography over silica gel in 15-50% EtOAc/Hex to give **332a** (64 mg, 50%, containing small traces of **315** and **332b**) and unreacted **315** (44 mg, containing >50% **332a**).

The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 2-iodothiophene as the coupling partner, *except 10 mol % Pd(OAc)$_2$ was used for the reaction*. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **332a** (31%), **332b** (<5%) and unreacted **315** (43%).

**332a**: yellow oil**.** $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.56 (dd, 1H, *J* = 4.1, 0.9 Hz), 8.17 (dd, 1H, *J* = 7.8, 1.0 Hz), 7.83 (td, 1H, *J* = 7.7, 1.7 Hz), 7.41 (ddd, 1H, *J* = 6.8, 5.5, 1.2 Hz), 7.14 (dd, 1H, *J* = 5.1, 1.0 Hz), 6.97-6.92 (m, 1H), 6.87 (dd, 1H, *J* = 2.3, 1.1 Hz), 3.54 (ddd, 1H, *J* = 14.0, 7.0, 6.8 Hz), 3.15-3.04 (m, 1H), 2.40-2.29 (m, 1H), 1.56-1.48 (m, 1H), 1.27-1.15 (m, 1H), 0.96-0.87 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.3, 150.2, 148.2, 142.6, 137.4, 127.0, 126.1, 125.9, 124.1, 122.3, 39.4, 19.2, 15.5, 11.3 ppm. FTIR (cm$^{-1}$) (neat): 3384, 2923, 2866, 2844, 1666, 1590, 1568, 1518, 1463, 1433, 1240, 1150. HRMS (ESI, Pos) calcd for $C_{14}H_{15}N_2OS$ [M+H]$^+$: 259.0900, found 259.0910 *m/z*.

**332b**: HRMS (ESI, Pos) calcd for $C_{18}H_{17}N_2OS_2$ [M+H]$^+$: 341.0777, found 341.0780 *m/z*.





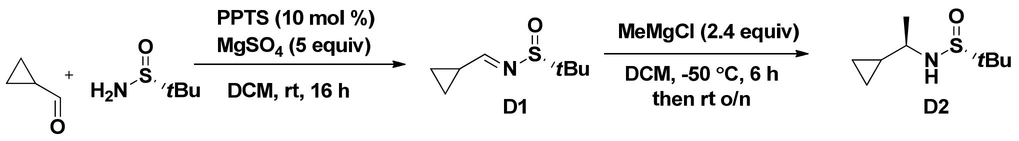
***N*-(((1R,2S)-2-(naphthalen-1-yl)cyclopropyl)methyl)picolinamide (333a) and *N*-(((1s,2R,3S)-2,3-di(naphthalen-1-yl)cyclopropyl)methyl)picolinamide (333b)**: The reaction was performed according to **Procedure L** on a 0.5 mmol scale, using 1-iodonaphthalene as the coupling partner and then purified via column chromatography over silica gel in 15-30% EtOAc/Hex to give **333a** and **333b** (67 mg, 44%, *trans*, as an inseparable 5:1 mixture of **333a:333b**), along with recovered **315** (46 mg, 52%).

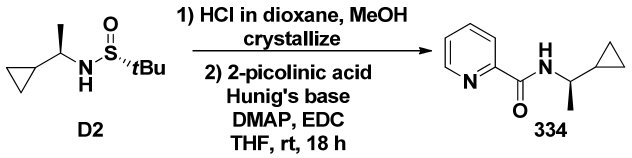
The reaction was performed according to **Procedure M** on a 0.5 mmol scale, using 1-iodonaphthalene as the coupling partner. After work-up, trimethoxybenzene was added and the $^1$H NMR yield determined: **333a** (19%) and unreacted **315** (80%).

Yellow oil, characterized as a 5:1 mixture of monoarylation and diarylation (*trans*).

**333a**: $^1$H NMR (CDCl$_3$, 500 MHz): δ 8.40-8.36 (m, 2H), 8.05 (d, 1H, *J* = 7.9 Hz), 7.88-7.86 (m, 1H), 7.78-7.75 (m, 2H), 7.70 (br. s, 1H), 7.54-7.48 (m, 1H), 7.43-7.40 (m, 1H), 7.37-7.34 (m, 2H), 3.18 (dt, 1H, *J* = 14.2, 7.0 Hz), 2.95-2.89 (m, 1H), 2.65-2.61 (m, 1H), 1.84-1.77 (m, 1H), 1.25 (td, 1H, *J* = 8.2, 5.3 Hz), 1.15-1.08 (q, 1H, *J* = 5.4 Hz) ppm. **333b**: $^1$H NMR (CDCl$_3$, 500 MHz): δ 8.51-8.50 (m, 1H), 8.13 (d, 1H, *J* = 7.7 Hz), 7.96 (br. s, 1H), 3.41-3.34 (m, 1H), 3.09-3.05 (m, 1H), 2.48-2.44 (m, 1H), 1.64-1.58 (m, 1H), 1.20-1.18 (m, 1H) ppm. **333a** + **333b**: $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 164.1, 164.0, 150.0, 148.1, 147.9, 137.4, 137.2, 135.9, 134.6, 133.8, 133.7, 132.4, 128.7, 128.1, 128.0, 127.7 (2), 127.4, 127.2, 126.4, 126.3, 126.1, 126.0, 125.8, 125.5, 124.4, 122.1, 39.6, 21.1, 19.2, 18.6, 18.3, 8.7, 8.3 ppm. FTIR (cm$^{-1}$) (neat): 3370, 2923, 2867, 1667, 1591, 1568, 1518, 1463, 1433, 1330, 1286, 1151, 1087, 1054. **333a**: HRMS (ESI, Pos) calcd for $C_{20}H_{19}N_2O$ [M+H]$^+$: 303.1492, found 303.1495 *m/z*. **333b**: HRMS (ESI, Pos) calcd for $C_{30}H_{25}N_2O$ [M+H]$^+$: 429.1967, found 429.2192 *m/z*.

*Synthesis of* **(*R*)-*N*-(1-cyclopropylethyl)picolinamide (334)**





Adapted from a literature procedure,[261] cyclopropanecarboxaldehyde (1.2 mL, 16 mmol, 2 equiv) was dissolved in 16 mL dry DCM under argon. To the stirring solution was added (*R*)-2-methylpropane-2-sulfinamide (Ellman's auxiliary) (970 mg, 8 mmol, 1 equiv), $Mg_2SO_4$ (9.86 g, 40 mmol, 5 equiv) and pyridinium *para*-toluenesulfonate (20 mg, 0.08 mmol, 1 mol %). The reaction was allowed to stir at room temperature overnight, then filtered over a pad of cotton and celite. The filtrate was concentrated and purified via flash chromatography over silica gel in 10-20% EtOAc/Hex, providing **D1** 866 mg (62%) clear oil, which corresponded to previously reported analytical data.[261]

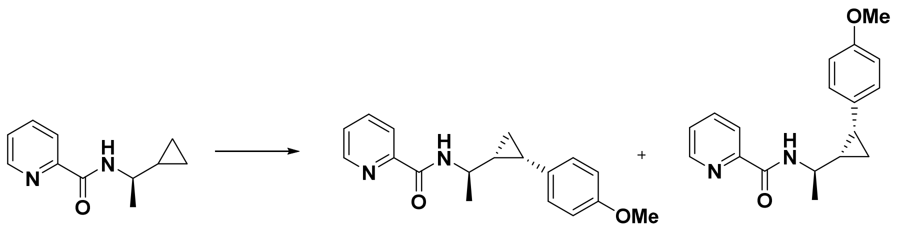
Adapted from a literature procedure,[261] a solution of **D1** (433 mg, 2.5 mmol, 1 equiv) in 15 mL dry DCM was cooled to -75 °C in a dry ice/acetone bath under Ar. Methylmagnesium chloride (3.12 M in THF, 1.9 mL, 6 mmol, 2.4 equiv) was added dropwise over 5 min. The reaction was allowed to warm up to -50 °C over 15 min, then stirred at this temperature for 6 h. The reaction was allowed to warm up to room temperature overnight, then quenched with sat. *aqueous* $NH_4Cl$ solution (10 mL), then transferred to a separatory funnel. The layers were separated and the *aqueous* layer was extracted with EtOAc (2x20 mL). The combined organic layers were washed with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. The residue was flashed in 40-80% EtOAc (product visible on TLC upon staining with $KMnO_4$). 448 mg (95%) clear oil **D2** were obtained, corresponding to previously reported analytical data.[261]

To a solution of **D2** (414 mg, 2.2 mmol, 1 equiv) in 1.5 mL freshly distilled methanol in a 10 mL round-bottom flask under Argon was added a solution of HCl in dioxane (1.09 mL of a 6.0 *M* solution, 3 equiv). The reaction was stirred at room temperature for 30 min, then concentrated. The resulting white solid was triturated with hexanes and dried under vacuum. The white solid (1.6 mmol) was taken and directly placed in a 100 mL dry round-bottom flask, to which dry THF (15 mL) was added. Diisopropylethylamine (0.86 mL, 4.8 mmol, 3 equiv) was added and the reaction was stirred for 5 min at room temperature. Then, the following reagents were added: 2-picolinic acid (302.8 mg, 2.46 mmol, 1.5 equiv), 4-dimethylaminopyridine (20.0 mg, 0.16 mmol, 0.1 equiv) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (381.9 mg, 22.46 mmol, 1.5 equiv). The reaction was stirred at room temperature for 16 h, then quenched with a solution of citric acid (10 mL, 0.8 *M*), transferred to a separatory funnel where EtOAc (30 mL) was added and the layers were separated. The organic layers was washed two more times with citric acid (10 mL), then saturated *aqueous* $NaHCO_3$ (10 mL), and brine (5 mL). The organic layer was dried ($Na_2SO_4$), filtered and concentrated. The residue was flashed in 20-30% EtOAc/Hex to give 171 mg (55%) of a white solid.

**334**: mp: 61-62 °C. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.51 (d, 1H, *J* = 4.7 Hz), 8.15 (dd, 1H, *J* = 7.8, 0.8 Hz), 8.01 (br. s, 1H), 7.79 (td, 1H, *J* = 7.7, 1.5 Hz), 7.37 (ddd, 1H, *J* = 7.5, 4.9, 1.0 Hz), 3.59-3.51 (m, 1H), 1.29 (d, 3H, *J* = 6.6 Hz), 0.96-0.89 (m, 1H), 0.52-0.48 (m, 1H), 0.43-0.41 (m, 1H), 0.39-0.35 (m, 1H), 0.27-0.22 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 163.5, 150.2, 148.0, 137.3, 126.0, 122.2, 49.7, 20.5, 17.5, 3.3, 3.1 ppm. FTIR ($cm^{-1}$) (neat): 3373, 2972, 2866, 1656, 1588, 1567, 1510, 1454, 1293, 1144, 1055, 1033. HRMS (ESI, Pos) calcd for $C_{11}H_{15}N_2O$ $[M+H]^+$: 191.1179, found 191.1182 *m/z*.

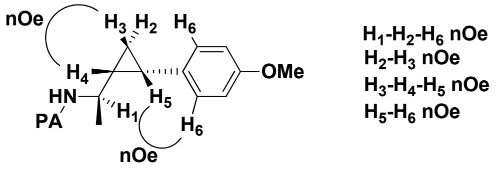
Compound **335** was synthesized in a similar matter as **334** and isolated in 53% yield for the last step. $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.49 (dd, 1H, *J* = 4.7, 0.5 Hz), 8.13 (dd, 1H, *J* = 7.8, 0.8 Hz), 7.76 (td, 1H, *J* = 7.7, 1.7 Hz), 7.34 (ddd, 1H, *J* = 7.5, 4.8, 1.2 Hz), 3.29 (td, 1H, *J* = 9.4, 5.8 Hz, 2.00-1.89 (m, 1H), 0.97 (dd, 6H, *J* = 6.8, 3.4 Hz), 0.93-0.83 (m, 1H), 0.56-0.49 (m, 1H), 0.38-0.30 (m, 1H) ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 163.7, 150.2, 148.0, 137.3, 126.0, 122.3, 59.0, 33.4, 19.4, 18.6, 14.0, 4.9, 2.2 ppm.

### *Synthesis of* ***N*****-((R)-1-((1R,2S)-2-(4-methoxyphenyl)cyclopropyl)ethyl)picolinamide (334a) and N-((R)-1-((1R,2R)-2-(4-methoxyphenyl)cyclopropyl)ethyl)picolinamide (334b)**



334 334a 334b

The reaction was performed according to **Procedure L** on a 0.2 mmol scale using **334** as the auxiliary and 4-iodoanisole as the coupling partner, and then purified via column chromatography over silica gel in 10-25% EtOAc/Hex. Obtained **334a** (42 mg, 71%, containing traces of diarylation) and **334b** (6 mg, 10%). The stereochemistry was determined via 1D nOe (it is difficult to know which diastereomer is which).

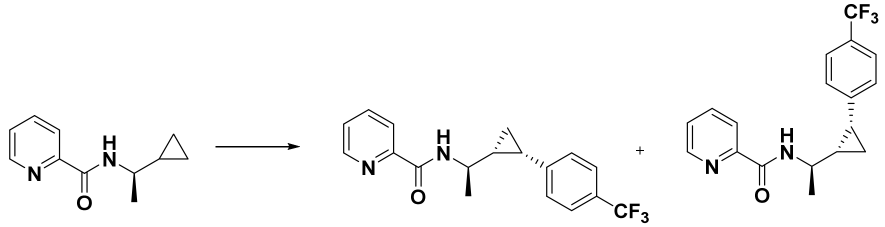


334a

**334a**: clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 8.56-8.52 (m, 1H), 8.04 (d, 1H, $J$ = 7.8 Hz), 7.86 (br. s, 1H), 7.79 (td, 1H, $J$ = 7.7, 1.7 Hz), 7.39 (ddd, 1H, $J$ = 7.6, 4.8, 1.2 Hz), 7.09 (d, 2H, $J$ = 8.4 Hz), 6.66-6.58 (m, 2H), 3.69 (s, 3H), 3.27-3.17 (m, 1H), 2.26-2.14 (m, 1H), 1.40-1.13 (m, 4H), 1.08 (td, 1H, $J$ = 8.6, 5.3 Hz), 0.86-0.80 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 163.0, 158.0, 150.3, 148.0, 137.3, 130.3, 129.7, 125.9, 122.1, 113.5, 55.3, 46.7, 24.3, 21.2, 20.7, 8.4 ppm. FTIR (cm$^{-1}$) (neat): 3680, 2967, 2866, 2844, 1670, 1611, 1590, 1510, 1463, 1290, 1178. HRMS (ESI, Pos) calcd for $C_{18}H_{21}N_2O_2$ [M+H]$^+$: 297.1598, found 297.1594 *m/z*.

**334b**: clear oil. $^1$H NMR (CDCl$_3$, 500 MHz): δ 8.56 (d, 1H, $J$ = 4.1 Hz), 8.18 (d, 1H, $J$ = 7.8 Hz), 8.08 (br d), 7.84 (td, 1H, $J$ = 7.7, 1.7 Hz), 7.41 (ddd, 1H, $J$ = 7.6, 4.8, 1.2 Hz), 7.21 (d, 2H, $J$ = 8.5 Hz), 6.86 (d, 2H, $J$ = 8.7 Hz), 3.8 (s, 3H), 3.48-3.38 (m, 1H), 2.27-2.18 (m, 1H), 1.27-1.20 (m, 1H), 1.18-1.12 (m, 1H), 1.10 (d, 3H, $J$ = 6.6 Hz), 0.97 (td, 1H, $J$ = 8.4, 5.4 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 163.5, 158.1, 150.4, 148.1, 137.5, 129.9, 129.8, 126.1, 122.4, 113.8, 55.4, 46.0, 26.1, 20.9 (2), 8.5 ppm. FTIR (cm$^{-1}$) (neat): 3680, 2972, 2844, 1669, 1569, 1455, 1433, 1033. HRMS (ESI, Pos) calcd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$: 297.1598, found 297.1595 *m/z*.

### *Synthesis of* ***N*-((R)-1-((1R,2S)-2-(4-(trifluoromethyl)phenyl)cyclopropyl)ethyl)picolinamide (334c)**



**334** **334c** **334d**

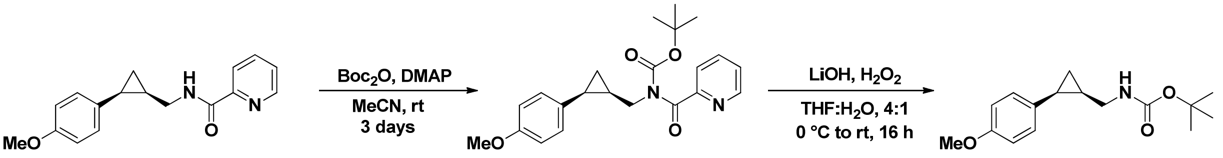
The reaction was performed according to **Procedure L** on a 0.2 mmol scale using **334** as the auxiliary and 4-iodobenzotrifluoride as the coupling partner, and then purified via column chromatography over silica gel in 10-50% EtOAc/Hex. Obtained **334c** and **334d** as an inseparable mixture (46 mg, 69%, 8:1). Traces of diarylation <3% also observed.

