Palladium-Catalyzed $C(sp^2)$-$C(sp^3)$ Bond Formation

By

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Dedicated to Keith Fagnou

Abstract

Palladium-catalyzed reactions for carbon-carbon bond formation have had a significant impact on the field of organic chemistry in recent decades. Illustrative is the 2010 Nobel Prize, awarded for "*palladium-catalyzed cross couplings in organic synthesis*", and the numerous applications of these transformations in industrial settings. This thesis describes recent developments in $C(sp^2)$-$C(sp^3)$ bond formation, focusing on alkane arylation reactions and arylative dearomatization transformations.

In the first part, our contributions to the development of intramolecular $C(sp^3)$-H arylation reactions from aryl chlorides are described (Chapter 2). The use of catalytic quantities of pivalic acid was found to be crucial to observe the desired reactivity. The reactions are highly chemoselective for arylation at primary aliphatic C-H bonds. Theoretical calculations revealed that C-H bond cleavage is facilitated by the formation of an agostic interaction between the palladium centre and a geminal C-H bond.

In the following section, the development of an alkane arylation reaction adjacent to amides and sulfonamides is presented (Chapter 3). The mechanism of $C(sp^3)$-H bond cleavage in alkane arylation reactions is also addressed through an in-depth experimental and theoretical mechanistic study. The isolation and characterization of an intermediate in the catalytic cycle, the evaluation of the roles of both carbonate and pivalate bases in reaction mechanism as well as kinetic studies are reported.

Our serendipitous discovery of an arylation reaction at cyclopropane methylene C-H bonds is discussed in Chapter 4. Reaction conditions for the conversion of cyclopropylanilines to quinolines/tetrahydroquinolines via one-pot palladium(0)-catalyzed $C(sp^3)$-H arylation with subsequent oxidation/reduction are described. Initial studies are also presented, which suggest that this transformation is mechanistically unique from other Pd-catalyzed cyclopropane ring-opening reactions.

Preliminary investigations towards the development of an asymmetric alkane arylation reaction are highlighted in Chapter 5. Both chiral carboxylic acid additives and phosphine ligands have been examined in this context. While high yields and enantiomeric

excesses were never observed, encouraging results have been obtained and are supported by recent reports from other research groups.

Finally, in part two, the use of Pd(0)-catalysis for the intramolecular arylative dearomatization of phenols is presented (Chapter 7). These reactions generate spirocyclohexadienones bearing all-carbon quaternary centres in good to excellent yields. The nature of the base, although not well understood, appears to be crucial for this transformation. Preliminary results in the development of an enantioselective variant of this transformation demonstrate the influence of catalyst activation on levels of enantiomeric excess.

Acknowledgments

"Really great people make you feel that you, too,

can become great." – Mark Twain

There are so many people that I need to thank for enabling me to reach this point. The last four and a half years have been a roller coaster of emotions and I don't know if I will truly be able to find the words to express the depth of my gratitude…

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snacks (and the zumba classes we had to take because of them!), the shopping and always finding a new restaurant to try. I would also like to acknowledge Jorge for teaching me the ropes in the lab when I arrived and sharing his great project.

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Sometimes the questions are complicated and the answers are simple.

Dr. Seuss

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List of Abbreviations

Ac – acetyl
agos – agostic
t-amyl – *tert*-amyl
aq – aqueous
Ar – aryl
atm – atmosphere
Bn – benzyl
Boc – *tert*-butyloxycarbonyl
BQ – benzoquinone
Bu – butyl
n-Bu – butyl
t-Bu – *tert*-butyl
Bz – benzoyl
cat. – catalytic
CBz – carbobenzyloxy
CMD – concerted metalation-deprotonation
Cy – cyclohexyl
Cyp – cyclopentyl
d – days
dba – dibenzylideneacetone
DDQ – 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT – density functional theory
DG – directing group
DIAD – diisopropyl azodicarboxylate
DIBAL – diisobutylaluminium hydride
DMA – *N*,*N*-dimethylacetamide
DMAP – 4-dimethylaminopyridine
DMF – *N*,*N*-dimethylformamide
DMP – Dess-Martin periodinane
DMSO – dimethyl sulfoxide
DPPA – diphenylphosphoryl azide
dr – diastereomeric ratio
E – electrophile
EDG – electron-donating group
ee – enantiomeric excess
equiv - equivalent
Et – ethyl
EWG – electron-withdrawing group
FG – functional group
GC – gas chromatography
GC-MS – gas chromatography-mass spectrometry
h – hour
Het – heteroaryl
hfacac - hexafluoroacetylacetonate
HFIP – hexafluoroisopropanol
HMDS - hexamethyldisilazide
HPLC – high-performance liquid chromatography
HRMS – high resolution mass spectrometry
imid – imidazole
IR – infrared
k – reaction rate
K – kelvin
kcal – kilocalorie
KIE – kinetic isotope experiment
(l) – liquid
L – generic ligand
L* – generic chiral ligand
LG – leaving group
M – generic metal
M – mol/L
mand – mandelate
Me – methyl
Mes – Mesitylene
min – minute
MOM – methoxymethyl
MS – molecular sieves
MW – microwave
NHC – *N*-heterocyclic carbene
NMR – nuclear magnetic resonance
Ns – *p*-nitrobenzenesulfonyl
Nu – nucleophile
obs – observed
Ph – phenyl
Phth – phthaloyl
PIDA – phenyliodonium diacetate
PIFA – phenyliodonium bis(trifluoroacetate)

Pin - pinacol
Piv – pivaloyl
PivOH – pivalic acid
Pr – propyl
i-Pr – *i*-propyl
n-Pr – propyl
pyr – pyridine
R – generic organic fragment
rt – room temperature
s – second
sat. – saturated
S_EAr – electrophilic aromatic substitution
SIPr – 1,3-bis(2,6-diisopropylphenyl)imidazolidene
TBAF – tetrabutylammonium fluoride
TBS – *tert*-butyldimethylsilyl
Temp – temperature
TES – triethylsilyl
Tf – trifluoromethanesulfonyl
TFA – trifluoroacetic acid
TFAA – trifluoroacetic anhydride
TFE – 2,2,2-trifluoroethanol
THF – tetrahydrofuran
TIPS – triisopropylsilyl
TLC – thin layer chromatography
TMS – trimethylsilyl
Tol – tolyl
Ts – *p*-toluenesulfonyl
TS – transition state
X – generic halide
Xyl – xylene
Y – generic atom except H
°C – degrees Celsius
κ – denticity
Δ – heat

1 Arylation at C(sp^3)-H Bonds – Introduction

The 2010 Nobel Prize in Chemistry was awarded to Richard F. Heck, Ei-ichi Negishi and Akira Suzuki for their contributions to *"palladium-catalyzed cross couplings in organic synthesis."* The ability to generate carbon-carbon bonds in a highly selective manner has revolutionized the pharmaceutical and agricultural industries as well as the field of material science.[1,2] Indeed, recent surveys of reactions performed within these contexts have demonstrated a remarkable increase over the last decade in the use of Pd-catalyzed carbon-carbon bond-forming reactions.[3] This observation further illustrates the utility and the robustness of these processes. Thus, the development of novel Pd-catalyzed transformations for the formation of carbon-carbon bonds is an attractive and valuable research area. Accordingly, the first portion of this body of work will discuss the development of Pd(0)-catalyzed arylation reactions at C(sp^3)-H bonds (Chapters 1-5). In a second part, the Pd(0)-catalyzed arylative dearomatization of phenols, via C(sp^2)-C(sp^3) bond formation, will be presented (Chapters 6-7).

[1] For recent reviews on the impact of catalysis in the pharmaceutical industry, see: (a) Magano, J.; Dunetz, J. R. *Chem. Rev.* **2011**, *111*, 2177-2250; (b) Busacca, C. A.; Fandrick, D. R. ; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2011**, *353*, 1825-1864.

[2] For a recent review on the application of cross-coupling in the synthesis of functional materials, see: Carsten, B.; He, F.; Son, H. J.; Xu, T.; Yu, L. *Chem. Rev.* **2011**, *111*, 1493-1528.

[3] (a) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Process Res. Dev.* **2005**, *9*, 253-258; (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.

1.1 Transition Metal-Catalyzed Reactions at C(sp^3)-H Bonds

The advent of transition metal-catalyzed transformations at C-H bonds has enabled the efficient formation of a wide range of carbon-carbon and carbon-heteroatom bonds from simple C-H bonds.[4] While these processes represent a chemical ideal from the standpoint of atom economy and synthetic efficiency, the ubiquitous nature of C-H bonds and their relative strength[5] pose a significant challenge for selectivity and reactivity that has been the focus of research efforts over the past decade.

Synthetic approaches towards transition metal-catalyzed transformations at C-H bonds are divided amongst two distinct mechanisms (Scheme 1.1).[6] Outer-sphere mechanisms (*coordination chemistry*) proceed *via* the direct interaction of the C-H bond being functionalized with a ligand coordinated to the transition metal. These processes typically involve weaker aliphatic positions, such as tertiary, allylic and benzylic C(sp^3)-H bonds.[7] Indeed, this mechanism has been exploited in metal-catalyzed carbene/nitrene insertions into C(sp^3)-H bonds as well as metal-oxo catalyzed C(sp^3)-H oxidations for example.[8] On the other hand, inner-sphere mechanisms (*organometallic chemistry*) involve the formation of a

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[4] For selected general reviews on catalytic transformations at C-H bonds for C-C and C-X bond formation, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698-1712; (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1769; (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077-1101; (d) *Handbook of C-H Transformations*; Dyker, G., Ed.; Wiley-VCH: Weinheim, **2005**; (e) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439-2463; (f) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173-1193; (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115; (h) Thansandote, P.; Lautens, M. *Chem. Eur. J.* **2009**, *15*, 5874-5883; (i) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242-3272; (j) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087-4109; (k) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. Eur. J.* **2010**, *16*, 2654-2672; (l) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147-1169; (m) *Top. Curr. Chem.* **2010**, *292*, 1-383; (n) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605-616; (o) Li, H.; Li, B.-J.; Shi, Z.-J. *Cat. Sci. Technol.* **2011**, *1*, 191-206.

[5] Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003, Chapter 3.