**334c**: white solid. mp 55-56 °C. $^1$H NMR ($CDCl_3$, 500 MHz): δ 8.43 (ddd, 1H, *J* = 4.8, 1.6, 0.9 Hz), 7.89 (dt, 1H, *J* = 7.8, 1.0 Hz), 7.70 (dt, 1H, *J* =7.7, 1.7 Hz), 7.69 (br. s, 1H), 7.31 (ddd, *J* = 7.5, 4.8, 1.2 Hz), 7.23 (d, 2H, *J* = 8.3 Hz), 7.18 (d, 2H, *J* = 8.3 Hz), 3.27-3.15 (m, 1H), 2.26-2.17 (m, 1H), 1.45-1.36 (m, 1H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.12 (td, 1H, *J* = 8.5, 5.6 Hz), 0.94-0.89 (m, 1H) ppm. $^{19}$F NMR ($CDCl_3$, 282 MHz): δ -63.8 ppm. $^{13}$C NMR ($CDCl_3$, 125 MHz): δ 162.8, 150.0, 147.9, 142.2, 137.4, 129.3, 129.0, 128.4 (q, $J_{C\text{-}F}$ = 32 Hz), 124.9 (q, $J_{C\text{-}F}$ = 3.5 Hz), 122.1, 46.5, 25.2, 21.4, 21.3, 9.0 ppm. FTIR ($cm^{-1}$) (neat): 3680, 2973, 2866, 1656, 1618, 1569, 1510, 1456, 1157. HRMS (ESI, Pos) calcd for $C_{18}H_{18}F_3N_2O$ $[M+H]^+$: 335.1366, found 335.1367 *m/z*.

*Reaction Scale Up*

To a 20 mL microwave vial (previously kept in an oven and cooled to room temperature under a stream of Argon) was added *N*-(pyridin-2-ylmethyl)cyclopropanecarboxamide (881.1 mg, 5 mmol, 1 equiv) and 4-iodoanisole (1.75 g, 7.5 mmol, 1.5 equiv). The vial was placed in a glove-box, where $Pd(OAc)_2$ (22.4 mg, 0.01 mmol, 0.02 equiv), sodium carbonate (159 mg, 1.5 mmol, 0.3 equiv), and silver phosphate (1.05 g, 2.5 mmol, 0.5 equiv) were added. The vial was crimped and taken out of the glove-box. Then, 10 mL dry toluene was added via syringe. The reaction was placed in an oil bath and stirred at 130 °C for 24 h. The reaction was allowed to cool to room temperature and filtered over a pad of silica and celite, rinsing with EtOAc (20 mL) and MeOH (5 mL). The filtrate was concentrated, then purified via flash chromatography in 15-30% EtOAc/Hex to provide 1.05 g **316** (74%), 110 mg **317** (6%), along with 148 mg **315** (17%).

*Auxiliary cleavage*



**316** **D3** **322**

Adapted from a literature procedure;[262] to a 10 mL round-bottom flask, previously flame-dried and cooled to room temperature under a stream of Ar, was added **316** (56.5 mg, 0.2 mmol, 1 equiv), 4-dimethylaminopyridine (4.9 mg, 0.04 mmol, 0.2 equiv), di-*tert*-butyl dicarbonate (87.3 mg, 0.4 mmol, 2 equiv) and dry acetonitrile (1.0 mL). The reaction was stirred for one day at room temperature. As the reaction was not complete, further 4-dimethylaminopyridine (4.9 mg, 0.04 mmol, 0.2 equiv) and di-*tert*-butyl dicarbonate (87.3 mg, 0.4 mmol, 2 equiv) were added for the next two days. The reaction was then concentrated in vacuo and flashed in 10% EtOAc/Hex to provide 25 mg (33%) desired product **D3**.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 8.59-8.52 (m, 1H), 7.78 (td, 1H, *J* = 7.7, 1.6 Hz), 7.63 (d, 1H, *J* = 7.9 Hz), 7.39-7.32 (m, 1H), 7.23 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.6 Hz), 3.83 (dd, 1H, *J* = 14.1, 4.1 Hz), 3.78 (s, 3H), 3.20 (dd, 1H, *J* = 14.1, 10.7 Hz), 2.21 (d, 1H, *J* = 6.4 Hz), 1.67-1.56 (m 1H), 1.17 (s, 9H), 1.14-1.06 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 125 MHz): δ 171.8, 158.1, 155.1, 153.6, 148.3, 136.8, 130.3, 130.1, 125.2, 122.7, 113.7, 82.9, 55.4, 46.3, 27.5, 20.0, 17.5, 9.3 ppm. FTIR (cm$^{-1}$) (neat): 2978, 2935, 1734, 1669, 1612, 1588, 1514, 1457, 1034. HRMS (ESI, Pos) calcd for $C_{22}H_{27}N_2O_4$ [M+H]$^+$: 383.1965, found 383.1949 *m/z*.

Adapted from a literature procedure;[262] to a 10 mL round-bottom flask, previously flame-dried and cooled under a stream of Ar, was added **D3** (25 mg, 0.065 mmol, 1 equiv) as a solution in 0.8 mL THF, followed by 0.2 mL distilled $H_2O$. The solution was cooled in an ice/water bath, then lithium hydroxide monohydrate (8.3 mg, 0.2 mmol, 3 equiv) and 30% $H_2O_2$ (37.1 mg, 0.33 mmol, 5 equiv) were added. The reaction was allowed to warm up to room temperature, then stirred at this temperature for 16 h. The reaction was quenched by the addition of a solution of saturated *aqueous* $Na_2SO_3$ (5 mL) and extracted with EtOAc (3x10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. The residue was purified by flash chromatography in 10% EtOAc/Hex to provide 16.9 mg (93%) of a clear oil. **322**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.12 (d, 2H, *J* = 8.2 Hz), 6.82 (d, 2H, *J* = 8.7 Hz), 4.36 (br. s, 1H), 3.78 (s, 3H), 2.95 (ddd, 1H, *J* = 13.9, 6.9, 6.8), 2.78-2.69 (m, 1H), 2.15 (td, 1H, *J* = 8.5, 6.2 Hz), 1.40 (s, 9H), 1.35-1.26 (m, 1H), 0.97 (td, 1H, *J* = 8.4, 5.3 Hz), 0.73 (q, 1H, *J* = 5.6 Hz) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 158.2, 155.9, 130.2, 130.0, 113.9, 79.2, 55.4, 40.8, 28.5, 19.9, 18.4, 8.4 ppm. FTIR ($cm^{-1}$) (neat): 3357, 2976, 2930, 1701, 1456, 1391, 1246. HRMS (ESI, Pos) calcd for $C_{16}H_{23}NO_3$ $[M+Na]^+$: 300.1570, found 300.1559 *m/z*.

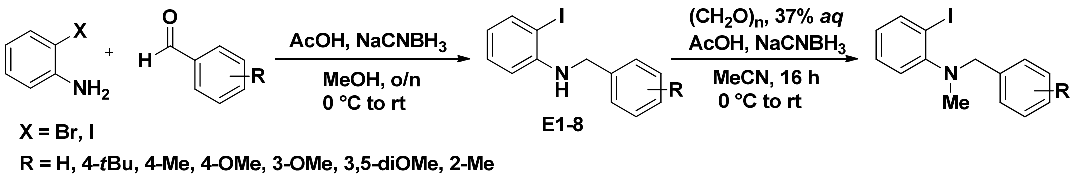
# Experimental section of chapter 5

*Aryl ether synthesis*

The aryl ether substrates **145** and **378** were prepared according to the literature procedure and **145** matches the literature data.[263]

**378**: Synthesized on a 2.27 mmol scale. Obtained **378** as a white solid (686 mg, 83%), mp: 64-66 °C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.82 (dd, 1H, *J* = 7.7, 1.6 Hz), 7.45 (d, 4H, *J* = 1.6 Hz), 7.32-7.29 (m, 2H), 6.90 (dd, 1H, *J* = 8.3, 1.3 Hz), 6.75 (td, 1H, *J* = 7.7, 1.3 Hz), 5.15 (s, 2H), 1.36 (s, 9H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 157.0, 150.4, 139.2, 133.1, 129.1, 126.5, 125.2, 122.3, 112.4, 86.5, 70.6, 34.3, 31.1 ppm. FTIR ($cm^{-1}$) (neat): 3060, 2961, 1471, 1275. HRMS (ESI Pos): expe. for $C_{17}H_{19}INaO$ $[M+Na]^+$: 389.0374, calc. 389.0373 *m/z*.

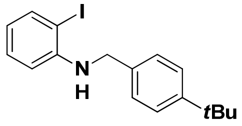
*Aryl amine synthesis*



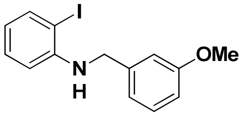
**Procedure N**: In a flame-dried 100 mL round bottom flask, 2-iodoaniline (1.0 equiv) and the corresponding aldehyde (1.5 equiv) were dissolved in 20 mL MeOH. Acetic acid (1.5 equiv) was added and the reaction was stirred at rt for 30 min. Then, the reaction was cooled down to 0 °C and sodium cyanoborohydride (1.3 equiv) was added in two portions over 30 min. The reaction was allowed to stir from 0 °C to rt overnight (or until complete by TLC). The reaction was quenched with a saturated *aqueous* solution of $NaHCO_3$ (30 mL) and then extracted with $Et_2O$ (3x30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The crude was flashed in 5% DCM/petroleum ether.

**Procedure O**: In a flame-dried 100 mL round bottom flask, **E1-8** (1.0 equiv) and 37% *aqueous* paraformaldehyde (10 equiv) were dissolved in 20 mL MeCN. Acetic acid (15 equiv) was added and the reaction was stirred at rt for 30 min. Then, the reaction was cooled down to 0 °C and sodium cyanoborohydride (1.3 equiv) was added in two portions over 30 min. The reaction was allowed to stir from 0 °C to rt overnight (or until complete by TLC). The reaction was quenched with a saturated *aqueuos* solution of $NaHCO_3$ (30 mL) and then extracted with $Et_2O$ (3x30 mL). The combined organic layers were dried with $Na_2SO_4$, filtered and the solvent was removed under reduced pressure. The crude was flashed in 5% DCM/petroleum ether to give the title compound.

For R = H,[264] 4-OMe,[265] 4-Me,[266] the intermediates **E1-2,4-5** matched the reported literature data. For R = H,[267] the methylated amine also matched the reported literature data.

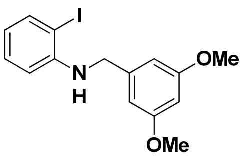


***N*-(4-tert-butylbenzyl)-2-iodoaniline** (**E3**): Synthesized according to **Procedure N** on a 2.28 mmol scale to give a white solid (624 mg, 75 %), mp: 81-83 °C. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.69 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.42-7.30 (m, 4H), 7.22-7.16 (m, 1H), 6.60 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.50-6.45 (m, 1H), 4.60 (br s, 1H), 4.37 (s, 2H), 1.35 (s, 9H) ppm. $^{13}C$ NMR ($CDCl_3$, 300 MHz): δ 151.4, 148.0, 140.2, 136.8, 130.3, 127.8, 126.7, 119.7, 111.6, 85.9, 49.0, 35.5, 32.2 ppm. FTIR ($cm^{-1}$) (neat): 3382, 2953, 1586, 1491, 1315, 1006. HRMS (ESI Pos): expe. for $C_{17}H_{21}IN$ $[M+H]^+$: 366.0709, calc. 366.0713 *m/z*.

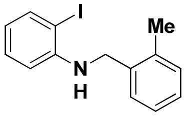


**2-iodo-*N*-(3-methoxybenzyl)aniline** (**E6**): Synthesized according to **Procedure N** on a 4.57 mmol scale to give a yellow oil (1.32 g, 85%). $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.68 (dd, 1H, *J*

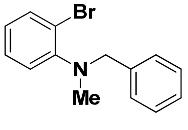
= 7.8, 1.4 Hz), 7.42-7.30 (t, 1H, *J* = 7.8 Hz), 7.16 (td, 1H, *J* = 8.3, 1.1 Hz), 6.95 (d, 1H, *J* = 8.2 Hz), 6.92 (s, 1H), 6.82 (dd, 1H, *J* = 8.2, 2.4 Hz), 6.54 (dd, 1H, *J* = 8.1, 1.3 Hz), 6.45 (td, 1H, *J* = 7.4, 1.4 Hz), 4.63 (br s, 1H), 4.38 (d, 2H, *J* = 5.6 Hz), 3.81 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 160.3, 147.4, 140.7, 139.3, 130.1, 129.7, 119.7, 119.2, 113.1, 113.0, 111.3, 85.6, 55.5, 48.6 ppm. FTIR (cm$^{-1}$) (neat): 3399, 2933, 1589, 1491, 1317, 1263, 743. HRMS (ESI Pos): expe. for $C_{14}H_{15}INO$ [M+H]$^+$: 340.0184, calc. 340.0193 *m/z*.



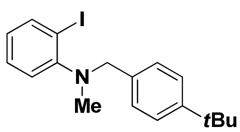
***N*-(3,5-dimethoxybenzyl)-2-iodoaniline** (**E7**): Synthesized according to **Procedure N** on a 2.28 mmol scale to give a white solid (651 mg, 77%). mp: 64-65 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.20 (t, 1H, *J* = 7.9 Hz), 6.58-6.55 (m, 3H), 6.49 (t, 1H, *J* = 7.8 Hz), 6.45-6.41 (m, 1H), 4.68 (br s, 1H), 4.37 (d, 2H, *J* = 6.3 Hz), 3.82 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 160.8, 146.7, 141.0, 138.7, 129.3, 118.6, 110.6, 104.7, 98.9, 85.0, 55.2, 48.2 ppm. FTIR (cm$^{-1}$) (neat): 3393, 2934, 1587, 1451, 1426, 1315, 1202, 1149. HRMS (ESI Pos): expe. for $C_{15}H_{17}INO_2$ [M+H]$^+$: 370.0297, calc. 370.0298 *m/z*.



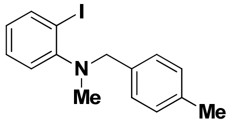
**2-iodo-*N*-(2-methylbenzyl)aniline** (**E8**): Synthesized according to **Procedure N** on a 2.28 mmol scale to give a white solid (469 mg, 64%). mp: 64-66 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71 (dd, 1H, *J* = 7.8, 1.4 Hz), 7.33 (d, 1H, *J* = 6.7 Hz), 7.25-7.19 (m, 4H), 6.58 (dd, 1H, *J* = 8.2, 1.0 Hz), 6.49 (td, 1H, *J* = 7.7, 1.4 Hz), 4.45 (bs, 1H), 4.33 (d, 2H, *J* = 5.3 Hz), 2.39 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 147.5, 139.3, 136.5, 130.8, 129.8, 128.1, 127.8, 126.6, 119.1, 111.1, 85.5, 46.9, 19.3 ppm. FTIR (cm$^{-1}$) (neat): 3398, 1588, 1501, 1315. HRMS (ESI Pos): expe. for $C_{14}H_{15}IN$ [M+H]$^+$: 324.0244, calc. 324.0244 *m/z*.



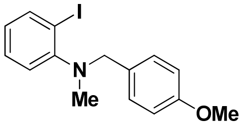
***N*-benzyl-2-bromo-*N*-methylaniline** (**E10**): Synthesized according to **Procedure O** to give a clear oil (95%). $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.60 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.45-7.41 (dm, 2H, *J* = 5.9 Hz), 7.36-7.31 (tm, 2H, *J* = 8.5 Hz), 7.28-7.23 (m, 2H), 7.09 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.92 (td, 2H, *J* = 7.3, 1.6 Hz), 4.19 (s, 2H), 2.67 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 151.3, 138.4, 134.0, 128.6, 128.4, 128.3, 128.1, 127.2, 124.4, 122.3, 120.2, 60.6, 40.6 ppm. FTIR (cm$^{-1}$) (neat): 2793, 1585, 1474, 1025, 753, 696. HRMS (ESI Pos): expe. for $C_{14}H_{15}BrN$ [M+H]$^+$: 276.0388, calc. 276.0382 *m/z*.



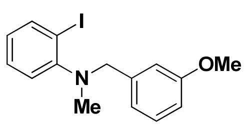
***N*-(4-tert-butylbenzyl)-2-iodo-*N*-methylaniline** (**380**): Synthesized according to **Procedure O** on a 1.37 mmol scale to give a white solid (480 mg, 92%). mp: 51-52 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.90 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.45-7.31 (m, 5H), 7.13 (dd, 1H, *J* = 8.0, 1.0 Hz), 6.81 (td, 1H, *J* = 7.8, 1.3 Hz), 4.10 (s, 2H), 2.63 (s, 3H), 1.35 (s, 9H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 155.3, 150.7, 140.8, 136.3, 129.9, 126.2, 125.9, 123.0, 99.4, 61.7, 42.4, 35.3, 32.3 ppm. FTIR (cm$^{-1}$) (neat): 2959, 1579, 1467, 1360, 1014. HRMS (ESI Pos): expe. for $C_{18}H_{23}IN$ [M+H]$^+$: 380.0870, calc. 380.0870 *m/z*.



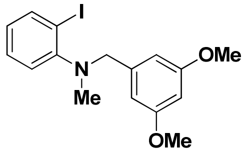
**2-iodo-*N*-methyl-*N*-(4-methylbenzyl)aniline** (**382**): Synthesized according to **Procedure O** on a 1.25 mmmol scale to give a white solid (332 mg, 80%). mp: 51-52 °C. $^{13}$H NMR (CDCl$_3$, 300 MHz): δ 7.90 (dd, 1H, *J* = 7.8, 1.5 Hz), 7.30-7.40 (m, 3H), 7.18-7.08 (m, 3H), 6.80 (td, 1H, *J* = 7.8, 1.6 Hz), 4.10 (s, 2H), 2.63 (s, 3H), 2.36 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75MHz): δ 155.0, 140.9, 137.5, 135.9, 129.8, 129.7, 129.5, 126.2, 123.1, 99.4, 61.7, 42.3, 22.0 ppm. FTIR (cm$^{-1}$) (neat): 2844, 1579, 1467, 1360, 1097. HRMS (ESI Pos): expe. for $C_{15}H_{17}N$ [M+H]$^+$: 338.0398, calc. 338.0400 *m/z*.



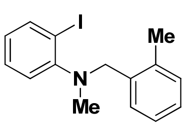
**2-iodo-*N*-(4-methoxybenzyl)-*N*-methylaniline** (**384**): Synthesized according to **Procedure O** on a 1.47 mmol scale to give a clear oil (451 mg, 87%). $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.89 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.41-7.37 (m, 2H), 7.35-7.29 (m, 1H), 7.10 (dd, 1H, *J* = 8.0, 1.5 Hz), 6.90-6.80 (m, 2H), 4.08 (s, 2H), 3.83 (s, 3H), (2.63 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 300 MHz): δ159.6, 154.9, 140.9, 131.0, 130.7, 129.8, 126.2, 123.2, 114.4, 99.5, 61.3, 56.1, 42.3 ppm. FTIR (cm$^{-1}$) (neat): 2920, 1609, 1569, 1457, 1219. HRMS (ESI, Pos): expe. for $C_{15}H_{17}NO$ [M+H]$^{+}$: 354.0351, found 354.0349 *m/z*.



**2-iodo-*N*-(3-methoxybenzyl)-*N*-methylaniline** (**386**): Synthesized according to **Procedure O** on a 0.59 mmol scale, to give a light yellow oil (205 mg, 95%). $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.89 (dd, 1H, *J* = 7.8, 1.4 Hz), 7.31 (td, 1H, *J* = 8.5, 1.4 Hz), 7.23 (t, 1H, *J* = 7.8 Hz), 7.11 (dd, 2H, *J* = 7.9, 1.4 Hz), 7.01 (d, 1H, *J* = 7.5 Hz), 6.83-6.79 (m, 2H), 4.11 (s, 2H), 3.81 (s, 3H), 2.64 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 160.0, 154.4, 140.4, 140.3, 129.4, 125.9, 122.7, 121.2, 114.1, 113.3, 99.0, 61.3, 55.6, 42.2 ppm. FTIR (cm$^{-1}$) (neat): 2832, 1600, 1583, 1466, 1258, 1044. HRMS (ESI Pos): expe. for $C_{15}H_{17}INO$ [M+H]$^{+}$: 354.0349, calc. 354.0350 *m/z*.

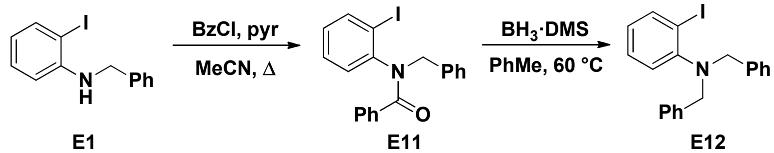


***N*-(3,5-dimethoxybenzyl)-2-iodo-*N*-methylaniline** (**388**): Synthesized according to **Procedure O** on a 1.25 mmol scale to give a clear oil (381 mg, 80%). $^{1}$H NMR ($CDCl_3$, 300 MHz): δ 7.91 (dd, 1H, *J* = 8.1, 1.5 Hz), 7.35-7.29 (m, 1H), 7.14 (dd, 1H, *J* = 8.1, 2.2 Hz), 6.82 (td, 1H, *J* = 7.5, 1.7 Hz), 6.70 (d, 2H, *J* = 2.2 Hz), 6.37-6.34 (m, 1H), 4.09 (s, 2H), 3.81 (s, 6H), 3.06 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 161.6, 154.8, 141.7, 140.9, 129.9, 126.4, 123.4, 107.1 100.1, 99.5, 61.8, 56.2, 42.9 ppm. FTIR (cm$^{-1}$) (neat): 2936, 1595, 1465, 1202, 1151. HRMS (ESI Pos): expe. for $C_{16}H_{19}INO_2$ [M+H]$^{+}$: 384.0454, calc. 384.0455 *m/z*.



**2-iodo-*N*-methyl-*N*-(2-methylbenzyl)aniline** (**400**): Synthesized according to **Procedure O** on a 0.93 mmol scale to give a clear oil (96%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.90 (dd, 1H, *J* = 7.9, 1.3 Hz), 7.57-7.54 (m, 1H), 7.36 (td, 1H, *J* = 7.3, 1.5 Hz), 7.23-7.19 (m, 4H), 6.83 (td, 1H, *J* = 7.8, 1.6 Hz), 4.14 (s, 2H), 2.67 (s, 3H), 2.36 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 155.0, 140.6, 137.3, 136.4, 130.6, 129.9, 129.4, 127.4, 126.0, 125.7, 122.4, 98.6, 58.7, 42.8, 19.8 ppm. FTIR (cm$^{-1}$) (neat): 2841, 1578, 1470, 1093. HRMS (ESI Pos): expe. for $C_{15}H_{17}IN$ $[M+H]^+$: 338.0403, calc. 338.0400 *m/z*.

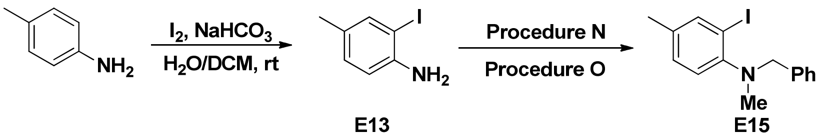
*Synthesis of* ***N*,*N*-dibenzyl-2-iodoaniline (E12)**



***N*-benzyl-*N*-(2-iodophenyl)benzamide** (**E11**): A solution of benzoyl chloride (3.9 mmol) in $CH_3CN$ (13 mL) was added to a suspension of **E1 (**3.2 mmol) and pyridine (9.7 mmol) in $CH_3CN$ (22 mL) at 0 °C dropwise. The mixture was warmed up to rt, and refluxed overnight and then cooled down to rt. The reaction mixture was diluted with $H_2O$, and extracted with EtOAc (3x15 mL). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The filtrate was concentrated, and purified by flash chromatography (10-15% EtOAc/Hex), affording a white solid in 84%. mp: 88-89 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.77 (d, 1H, *J* = 7.8 Hz), 7.37 (d, 1H, *J* = 7.3 Hz), 7.27 (s, 6H), 7.20 (t, 1H, *J* = 7.2 Hz), 7.13 (t, 1H, *J* = 7.2 Hz), 7.00 (t, 1H, *J* = 7.4 Hz), 6.83 (t, 1H, *J* = 7.3 Hz), 6.62 (d, 1H, *J* = 7.8 Hz), 5.82 (d, 1H, *J* = 14.2 Hz), 4.27 (d, 1H, *J* = 14.2 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 170.6, 144.8, 140.4, 137.1, 136.1, 132.4, 130.0, 129.8, 129.4, 128.9, 128.7, 128.5, 127.9, 127.8, 100.3, 52.7 ppm. FTIR (cm$^{-1}$) (neat): 3028, 1641, 1467, 1378, 1292, 696. HRMS (ESI Pos): expe. for $C_{20}H_{17}INO$ $[M+H]^+$: 414.0357, calc. 414.0349 *m/z*.

***N*,*N*-dibenzyl-2-iodoaniline** (**E12**): A $BH_3 \cdot DMS$ solution (6 mmol) was added to a solution of **E11** (1.9 mmol) in toluene (8 mL). The resulting mixture was heated at 60 °C overnight, and then cooled down to rt. The reaction was quenched by adding $H_2O$ at 0 °C, and stirred until the evolution of $H_2$ gas ceased. The mixture was extracted with DCM (3x10 mL), and the combined organic layers were washed with brine. After drying the organic layers with anhydrous $MgSO_4$, the crude was concentrated and purified by flash chromatography (5% EtOAc/Hex), affording a pale yellow oil in 87% yield. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.88 (d, 1H, *J* = 7.8 Hz), 7.35-7.16 (m, 11H), 6.88 (d, 1H, *J* = 8.0 Hz), 6.76 (t, 1H, *J* = 7.8 Hz), 4.14 (s, 4H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 151.9, 140.4, 138.1, 129.3, 128.8, 128.5, 127.4, 126.1, 124.9, 100.1, 57.4 ppm. FTIR (cm$^{-1}$) (neat): 3026, 2923, 1579, 1466, 719, 695. HRMS (ESI Pos): expe. for $C_{20}H_{19}IN$ $[M+H]^+$: 400.0567, calc. 400.0557 *m/z*.

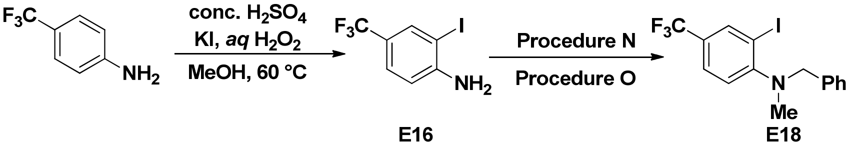
*Synthesis of* ***N*****-benzyl-2-iodo-*****N*****,4-dimethylaniline (E15)**



**2-Iodo-4-methylaniline** (**E13**): *p*-Toluidine (5 mmol), iodine (5 mmol) and $NaHCO_3$ (15 mmol) were dissolved in a mixture of DCM (20 mL) and $H_2O$ (10 mL), and stirred overnight at rt. The organic layer was separated and the aqueous layer was extracted with DCM (2x10 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous $MgSO_4$. The filtrate was concentrated and the crude mixture was purified by flash chromatography (5% EtOAc/Hex), affording a white solid in 79%. The observed characterization data ($^1$H and $^{13}$C) were consistent with the one previously reported in the literature.[268]

***N*****-benzyl-2-iodo-4-methylaniline (E14)**: Synthesized according to **Procedure N** to give a yellow oil in >95% yield. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, 1H, *J* = 1.3 Hz), 7.36-7.33 (m, 4H), 7.31-7.27 (m, 1H), 6.97 (d, 1H, *J* = 7.9 Hz), 6.45 (d, 1H, *J* = 8.2 Hz), 4.46 (br. s, 1H), 4.38 (d, 2H, *J* = 5.6 Hz), 2.21 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 145.2, 139.6, 139.2, 130.3, 129.0, 128.6, 127.6, 127.5, 111.2, 85.7, 48.9, 20.1 ppm. FTIR (cm$^{-1}$) (neat): 3402, 2918, 1603, 1508, 1026, 695. HRMS (ESI Pos): expe. for $C_{14}H_{15}IN$ $[M+H]^+$: 324.0244, calc. 324.0244 *m/z*.

***N*-benzyl-2-iodo-*N*,4-dimethylaniline (E15)** : Synthesized according to **Procedure O** to give a pale yellow oil (>95%). $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 7.72 (s, 1H), 7.47 (d, 2H, *J* = 7.3 Hz), 7.33 (t, 2H, *J* = 7.3 Hz), 7.26 (t, 1H, *J* = 7.3 Hz), 7.11 (d, 1H, *J* = 8.0 Hz), 7.00 (d, 1H, *J* = 8.0 Hz), 4.08 (s, 2H), 2.59 (s, 3H), 2.27 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 151.9, 140.7, 138.7, 135.7, 130.1, 129.1, 128.5, 127.4, 122.2, 99.1, 61.7, 42.1, 20.5 ppm. FTIR (cm$^{-1}$) (neat): 3025, 2792, 1484, 1450, 1032, 696. HRMS (ESI Pos): expe. for $C_{15}H_{17}IN$ [M+H]$^+$: 338.0410, calc. 338.0400 *m/z*.

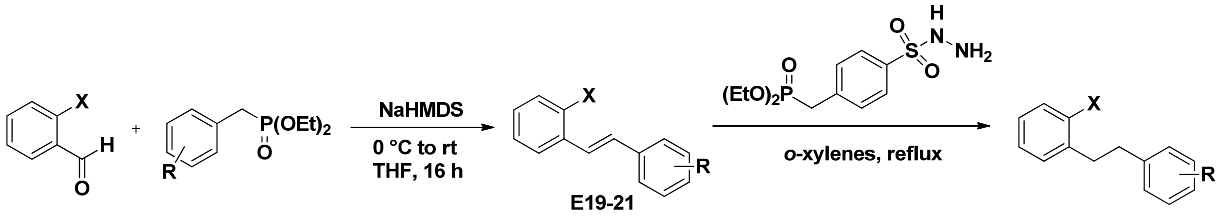


**2-Iodo-4-trifluoromethylaniline** (**E16**): Using a literature procedure,[269] the title intermediate **E16** was obtained as an orange solid in 72% yield. The observed characterization data ($^{1}$H and $^{13}$C) were consistent with the one previously reported in the literature.

***N*-benzyl-2-iodo-4-(trifluoromethyl)aniline** (**E17**): Synthesized according to **Procedure N** to give a yellow oil (25%). $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 7.90 (d, 1H, *J* = 1.4 Hz), 7.40-7.29 (m, 6H), 6.52 (d, 1H, *J* = 8.6 Hz), 4.99 (br s, 1H), 4.45 (d, 2H, *J* = 5.6 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 149.6, 137.9, 136.3, 129.1, 127.9, 127.3, 127.0, 125.3, 122.6, 120.7, 120.4, 109.9, 83.9, 48.3 ppm. FTIR (cm$^{-1}$) (neat): 3396, 3031, 1603, 1525, 1316, 729. HRMS (ESI Pos): expe. for $C_{14}H_{12}F_3IN$ [M+H]$^+$: 377.9962, calc. 377.9961 *m/z*.

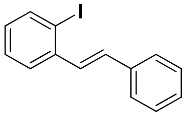
***N*-benzyl-2-iodo-*N*-methyl-4-(trifluoromethyl)aniline** (**E18**): Synthesized according to **Procedure O** to give a pale orange oil (83%). $^{1}$H NMR (CDCl$_3$, 400 MHz): δ 8.13 (d, 1H, *J* = 1.4 Hz), 7.55 (dd, 1H, *J* = 8.4, 1.4 Hz), 7.43 (dd, 2H, *J* = 8.3, 1.4 Hz), 7.35 (td, 2H, *J* = 7.0, 1.2 Hz), 7.31-7.27 (m, 1H), 7.10 (d, 1H, *J* = 8.4 Hz), 4.22 (s, 2H), 2.70 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 157.5, 137.7, 128.8, 128.7, 127.7, 127.1, 126.8, 126.3, 124.9, 122.2, 121.9, 119.5, 96.8, 60.8, 41.6 ppm. FTIR (cm$^{-1}$) (neat): 3029, 2802, 1601, 1320, 1121, 697. HRMS (ESI Pos): expe. for $C_{15}H_{14}F_3IN$ [M+H]$^+$: 392.0123, calc. 392.0118 *m/z*.

*Synthesis of carbon iodoarenes*

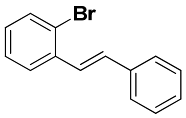


**Procedure P**: To a flame-dried 100 mL round-bottom flask was added NaHMDS (1 equiv) in a dry box. The flask was fitted with a septum and taken outside of the dry box. THF (20 mL) were added and the solution was cooled down to 0 °C. A solution of the corresponding phosphonate (1 equiv) in THF (2 mL) was added to the reaction dropwise. The reaction was stirred for a further 10 min at 0 °C, then a solution of the haloaldehyde (1 equiv) in THF (2 mL) was added to the reaction dropwise. The reaction was stirred from 0 °C to rt overnight (or until complete by TLC). The reaction was quenched with water (10 mL), and the *aqueous* layer was extracted with $Et_2O$ (3x25 mL). The combined organic layers were washed with 10% *aq* $NaHSO_3$ (2x10 mL) and brine (10 mL). The crude was purified by flash chromatography in 5% DCM/Pet. $Et_2O$ to give **E19-21** as a mixture of *E/Z* isomers.

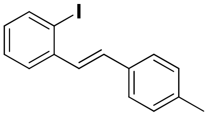
**Procedure Q**: **E19-20** (1 equiv) was dissolved in 2 mL *o*-xylenes. Hydrazide[270] (1 equiv) was added. The reaction was refluxed for 10 min, then an additional equivalent of hydrazide was added to the reaction every 15 min until complete reduction (usually a total of 4 equiv). The reaction was filtered through a pad of celite and purified by flash chromatography (2% EtOAc/Hex) to give the title compound.



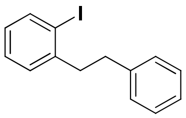
**(*E*)-1-iodo-2-styrylbenzene** (**E19**): Synthesized according to **Procedure P** on a 4.13 mmol scale, to give a white solid (957 mg, 76%, *E/Z* >10:1, mixture). mp: <50 °C (decomposition). *E* isomer: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.91 (dd, 1H, *J* = 7.9, 1.3 Hz), 7.65 (dd, 1H, *J* = 7.8, 1.3 Hz), 7.61-7.58 (m, 2H), 7.44-7.31 (m, 5H), 7.02-6.97 (m, 2H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 140.0, 139.3, 136.6, 132.1, 131.3, 128.7, 128.4, 128.1, 127.7, 126.5, 126.0, 99.9 ppm. FTIR ($cm^{-1}$) (neat): 2922, 1461, 1010, 957. HRMS (ESI Pos): expe. for $C_{14}H_{11}AgI$ $[M+Ag]^+$: 412.8949, calc. 412.8951 *m/z*.



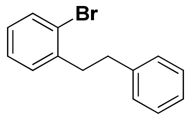
**(*E*)-1-bromo-2-styrylbenzene** (**E20** Synthesized according to **Procedure P** on a 5.4 mmol scale to give a clear oil (966 mg, 72%, *E/Z* >10:1, mixture). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71 (d, 1H, *J* = 8.0 Hz), 7.64-7.59 (m, 3H), 7.52 (d, 1H, *J* = 16.2 Hz), 7.43 (t, 2H, *J* = 7.6 Hz), 7.37-7.32 (m, 2H), 7.18-7.14 (m, 1H), 7.08 (d, 1H, *J* = 16.2 Hz) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.0, 137.9, 133.9, 132.3, 129.7, 129.6, 128.9, 128.3, 127.7, 127.6, 125.0 ppm. FTIR (cm$^{-1}$) (neat): 3057, 1585, 1464, 1022, 957. HRMS (ESI Pos): expe. for $C_{14}H_{11}AgBr$ [M+Ag]$^+$: 364.9094, calc. 364.9090 *m/z*.