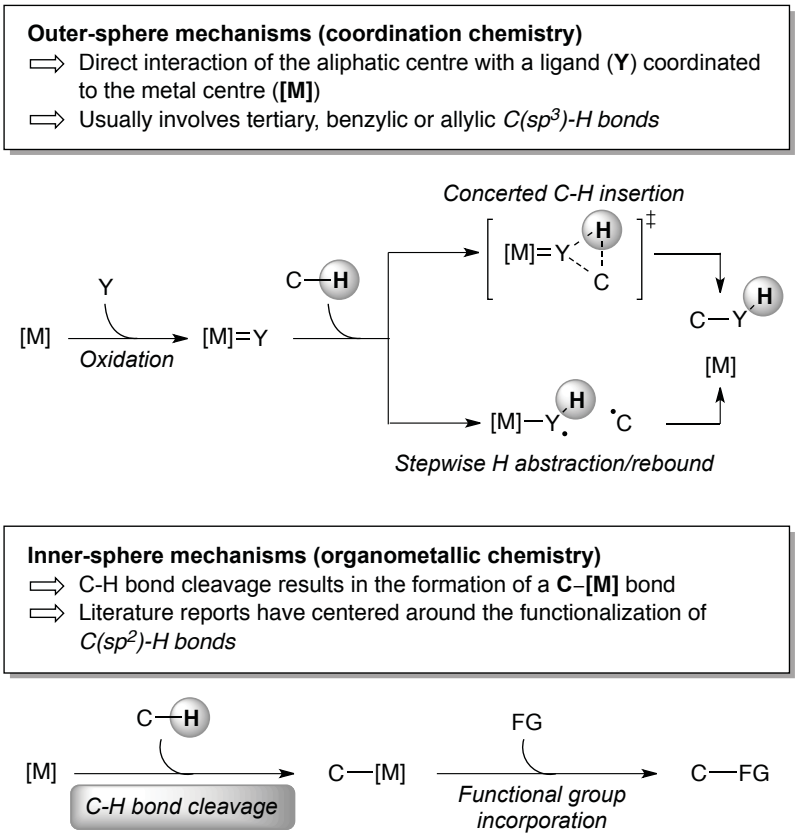
[6] For selected reviews that highlight these mechanistic differences, see: (a) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437-2450. See also ref 4e.

[7] Bond dissociation energies for C-H bonds: arene = 113 kcal/mol (benzene); alkene = 111 kcal/mol (ethylene); 1º aliphatic = 105 kcal/mol (methane); 2º aliphatic = 101 kcal/mol (ethane); 3º aliphatic = 96 kcal/mol (isobutane); benzylic = 89 kcal/mol (toluene); allylic = 88 kcal/mol (propene). See ref 5.

[8] For selected reviews, see: (a) Davies, H. M. L.; Beckwith, R. E. J.; *Chem. Rev.* **2003**, *103*, 2861-2903; (b) Que, L., Jr; Tolman, W. B.; *Nature* **2008**, *455*, 333-340; (c) Davies, H. M. L.; Manning, J. R.; *Nature* **2008**, *451*, 417-424; (d) Diaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379-3394; (e) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061-5074; (f) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704-724; (g) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347-378; (h) Gunay, A.; Theopold, K. H. *Chem. Rev.* **2010**, *110*, 1060-1081.

carbon-metal bond as a result of C-H bond cleavage.[9] Significantly, in this latter form of reactivity, also referred to as C-H activation or C-H functionalization in the literature, the transition metal is intimately involved in the transformation, leading to opportunities for new reactivity by tuning its electronic and steric properties. Unlike *coordination chemistry*, *organometallic chemistry* has traditionally involved the functionalization of arene C-H bonds (*vide infra*).

Scheme 1.1 Outer- vs inner-sphere transition metal-catalyzed transformations at C-H bonds



[9] For selected reviews related to the mechanism of transformations at C-H bonds proceeding through an inner-sphere pathway, see: (a) Ryabov, A. D.; *Chem. Rev.* **1990**, *90*, 403-424; (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev*. **1997**, *97*, 2879-2932; (c) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083-4091; (d) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820-5831; (e) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749-823. See also ref 6a.

In recent years, the development of selective direct C-H arylation reactions has been of particular interest.[10,11] These transformations present an attractive alternative to traditional cross-coupling reactions, due to the minimization of the stoichiometric, sometimes toxic, organometallic waste and the costs of starting material synthesis associated with the latter.[12] While numerous methods have been developed and exploited for the arylation of C(sp^2)-H bonds,[10] transformations at aliphatic *unactivated* C-H bonds have been significantly less investigated.[11,13] The difficulty in functionalizing these positions has been attributed to the lack of beneficial catalyst-substrate interactions through the π-system of the latter.[14] Palladium-catalyzed reactions at aliphatic positions are also inherently more challenging due to the possibility for byproduct formation *via* β-hydride elimination.[15] In this Chapter, a literature survey of different strategies for regioselective palladium-catalyzed C(sp^3)-H bond arylation will be presented (Section 1.2). This will be followed by an in-depth examination of the proposals for the mechanism of C-H bond cleavage in these transformations (Section 1.3).

1.2 Regioselective Palladium-Catalyzed C(sp^3)-H Bond Arylation

The selective functionalization of aliphatic C-H bonds in substrates containing several potential reaction sites poses a significant challenge for the development of synthetically useful transformations. Two general strategies have been developed to overcome this hurdle.

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[10] For selected reviews on the direct arylation of C(sp^2)-H bonds, see: (a) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrich. Chim. Acta* **2007**, *40*, 35-41; (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200-205; (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238; (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792-9826; (e) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269-10310. See also ref 4f.

[11] For a review on the direct arylation of C(sp^3)-H bonds, see: Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902-4911.

[12] For reviews on traditional transition metal-catalyzed cross-coupling reactions, see: (a) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470; (b) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: New-York, **2004**.

[13] The term *unactivated* refers to non-acidic C(sp^3)-H bonds (i.e. that are not adjacent to electron-withdrawing groups). For a review on transition metal-catalyzed arylation of *activated* C(sp^3)-H bonds, see: Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082-1146.

[14] For a review on the general mechanistic understanding of transition metal-catalyzed C(sp^3)-H bond functionalization, see: Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507-514.

[15] For a review on palladium-catalyzed cross-coupling reactions of alkyl electrophiles, see: Netherton, M. R.; Fu, G. C. *Top. Organomet. Chem.* **2005**, *14*, 85-108.

The use of biased substrates containing Lewis-basic directing groups,[16] which act as ligands for the metal, can be used to guide site-specific palladation (Section 1.2.1). On the other hand, intramolecular reactions can also eliminate some of the problems of regioselectivity. In these cases, selective C-H bond functionalization is generally governed by the size of the metallacyclic intermediate that is formed during the catalytic cycle (Section 1.2.2).

1.2.1 Heteroatom-Directed Alkane Arylation

The use of Lewis-basic directing groups within the substrate to mediate carbon-carbon or carbon-heteroatom bond formation at C-H bonds through the formation of stable five- or six-membered metalacyclic intermediates has been well documented.[16] Since initial examples of stoichiometric cyclometalation reactions using Ru, Rh, Pt and Pd first appeared in the literature,[17] several catalytic processes employing this strategy have been reported. A preference for palladium(II) catalysis has emerged due to its compatibility with a broad scope of directing groups and its ability to functionalize both sp^2 and sp^3 C-H bonds.[4l] Lewis-basic directing groups including, but not limited to, pyridines, picolinamides, carboxylic acids, amides and hydroxamic acids have all been employed in these transformations (Scheme 1.2). One should note, however, that while this strategy efficiently overcomes the hurdle of C-H bond selectivity in targets containing multiple potential reaction sites, its application in the synthesis of complex natural products has been less forthcoming. This may be attributed to the nature of some of these directing groups, which may be irremovable, such as pyridine, and unfortunately not desired in the final target. Significant strides are currently being made to develop directing groups that may be easily removed or transformed into other desirable functional groups.[16c] Selected examples of heteroatom-directed alkane arylation will be highlighted in the upcoming section, providing a broad perspective of the progress (and limitations) in this area of C-H bond functionalization. These examples will be divided according to arene sources (i.e. aryl boronic acids/esters, aryl iodonium salts and aryl halides) and catalytic cycle oxidation states (i.e. Pd(II)/Pd(0), Pd(II)/Pd(IV), Pd(0)/Pd(II)).

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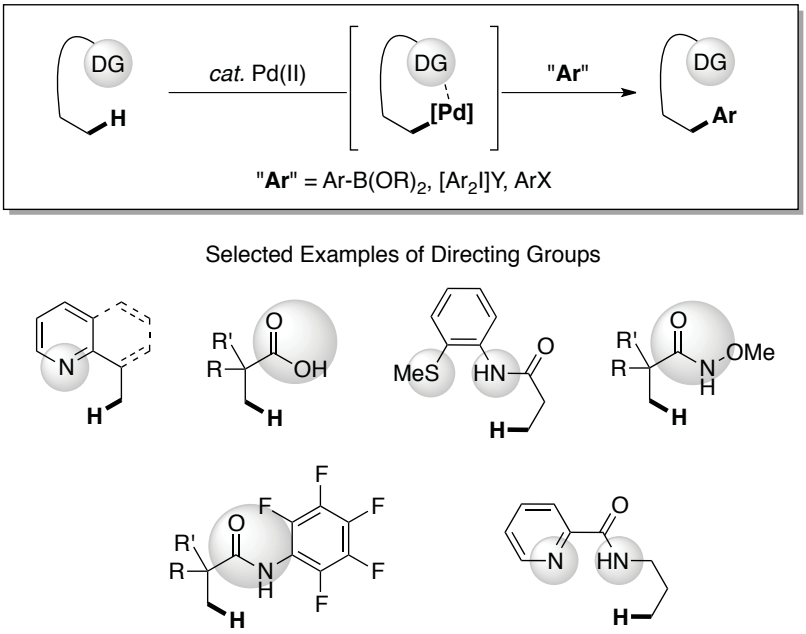
[16] For selected reviews on ligand-directed C-H bond functionalization, see: (a) Yu, J.-Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041-4047; (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074-1086; (c) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450-2494. See also ref 4l.

[17] For selected reviews, see: (a) Bruce, M. I. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 73-86; (b) Ryabov, A. D. *Synthesis* **1985**, 233-252. See also ref 9a.

Scheme 1.2 General strategy for heteroatom-directed alkane arylation

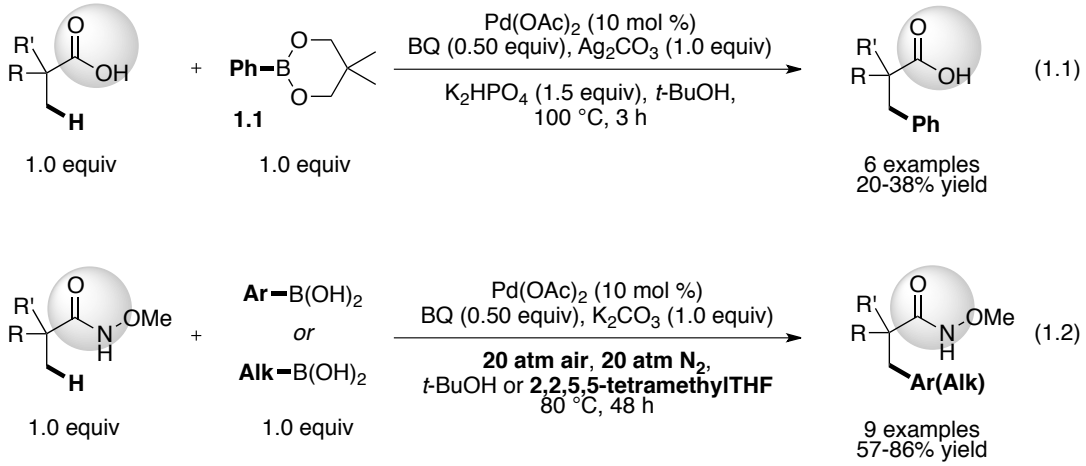


1.2.1.1 Pd(II)/Pd(0)-Catalyzed Alkane Arylation with Boronic Acids/Esters

In 2007, Yu and coworkers reported a Pd(II)/Pd(0)-catalyzed protocol for the β-C-H arylation of carboxylic acids (eq 1.1).[18] Using 10 mol % $Pd(OAc)_2$, primary and secondary C(sp^3)-H bonds of aliphatic carboxylic acids were coupled with phenylboronate **1.1** in 20-38% yield. Of note, the reaction is highly selective for mono-arylation, with less than 2% diarylated product observed by ^{1}H NMR. While the first report of C(sp^3)-H arylation using organometallic arylating reagents, this protocol presents important limitations such as mediocre product yields. In a subsequent communication, the Yu group found that modifying the carboxylic acid to a stronger binding *O*-methyl hydroxamic acid directing group afforded improved reactivity (eq 1.2).[19] Indeed, while their initial protocol was limited to the use of phenylboronate **1.1** as a coupling partner, these second-generation conditions allowed for C(sp^3)-H arylation/alkylation in good to excellent yields using a range of boronic acids. However, while the use of stoichiometric amounts of silver salts (Ag_2CO_3)

[18] Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510-3511.
[19] Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190-7191.

could be avoided under these conditions, a total of 40 atmospheres of pressure (20 atm air, 20 atm N_2) were required to obtain the desired reactivity. Additionally, the solvent 2,2,5,5-tetramethyltetrahydrofuran is commercially available from limited suppliers and is expensive.[20] Unfortunately, this limits the potential future application of this methodology in industrial settings.