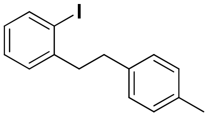
**(*E*)-1-iodo-2-(4-methylstyryl)benzene** (**E21**): Synthesized according to **Procedure P** on a 4.3 mmol scale to give a clear oil (688 mg, 50%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.87 (dd, 1H, *J* = 7.8, 1.1 Hz), 7.62 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.46 (dd, 1H, *J* = 7.9 Hz), 7.37-7.30 (m, 1H), 7.27-7.25 (m, 1H), 7.20 (d, 2H, *J* = 8.3 Hz), 7.00-6.93 (m, 2H), 2.39 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 141.4, 140.5, 138.9, 135.0, 132.4, 132.3, 130.3, 129.6, 129.2, 127.6, 127.0, 101.2, 22.1 ppm. FTIR (cm$^{-1}$) (neat): 2921, 1514, 1464, 1011. HRMS (ESI Pos): expe. for $C_{15}H_{13}AgI$ [M+Ag]$^+$: 426.9101, calc. 426.9107 *m/z*.



**1-iodo-2-phenethylbenzene** (**E22**): Synthesized according to **Procedure Q** on a 1.5 mmol scale to give a clear oil (355 mg, 70%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.88 (d, 1H, *J* = 7.8 Hz), 7.38-7.21 (m, 7H), 6.94 (t, 1H, *J* = 7.4 Hz), 3.08-3.04 (m, 2H), 2.95-2.91 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 143.9, 141.0, 139.2, 129.3, 128.2, 128.1, 127.6, 125.8, 100.2, 42.8, 36.0 ppm. FTIR (cm$^{-1}$) (neat): 2925, 1561, 1453, 1009. HRMS (ESI Pos): expe. for $C_{14}H_{13}AgI$ [M+Ag]$^+$: 414.9121, calc. 414.9107 *m/z*.



**1-bromo-2-phenethylbenzene** (**E23**): Synthesized according to **Procedure Q** on a 1.5 mmol scale to give a clear oil (322 mg, 82%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.59 (dd, 1H, *J* = 8.0, 1.0 Hz), 7.36-7.19 (m, 7H), 7.11 (td, 1H, *J* = 8.0, 2.0 Hz), 3.09-3.05 (m, 2H), 2.97-2.93 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 142.3, 141.8, 131.3, 129.3, 129.2, 128.6, 128.3, 126.9, 125.3, 39.3, 37.1 ppm. FTIR (cm$^{-1}$) (neat): 3025, 1602, 1470, 1024. HRMS (ESI Pos): expe. for $C_{14}H_{13}AgBr$ [M+Ag]$^+$: 366.9254, calc. 366.9246 *m/z*.



**1-iodo-2-(4-methylphenethyl)benzene** (**392**): Synthesized according to **Procedure Q** on a 1.25 mmol scale to give a clear oil (314 mg, 78%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.88 (dd, 1H, *J* = 8.0, 1.2 Hz), 7.31 (td, 1H, *J* = 7.5, 1.5 Hz), 7.24-7.16 (m, 5H), 6.94 (td, 1H, *J* = 7.6, 1.7 Hz), 3.07-3.02 (m, 2H), 2.92-2.88 (m, 2H), 2.39 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 144.0, 139.2, 138.0, 135.2, 129.2, 128.8, 128.0, 127.5, 100.2, 42.8, 35.7, 20.7 ppm. FTIR (cm$^{-1}$) (neat): 2921, 1514, 1464, 1443, 1010. HRMS (ESI Pos): expe. for $C_{15}H_{15}AgI$ [M+Ag]$^+$: 428.9267, calc. 428.9264 *m/z*.

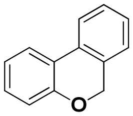
The amide substrates were prepared according to the literature procedure and matched the reported spectra.[271,89a]

*KOtBu-promoted intramolecular arylation*

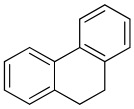
**Procedure R**: A microwave vial was charged with a stir bar and freshly sublimed KO*t*Bu (1 mmol, 2 equiv) in a glove box. The vial was crimped and taken out of the glove box. A solution of the starting material (0.5 mmol, 1 equiv) in freshly distilled pyridine (3.7 mL, 0.13 M) was added to the vial via syringe under a positive pressure of Ar. The reaction was stirred at rt for 1 min, then heated in a microwave at 160 °C for 10 min. The reaction mixture was filtered on a pad of silica and celite, rinsing with EtOAc (20 mL). The solvent was removed *in* *vacuo*, and the crude was purified by flash chromatography in 1-2% $Et_2O$/Pet. ether. The product was occasionally recovered with a small impurity of reduced starting material.

**Procedure S**: A microwave vial was charged with a stir bar, phenanthroline (0.05 mmol, 0.1 equiv), and freshly sublimed KO*t*Bu (1 mmol, 2 equiv) in a glove box. The vial was crimped and taken out of the glove box. A solution of the starting material (0.5 mmol, 1 equiv) in freshly distilled pyridine (3.7 mL, 0.13 M) was added to the vial via syringe under a positive pressure of Ar. The reaction was stirred at rt for 1 min, then heated in a microwave at 160 °C for 10 min. The reaction mixture was filtered on a pad of silica and celite, rinsing with EtOAc (20 mL). The solvent was removed *in vacuo*, and the crude was purified by flash chromatography in 1-2% $Et_2O$/Pet. ether. The product was occasionally recovered with a small impurity of reduced starting material.

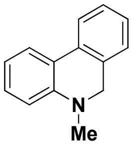
The phenanthridine products had a high propensity to oxidize at room temperature,[210b] but were stable at –20 °C for several weeks.



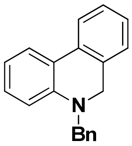
**6*H*-benzo[*c*]chromene (152)**: Synthesized according to **Procedure R** to give a clear oil (72 mg, 79%, for X = I, along with 2% **368**). Matches reported literature data.[272] Synthesized according to **Procedure S** to give a clear oil (68 mg, 75%, for X = Br, along with 2% **368**).



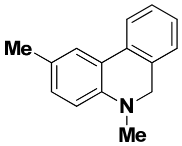
**9,10-dihydrophenanthrene (373)**: Synthesized according to **Procedure R** to give a clear oil (X = I, 80 mg, 89%). Synthesized according to **Procedure S** to give a clear oil (X = Br, 63 mg, 71%). Matches reported data.[273]



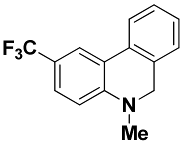
**5-methyl-5,6-dihydrophenanthridine** (**375**): Synthesized according to **Procedure R** to give a clear oil (80 mg, 82% for X = I). Synthesized according to **Procedure S** to give a clear oil (62 mg, 64% for X = Br). Matches reported data.[274]



**5-benzyl-5,6-dihydrophenanthridine** (**374**): Synthesized according to **Procedure R** to give a yellow oil (88 mg, 65%).$^1$H NMR (CDCl$_3$, 400 MHz): δ 7.82 (t, 1H, *J* = 6.4 Hz), 7.42-7.21 (m, 8H), 7.10 (d, 1H, *J* = 7.4 Hz), 6.87 (t, 1H, *J* = 7.3 Hz), 6.83 (d, 1H, *J* = 8.1 Hz), 4.56 (s, 2H), 4.36 (s, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 147.2, 138.6, 133.8, 133.0, 129.9, 129.5, 128.5, 127.9, 127.8, 126.4, 124.5, 124.0, 123.3, 119.2, 113.9, 55.7, 53.4 ppm. FTIR (cm$^{-1}$) (neat): 3027, 1649, 1603, 1493, 1442, 1286. HRMS (ESI Pos): expe. for $C_{20}H_{18}N$ [M+H]$^+$: 272.1431, calc. 272.1434 *m/z*.

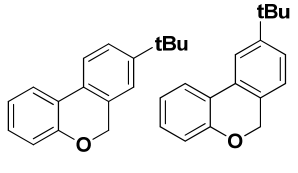


**2,5-dimethyl-5,6-dihydrophenanthridine (376)**: Synthesized according to **Procedure R** to give a yellow oil in 64% yield, along with traces of dehalogenated arene. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.77 (d, 1H, *J* = 7.8 Hz), 7.60 (s, 1H), 7.36 (t, 1H, *J* = 7.4 Hz), 7.26 (t, 1H, *J* = 7.3 Hz), 7.18 (d, 1H, *J* = 7.4 Hz), 7.11 (d, 1H, *J* = 8.2 Hz), 6.72 (d, 1H, *J* = 8.2 Hz), 4.17 (s, 2H), 2.94 (s, 3H), 2.40 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 145.4, 133.8, 132.5, 129.9, 128.0, 127.9, 127.2, 125.9, 124.5, 123.7, 122.7, 112.7, 55.6, 39.0, 21.0 ppm. FTIR (cm$^{-1}$) (neat): 3027, 2788, 1504, 1446, 1283, 1203. HRMS (ESI Pos): expe. for $C_{15}H_{16}N$ [M+H]$^+$: 210.1279, calc. 210.1277 *m/z*.

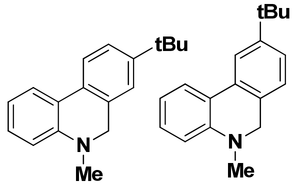


**5-methyl-2-(trifluoromethyl)-5,6-dihydrophenanthridine (377)**: Synthesized according to **Procedure R** to give a yellow oil in 31% yield (41 mg), along with dehalogenated arene

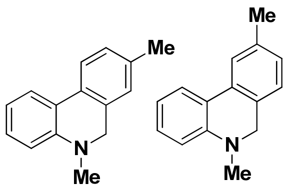
(~13%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.91 (d, 1H, *J* = 1.6 Hz), 7.73 (d, 1H, *J* = 7.8 Hz), 7.44 (dd, 1H, *J* = 8.4, 1.5 Hz), 7.35 (q, 1H, *J* = 7.8 Hz), 7.27 (td, 1H, *J* = 7.4, 1.1 Hz), 7.13 (d, 1H, *J* = 7.4 Hz), 6.74 (d, 1H, *J* = 8.5 Hz), 4.31 (s, 2H), 2.97 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 149.7, 133.0, 131.3, 129.2, 128.4, 128.2, 126.8, 126.4, 126.2, 123.1, 123.0, 120.8, 112.2, 55.0, 38.9 ppm. FTIR (cm$^{-1}$) (neat): 2959, 1617, 1330, 1272, 1106, 815. HRMS (ESI Pos): expe. for $C_{15}H_{13}F_3N$ [M+H]$^+$: 264.1001, calc. 264.0995 *m/z*.



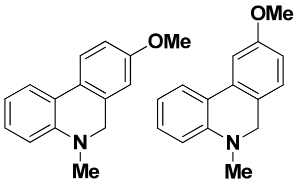
**8-*tert*-butyl-6*H*-benzo[*c*]chromene (379a) and 9-(*tert*-butyl)-6*H*-benzo[*c*]chromene (379b)**: Synthesized according to **Procedure S** to give a clear oil (108 mg, 91%) 5:1 mixture of inseparable regioisomers, along with 7% reduced starting material. **379a**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.75 (dd, 1H, *J* = 7.9, 1.6 Hz), 7.65 (d, 1H, *J* = 8.2 Hz), 7.43 (m, 1H), 7.24 (m, 1H), 7.19 (d, 1H, *J* = 1.5 Hz), 7.07 (td, 1H, *J* = 7.5, 1.2 Hz), 7.01 (dd, 1H, *J* = 8.0, 1.2 Hz), 5.15 (s, 2H), 1.38 (s, 9H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 155.5, 151.9, 132.0, 129.8, 128.2, 126.3, 123.9, 123.8, 122.9, 122.6, 122.4, 118.0, 69.7, 35.5, 32.2 ppm. FTIR (cm$^{-1}$) (neat): 2960, 1607, 1479, 1241. HRMS (ESI Pos): expe. for $C_{17}H_{19}O$ [M+H]$^+$: 239.1428, calc. 239.1430 *m/z*. Structure was assigned based on 1D nOe experiments.[275] **379b** (mass confirmed by GC-MS) could not be characterized. Structure was assigned based on proposed mechanism for *para* isomer.



**8-*tert*-butyl-5-methyl-5,6-dihydrophenanthridine (381a) and 8-*tert*-butyl-5-methyl-5,6-dihydrophenanthridine (381b)**: Synthesized according to **Procedure R** to give a yellow oil (107 mg, 86%) 10:1 inseparable mixture of isomers, with <2% reduced starting material). **381a**: $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.72-7.66 (m, 2H), 7.36 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.26-7.20 (m, 1H), 7.17 (d, 1H, *J* = 2.0 Hz), 6.87 (td, 1H, *J* = 7.7, 1.3 Hz), 6.75 (d, 1H, *J* = 8.3 Hz), 4.20 (s, 2H), 2.93 (s, 3H), 1.34 (s, 9H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 150.6, 147.5, 133.2, 129.8, 129.1, 125.1, 123.8, 123.0, 122.6, 119.0, 112.7, 112.6, 55.9, 39.1, 35.0, 31.8 ppm. FTIR (cm$^{-1}$) (neat): 2959, 1651, 1604, 1271, 1206. HRMS (ESI Pos): expe. for $C_{18}H_{22}N$ $[M+H]^+$: 252.1747, calc. 252.1747 *m/z*. Structure was assigned based on 1D nOe experiments.[275] **381b** (mass confirmed by GC-MS) could not be characterized. Structure was assigned based on proposed mechanism for *para* isomer.



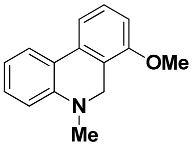
**5,8-dimethyl-5,6-dihydrophenanthridine (383a) and 5,9-dimethyl-5,6-dihydrophenanthridine (383b)**: Synthesized according to **Procedure R** to give a clear oil (107 mg, 82%, inseparable mixture of two isomers, >15:1). **383a**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.72 (dd, 1H, *J* = 7.8, 1.7 Hz), 7.65 (d, 1H, *J* = 8.0 Hz), 7.28-7.24 (m, 1H), 7.18-7.16 (m, 1H), 6.99 (s, 1H), 6.90 (td, 1H, *J* = 7.6, 1.4 Hz), 6.80-6.77 (m, 1H), 4.2 (s, 3H), 2.95 (s, 3H), 2.40 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 146.6, 136.5, 132.8, 129.0, 128.3, 125.9, 123.2, 122.9, 122.1, 118.2, 111.9, 54.5, 38.3, 20.9 ppm. FTIR (cm$^{-1}$) (neat): 1648, 1492, 1291, 1204. HRMS (ESI Pos): expe. for $C_{15}H_{16}N$ $[M+H]^+$: 210.1274, calc. 210.1273 *m/z*. Structure was assigned based on 1D nOe experiments.[275] **383b** (mass confirmed by GC-MS) could not be characterized. Structure was assigned based on proposed mechanism for *para* isomer.



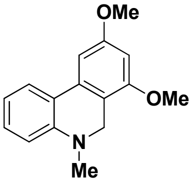
**8-methoxy-5-methyl-5,6-dihydrophenanthridine (385a) and 9-methoxy-5-methyl-5,6-dihydrophenanthridine (385b)**: Synthesized according to **Procedure R** to give white solids (93 mg, 83%, **385a**:**385b**, 10:1).

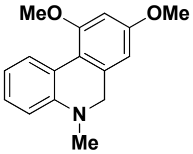
**385a**: mp: 78-80 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.69-7.65 (m, 2H), 7.22 (t, 1H, *J* = 7.7 Hz), 6.92-6.87 (m, 2H), 6.76 (d, 1H, *J* = 8.3 Hz), 6.71 (d, 1H, *J* = 2.3 Hz), 4.2 (s, 2H), 3.86 (s, 3H), 2.94 (s, 2H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 158.6, 146.0, 134.4, 127.8, 124.7, 123.5, 123.1, 122.4, 118.3, 113.1, 111.9, 110.5, 55.0, 54.9, 38.3 ppm. FTIR (cm$^{-1}$) (neat): 1611, 1493, 1291, 1035. HRMS (ESI Pos): expe. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1217, calc. 226.1226 *m/z*. Structure was assigned based on 1D nOe experiments.[275]

**385b**: mp: 57-58 °C. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.69 (dd, 1H, *J* = 7.8, 1.3 Hz), 7.27-7.23 (m, 2H), 7.07 (d, 1H, *J* = 8.4 Hz), 6.88 (t, 1H, *J* = 7.5 Hz), 6.82-6.75 (m, 2H), 4.15 (s, 2H), 3.88 (s, 3H), 2.94 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 160.2, 148.2, 134.1, 130.1, 127.5, 126.7, 124.4, 124.1, 119.3, 113.6, 113.2, 108.7, 56.2, 55.4, 39.5 ppm. FTIR (cm$^{-1}$) (neat): 1646, 1610, 1500, 1207, 1039. HRMS (ESI Pos): expe. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1223, calc. 226.1226 *m/z*. Structure was assigned based on comparison to literature spectra of oxidized **385b**.[276]



**7-methoxy-5-methyl-5,6-dihydrophenanthridine** (**387a**): Synthesized according to **Procedure R** to give a yellow oil in 67% yield (75 mg), along with dehalogenated arene. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.69 (dd, 1H, *J* = 7.7, 1.3 Hz), 7.36 (d, 1H, *J* = 7.8 Hz), 7.28 (t, 1H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 7.2 Hz), 6.86 (td, 1H, *J* = 7.5, 1.0 Hz), 6.80 (d, 1H, *J* = 8.1 Hz), 6.74 (d, 1H, *J* = 8.1 Hz), 4.29 (s, 2H), 3.87 (s, 3H), 2.94 (s, 3H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 155.2, 147.4, 133.6, 129.5, 128.2, 124.2, 123.4, 122.3, 119.3, 115.2, 112.7, 109.0, 55.8, 48.9, 38.9 ppm. FTIR (cm$^{-1}$) (neat): 2953, 1606, 1467, 1255. HRMS (ESI Pos): expe. for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1226, calc. 226.1226 *m/z*.

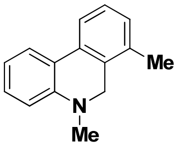




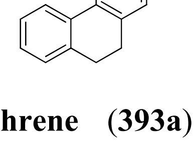
**7,9-dimethoxy-5-methyl-5,6-dihydrophenanthridine (389a) and 8,10-dimethoxy-5-methyl-5,6-dihydrophenanthridine (389b)**: Synthesized according to **Procedure R** to give a clear oil (78 mg, 62%, **389a**:**389b**, 7:1).

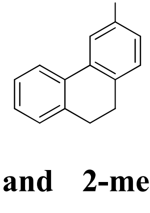
**389a**: mp: 61-62 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.67 (dd, 1H, *J* = 7.7, 1.5 Hz), 7.27-7.21 (m, 1H), 6.88-6.82 (m, 1H), 6.75 (d, 1H, *J* = 2.4 Hz), 4.22 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 2.94 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 160.8, 156.8, 148.2, 134.5, 130.1, 124.6, 123.9, 118.9, 115.7, 112.9, 99.4, 98.0, 56.3, 49.2, 39.4 ppm. FTIR (cm$^{-1}$) (neat): 1607, 1422, 1204. HRMS (ESI Pos): expe. for $C_{16}H_{18}NO_2$ [M+H]$^+$: 256.1327, calc. 256.1332 *m/z*.

**389b**: mp: 64-65 °C. $^1$H NMR (CDCl$_3$, 300 MHz): δ 8.31 (dd, 1H, *J* = 8.3, 1.5 Hz), 7.24-7.19 (m, 1H), 6.91 (t, 1H, *J* = 7.4 Hz), 6.79 (d, 1H, *J* = 7.7 Hz), 6.51 (d, 1H, *J* = 2.3 Hz), 6.37 (d, 1H, *J* = 2.3 Hz), 4.02 (s, 2H), 3.91 (s, 3H), 3.87 (s, 3H), 2.92 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 160.3, 158.9, 148.2, 138.5, 128.8, 128.2, 123.8, 119.5, 115.2, 112.9, 103.4, 99.3, 57.1, 56.5, 56.2, 39.7 ppm. FTIR (cm$^{-1}$) (neat): 1607, 1455, 1422, 1277. HRMS (ESI Pos): expe. for $C_{16}H_{18}NO_2$ [M+H]$^+$: 256.1328, calc. 256.1332 *m/z*. Structures assigned based on 1D nOe experiments.[275]



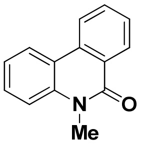
**5,10-dimethyl-5,6-dihydrophenanthridine** (**391a**): Synthesized according to **Procedure R** to give a clear oil (26 mg, 25%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.71 (dd, 1H, *J* = 7.8, 1.5 Hz), 7.31-7.16 (m, 2H), 7.09-7.05 (m, 1H), 6.95 (t, 1H, *J* = 7.6 Hz), 6.86 (d, 1H, *J* = 8.1 Hz), 3.99 (s, 2H), 2.94 (s, 3H), 2.66 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 149.1, 136.5, 133.8, 131.1, 128.0, 126.0, 124.6, 122.9, 117.8, 112.1, 56.2, 38.3, 22.9 ppm. FTIR (cm$^{-1}$) (neat): 2952, 1600, 1496, 1281, 1203. HRMS (ESI Pos): expe. for $C_{15}H_{16}N$ [M+H]$^+$: 210.1281, calc. 210.1277 *m/z*. Structure was assigned based on 1D nOe experiments of **391a** and oxidized **391a**.[275]





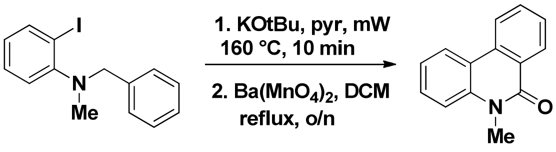
**3-methyl-9,10-dihydrophenanthrene** (**393a**) and **2-methyl-9,10-dihydrophenanthrene** (**393b**): Synthesized according to **Procedure R** to give a clear oil ( mg, 92%, **393a**:**393b**, 1:2.3, inseparable, with <5% reduced starting material). Mixture: $^1$H NMR (CDCl$_3$, 500

MHz): δ 7.81 (d, 1H, $J$ = 8.0 Hz, major), 7.78 (d, 1H, $J$ = 8.0 Hz, minor), 7.71 (d, 1H, $J$ = 8.0 Hz, minor), 7.64 (s, 1H, major), 7.38-7.34 (m, 1H, major; m, 1H, minor), 7.30-7.24 (m, 2H, major; m, 1H, minor), 7.19-7.16 (m, 1H, major; m, 2H, minor), 7.12-7.10 (m, 1H, major; m, 1H, minor), 2.96-2.88 (m, 4H, major; m, 4H, minor), 2.47 (s, 3H, major), 2.43 (s, 3H, minor) ppm. $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 137.2, 137.0, 136.8, 136.7, 136.0, 134.2, 134.1, 134.0, 131.4, 128.7, 128.5, 128.1, 128.0, 127.8, 17.7, 127.7, 127.6, 127.3, 126.9, 126.6, 126.5, 124.1, 123.3, 123.1, 28.9, 28.8, 28.7, 28.3, 21.1, 20.8 ppm. FTIR (cm$^{-1}$) (neat): 3025, 2930, 1491, 1448. HRMS (ESI Pos): expe. for $C_{15}H_{14}$ [M*+]: 194.1085, calc. 194.1090 *m/z*.



**5-methylphenanthridin-6(5*H*)-one (399):** Synthesized according to **Procedure S** to give a light brown solid (45 mg, 43%). Matches reported literature data.[277]

*Oxidation to phenanthridone*



399

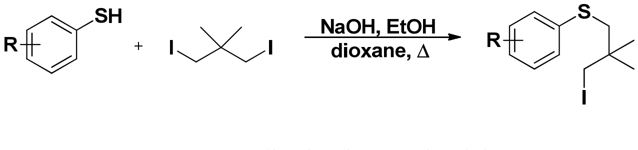
A microwave vial was charged with a stir bar and freshly sublimed KO*t*Bu (1 mmol, 2 equiv) in a dry box. The vial was capped and taken out of the dry box. A solution of *N*-benzyl-2-iodo-*N*-methylaniline (0.5 mmol, 1 equiv) in freshly distilled pyridine (3.7 mL, 0.13 M) was added to the vial via syringe under a positive pressure of Ar. The reaction was stirred at rt for 1 min, then heated in a microwave at 160 °C for 10 min. The reaction mixture was filtered on a pad of silica and celite, rinsing with EtOAc (20 mL). The solvent was removed *in vacuo*, and the crude dihydrophenanthridine **374** (1 equiv) was dissolved in DCM (0.1 *M*) in a microwave vial. $Ba(MnO_4)_2$ (5 equiv) was added, the vial was crimped and reaction was refluxed at 45 °C overnight (or until complete by TLC). The reaction was allowed to cool down to rt, and filtered through a celite cake. Purification by flash chromatography in 30-50% EtOAc/Hex provided 70 mg of the phenanthridone **399** (67% overall yield).

*Radical Scavenging Studies*

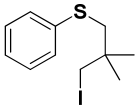
Using **Procedure R**, except that one equivalent of the corresponding radical inhibitor was added to the reaction as a solution in pyridine. Yields determined by $^1$H NMR using trimethoxybenzene as internal standard.

# Experiment section of Chapter 6

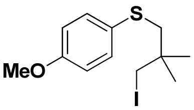
*Synthesis of phenylsulfanes*



**Procedure T**: To a flask charged with NaOH (1.0 equiv) in EtOH (0.5 mL/mmol NaOH) was added thiophenol (1.0 equiv) in one portion at rt. The reaction mixture was refluxed until dissolution of the NaOH. A solution of 1,3-diiodo-2,2-dimethylpropane[278] (4.0 equiv) in dioxane (0.17 mL/mmol 1,3-diiodo-2,2-dimethylpropane) was added in one portion and the yellow solution was refluxed for 16 h. The reaction was cooled to rt and then poured into ice water (20 mL). Et$_2$O (20 mL) was added and the layers were separated. The aqueous layer was extracted with Et$_2$O (2x20 mL). The combined organic layers were dried over MgSO$_4$, filtered, then concentrated *in vacuo*.

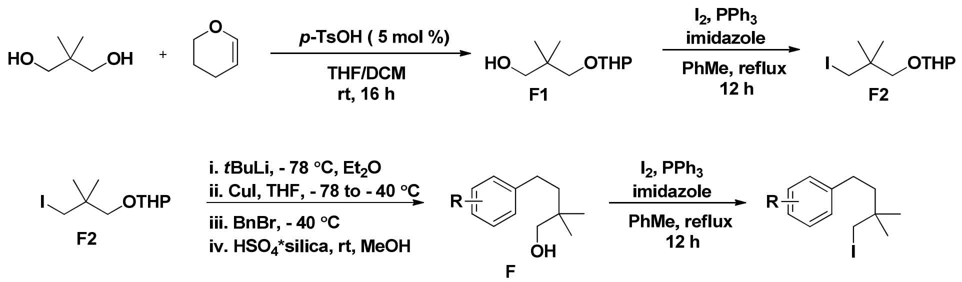


**(3-iodo-2,2-dimethylpropyl)(phenyl)sulfane (450):** Synthesized according to **Procedure T** on a 3 mmol scale. The crude product was purified by flash chromatography (2-3% EtOAc/Hex) affording the title compound (817 mg, 89%) as a pale yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.41-7.16 (m, 5H), 3.33 (s, 2H), 3.03 (s, 2H), 1.15 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 137.3, 129.8, 129.0, 126.3, 46.1, 35.5, 26.7, 22.2. IR (film) cm$^{-1}$ 2960, 1582, 1479, 1438, 1381, 1365, 1088, 1024. HRMS (ESI, Pos) calcd for $C_{11}H_{15}Ag_1I_1S_1$ [M+Ag]$^+$: 412.8985, found 412.8990 *m/z*.

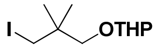


**(3-iodo-2,2-dimethylpropyl)(4-methoxyphenyl)sulfane (453)**: Synthesized according to **Procedure T** on a 4 mmol scale. The residue was purified by flash chromatography (2-3% EtOAc/Hex), affording the title compound (945 mg, 70%) as a clear oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 7.38 (d, 2H, $J$ = 8.8 Hz), 6.83 (d, 2H, $J$ = 8.8 Hz), 3.79 (s, 3H), 3.30 (s, 2H), 2.94 (s, 2H), 1.13 (s, 6H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 158.7, 133.6, 127.7, 114.5, 55.6, 48.5, 36.2, 26.7, 22.5. IR (film) cm$^{-1}$ 2958, 1592, 1492, 1461, 1283, 1240, 1172, 1030, 822, 639, 604, 522. HRMS (ESI, Pos) calcd for $C_{12}H_{17}I_1O_1S_1$ $[M]^+$: 336.0039, found 336.0038 *m/z*.

***Route 1***



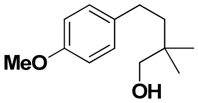
Mono-protected diol **F1** was synthesized according to the literature procedure and is in accordance to the given spectra.[279]



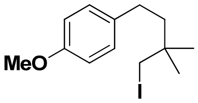
**2-(3-iodo-2,2-dimethylpropoxy)tetrahydro-2H-pyran (F2):** To a solution of **F1** (28.5 mmol, 1.0 equiv) in toluene (100 mL) was added $I_2$ (31.3 mmol, 1.1 equiv), $PPh_3$ (31.3 mmol, 1.1 equiv) and imidazole (113.8 mmol, 4.0 equiv). The reaction was stirred under reflux for 12 h (or until complete by TLC). The reaction was allowed to cool down to rt, then quenched with a saturated aqueous solution of $NaHSO_3$. The layers were separated, and the organic layer was concentrated. The resulting solid suspension was triturated several times with hexanes. The filtrate was concentrated and then purified by flash chromatography in 0-5% EtOAc/Hex, giving 6.26 g (74%) of a clear, colourless oil. $^1$H NMR ($CDCl_3$, 300 MHz): δ 4.56 (s, 1H), 3.86-3.78 (m, 1H), 3.54-3.45 (m, 2H), 3.21 (q, 2H, $J$ = 9.7 Hz), 3.09 (d, 1H, $J$ = 9.7 Hz), 1.82-1.46 (m, 6H), 1.04 (s, 3H), 0.99 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75 MHz): δ 98.9, 74.4, 61.9, 34.9, 30.5, 25.5, 24.5, 24.4, 20.7, 19.3. IR (film) cm$^{-1}$ 2939, 2869, 1473, 1379, 1350, 1200, 1121, 1063, 1032. HRMS (ESI, Pos) calcd for $C_{10}H_{19}Na_2O_2$ $[M+Na]^+$: 321.0322, found 321.0320 *m/z*.

**Procedure U**: To a solution of **F2** (6.9 mmol, 2.3 equiv) in $Et_2O$ (7.0 mL) in a flame-dried flask under Argon was cannulated *t*BuLi (1.5 *M* in pentane, 14.4 mmol, 4.8 equiv) at – 78 °C. The reaction was stirred at – 78 °C for 1 h, then allowed to warm up to rt in 5 min. The resulting organolithium was then cannulated to a suspension of CuI (3.6 mmol, 1.2 equiv) in THF (6 mL) at – 78 °C. The reaction was transferred to a cryostat bath at – 40 °C. After 30 min, the corresponding benzyl bromide (3.0 mmol, 1.0 equiv) was added dropwise (neat, or as a solution in THF if solid), and the reaction was stirred at – 40 °C for 16 h. The reaction was quenched with a saturated *aqueous* ammonium sulfate solution (20 mL), filtered, and extracted with ether (3x25 mL). The combined organic layers were washed with brine, dried with $Na_2SO_4$, and concentrated. The concentrate was dissolved in 6 mL MeOH, and 225 mg of $HSO_4$**.**silica was added. The reaction was stirred for 30 min at rt, then filtered and concentrated.

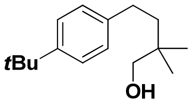
**Procedure V**: To a solution of the corresponding alcohol (1.0 equiv) in toluene was added $I_2$ (1.1 equiv), $PPh_3$ (1.1 equiv) and imidazole (4.0 equiv). The reaction was stirred under reflux for 12 h (or until complete by TLC). The reaction was allowed to cool down to rt, then quenched with a saturated *aqueous* solution of $NaHSO_3$. The layers were separated, and the organic layer was concentrated. The residue was purified by flash chromatography.



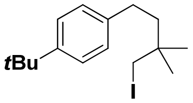
**4-(4-methoxyphenyl)-2,2-dimethylbutan-1-ol (F3):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (251 mg, 40%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.14–7.08 (m, 2H), 6.85–6.80 (m, 2H), 3.78 (s, 3H), 3.37 (s, 2H), 2.56–2.49 (m, 2H), 1.56–1.50 (m, 2H), 1.40 (br s, 1H), 0.95 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 157.7, 135.3, 129.2, 113.8, 71.8, 55.3, 41.2, 35.3, 29.6, 23.9 (2). IR (film) cm$^{-1}$ 3428, 2954, 1512, 1245, 1036. HRMS (ESI, Pos) calcd for $C_{13}H_{20}AgO_2$ $[M+Ag]^+$: 315.0509, found 315.0509 *m/z*.



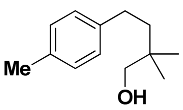
**1-(4-iodo-3,3-dimethylbutyl)-4-methoxybenzene (457):** Synthesized according to **Procedure V** on a 1.2 mmol scale. The residue was purified by flash chromatography (2% EtOAc/Hex), affording the title compound (282 mg, 74%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.18–7.10 (m, 2H), 6.90–6.82 (m, 2H), 3.81 (s, 3H), 3.24 (s, 2H), 2.55–2.47 (m, 2H), 1.67–1.60 (m, 2H), 1.12 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 157.8, 134.6, 129.3, 113.9, 55.4, 43.7, 33.6, 30.0, 26.8, 24.0. IR (film) cm$^{-1}$ 2956, 1612, 1510, 1463, 1243, 1176, 1035. HRMS (ESI, Pos) calcd for $C_{13}H_{19}NAgIO$ $[M+Ag]^+$: 424.9526, found 424.9515 *m/z*.



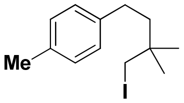
**4-(4-tert-butylphenyl)-2,2-dimethylbutan-1-ol (F4):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (241 mg, 35%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, 2H, *J* = 8.0 Hz), 7.21 (d, 2H, *J* = 8.0 Hz), 3.44 (s, 2H), 2.65-2.60 (m, 2H), 1.90 (br s, 1H), 1.66-1.62 (m, 2H), 1.39 (s, 9H), 1.03 (s, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 148.5, 140.2, 128.0, 125.3, 71.9, 40.9, 35.4, 34.4, 31.6, 30.0, 23.9. IR (film) cm$^{-1}$ 3355, 2955, 2867, 1109. HRMS (ESI Pos): calc. for $C_{16}H_{26}NaO$ $[M+Na]^+$: 257.1876, found 257.1872 *m/z*.