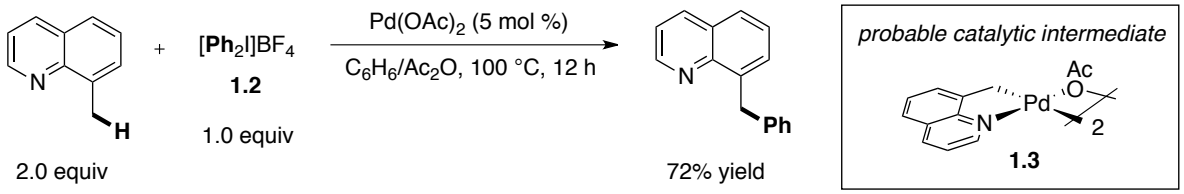
1.2.1.2 Pd(II)/Pd(IV)-Catalyzed Alkane Arylation with Aryl Iodonium Salts

Pyridine derivatives have seen the most widespread use as directing groups in Pd-catalyzed alkane arylation. The Sanford group first reported, in 2005, the *N*-directed benzylic arylation of 8-methylquinoline using phenyl iodonium salt **1.2** (Scheme 1.3).[21] 8-Benzylquinoline was produced in 72% yield when 2.0 equivalents of 8-methylquinoline and 1.0 equivalent of reagent **1.2** were subjected to 5 mol % $Pd(OAc)_2$ in a 1:1 mixture of C_6H_6 and Ac_2O at 100 °C. Initial mechanistic investigations, including the addition of Hg(0) and free radical inhibitors to the standard reaction conditions, excluded the involvement of palladium nanoparticles and free radical intermediates in product formation. As well, the absence of reactivity when iodonium salt **1.2** was replaced by Ph-I or Ph-OTf provided evidence against a Pd(0)/Pd(II) catalytic cycle, favouring direct C-H bond cleavage by Pd(II) to generate palladacycle **1.3**. Recent mechanistic investigations for the analogous C(sp^2)-H

[20] Alfa Aesar: 10 g (0.810 g/mL) for 70.70 CAD$. Aldrich and Acros have recently discontinued the production of 2,2,5,5-tetramethyltetrahydrofuran.
[21] Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330-7331.

arylation favour a mechanistic pathway which proceeds via a high oxidation state dimeric Pd(IV)-Pd(II) or Pd(III)-Pd(III) intermediate.[22,23]

Scheme 1.3 Pd(II)-catalyzed arylation of 8-methylquinoline using aryl iodonium salts



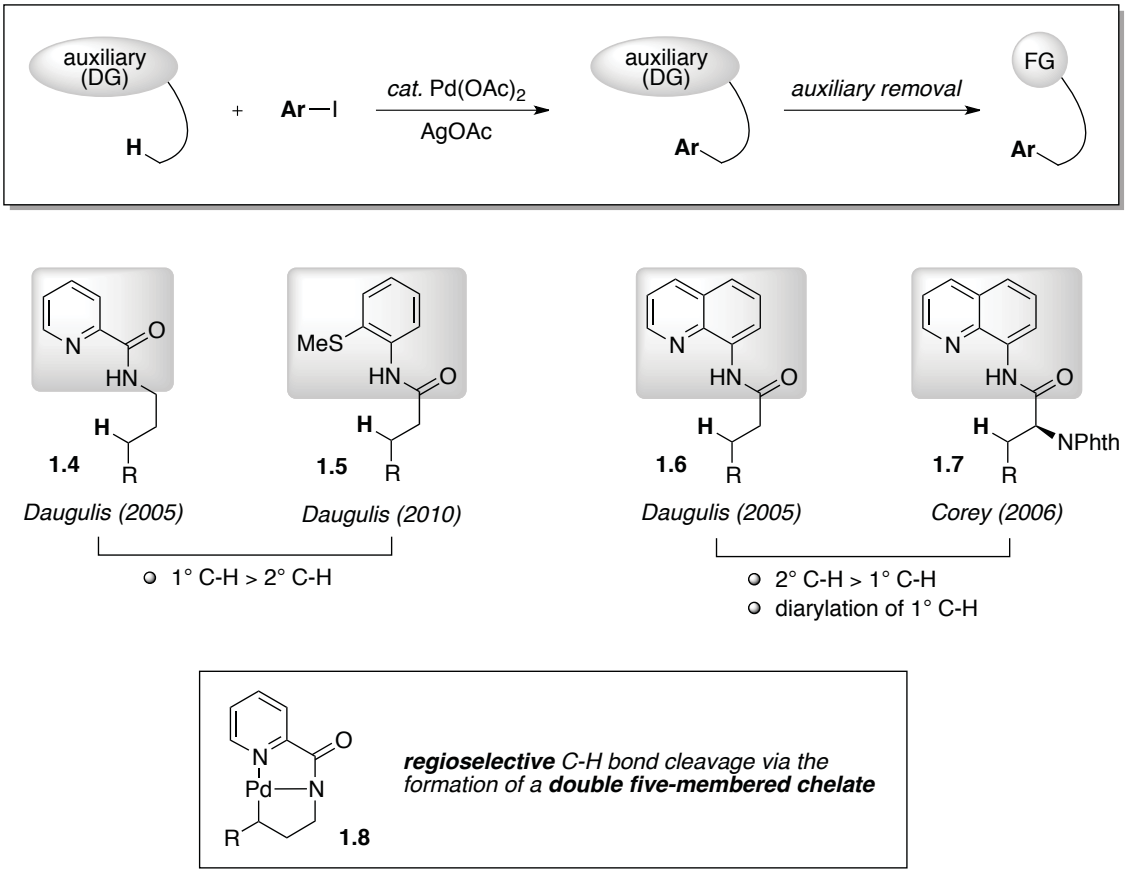
1.2.1.3 Pd(II)/Pd(IV)-Catalyzed Alkane Arylation with Aryl Iodides

In 2005, Daugulis and coworkers reported a highly regioselective Pd(II)-catalyzed arylation of aliphatic C-H bonds using pyridine directing groups as removable auxiliaries (Scheme 1.4).[24] Since this original communication, several removable auxiliary directing groups for Pd(II)-catalyzed alkane arylation have appeared in the literature.[25] Structurally, these auxiliaries all contain two binding sites for the electrophilic Pd(II) species, facilitating regioselective C-H bond cleavage via the formation of a double five-membered chelate intermediate **1.8** (see Chapter 1, Section 1.3.1 for further mechanistic insight). *N*-Alkylpicolinamides **1.4**, 8-aminoquinoline amides **1.6** and **1.7** (derived from the corresponding α-amino acids) as well as 2-methylthioanilines **1.5** efficiently underwent regioselective arylation when treated with catalytic amounts of $Pd(OAc)_2$, stoichiometric amounts of AgOAc and an excess (3-4 equivalents) of the aryl iodide coupling partner. Subsequent hydrolysis of the auxiliary yielded γ-arylated amines and β-arylated (amino)acids. Picolinamide **1.4** and 2-methylthioaniline **1.5** auxiliaries typically favour monoarylation of primary C-H bonds due to sluggish reactions at methylene positions. However, secondary C-H bonds react faster than primary C-H bonds when 8-aminoquinoline

[22] Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234-11241.
[23] For reviews on the role of Pd(III)-intermediates in catalysis, see: (a) Powers, D. C.; Ritter, T. *Top. Organomet. Chem.* **2011**, *35*, 129-156; (b) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2011**, *In press*, doi: 10.1021/ar2001974.
[24] Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154-13155.
[25] (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391-3394; (b) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414-3417; (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965-3972; (d) He, G.; Chen, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 5192-5196.

amine **1.6** or **1.7** are employed. Therefore, **1.6** or **1.7** are the auxiliary of choice for arylation of methylene positions. Unfortunately, in these cases, monoarylation is challenging and products of diarylation are obtained. The means to dictate selective C(sp^3)-H bond cleavage according to the nature of the auxiliary, and more importantly the ability to subsequently remove the latter, represents a significant achievement in the field of Pd-catalyzed alkane arylation. However, the use of an excess (3-4 equivalents) of the aryl iodide coupling partner remains a challenge to be addressed.

Scheme 1.4 Auxiliary-directed arylation of primary and secondary C(sp^3)-H bonds

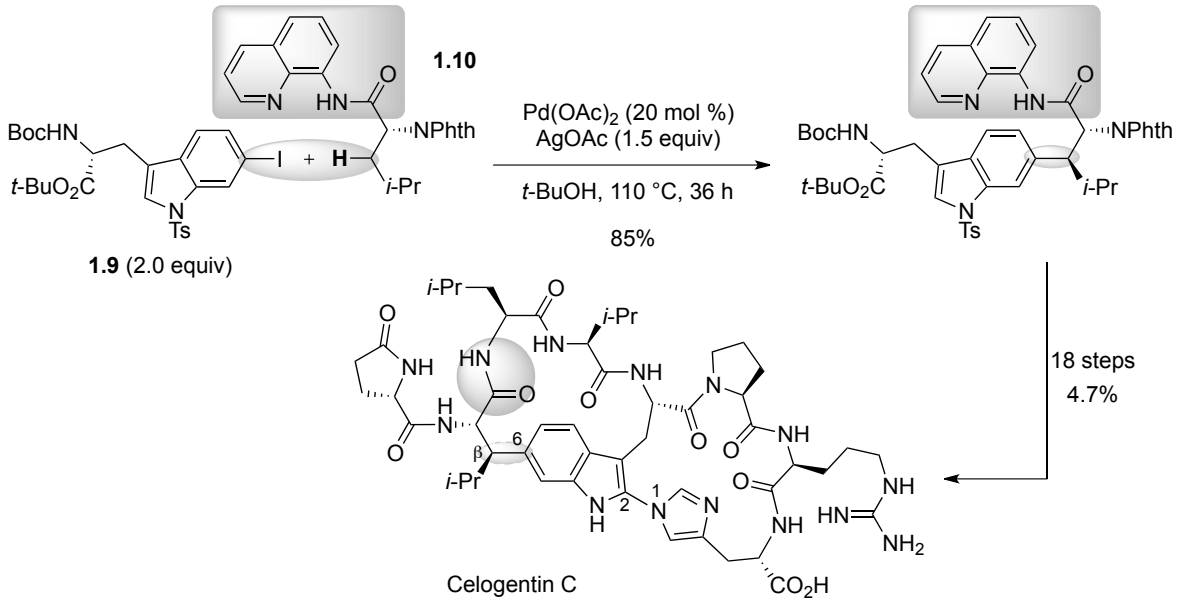


The impact of this alkane arylation strategy as a synthetic tool is evidenced by its recent use in natural product total synthesis.[26] In their total synthesis of celogentin C,[27] Feng

[26] For reviews on the application of transition-metal catalyzed C-H functionalization strategies in natural product synthesis, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67-72; (b) McMurray, L.; O'Hara, F.;

and Chen employed the 8-aminoquinoline amide auxiliary developed by Daugulis[24] and Corey[25a] to construct the extremely rare (and synthetically challenging) "Trp C6" - "Leu Cβ" amino acid linkage (Scheme 1.5). The C(sp^3)-H arylation of *N*-phthaloyl leucine derivative **1.9** (2 equiv) with **1.10** was effected by $Pd(OAc)_2$ (0.2 equiv) and AgOAc (1.5 equiv) in *t*-BuOH at 110 °C over 36 hours in 85% yield. This reaction was performed on a 4 gram scale to afford the desired product as a single diastereomer, demonstrating the robustness of this method.

Scheme 1.5 Total synthesis of celogentin C employing an auxiliary-directed Pd(II)-catalyzed alkane arylation strategy



In 2011, Gutekunst and Baran prepared piperarborenine B by *sequential* 2-methylthioaniline-directed cyclobutane C(sp^3)-H arylation reactions (Scheme 1.6).[28] Cyclobutane **1.11**, prepared from methyl coumalate in 61% yield (3 steps), was first monoarylated with aryl iodide **1.12**. The authors hypothesized that the *cis* orientation of the directing group and the ester functional group would lower the rate of a second arylation,

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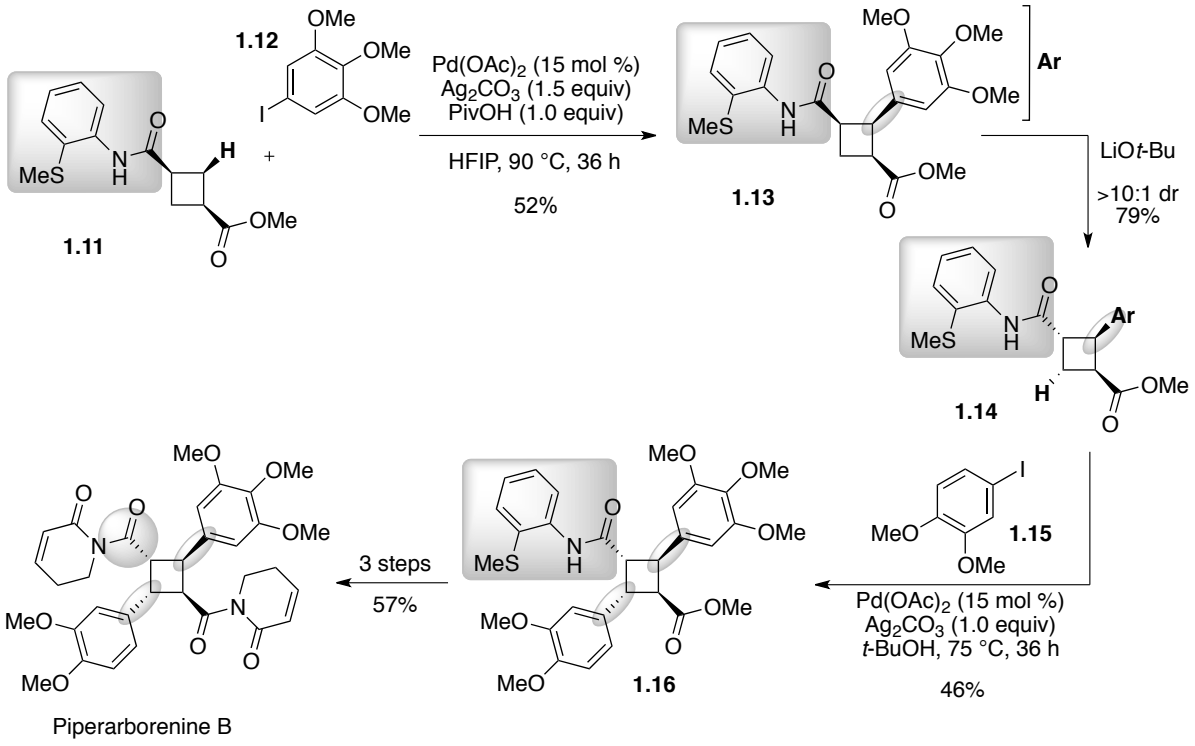
Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885-1898; (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976-1991.

[27] Feng, Y.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958-961.

[28] Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076-19079.

favouring formation of monoarylated **1.13**. Significant optimization revealed that the use of hexafluoroisopropanol (HFIP) and pivalic acid as additives, relative to Daugulis' original conditions,[25c] provided optimal catalyst turnover while avoiding diarylated byproducts. Using 15 mol % $Pd(OAc)_2$ and 1.5 equivalents of Ag_2CO_3, cyclobutane **1.13** was obtained in 52% yield (1.0 gram scale) with trace amounts of diarylated product. Selective stereocenter epimerization using LiO*t*-Bu in toluene provided **1.14** in 79% yield. Cyclobutane **1.14** was regioselectively coupled to aryl iodide **1.15** using 15 mol % $Pd(OAc)_2$ and 1.0 equivalent of Ag_2CO_3 in *t*-BuOH (1.0 M), providing diarylated cyclobutane **1.16** in 46% yield (1.1 gram scale). Surprisingly, the use of HFIP and pivalic acid for this second arylation resulted in poor reactivity. Piperarborenine B was finally obtained from cyclobutane **1.16** in three additional steps.

Scheme 1.6 Total synthesis of piperarborenine B employing sequential auxiliary-directed cyclobutane alkane arylations



1.2.1.4 Pd(0)/Pd(II)-Catalyzed Alkane Arylation with Aryl Iodides, Bromides and Chlorides

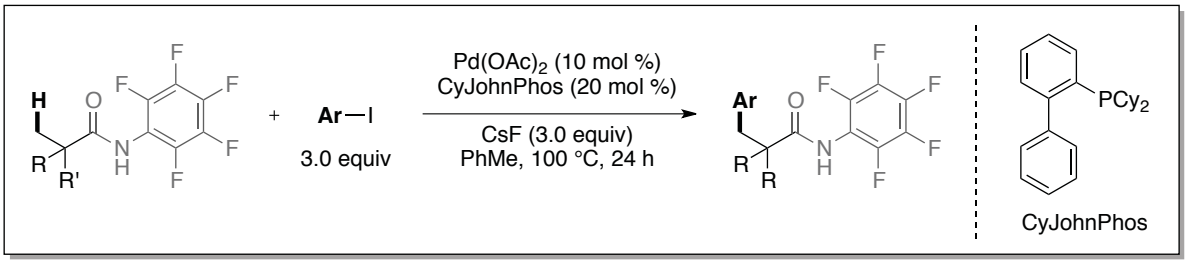
Heteroatom-directed alkane arylation has also been reported using Pd(0) catalysis. Beyond the tolerance for a wide range of functional groups in Pd(0) catalysis, the ability to

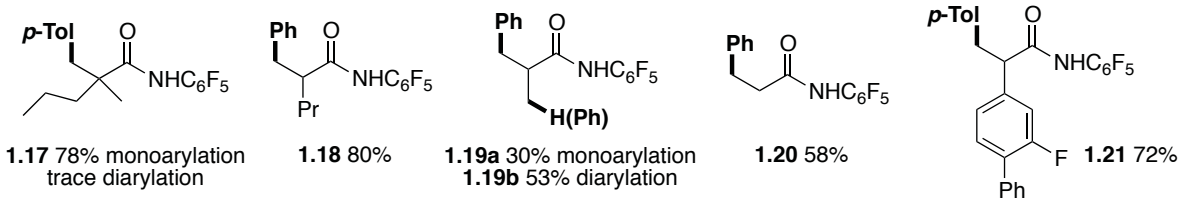
use inexpensive, commercially available (or easily prepared) aryl bromides and chlorides as coupling partners presents an attractive alternative to Pd(II) catalysis. While the aryl halide remains an element of pre-activation in the coupling process, it also enables the necessary change in oxidation state for C-H bond cleavage to occur.

Yu and coworkers have developed a Pd(0)/PR_3-catalyzed intermolecular β-C-H arylation of carboxylic acid derivatives (Scheme 1.7).[29] Based on their initial results in this field (eqs 1.1 and 1.2),[19] the use of amide directing groups to direct C-H bond cleavage was investigated. *N*-Aryl amides provided optimal results, since their diminished nucleophilicity suppressed potential competitive Buchwald-Hartwig aminations, which are well documented to occur under similar Pd(0)-catalysis conditions.[30] Use of *N*-(perfluorophenyl)amide as the directing group with 10 mol % $Pd(OAc)_2$, 20 mol% biaryl phosphine ligand Cyclohexyl JohnPhos (CyJohnPhos) [31] and 3.0 equivalents of CsF as the base enabled the functionalization of methyl groups with aryl iodides. These reactions were highly selective for arylation of primary C(sp^3)-H bonds (**1.17**, **1.18** and **1.21**), however mixtures of mono- and diarylated products were often obtained when multiple arylation sites were available (**1.19a** and **1.19b**). Diarylation most likely occurs due to the presence of aryl iodide in excess (3.0 equivalents) under the optimized reaction conditions. These product mixtures demonstrate the challenge in developing synthetically useful, highly selective intermolecular alkane arylation reactions. Substrates containing α-hydrogen atoms were tolerated (**1.18-1.21**) as well as potentially problematic aromatic substituents containing sites for C(sp^2)-H bond arylation (**1.21**). The authors proposed the formation of catalytic intermediate **1.22** for selective C-H bond cleavage to occur, although direct mechanistic evidence has yet to be obtained to support this hypothesis.

[29] Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886-9887.
[30] For selected reviews on Buchwald-Hartwig amination, see: (a) Hartwig, J. F. *Nature* **2008**, *455*, 314-322; (b) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27-50.
[31] For selected reviews on biaryl phosphine ligands in Pd(0)-catalysis, see: (a) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461-1473; (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338-6361.