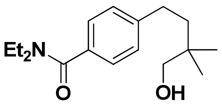
**1-tert-butyl-4-(4-iodo-3,3-dimethylbutyl)benzene (459):** Synthesized according to **Procedure V** on a 1 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (279 mg, 81%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.38 (d, 2H, *J* = 8.2 Hz), 7.20 (d, 2H, *J* = 8.2 Hz), 3.23 (s, 2H), 2.60-2.55 (m, 2H), 1.73-1.69 (m, 2H), 1.38 (s, 9H), 1.17 (s, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 148.7, 139.5, 128.1, 125.4, 43.4, 34.4, 33.7, 31.6, 30.4, 26.8, 24.0 ppm. IR (film) cm$^{-1}$ 2958, 1364, 1268. LRMS (CI, Pos) calcd for $C_{16}H_{26}I_1$ $[M+H]^+$ : 345.3 m/z, found 345.2 m/z.



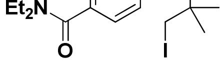
**2,2-dimethyl-4-p-tolylbutan-1-ol (F5):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (208 mg, 36%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.17 (s, 4H), 3.41 (s, 2H), 2.64-2.58 (m, 2H), 2.39 (s, 3H), 1.65-1.59 (m, 2H), 1.02 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 140.2, 135.0, 129.1, 128.2, 71.9, 41.2, 35.3, 30.1, 23.9, 21.1. IR (film) cm$^{-1}$ 2959, 1514, 1466, 807. LRMS (CI, Pos): calc. for $C_{13}H_{19}^{\bullet}$ [M-OH$^{\bullet}$]: 175.2 *m/z*, found 175.1 *m/z*.



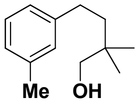
**1-(4-iodo-3,3-dimethylbutyl)-4-methylbenzene (461):** Synthesized according to **Procedure V** on a 1.1 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (243 mg, 75%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.15 (s, 4H), 3.26 (s, 2H), 2.57-2.53 (m, 2H), 2.38 (s, 3H), 1.70-1.65 (m, 2H), 1.15 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 139.5, 135.3, 129.2, 128.3, 43.6, 33.7, 30.5, 26.9, 24.0, 21.1. IR (film) cm$^{-1}$ 2959, 2861, 1514, 1466, 1383, 1365, 1207, 1162. LRMS (CI, Pos) calcd for $C_{13}H_{20}I_1$ [M+H]$^+$: 303.1, found 303.0 *m/z*.



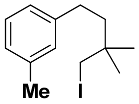
**N,N-diethyl-4-(4-hydroxy-3,3-dimethylbutyl)benzamide (F6):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (20-30% EtOAc/Hex), affording the title compound (371 mg, 45%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.27 (d, 2H, $J$ = 8.1 Hz), 7.20 (d, 2H, $J$ = 8.1 Hz), 3.53-3.27 (m, 4H), 3.34 (s, 2H), 2.60-2.56 (m, 2H), 2.16 (br s, 1H), 1.57-1.52 (m, 2H). 1.23-1.11 (m, 6H), 0.94 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 171.7, 144.6, 134.6, 128.4, 126.5, 71.6, 40.8, 35.4, 30.5, 25.8, 24.0, 14.3, 13.1 ppm. IR (film) cm$^{-1}$ 3407, 2937, 1608, 1460. HRMS (ESI Pos): expe. for $C_{17}H_{27}NNaO_2$ [M+Na]$^+$: 300.1938, calc. 300.1934 *m/z*.



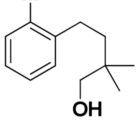
**N,N-diethyl-4-(4-iodo-3,3-dimethylbutyl)benzamide (465):** Synthesized according to **Procedure V** on a 1.3 mmol scale. The residue was purified by flash chromatography (10-20% EtOAc/Hex), affording the title compound (318 mg, 63%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.27 (d, 2H, *J* = 7.9 Hz), 7.20 (d, 2H, *J* = 7.9 Hz), 3.53-3.27 (m, 4H), 3.21 (s, 2H), 2.56-2.52 (m, 2H), 1.64-1.60 (m, 2H), 1.22-1.11 (m, 6H), 1.11 (s, 6H) ppm. $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 171.1, 143.9, 134.6, 128.2, 126.6, 43.4, 33.7, 31.1, 27.8, 23.5, 14.3, 12.9 ppm. IR (film) cm$^{-1}$ 2961, 1608, 1462, 1282, 1094. HRMS (ESI Pos): expe. for $C_{17}H_{26}INNaO$ $[M+Na]^+$: 410.0963, calc. 410.0951 *m/z.*



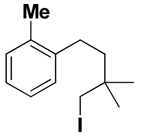
**2,2-dimethyl-4-m-tolylbutan-1-ol (F7):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (189 mg, 32%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.19 (t, 1H, *J* = 7.0 Hz), 7.04-7.01 (m, 3H), 3.39 (s, 2H), 2.59-2.54 (m, 2H), 2.36 (s, 3H), 1.67 (br s, 1H), 1.60-1.56 (m, 2H), 0.98 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 143.2, 137.9, 129.2, 128.3, 126.4, 125.4, 71.9, 41.1, 35.4, 30.6, 23.9, 21.5. IR (film) cm$^{-1}$ 3469, 2943, 2869, 1753, 1445, 1378, 1038, 1018. HRMS (ESI Pos): expe. for $C_{13}H_{19}$ $[M-H_2O]^+$: 175.1475, calc. 175.1481 *m/z.*



**1-(4-iodo-3,3-dimethylbutyl)-3-methylbenzene (469):** Synthesized according to **Procedure V** on a 0.96 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (190 mg, 62%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.25 (t, 1H, *J* = 7.5 Hz), 7.09-7.06 (m, 3H), 3.26 (s, 2H), 2.59-2.55 (m, 2H), 2.41 (s, 3H), 1.72-1.68 (m, 2H), 1.17 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 142.5, 138.1, 129.3, 128.4, 126.6, 125.5, 43.5, 33.7, 30.9, 26.8, 23.9, 21.5. IR (film) cm$^{-1}$ 2959, 1608, 1466, 1383, 1365, 1225, 1206. LRMS (CI, Pos) calcd for $C_{13}H_{20}I_1$ $[M+H]^+$: 303.1, found 303.0 *m/z*.

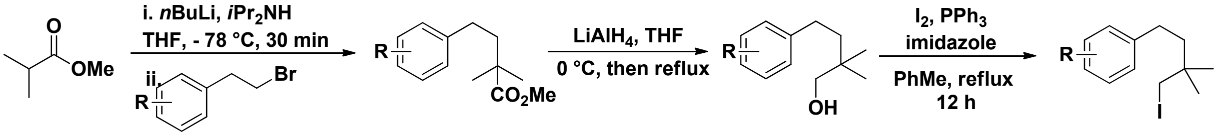


**2,2-dimethyl-4-o-tolylbutan-1-ol (F8):** Synthesized according to **Procedure U**. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (90 mg, 16%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.15-7.08 (m, 4H), 3.43 (s, 2H), 2.60-2.56 (m, 2H), 2.37 (s, 3H), 1.55 (br s, 1H), 1.55-1.48 (m, 2H), 1.04 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 141.4, 135.8, 130.3, 128.9, 126.2, 126.0, 72.0, 39.7, 35.5, 28.0, 23.8, 19.4 ppm. IR (film) cm$^{-1}$ 3457, 2942, 2868, 1732, 1363, 1125, 1105, 1017. HRMS (ESI Pos): expe. for $C_{13}H_{20}AgO$ [M+Ag]$^+$: 299.0556, calc. 299.0560 *m/z*.



**1-(4-iodo-3,3-dimethylbutyl)-2-methylbenzene (471):** Synthesized according to **Procedure V** on a 0.83 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (150 mg, 60%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.18-7.11 (m, 4H), 3.27 (s, 3H), 2.58-2.52 (m, 2H), 2.37 (s, 3H), 1.62-1.55 (m, 2H), 1.18 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 140.6, 135.8, 130.4, 129.0, 126.3, 126.1, 42.2, 33.8, 28.3, 26.8, 23.8, 19.4 ppm. IR (film) cm$^{-1}$ 2958, 2860, 1608, 1466, 1383, 1366, 1255, 1130. LRMS (CI, Pos) calcd for $C_{13}H_{20}I_1$ [M+H]$^+$: 303.1, found 303.0 *m/z*.

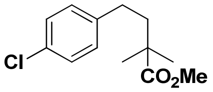
***Route 2***



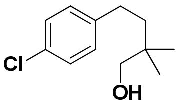
**Procedure W**: To a solution of *i*Pr$_2$NH (1.2 equiv) in THF (0.33 mL/mmol *i*Pr$_2$NH) at 0 °C was added *n*BuLi (2.5 *M* in hexanes, 1.25 equiv). The reaction was stirred for 15 min at 0 °C, then cooled down to - 78 °C. Then, the LDA solution was slowly cannulated to a solution of methyl isobutyrate (1.0 equiv) in THF (15 mL), previously cooled down to - 78 °C. The resulting reaction was stirred for 30 min, then the corresponding phenethyl bromide (1.2 equiv) was added dropwise. The reaction was stirred for another 15 min at - 78 °C, then allowed to warm up to rt overnight. The reaction was acidified with 2*M* HCl, extracted with

$Et_2O$ (3x30 mL). The combined organic layers were washed with brine, dried with $Na_2SO_4$, filtered and concentrated under vacuum.

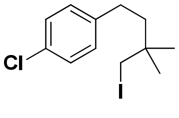
**Procedure X**: To a suspension of $LiAlH_4$ (2.0 equiv) in THF (12 mL) at 0 °C, a solution of the methyl ester (1.0 equiv), in THF (5 mL) was added dropwise. The reaction was fitted with a reflux condenser and refluxed for 2 h. The reaction was then cooled down to 0 °C, where water and 15% NaOH were added (*n* mL $H_2O$, *n* mL 15% NaOH, and *3n* mL $H_2O$, where *n* = grams of $LiAlH_4$ used). The mixture was filtered on a pad of celite, eluted with $Et_2O$, dried with $Na_2SO_4$, filtered and concentrated *in vacuo*.



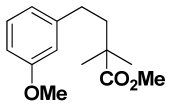
**methyl 4-(4-chlorophenyl)-2,2-dimethylbutanoate (F9):** Synthesized according to **Procedure W** on a 10 mmol scale. The residue was purified by flash chromatography (2-3% EtOAc/Hex), affording the title compound (84 mg, 88%) as a clear oil. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.23–7.16 (m, 2H), 7.11–7.02 (m, 2H), 3.65 (s, 3H), 2.54–2.43 (m, 2H), 1.83–1.73 (m, 2H), 1.23 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 177.8, 140.6, 131.4, 129.6, 128.3, 51.6, 42.4, 42.2, 30.8, 25.1 (2). IR (film) cm$^{-1}$ 2951, 1721, 1492, 1453, 1259, 1192, 1170, 1130, 1088, 1041, 811, 520. HRMS (ESI, Pos) calcd for $C_{13}H_{17}Cl_1Na_1O_2$ $[M+Na]^+$: 263.0809, found 263.0806 *m/z*.



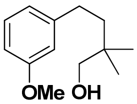
**4-(4-chlorophenyl)-2,2-dimethylbutan-1-ol (F10):** Synthesized according to **Procedure X** on a 2.5 mmol scale. The title compound (539 mg, quant.) was obtained as a clear oil. $^1H$ NMR ($CDCl_3$, 300 MHz): δ 7.14–7.06 (m, 2H), 7.02–6.94 (m, 2H), 3.22 (s, 2H), 2.46–2.37 (m, 2H), 2.33 (br s, 1H), 1.45–1.35 (m, 2H), 0.82 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 75 MHz): δ 141.6, 131.2, 129.7, 128.4, 71.6, 40.7, 35.2, 29.9, 23.8 (2). IR (film) cm$^{-1}$ 3322, 2954, 2865, 1572, 1492, 1304, 1260, 1159, 1093, 1015, 807. HRMS (ESI, Pos) calcd for $C_{12}H_{17}Cl_1Li_1O_1$ $[M+Li]^+$: 218.1114, found 218.1113 *m/z.*



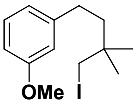
**1-chloro-4-(4-iodo-3,3-dimethylbutyl)benzene (463):** Synthesized according to **Procedure V** on a 2.5 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (699 mg, 87%) as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.16–7.08 (m, 2H), 7.04–6.97 (m, 2H), 3.08 (s, *2*H), 2.42–2.33 (m, 2H), 1.53–1.43 (m, 2H), 0.98 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 140.9, 131.5, 129.7, 128.5, 43.3, 33.5, 30.2, 26.7(2C), 23.6. IR (film) cm$^{-1}$ 2959, 2865, 1491, 1467, 1384, 1365, 1204, 1162, 1092, 1014, 805, 660, 607, 519. LRMS (EI) calcd for $C_{14}H_{19}Cl_1I_1$ [M]: 322.0, found 322.0 *m/z*.



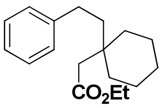
**methyl 4-(3-methoxyphenyl)-2,2-dimethylbutanoate (F11):** Synthesized according to **Procedure W** on a 1.2 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (219 mg, 77%) as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.27-7.18 (m, 1H), 6.80-6.74 (m, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 2.58-2.52 (m, 2H), 1.90-1.83 (m, 2H), 1.28 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 178.2, 159.8, 143.9, 129.4, 120.7, 114.2, 111.2, 55.1, 51.7, 42.7, 42.3, 31.6, 25.2. IR (film) cm$^{-1}$ 2950, 1730, 1602, 1489, 1455, 1262, 1193, 1151, 1128, 1046. HRMS (ESI, Pos) calcd for $C_{14}H_{20}Na_1O_3$ [M+Na]$^+$: 259.1305, found 259.1300 *m/z*.



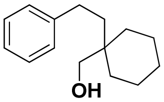
**4-(3-methoxyphenyl)-2,2-dimethylbutan-1-ol (F12):** Synthesized according to **Procedure X** on a 0.75 mmol scale. The title compound (158 mg, quant.) was obtained as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.23 (t, 1H, *J* = 7.9 Hz), 6.84-6.76 (m, 3H), 3.82 (s, 3H), 3.40 (s, 2H), 2.62-2.58 (m, 2H), 1.94 (br s, 1H), 1.62-1.58 (m, 2H), 1.00 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 159.8, 145.1, 129.5, 120.9, 114.1, 111.1, 71.8, 55.2, 40.8, 35.2, 30.7, 23.9. IR (film) cm$^{-1}$ 3373, 2950, 2871, 1601, 1585, 1489, 1455, 1259, 1152, 1048. HRMS (ESI, Pos) calcd for $C_{13}H_{20}Na_2O_2$ [M+Na]$^+$: 231.1356, found 231.1347 *m/z*.



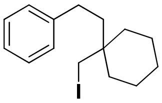
**1-(4-iodo-3,3-dimethylbutyl)-3-methoxybenzene (467):** Synthesized according to **Procedure V** on a 0.73 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (203 mg, 87%) as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.22 (t, 1H, $J$ = 7.8 Hz), 6.83-6.73 (m, 3H), 3.81 (s, 3H), 3.22 (s, 2H), 2.57-2.51 (m, 2H), 1.69-1.63 (m, 2H), 1.12 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 159.8, 144.2, 129.6, 120.8, 114.2, 111.1, 55.2, 43.3, 39.7, 31.0, 26.8, 23.6. IR (film) cm$^{-1}$ 2957, 1601, 1489, 1465, 1260, 1152, 1048. HRMS (ESI, Pos) calcd for $C_{13}H_{19}INaO$ [M+Na]$^+$: 341.0373, found 341.0364 *m/z*.



**ethyl 1-phenethylcyclohexanecarboxylate (F13):** Synthesized according to **Procedure W** on a 7.6 mmol scale. The residue was purified by flash chromatography (2-3% EtOAc/Hex), affording the title compound (1.34 g, 68%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.31-7.27 (m, 2H), 7.21-7.16 (m, 3H), 4.20 (q, 2H, $J$ = 7.2 Hz), 2.55-2.51 (m, 2H), 2.17-2.14 (m, 2H), 1.84-1.79 (m, 2H), 1.59-1.56 (m, 3H), 1.46-1.27 (m, 5H), 1.32 (t, 3H, $J$ = 7.2 Hz). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 176.1, 142.2, 128.2, 128.1, 126.6, 59.5, 46.7, 42.4, 34.1, 30.5, 25.8, 23.1, 14.2. IR (film) cm$^{-1}$ 2930, 2854, 1722, 1452, 1173, 1129, 1026. HRMS (ESI, Pos) calcd for $C_{17}H_{24}Na_1O_2$ [M+Na]$^+$: 283.1669, found 283.1659 *m/z*.

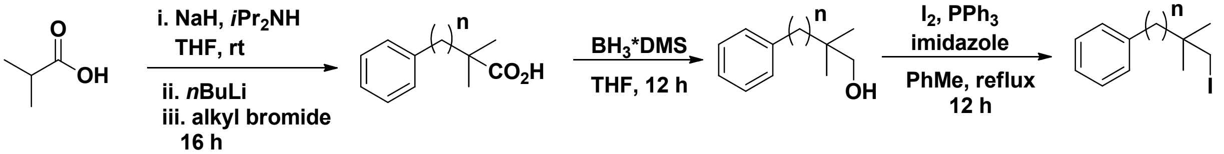


**(1-phenethylcyclohexyl)methanol (F14):** Synthesized according to **Procedure X** on a 5.0 mmol scale. The residue was purified by flash chromatography (5-20% EtOAc/Hex), affording the title compound (966 mg, 88%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.36-7.21 (m, 5H), 3.55 (s, 2H), 2.64-2.59 (m, 2H), 1.94 (br s, 1H), 1.75-1.63 (m, 2H), 1.55-1.45 (m, 10H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 143.5, 128.4 (2), 125.6, 68.4, 37.3, 37.0, 32.4, 29.7, 26.5, 21.6. IR (film) cm$^{-1}$ 3344, 2922, 2850, 1452, 1031. HRMS (ESI, Pos) calcd for $C_{15}H_{22}Na_1O_1$ [M+Na]$^+$: 241.1563, found 241.1565 *m/z*.