Scheme 1.7 Pd(0)-catalyzed intermolecular arylation of methyl groups directed by *N*-(perfluorophenyl)amide





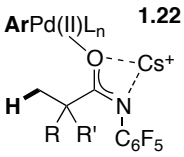
1.17 78% monoarylation
trace diarylation

1.18 80%

1.19a 30% monoarylation
1.19b 53% diarylation

1.20 58%

1.21 72%



Proposed catalytic intermediate
(precursor to C-H bond cleavage)

In 2008, the Fagnou and Charette groups independently reported the C(sp^3)-H arylation of picoline *N*-oxide and 2-methyl-*N*-iminopyridinium ylide respectively (Scheme 1.8).[32,33] Fagnou and coworkers found that modifying the nature of the catalyst and the base enabled a reversal in site-selectivity from C(sp^2)-H arylation *ortho* to the *N*-oxide moiety to C(sp^3)-H arylation. Indeed, the use of a catalyst based on Pd_2dba_3/XPhos in combination with 3.0 equivalents of NaO*t*-Bu in toluene under microwave (MW) heating led to exclusive selectivity for benzylic arylation. Electron-rich (**1.23**), electron-deficient (**1.24**) and heterocyclic (**1.25**) aryl bromides were all well tolerated. Other azine *N*-oxides (**1.26**) reacted with similar selectivities for C(sp^3)-H arylation and methylene functionalization proved possible (**1.27**). Mechanistic experiments determined that the choice of base was responsible for aryl vs alkyl C-H bond selectivity.[32b] Indeed, strong bases, such as NaO*t*-Bu,

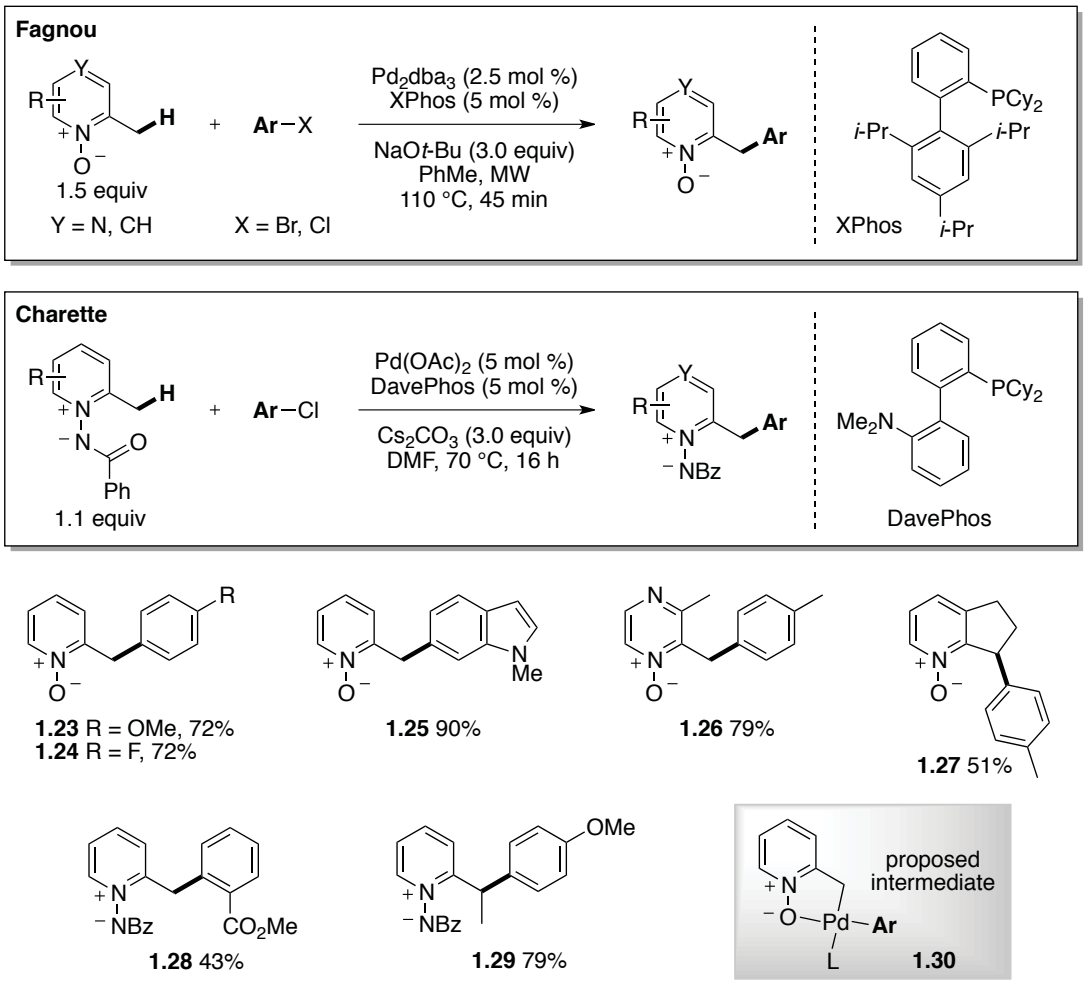
[32] (a) Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 3266-3267; (b) Schipper, D. J.; Campeau, L. C.; Fagnou, K. *Tetrahedron* **2009**, *65*, 3155-3164.
[33] Mousseau, J. J.; Larivée, A.; Charette, A. B. *Org. Lett.* **2008**, *10*, 1641-1643.

can deprotonate the more acidic benzylic C-H bonds, favouring the formation of intermediate **1.30** and C(sp^3)-H bond arylation. However, weaker carbonate bases, such as K_2CO_3, cannot deprotonate the benzylic position and therefore promote C(sp^2)-H bond arylation via a concerted metalation-deprotonation transition state (*vide infra*).[34] Thus, this method for C(sp^3)-H arylation is inherently limited to the use of substrates with relatively acidic benzylic positions and may be mechanistically more similar to the alkane arylation of "activated" C-H bonds.[13]

Charette and coworkers also found that 2-methyl-*N*-iminopyridinium ylides could be selectively arylated at the aliphatic C-H bond using aryl chloride coupling partners (Scheme 1.8).[33] A combination of 5 mol% $Pd(OAc)_2$, 12 mol % DavePhos and 3.0 equivalents of Cs_2CO_3 in DMF at 70 °C afforded optimal yields of the desired product. Under these conditions, no C(sp^2)-H arylated product could be detected by ^{1}H NMR of the crude reaction mixture. The reaction scope with respect to electron-rich (**1.29**) and electron-poor (**1.28**) aryl chloride coupling partners was found to be relatively broad. Arylation of secondary C(sp^3)-H bonds was also achieved under these reaction conditions (**1.29**).

[34] For a study on the mechanism of Pd(0)-catalyzed azine *N*-oxide direct arylation, see: Sun, H.-Y.; Gorelsky, S. I.; Stuart, D. R.; Campeau, L.-C.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 8180-8189.

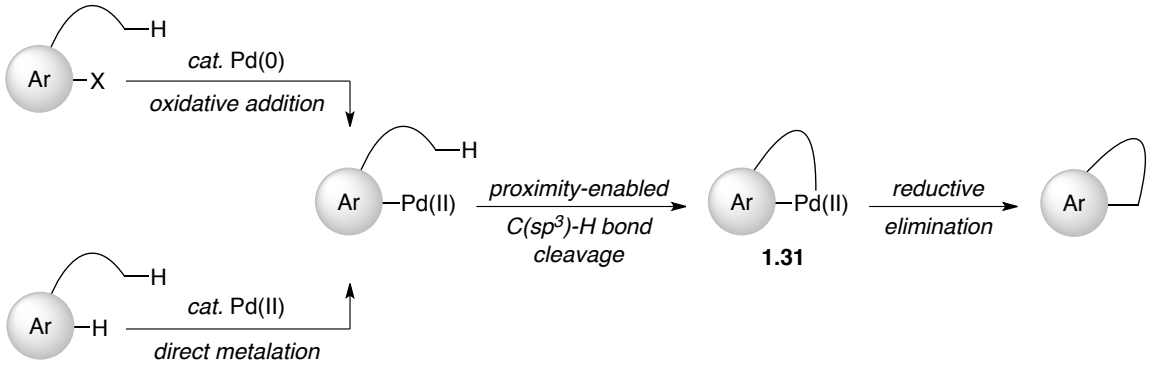
Scheme 1.8 Benzylic arylation of picoline *N*-oxide and 2-methyl-*N*-iminopyridinium ylide



1.2.2 Oxidative Addition/Metalation-Induced Alkane Arylation

In the absence of Lewis-basic directing groups, intramolecular reactions can be exploited for regioselective Pd-catalyzed C(sp^3)-H bond arylation.[4k,11] Two main strategies, which will be discussed in the upcoming section, have been adopted towards this goal: (1) oxidative addition of a Pd(0) catalyst into an aryl-halide bond, and (2) direct palladation of an electron-rich heteroarene by a Pd(II) species (Scheme 1.9). In both cases, an electrophilic Pd(II) species, which lies in close proximity to the aliphatic position to be functionalized, is generated and "proximity-enabled" C-H bond cleavage can occur. Regioselectivity is governed by the size of palladacycle **1.31** that is formed.

Scheme 1.9 Strategies for intramolecular Pd-catalyzed alkane arylation

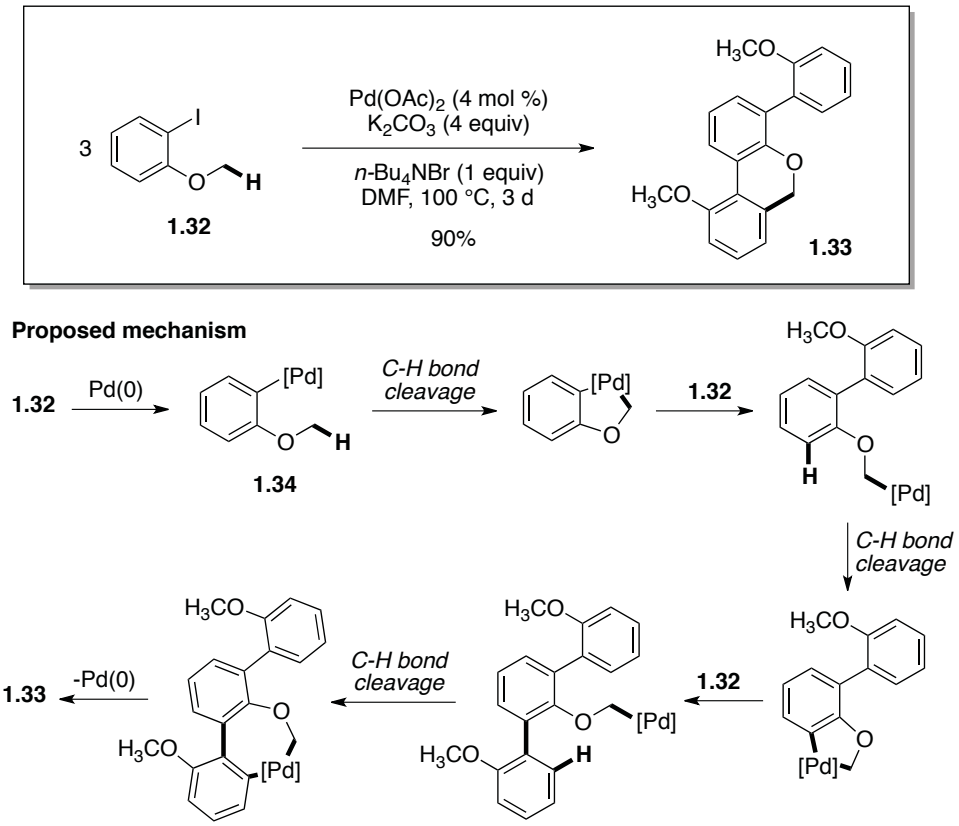


1.2.2.1 Oxidative Addition-Induced Pd(0)-Catalyzed Alkane Arylation

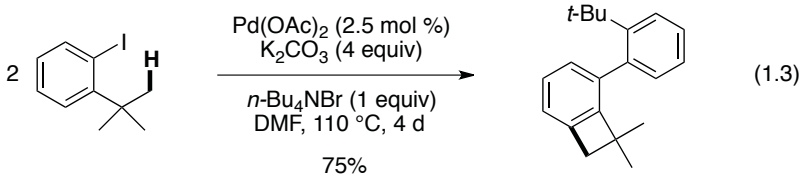
Pioneering work by Dyker revealed that arylation of methoxy C(sp^3)-H bonds with aryl iodides occurred in excellent yield using Pd(0)-catalysis (Scheme 1.10).[35] Treatment of 3.0 equivalents of 2-iodoanisole **1.32** with 4 mol % $Pd(OAc)_2$, 1.0 equivalent of tetrabutylammonium bromide and 4.0 equivalents of K_2CO_3 in DMF at 100 ºC for 3 days generated **1.33** in 90% yield. This domino reaction involves three distinct C-H functionalization processes: initial aliphatic C-H bond cleavage from the oxidative addition complex **1.34** followed by two subsequent C(sp^2)-H bond cleavage steps. Dyker suggested that the mechanism of this transformation could involve Pd(0)-Pd(II)-Pd(IV) catalytic species, however no direct evidence was obtained to support this proposal.

[35] Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023-1025.

Scheme 1.10 Domino Pd(0)-catalyzed C(sp^3)-H and C(sp^2)-H functionalization of 2-iodoanisole



A similar domino C-H functionalization/arylation reaction was later observed with 1-*tert*-butyl-2-iodobenzene (eq 1.3).[36] Notably, Dyker's reports highlighted the potential for aliphatic C-H bond cleavage/palladation to occur from oxidative addition intermediates similar to **1.34**.

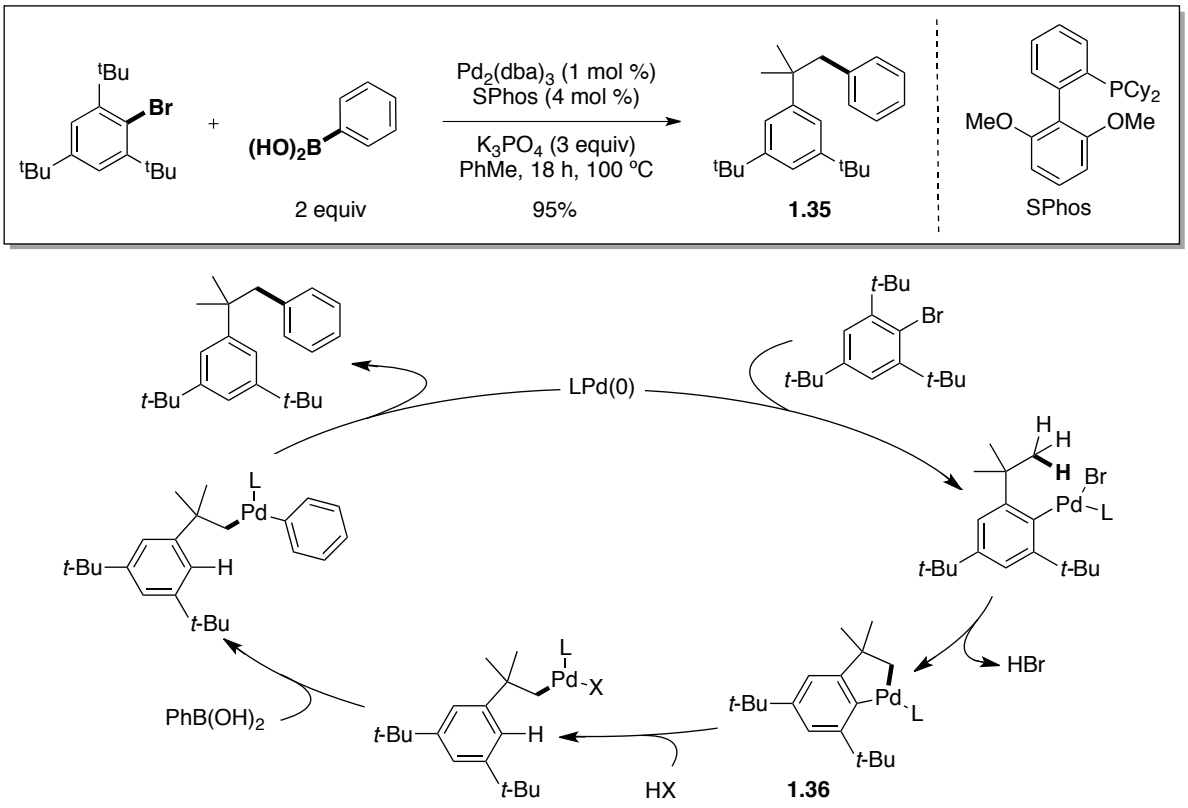


(1.3)

[36] Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 103-105.

Since these original publications, there have been a handful of reports of alkane arylation reactions proceeding through an ArPdX intermediate. During a study of Suzuki-Miyaura couplings using sterically hindered aryl bromides, Buchwald and coworkers observed an intriguing C(sp^3)-H arylation side reaction instead of the desired transformation (Scheme 1.11).[37] Indeed, coupling of 2,4,6-tri(*tert*-butyl)bromobenzene with phenylboronic acid using 1 mol % Pd_2dba_3 and 4 mol % SPhos afforded product **1.35** in 95% yield. Following oxidative addition, the reaction is proposed to proceed via C(sp^3)-H bond cleavage/cyclopalladation of a *tert*-butyl group. Subsequent protodepalladation of **1.36**, transmetalation and reductive elimination provides **1.35** while regenerating the Pd(0) catalyst. The formation of **1.35** rather than the expected cross-coupled product or the benzocyclobutene resulting from reductive elimination at intermediate **1.36** underlines the influence of steric effects on the reaction outcome.

Scheme 1.11 Domino C(sp^3)-H functionalization/Suzuki-Miyaura coupling of sterically hindered aryl bromides



[37] Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

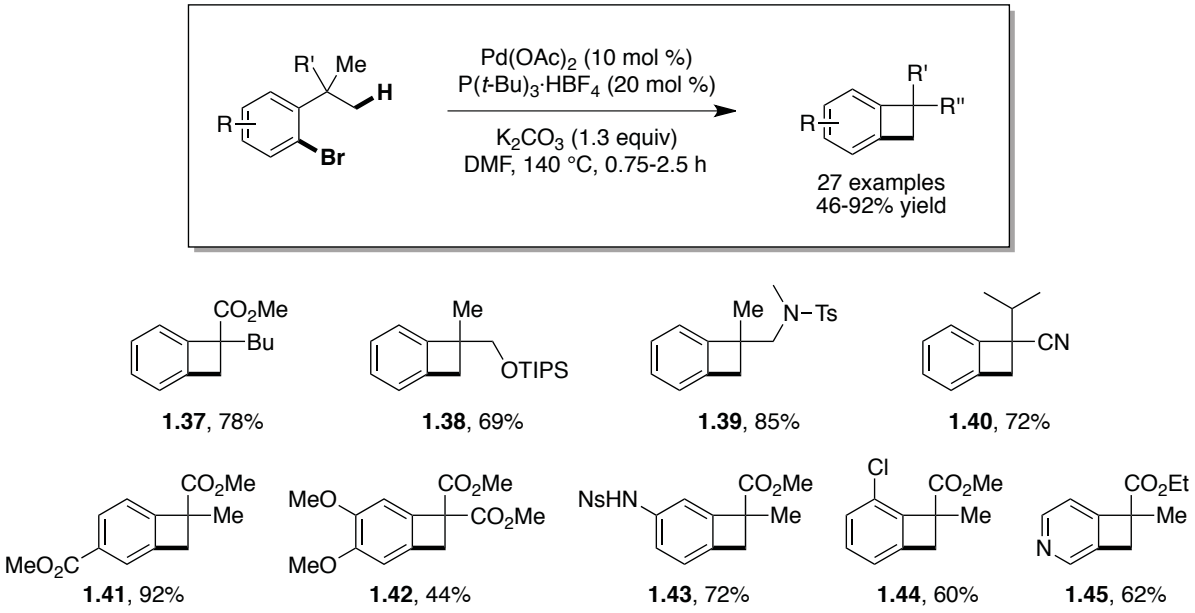
These initial reports of alkane arylation reactions were limited to single, very specific examples. The groups of Baudoin,[38] Fagnou[39] and Fujii and Ohno[40] have employed intramolecular alkane arylation reactions for the synthesis of fused carbocycles and heterocycles. Theoretical mechanistic studies have been performed for these systems, elucidating key aspects of C(sp^3)-H bond cleavage (see Chapter 1, Section 1.3.2 for a mechanistic discussion).

Baudoin and co-workers have developed a general Pd(0)-catalyzed C(sp^3)-H bond arylation reaction for the synthesis of benzocyclobutenes.[38c] The importance of benzocyclobutenes (BCBs) as synthetic intermediates has been widely recognized.[41] For example, their inherent ring strain allows them to undergo eletrocyclic ring-opening under thermal conditions, affording useful precursors for the synthesis of more complex structures via pericyclic reactions. Reaction optimization revealed that a combination of 10 mol % $Pd(OAc)_2$, 20 mol % $P(t\text{-}Bu)_3 \cdot HBF_4$,[42] 1.3 equivalents of K_2CO_3 in DMF at 140 °C catalyzed the intramolecular arylation of methyl C-H bonds in *ortho*-substituted arylbromides (Scheme 1.12). The absence of oligomerization products, reminiscent of Dyker's seminal reports (Scheme 1.10 and eq 1.3), can be attributed to the presence of a phosphine ligand. The transformation demonstrated complete selectivity for functionalization of methyl groups over methylene (**1.37**, **1.38** and **1.39**) or methyne (**1.40**) positions. However, only substrates bearing quaternary benzylic carbons yielded the desired cyclized product. In the presence of benzylic hydrogens, the starting material is converted, in majority, to proto-debrominated material as well as to minor amounts of styrene resulting from β-hydride elimination. The scope, with respect to the aliphatic component, was relatively broad. Functional groups including esters (**1.37**, **1.41**-**1.45**), silyl-protected alcohols (**1.38**), amines (**1.39**) and nitriles (**1.40**) were well tolerated. On the aromatic ring,

[38] (a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736-5740; (b) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792-799; (c) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157-15166; (d) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179-182; (e) Pierre, C.; Baudoin, O. *Org. Lett.* **2011**, *13*, 1816-1819; (f) Guyonnet, M.; Baudoin, O. *Org. Lett.* **2012**, *14*, 398-401.
[39] Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570-14571.
[40] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759-1762.
[41] Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539–1602.
[42] For the report of air-stable trialkylphosphine precursors, see: Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295-4298.