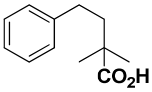
**(2-(1-(iodomethyl)cyclohexyl)ethyl)benzene (473):** Synthesized according to **Procedure V** on a 3.0 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (777 mg, 79%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.30-7.14 (m, 5H), 3.31 (s, 2H), 2.48-2.42 (m, 2H), 1.66-1.60 (m, 2H), 1.53-1.37 (m, 10 H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 142.5, 128.4 (2 C's), 125.8, 40.5, 35.1, 35.0, 29.3, 2621, 21.9, 21.8. IR (film) cm$^{-1}$ 2923, 2848, 1496, 1452, 1220, 1168. HRMS (ESI Pos): expe. for $C_{15}H_{21}Ag$ [M+Ag]$^+$: 434.9741, calc. 434.9733 *m/z*.

***Route 3***

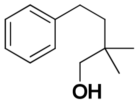


**Procedure Y**: To a solution of NaH (1.1 equiv) and *i*Pr$_2$NH (1.0 equiv) in THF (2.5 mL/mmol *i*Pr$_2$NH) was added dropwise isobutyric acid (1.0 equiv) at rt. The reaction was refluxed for 15 min, then cooled down to 0 °C. *n*BuLi (2.5 *M* in hexanes, 1.0 equiv) was added dropwise. The reaction was stirred at 0 °C for 20 min, then at 35 °C for 30 min. The reaction was cooled down to 0 °C, and the alkyl bromide (1.0 equiv) was added dropwise. The reaction was stirred at 0 °C for 30 min, then at 35 °C for 1 h. Then, the reaction was cooled to 0 °C and quenched slowly with water (20 mL). The layers were separated. The organic layer was washed with water (20 mL). The combined organic layers were extracted with 20 mL Et$_2$O. The combined aqueous layers were acidified with 2 *M* HCl, then back-extracted with 2x30 mL Et$_2$O. The combined organic layers from the back-extraction were washed with brine, dried with Na$_2$SO$_4$, filtered and concentrated *in vacuo*.

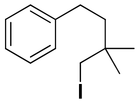
**Procedure Z**: To a solution of the carboxylic acid (1.0 equiv) in THF (0.23 mL/mmol carboxylic acid) at 0 °C was added dropwise a solution of BH$_3$•DMS (1.5 equiv) in THF (0.48 mL/mmol BH$_3$•DMS). The reaction was stirred at 0 °C for 1 h, then allowed to warm up to rt overnight (or when complete by TLC). The reaction was cooled down to 0 °C, then quenched slowly with water (20 mL). The reaction was extracted with DCM 3x20 mL. The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated *in vacuo*.



**2,2-dimethyl-4-phenylbutanoic acid (F15):** Synthesized according to **Procedure Y** on a 55 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (7.43 g, 71%) as a white solid. mp: 80-83 °C. $^1$H NMR (CDCl$_3$, 400 MHz): δ 12.05 (br s, 1H), 7.35-7.31 (m, 2H), 7.25-7.21 (m, 3H), 2.69-2.65 (m 2H), 1.95-1.91 (m, 2H), 1.34 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 185.1, 142.4, 128.5 (2 C's), 125.0, 42.6, 42.4, 31.6, 25.1. IR (film) cm$^{-1}$ 2973, 2933, 1698, 1473, 1236, 1203, 935, 744, 698, 546, 501. HRMS (ESI, Pos) calcd for $C_{13}H_{18}Na_1O_2$ [M+Na]$^+$: 215.1043, found 215.1041 *m/z*.

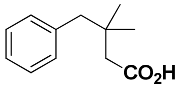


**2,2-dimethyl-4-phenylbutan-1-ol (F16):** Synthesized according to **Procedure Z** on a 35 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (4.62 g, 74%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.34-7.29 (m, 2H), 7.25-7.20 (m, 3H), 3.42 (s, 2H), 2.65-2.60 (m, 2H), 1.64 (br s, 1H), 1.63-1.59 (m, 2H), 1.01 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 143.3, 128.5, 128.4, 125.8, 71.9, 41.0, 35.4, 30.6, 24.5, 23.9. IR (film) cm$^{-1}$ 3353, 2952, 2868, 1496, 1454, 1415, 1382, 1337, 1047, 736, 697. HRMS (ESI, Pos) calcd for $C_{12}H_{18}Li_1O_1$ [M+Li]$^+$: 184.1503, found 184.1503 *m/z*.

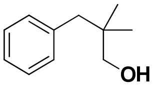


**(4-iodo-3,3-dimethylbutyl)benzene (455):** Pyridine (10 mL) was cooled in an ice/salt bath and *p*-TsCl (4.82 g, 23.0 mmol) was added as a solid portionwise. A solution of **F16** in pyridine (10 mL) was added and the reaction was allowed to warm to rt. The reaction mixture was stirred at rt for 16 h, then partitioned between DCM (100 mL) and 1 *M* aqueous HCl solution (50 mL). The layers were separated and the organic layer was sequentially washed with 1 *M* aqueous HCl solution (25 mL), $H_2O$ (25 mL), 1 *M* aqueous NaOH solution (25 mL) and $H_2O$ (25 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* affording the crude tosylate (8.00 g, 93%) as a red oil, which was used as such in the iodination reaction. The crude tosylate (7.85 g, 23.6 mmol) was dissolved in 2-ethoxyethanol

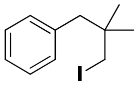
(25 mL) and NaI (7.08 g, 47.2 mmol) was added as a solid in one portion. The reaction mixture was heated to reflux for 16 h. The reaction was allowed to cool to room temperature and diluted with $H_2O$ (50 mL) and $Et_2O$ (100 mL). The layers were separated and the organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (Hex), affording the title compound (4.30 g, 66%) as a pale red oil. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.29-7.19 (m, 5H), 3.22 (s, 2H), 2.57-2.51 (m, 2H), 1.67-1.61 (m, 2H), 1.11 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 142.5, 128.5, 128.4, 125.9, 43.5, 33.7, 31.0, 26.8, 23.9. IR (film) cm$^{-1}$ 3025, 2959, 1497, 1454, 1384, 1365, 1204, 1163. LRMS (CI, Pos) calcd for $C_{12}H_{18}I_1$ $[M+H]^+$: 289.0, found 289.0 *m/z*.



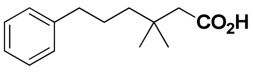
**2,2-dimethyl-3-phenylpropanoic acid (F17):** Synthesized according to **Procedure Y** on a 55 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (8.14 g, 84%) as a white solid. mp: 50-51 °C. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.29-7.13 (m, 5H), 2.88 (s, 2H), 1.20 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 184.8, 137.8, 130.4, 128.2, 126.7, 46.0, 43.6, 24.8. IR (film) cm$^{-1}$ 2972, 1685, 1470, 1456, 1289, 1223, 1134. HRMS (ESI, Pos) calcd for $C_{11}H_{14}Na_1O_2$ $[M+Na]^+$: 201.0886, found 201.0889 *m/z*.



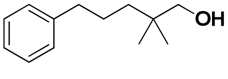
**2,2-dimethyl-3-phenylpropan-1-ol (F18):** Synthesized according to **Procedure Z**, on a 30 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (4.90 g, 99%) as a clear oil. $^1H$ NMR ($CDCl_3$, 400 MHz): δ 7.28-7.12 (m, 5H), 3.30 (d, 2H, $J$ = 6.0 Hz), 2.56 (s, 2H), 0.87 (s, 6H). $^{13}C$ NMR ($CDCl_3$, 100 MHz): δ 138.9, 130.6, 128.0, 126.1, 71.3, 44.9, 36.6, 24.1. IR (film) cm$^{-1}$ 3239, 2866, 1467, 1385, 1361, 1040. HRMS (ESI, Pos) calcd for $C_{11}H_{16}Na_1O_1$ $[M+Na]^+$: 187.1093, found 187.1092 *m/z*.



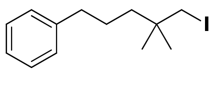
**(3-iodo-2,2-dimethylpropyl)benzene (F19):** Pyridine (20 mL) was cooled in an ice/salt bath and *p*-TsCl (5.80 g, 30.4 mmol) was added as a solid portionwise. A solution of **F18** in pyridine (10 mL) was added and the reaction was allowed to warm to rt. The reaction mixture was stirred at rt for 16 h, then partitioned between DCM (100 mL) and 1 *M* aqueous HCl solution (50 mL). The layers were separated and the organic layer was sequentially washed with 1 *M* aqueous HCl solution (25 mL), $H_2O$ (25 mL), 1 *M* aqueous NaOH solution (25 mL) and $H_2O$ (25 mL). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* affording the crude tosylate (7.99 g, 91%) as a pale yellow solid, which was used as such in the iodination reaction. The crude tosylate (7.99 g, 25.1 mmol) was dissolved in 2-ethoxyethanol (75 mL) and NaI (7.52 g, 50.2 mmol) was added as a solid in one portion. The reaction mixture was heated to reflux for 16 h. The reaction was allowed to cool to room temperature and diluted with $H_2O$ (50 mL) and $Et_2O$ (100 mL). The layers were separated and the organic layer was dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (Hex), affording the title compound (3.97 g, 58%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.32-7.19 (m, 5H), 3.14 (s, 2H), 2.66 (s, 2H), 1.06 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 138.3, 130.4, 128.0, 126.4, 46.4, 34.8, 27.2, 24.3. IR (film) cm$^{-1}$ 2959, 1453, 1364, 1212, 773. LRMS (CI, Pos) calcd for $C_{11}H_{16}I_1$ $[M+H]^+$: 275.0, found 275.0 *m/z*.



**2,2-dimethyl-5-phenylpentanoic acid (F20):** Synthesized according to **Procedure Y** on a 9.0 mmol scale. The residue was purified by flash chromatography (5% EtOAc/Hex), affording the title compound (310 mg, 17%) as a clear oil. $^1$H NMR ($CDCl_3$, 400 MHz): δ 12.18 (br s, 1H), 7.37-7.33 (m, 2H), 7.28-7.24 (m, 3H), 2.70-2.66 (m, 2H), 1.71-1.67 (m, 4H), 1.27 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 185.3, 142.3, 128.5, 125.6, 42.2, 40.3, 36.4, 26.9, 25.41. IR (film) cm$^{-1}$ 2942, 1697, 1475, 1453, 1278, 1199. HRMS (ESI, Pos) calcd for $C_{13}H_{18}Na_1O_2$ $[M+Na]^+$: 229.1202, found 229.1199 *m/z*.



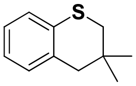
**2,2-dimethyl-5-phenylpentan-1-ol (F21):** Synthesized according to **Procedure Z** on a 1.5 mmol scale. The residue was purified by flash chromatography (5-10% EtOAc/Hex), affording the title compound (212 mg, 76%) as a clear oil. $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.32 (m, 2H), 7.25-7.23 (m, 3H), 3.35 (s, 2H), 2.65 (t, 2H, $J$ = 8.2 Hz), 1.69-1.61 (m, 3H), 1.37-1.33 (m, 2H), 0.92 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 142.8, 128.5 (2), 125.8, 72.0, 38.4, 37.0, 35.2, 26.1, 24.0. IR (film) cm$^{-1}$ 3354, 2936, 2864, 1495, 1471, 1453, 1389, 1363, 1028. HRMS (ESI Pos): expe. for $C_{13}H_{20}NaO$ $[M+Na]^+$: 215.1410, calc. 215.1406 *m/z*.



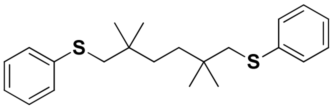
**(5-iodo-4,4-dimethylpentyl)benzene (F22):** Synthesized according to **Procedure V**, on a 1.1 mmol scale. The residue was purified by flash chromatography (Hex), affording the title compound (232 mg, 72%) as a clear oil. $^{1}$H NMR ($CDCl_3$, 400 MHz): δ 7.38-7.34 (m, 2H), 7.27-7.25 (m, 3H), 3.21 (s, 2H), 2.68 (t, 2H, $J$ = 7.6 Hz), 1.68-1.60 (m, 2H), 1.48-1.44 (m, 2H), 1.08 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 142.5, 128.4 (2C), 125.9, 40.8, 36.7, 33.6, 26.9, 26.6, 24.4. IR (film) cm$^{-1}$ 2958, 2934, 2858, 1495, 1466, 1453, 1384, 1365, 1222, 1205, 1161, 1030. LRMS (CI, Pos) calcd for $C_{13}H_{20}I_1$ $[M+H]^+$: 303.1, found 303.0 *m/z*.

*Nickel-catalyzed cyclization*

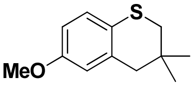
**Procedure AA**: In a glovebox, $Ni(PPh_3)_4$ (27.7 mg, 0.025 mmol, 0.05 equiv) and NaHMDS (137.5 mg, 0.75 mmol, 1.5 equiv) were added to a microwave vial containing a stir bar. The vial was crimped and taken out of the glovebox. A solution of the corresponding iodide (0.5 mmol, 1.0 equiv) in 1.5 mL dry benzene was cannulated into the microwave vial. The flask was rinsed with 2x1.5 mL benzene for a total volume of 4.5 mL. The reaction was stirred at 80 °C for 20 h. The reaction was allowed to cool down to rt, then filtered through a pad of silica and celite, concentrated and purified by flash chromatography.



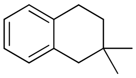
**3,3-dimethylthiochroman (451):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (62 mg, 70%) and dimer **452** (7 mg, 8%) as clear oils. $^{1}$H NMR ($CDCl_3$, 300 MHz): δ 7.13-6.94 (m, 4H), 2.76 (s, 2H), 2.58 (s, 2H), 1.13 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 132.9, 132.4, 130.8, 127.1, 126.0, 124.0, 43.5, 39.6, 28.5, 28.1. IR (film) cm$^{-1}$ 2953, 2913, 1467, 1437, 1249, 1070, 1039. LRMS (CI, Pos) calcd for $C_{11}H_{15}S_1$ [M+H]$^+$: 179.1, found 179.1 *m/z*.



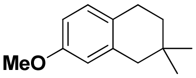
**(2,2,5,5-tetramethylhexane-1,6-diyl)bis(phenylsulfane) (452):** $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.36-7.34 (m, 4H), 7.28-7.24 (m, 3H), 7.16-7.13 (m, 3H), 2.88 (s, 4H), 1.30 (s, 4H), 1.00 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 138.5, 129.2, 128.9, 125.7, 49.9, 35.2, 34.8, 27.0. IR (film) cm$^{-1}$ 2956, 2056, 1583, 1479, 1438, 1384, 1365, 1089, 1025. HRMS (ESI, Pos) calcd for $C_{22}H_{31}S_2$ [M+H]$^+$: 359.1862, found 359.1874 *m/z*.



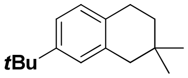
**6-methoxy-3,3-dimethylthiochroman (454):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (92 mg, 88%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.03-7.01 (m, 1H), 6.69-6.66 (m, 1H), 6.58-6.59 (m, 1H), 3.75 (s, 3H), 2.72 (s, 2H), 2.54 (s, 2H), 1.10 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 156.8, 134.4, 127.0, 123.3, 116.1, 112.8, 55.7, 43.9, 39.3, 29.1, 28.2. IR (film) cm$^{-1}$ 2953, 2933, 1599, 1482, 1312, 1230, 1151, 1034. HRMS (ESI, Pos) calcd for $C_{12}H_{17}O_1S_1$ [M+H]$^+$: 209.0995, found 209.0990 *m/z*.



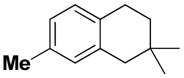
**2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (456):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (59 mg,74%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.15-7.04 (m, 4H), 2.84 (t, 2H, $J$ = 6.9 Hz), 2.58 (s, 2H), 1.60 (t, 2H, $J$ = 6.9 Hz), 1.04 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 136.7, 135.9, 129.6, 128.9, 125.6 (2), 43.7, 36.1, 29.6, 28.3, 26.8. IR (film) cm$^{-1}$ 2949, 2911, 1494, 1452, 1364. LRMS (CI, Pos) calcd for $C_{12}H_{17}$ [M+H]$^+$: 161.1, found 161.1 *m/z*.



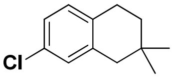
**7-methoxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (458):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (84 mg, 88%) as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.04–6.99 (m, 1H), 6.73–6.67 (m, 1H), 6.61–6.57 (m, 1H), 3.78 (s, 3H), 2.74 (t, 2H, $J$ = 6.8 Hz), 2.52 (s, 2H), 1.56 (t, 2H, $J$ = 6.8 Hz), 1.00 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 157.6, 137.7, 129.7, 128.0, 114.1, 111.8, 55.3, 43.9, 36.3, 29.5, 28.2 (2), 25.8. IR (film) cm$^{-1}$ 2948, 2908, 1610, 1502, 1463, 1364, 1269, 1242, 1219, 1156, 1042. LRMS (CI, Pos) calcd for $C_{14}H_{19}O_1$ [M+H]$^+$: 191.1, found 191.1 *m/z*.