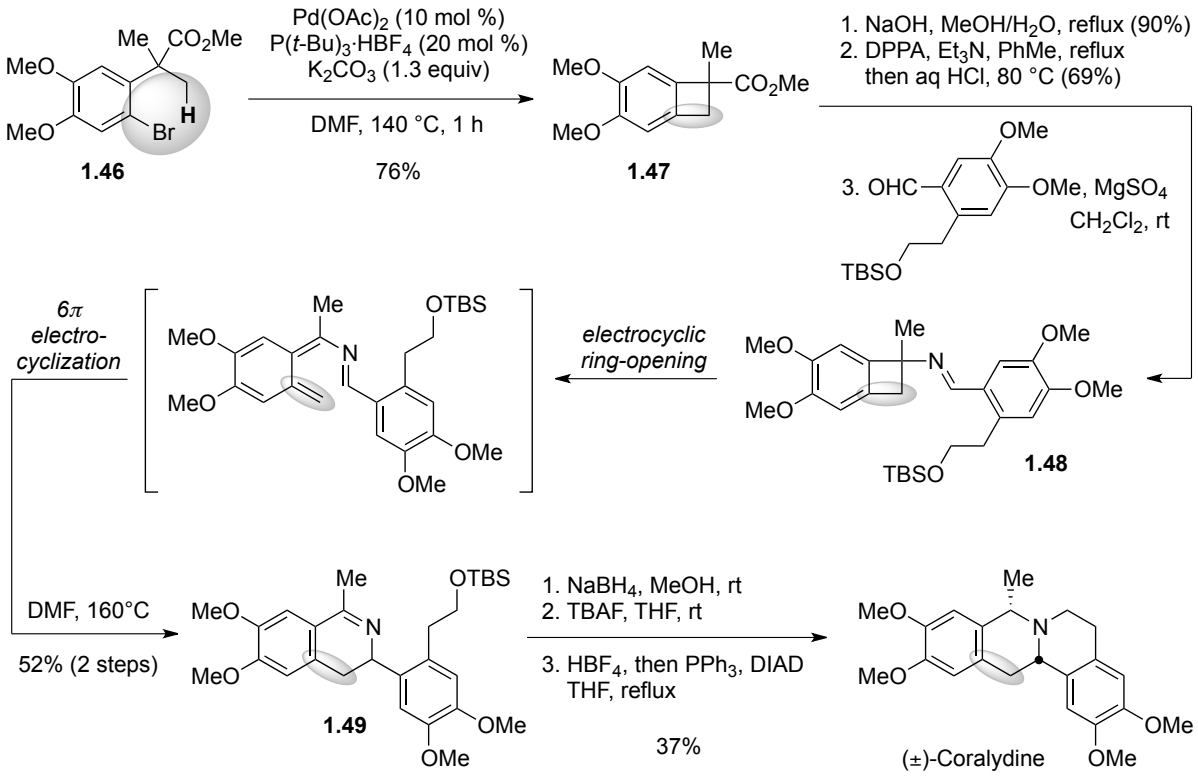
electron-withdrawing (**1.41**) as well as electron-donating (**1.42** and **1.43**) groups afforded the desired product. The reaction of a 2-bromo-6-chlorobenzene-derivative yielded benzocyclobutene **1.44**, with complete selectivity for oxidative addition at the C-Br bond. Finally, a π-deficient heterocycle also furnished the product of alkane arylation under these reaction conditions (**1.45**).

Scheme 1.12 Benzocyclobutene formation via intramolecular alkane arylation



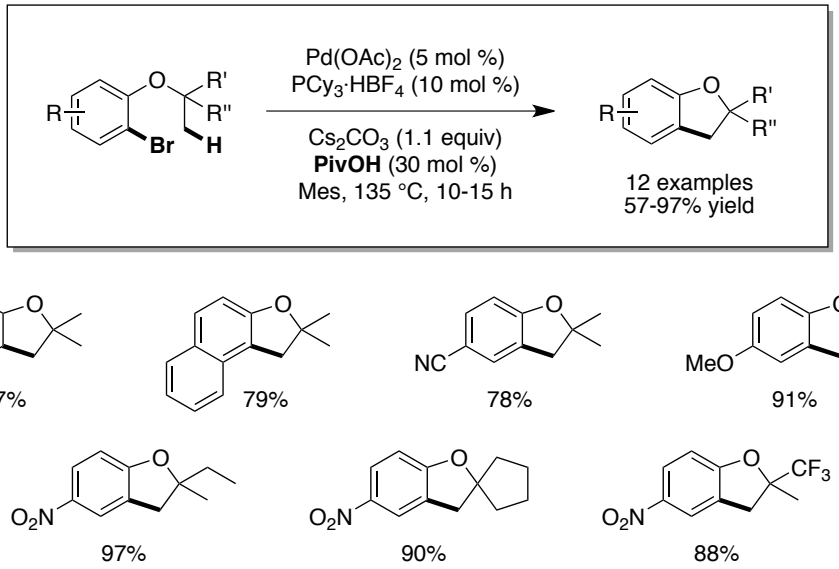
In 2009, Baudoin and coworkers synthesized (±)-coralydine, a tetrahydroprotoberberine alkaloid, employing their previously reported C(sp^3)-H arylation protocol followed by an interesting electrocyclization strategy to build its core (Scheme 1.13).[38d] Benzocyclobutene **1.47** was prepared in 76% yield by submitting aryl bromide **1.46** to their standard reaction conditions (Scheme 1.12). Following hydrolysis, Curtius rearrangement and imine formation, BCB **1.48** underwent a thermal electrocyclic ring-opening reaction and subsequent 6π-electrocyclization to produce dihydroisoquinoline **1.49**. Nearly quantitative imine reduction by $NaBH_4$ produced a 6:1 mixture of diastereomers in favour of the desired *cis* product. Isolation of the major diastereomer, TBAF-promoted desilylation and Mitsonobu reaction afforded (±)-coralydine.

Scheme 1.13 Total synthesis of (±)-coralydine using a C(sp^3)-H arylation/electrocyclization strategy



Fagnou and coworkers have reported a similar alkane arylation strategy for the synthesis of 2,2-dialkyldihydrobenzofurans (Scheme 1.14).[39] Crucial to the success of these reactions is the use of a carbonate base in combination with a catalytic amount of a carboxylic acid additive; pivalic acid proved to be optimal (see Chapter 1, Section 1.3.2 for a discussion on the role of this additive). Once again, these reactions were found to be very selective for arylation of primary aliphatic C-H bonds. No reaction occurred at secondary or tertiary positions under the optimal reaction conditions. A quaternary carbon center adjacent to the methyl C-H bond is also necessary to observe the desired reactivity.

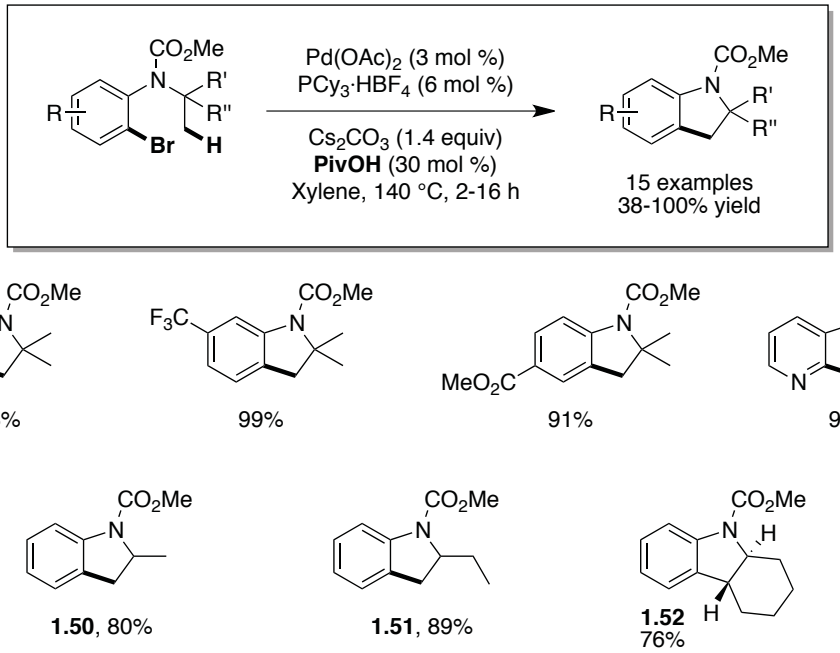
Scheme 1.14 Dihydrobenzofuran synthesis via intramolecular alkane arylation



Shortly after Fagnou, Fujii and Ohno reported a similar C(sp^3)-H bond arylation for the formation of indoline derivatives from the corresponding 2-bromo-*N*-*tert*-butylanilines (Scheme 1.15).[40] A catalytic quantity of pivalic acid was also used as an additive in these transformations to obtain optimal yields. While the authors found that aryl iodides, bromides and chlorides were all compatible coupling partners, aryl bromides led to significantly higher yields and were therefore chosen to explore the scope of the reaction. Of note for this substrate class is the ability to functionalize methyl groups (**1.50** and **1.51**) in the presence of β-hydrogens, which have proven problematic in previous reports.[38,43] Additionally, this work contains a rare example of methylene C(sp^3)-H arylation (**1.52**). The enantioselective formation of indoline **1.50-1.52** by asymmetric Pd(0)-catalyzed alkane arylation was recently presented by the groups of Kündig and Kagan (see Chapter 5, Section 5.1).[44]

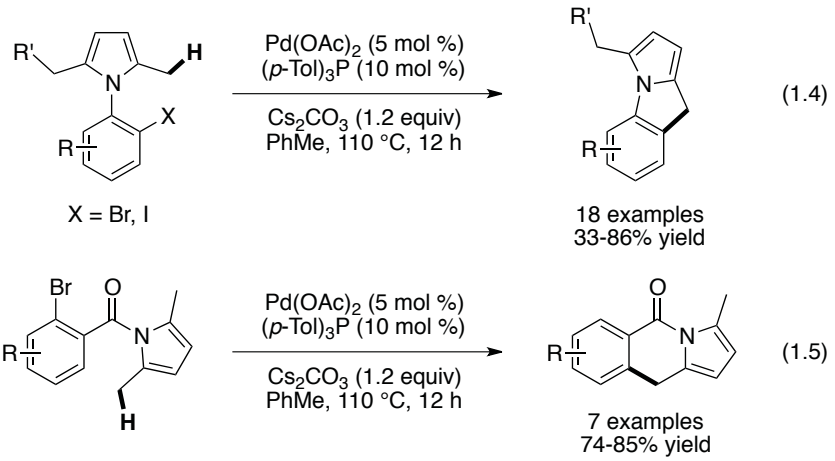
[43] Lafrance, M. *Development of New Palladium-Catalyzed Arylation Reactions*, Ph.D. Thesis, University of Ottawa, Ottawa, 2008.
[44] (a) Nakanishi, M.; Katayev, D.; Besnard, C.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438-7441; (b) Anas, S.; Cordi, A.; Kagan, H. B. *Chem. Commun.* **2011**, *47*, 11483-11485.