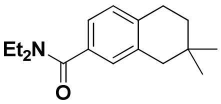
**7-tert-butyl-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (460):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (92 mg, 85%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.22-7.07 (m, 3H), 2.82 (t, 2H, $J$ = 6.8 Hz), 2.60 (s, 2H), 1.61 (t, 2H, $J$ = 6.8 Hz), 1.37 (s, 9H), 1.05 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 148.4, 136.1, 132.9, 128.5, 126.3, 122.6, 43.9, 36.2, 31.6, 28.5, 26.2 ppm. IR (film) cm$^{-1}$ 2950, 2906, 2868, 1460, 1433, 1363, 1339, 1256, 1089. LRMS (EI) calcd for $C_{16}H_{24}$ [M]: 216.2, found 216.2 *m/z*.



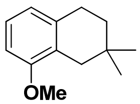
**2,2,7-trimethyl-1,2,3,4-tetrahydronaphthalene (462):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (75 mg, 86%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.05-6.90 (m, 3H), 2.81 (t, 2H, $J$ = 6.8 Hz), 2.54 (s, 2H), 2.33 (s, 3H), 1.60 (t, 2H , $J$ = 6.8 Hz), 1.03 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 136.4, 134.9, 132.7, 130.2, 128.8, 126.4, 43.6, 36.2, 29.6, 28.3, 26.2, 21.1. IR (film) cm$^{-1}$ 2949, 2913, 2868, 1504, 1450, 1433, 1383, 1364, 1167. LRMS (CI, Pos) calcd for $C_{13}H_{19}$ [M+H]$^+$: 175.2, found 175.2 *m/z*.

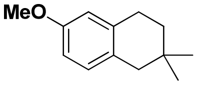


**7-chloro-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (464):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (72 mg, 74%) as a clear oil. $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.13–6.90 (m, 3H), 2.75 (t, 2H, $J$ = 6.6 Hz), 2.49 (s, 2H), 1.55 (t, 2H, $J$ = 6.8 Hz), 0.97 (s, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 138.5, 134.3, 131.0, 130.2, 129.3, 125.6, 43.4, 35.8, 29.4, 28.1 (2), 26.1. IR (film) cm$^{-1}$ 2950, 2918, 2869, 1486, 1449, 1431, 1365, 1089. LRMS (CI, Pos) calcd for $C_{12}H_{16}Cl_1$ [M+H]$^+$: 195.1, found 195.0 *m/z*.



***N,N*-diethyl-7,7-dimethyl-5,6,7,8-tetrahydronaphthalene-2-carboxamide (466):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (10-15% EtOAc/Hex), affording the title compound (90 mg, 70%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.10-7.00 (m, 3H), 3.52-3.28 (m, 4H), 2.79 (t, 2H, $J$ = 6.7 Hz), 2.52 (s, 2H), 1.56 (t, 2H, $J$ = 6.7 Hz), 1.21-1.12 (m, 6H), 0.97 (s, 6H) ppm. $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 171.7, 137.9, 137.1, 136.1, 134.7, 129.3, 128.6, 127.6, 126.9, 123.5, 43.5, 35.9, 29.5, 28.2, 26.5, 14.3, 13.0 ppm. IR (film) cm$^{-1}$ 2915, 1627, 1425, 1381, 1364, 1315, 1290, 1255, 1221, 1162, 1118. HRMS (ESI Pos): expe. for $C_{17}H_{25}NNaO$ [M+Na]$^+$: 282.1836, calc. 282.1828 *m/z*.

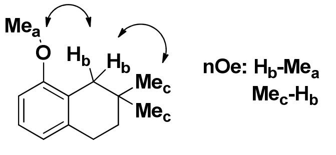




**8-methoxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (468a) and 6-methoxy-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene (468b)**: Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording **468a** (59 mg, 62%) and **468b** (22 mg, 23%) as clear oils.

**468a**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.14 (t, 1H, $J$ = 8.1 Hz), 6.80 (d, 1H, $J$ = 7.8 Hz), 6.71 (d, 2H, $J$ = 8.1 Hz), 3.87 (s, 3H), 2.85 (t, 2H, $J$ = 6.8 Hz), 2.51 (s, 2H), 1.59 (t, 2H, $J$ = 6.8 Hz), 1.06 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 157.7, 137.3, 125.8, 125.4, 121.2, 106.8, 55.3, 37.0, 35.6, 29.0, 28.7, 26.8. IR (film) cm$^{-1}$ 2948, 2914, 2869, 2843, 1585, 1467, 1252. LRMS (CI, Pos) calcd for $C_{13}H_{19}O_1$ [M+H]$^+$: 191.1, found 191.1 *m/z*.

**468b**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 6.97 (d, 1H, *J* = 8.5 Hz), 6.71-6.67 (m, 2H), 3.77 (s, 3H), 2.77 (t, 2H, *J* = 6.7 Hz), 2.47 (s, 2H), 1.54 (t, 2H, *J* = 6.7 Hz), 0.99 (s, 6H). $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 157.5, 136.9, 130.4, 128.7, 113.4, 111.9, 55.5, 42.9, 36.0, 29.7, 28.2, 27.0. IR (film) cm$^{-1}$ 2949, 2917, 1610, 1503, 1466, 1261, 1243, 1043. LRMS (CI, Pos) calcd for $C_{13}H_{19}O_1$ $[M+H]^+$: 191.1, found 191.1 *m/z*.



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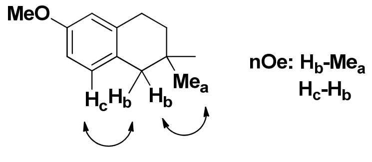

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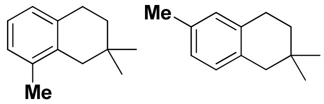
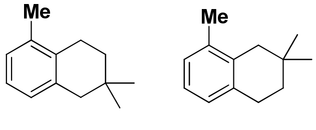


**2,2,8-trimethyl-1,2,3,4-tetrahydronaphthalene (470a) and 2,2,6-trimethyl-1,2,3,4-tetrahydronaphthalene (470b):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording an inseparable 3:1 mixture of **470a** and 47**0b** (71 mg, 81%) as a clear oil.

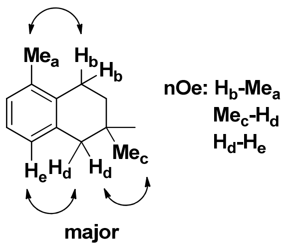
**470a**: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.10-6.98 (m, 3H), 2.87 (t, 2H, *J* = 6.7 Hz), 2.45 (s, 2H), 2.30 (s, 3H), 1.61 (t, 2H, *J* = 6.7 Hz), 1.07 (s, 6H). Minor: $^1$H NMR ($CDCl_3$, 400 MHz): δ 7.10-6.98 (m, 3H), 2.82 (t, 2H, *J* = 6.7 Hz), 2.58 (s, 2H), 2.35 (s, 3H), 1.62-1.59 (m, 2H), 1.04 (s, 6H). Major + minor $^{13}$C NMR ($CDCl_3$, 100 MHz): δ 136.8, 135.7, 135.6, 135.0, 134.8, 133.4, 129.4 (2 C's), 127.1, 126.7, 125.0, 43.2, 40.8, 36.1, 35.5, 29.6, 28.7, 27.0, 26.6, 21.0, 19.7. IR (film) cm$^{-1}$ 2948, 2911, 2864, 1458, 1384, 1363. LRMS (CI, Pos) calcd for $C_{13}H_{19}$ $[M+H]^+$: 175.2, found 175.1 *m/z*.



**2,2,5-trimethyl-1,2,3,4-tetrahydronaphthalene (472a) + 2,2,8-trimethyl-1,2,3,4-tetrahydronaphthalene (472b):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording an inseparable 10:1 mixture of **472a** and **472b** (59 mg, 71%) as a clear oil.

**472a**: $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.07-6.89 (m, 3H), 2.65 (t, 2H, *J* = 6.7 Hz), 2.57 (s, 2H), 2.24 (s, 3H), 1.62 (t, 2H, *J* = 6.7 Hz), 0.99 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 136.4 (2), 134.3, 127.4, 127.1, 125.4, 44.1, 36.2, 29.2, 28.1, 24.5, 19.7. IR (film) cm$^{-1}$ 2948, 2909, 2866, 1460, 1430, 1384, 1364. LRMS (CI, Pos) calcd for $C_{13}H_{19}$ [M+H]$^+$: 175.2, found 175.1 *m/z*.

**472b**: $^1$H NMR (CDCl$_3$, 300 MHz): δ 7.07-6.89 (m, 3H), 2.83 (t, 2H, *J* = 6.4 Hz), 2.40 (s, 2H), 2.23 (s, 3H), 1.56 (t, 2H, *J* = 6.7 Hz), 1.02 (s, 6H).



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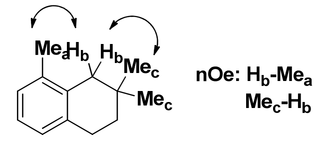

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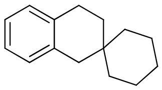
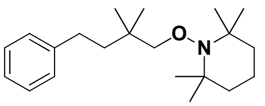


**3',4'-dihydro-1'*H*-spiro[cyclohexane-1,2'-naphthalene] (474):** Synthesized according to **Procedure AA**. The residue was purified by flash chromatography (Hex), affording the title compound (94 mg, 94%) as a clear oil. $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.15-7.08 (m, 4H), 2.82 (t, 2H, *J* = 6.7 Hz), 2.63 (s, 2H), 1.68 (t, 2H, *J* = 6.7 Hz), 1.57-1.47 (m, 6H), 1.40-1.37 (m, 4H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 136.4 (2), 129.7, 128.8, 125.6, 125.5, 41.4, 36.5, 33.4, 32.0, 26.9, 25.7, 21.9. IR (film) cm$^{-1}$ 2918, 2845, 1494, 1449, 745, 712. LRMS (CI, Pos) calcd for $C_{15}H_{21}$ [M+H]$^+$: 201.2, found 201.1 *m/z*.



**1-(2,2-dimethyl-4-phenylbutoxy)-2,2,6,6-tetramethylpiperidine (479):** Synthesized according to **Procedure AA** in presence of TEMPO (78.1 mg, 1 mmol). The residue was purified by flash chromatography (Hex), affording the TEMPO-adduct **479** (52 mg, 33%) as a clear oil and recovery of **455** (90 mg, 63%). $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.33-7.29 (m, 2H), 7.24-7.19 (m, 3H), 3.60 (s, 2H), 2.67-62 (m, 2H), 1.66-1.62 (m, 2H), 1.56-1.30 (m, 6H), 1.23 (s, 6H), 1.18 (s, 6H), 1.06 (s, 6H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 143.9, 128.7, 125.9, 84.9, 60.7, 42.7, 40.3, 35.8, 33.9, 31.3, 25.6, 20.6, 17.3. IR (film) cm$^{-1}$ 2928, 2870, 1470, 1373, 1133, 1059. HRMS (ESI, Pos) calcd for $C_{21}H_{36}N_1O_1$ $[M+H]^+$: 318.2791, found 318.2793 *m/z*.

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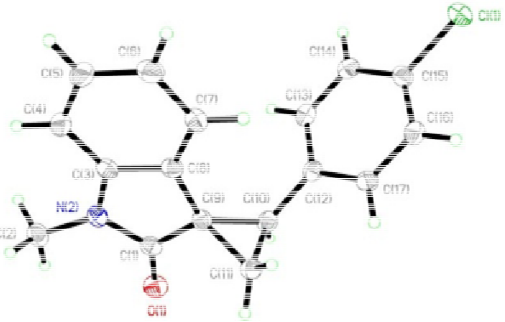
# Annex 1: X-Ray Data for Compounds 242a and 241b

**242a:**



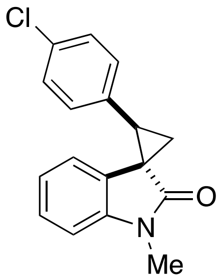
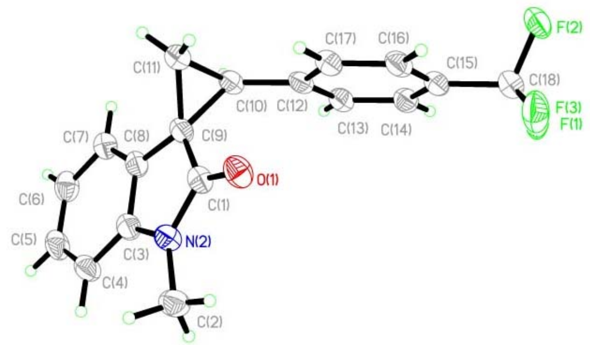


**Table 1.** Crystal data and structure refinement for C17 H14 Cl N O.

| | |
|---|---|
| Identification code | cha217 |
| Empirical formula | C17 H14 Cl N O |
| Formula weight | 283.74 |
| Temperature | 150K |
| Wavelength | 1.54178 Å |
| Crystal system | Orthorhombic |
| Space group | Pna21 |
| Unit cell dimensions | a = 12.5875(8) Å $\alpha$ = 90°<br>b = 17.8684(12) Å $\beta$ = 90°<br>c = 6.0173(4) Å $\gamma$ = 90° |
| Volume | 1353.40(15)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.393 g/cm$^3$ |
| Absorption coefficient | 2.440 mm$^{-1}$ |
| F(000) | 592 |
| Crystal size | 0.25 x 0.15 x 0.15 mm |
| Theta range for data collection | 4.30 to 69.70° |
| Index ranges | $-15 \leq h \leq 15$, $-21 \leq k \leq 21$, $-5 \leq \ell \leq 7$ |
| Reflections collected | 39869 |
| Independent reflections | 1968 [$R_{int}$ = 0.039] |

| | |
|---|---|
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.6935 and 0.5640 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1968 / 1 / 183 |
| Goodness-of-fit on $F^2$ | 1.080 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0299, $wR_2$ = 0.0791 |
| R indices (all data) | $R_1$ = 0.0299, $wR_2$ = 0.0791 |
| Absolute structure parameter | 0.127(18) |
| Largest diff. peak and hole | 0.254 and -0.251 e/Å$^3$ |

**241b:**



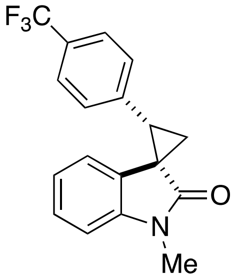


**Table 2.** Crystal data and structure refinement for C18 H14 F3 N O.

| | |
|---|---|
| Identification code | cha227 |
| Empirical formula | C18 H14 F3 N O |
| Formula weight | 317.30 |
| Temperature | 100K |
| Wavelength | 1.54178 Å |
| Crystal system | Monoclinic |
| Space group | P21/n |
| Unit cell dimensions | a = 15.2477(7) Å α = 90°<br>b = 5.8321(3) Å β = 90.669(3)°<br>c = 16.7963(9) Å γ = 90° |

| | |
|---|---|
| Volume | 1493.53(13)Å$^3$ |
| Z | 4 |
| Density (calculated) | 1.411 g/cm$^3$ |
| Absorption coefficient | 0.964 mm$^{-1}$ |
| F(000) | 656 |
| Crystal size | 0.22 x 0.04 x 0.02 mm |
| Theta range for data collection | 3.89 to 70.51° |
| Index ranges | $-18 \le h \le 18$, $-6 \le k \le 7$, $-20 \le \ell \le 20$ |
| Reflections collected | 18994 |
| Independent reflections | 2813 [$R_{int}$ = 0.042] |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.9809 and 0.7716 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2813 / 84 / 219 |
| Goodness-of-fit on $F^2$ | 1.112 |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.0453, $wR_2$ = 0.1269 |
| R indices (all data) | $R_1$ = 0.0515, $wR_2$ = 0.1323 |
| Largest diff. peak and hole | 0.358 and -0.253 e/Å$^3$ |

# Annex 2: Collaborator Contributions

| Collaborator | Page # | Scheme/Table/ Figure/Procedure | Structure # | Comments |
|---|---|---|---|---|
| Valentin Poiret (BSc) | 60 | Table 5 |  | Under my supervision |
| Carolyn Ladd (MSc) | 86 | Scheme 86 |  |  |
|  | 87 | Table 11 |  |  |
|  | 87 | Scheme 87 |  |  |
|  | 88 | Scheme 88 |  |  |
|  | 89 | Scheme 89 |  | The reaction for 3 h |
|  | 99 | Scheme 101 |  |  |
|  | 101 | Scheme 102 |  |  |
|  | 102 | Scheme 104 |  |  |
|  | 102 | Scheme 105B |  |  |
|  | 104 | Table 15 |  |  |
| Yoko Takahashi (PhD) | 143 | Scheme 142 | **376, 377** | Includes SM synthesis |
|  | 144-145 | Table 29, entries 5-7 |  | Includes SM synthesis |
|  | 145 | Scheme 143 | **394, 396, 397** |  |
|  | 272 | Procedures N and O |  | Y.T. optimized the procedures |
| Louis-Philippe Bonhomme-Beaulieu (PhD) | 159 | Scheme 161 |  | With F. Vallée |
|  | 160 | Table 30, entries 1-11 |  |  |
|  | 161-162 | Table 31, entries 1, 3, 4, 6, 7, 10-12 | **450, 451, 453, 455, 456, 457, 458, 461, 462, 463, 464, 469, 470, 471, 472, 473, 474** |  |
|  | 163 | Scheme 162 | **456** |  |
|  | 164 | Scheme 163 |  |  |
|  | 165-169 | All Section 6.2.3.2 |  | NMR experiments in collaboration with Dr. Cédric Malveau (University of Montreal, technician); $^1$H NMR in Figure 19 was double-checked by me, including work-up of the reaction |
|  | 291 |  | **F1, F2** | Beaulieu + Sustac |
| Frédéric Vallée (MSc) | 159 | Scheme 161 |  | With L.-P. Beaulieu |