Scheme 1.15 Indoline synthesis via intramolecular alkane arylation

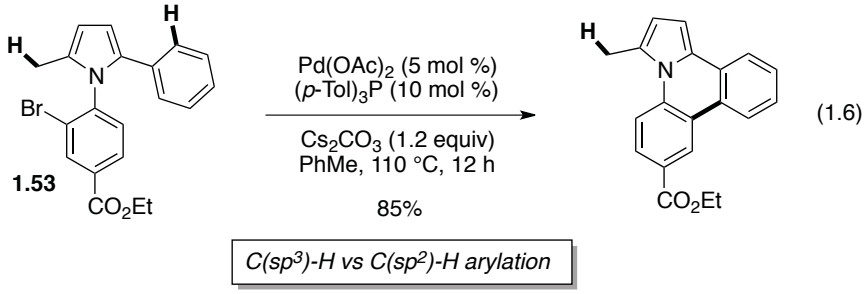


In 2006, Knochel and coworkers prepared a series of fused *N*-containing heterocycles via Pd(0)-catalyzed arylation of benzylic C-H bonds (eqs 1.4 and 1.5).[45] Using a catalyst based on $Pd(OAc)_2$/P(*p*-Tol)$_3$ in combination with 1.2 equivalents of Cs_2CO_3 in toluene at 110 °C, benzylic methyl groups were arylated in good to excellent yields. Both aryl iodides and bromides underwent ring closure to afford the desired products in similar yields. It should be noted that alkane arylation at *benzylic* positions is often viewed as more facile due to the proximity of the arene π-system, which can favour catalyst-substrate interactions, and the increased acidity of these C-H bonds.

[45] (a) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462-3465; (b) Ren, H.; Li, Z.; Knochel, P. *Chem. Asian. J.* **2007**, *2*, 416-433.



Substrate **1.53** highlights the greater reactivity of C(sp^2)-H bonds towards Pd(0)-catalyzed arylation compared to C(sp^3)-H bonds (eq 1.6). Exclusive arylation at the aromatic position via a higher energy 7-membered palladacycle is observed over arylation at the aliphatic position via a 6-membered palladacycle.

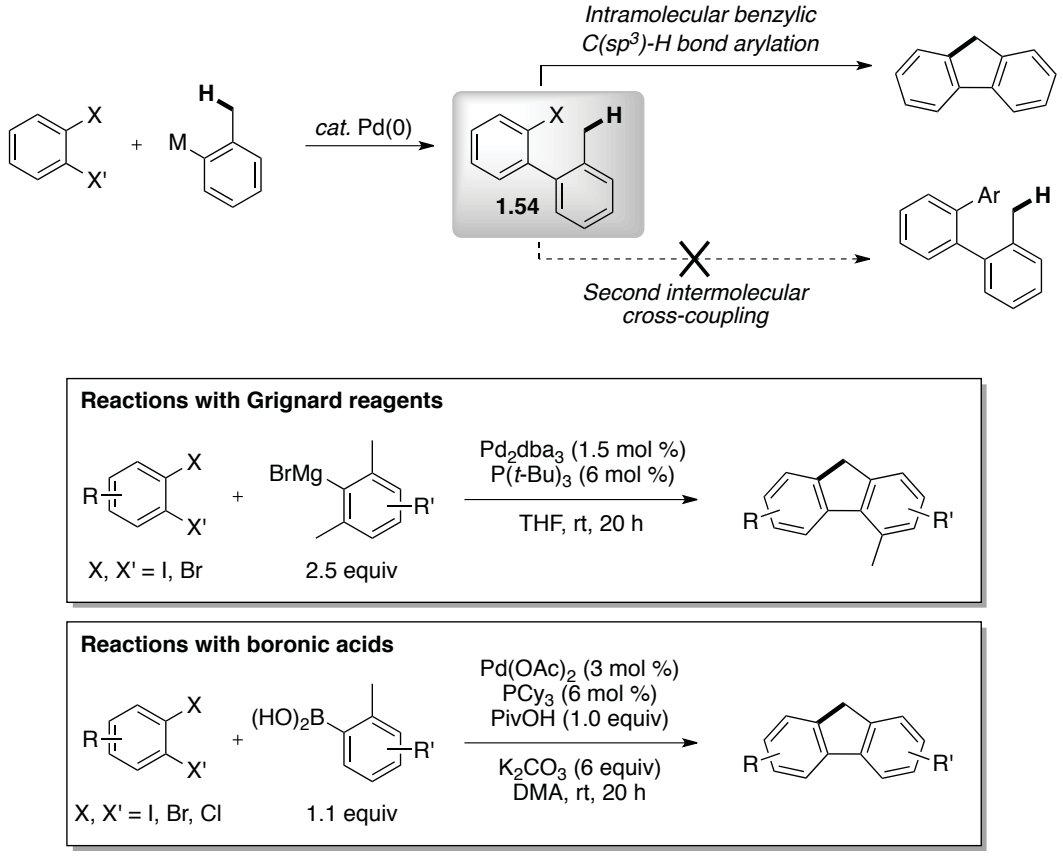


The Hu group has developed a series of Pd(0)-catalyzed domino processes, involving cross-coupling and C(sp^3)-H bond arylation of dihaloarenes with organometallic reagents.[46] Accordingly, a range of fluorene derivatives have been prepared in good to excellent yields (Scheme 1.16). The initial Pd(0)-catalyzed cross-coupling of a dihaloarene with an organometallic reagent produces intermediates of general structure **1.54**, which may undergo a traditional cross-coupling with a second equivalent of organometallic reagent or a

[46] (a) Dong, C.-G.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2289-2292; (b) Dong, C.-G.; Hu, Q.-S. *Org. Lett.* **2006**, *8*, 5057-5060; (c) Dong, C.-G.; Hu, Q.-S. *Tetrahedron* **2008**, *64*, 2537-2552; (d) Liu, T.-P.; Xing, C.-H.; Hu, Q.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 2909-2912.

"proximity-enabled" intramolecular benzylic C(sp^3)-H bond arylation. In their initial report, Dong and Hu found that the steric environment of the organometallic reagent dictated the fate of **1.54**.[46a] Indeed, the use of bulky (2,6-dimethylphenyl)magnesium bromide derivatives favoured benzylic C-H arylation by rendering the second intermolecular Kumada coupling challenging. While 1-bromo-2-iodoarenes and 1,2-dibromoarenes afforded the desired fluorenes, less expensive 1-chloro-2-haloarenes were not compatible substrates. The air and moisture sensitivity of Grignard reagents also decreased the synthetic utility of this transformation. Potentially the most important limitation of this method was the use of (2,6-dimethylphenyl)magnesium bromide derivatives, which provided fluorene derivatives bearing C-4 methyl groups. To avoid these limitations, the use of an organometallic reagent with diminished nucleophilicity was investigated, based on the hypothesis that it could decrease the rate of transmetalation and therefore disfavour the second intermolecular cross-coupling pathway without requiring additional steric bulk.[46d] Upon reoptimization of the reaction conditions, boronic acid derivatives proved to be optimal coupling partners. Beyond being air and moisture stable, these organometallic reagents did not require the same steric bias as their Grignard counterparts to favour intramolecular benzylic C-H arylation. The use of pivalic acid, as an additive, in combination with a carbonate base proved crucial to observing the desired reactivity, as had been previously observed in intramolecular alkane arylation reactions.[39,40] The later observations potentially suggest a common mechanism for C(sp^3)-H bond cleavage in these alkane arylation processes.

Scheme 1.16 Domino Pd(0)-catalyzed cross-coupling/benzylic C-H arylation of dihaloarenes with organometallic reagents



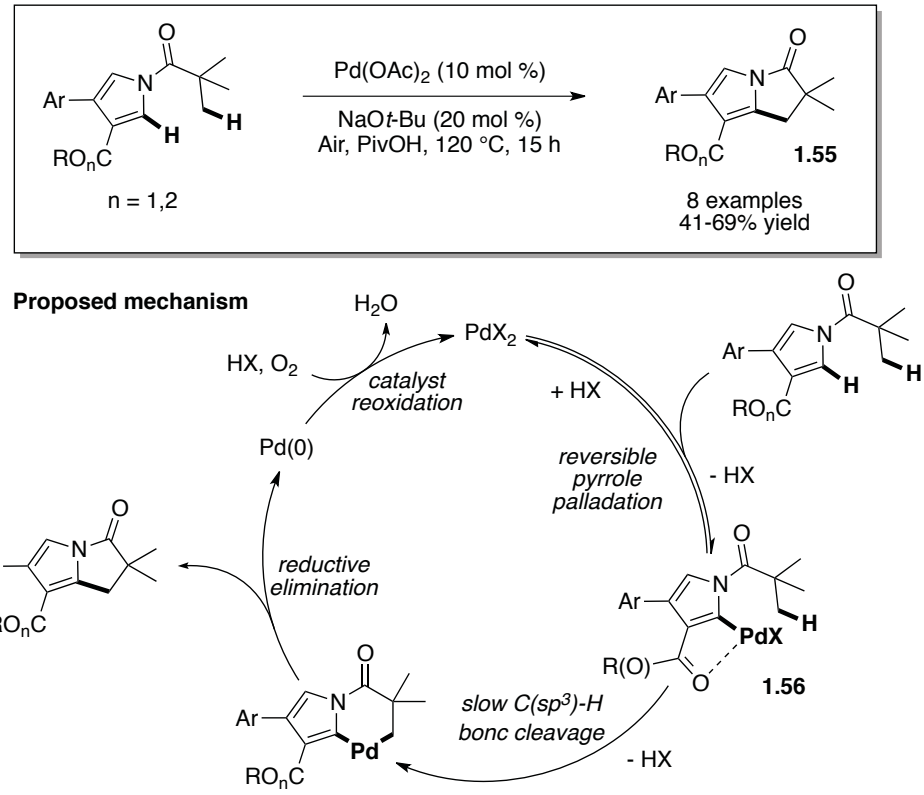
1.2.2.2 Metalation-Induced Pd(II)-Catalyzed Alkane Arylation

A single limited example of metalation-induced intramolecular Pd-catalyzed alkane arylation reaction has been reported to date, involving C(sp^2)-H/C(sp^3)-H oxidative coupling.[47] This type of transformation represents the chemical ideal for atom economy, since no elements of preactivation are required for C-C bond formation. As previously highlighted, direct palladation of an electron-rich heteroarene via C(sp^2)-H bond cleavage can generate an electrophilic Pd(II) species, which can promote C(sp^3)-H bond arylation (Scheme 1.9). In 2008, Liégault and Fagnou reported the intramolecular coupling of pyrroles with unactivated methyl groups, using air as the terminal oxidant (Scheme 1.17). The amount of base was found to be crucial: slightly more base than Pd source afforded

[47] Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841-4843.

optimal product yields. Using 10 mol % $Pd(OAc)_2$, 20 mol % NaO*t*-Bu in PivOH at 110 °C under an atmosphere of air, functionalized pyrroles (**1.55**) were obtained as single regioisomers in moderate to good yields. Significantly lower product yields were obtained in the absence of aromatic and electron-withdrawing (esters and ketones) substituents in the starting material. Deuterium-labeling studies led the authors to postulate a mechanism involving initial reversible pyrrole palladation with subsequent rate-determing C(sp^3)-H bond cleavage. Additionally, these experiments revealed that reversible palladation occurred at the 2- and 5-positions of the pyrrole ring, despite complete selectivity for C-C bond formation adjacent to the carbonyl group. The latter may therefore play a crucial role in stabilizing Pd(II)-intermediate **1.56**, allowing the slower aliphatic C-H bond-cleaving event to occur.

Scheme 1.17 Pd(II)-catalyzed intramolecular oxidative coupling of arenes and alkanes



1.3 Mechanistic Aspects of Pd-Catalyzed C(sp^3)-H Bond Arylation

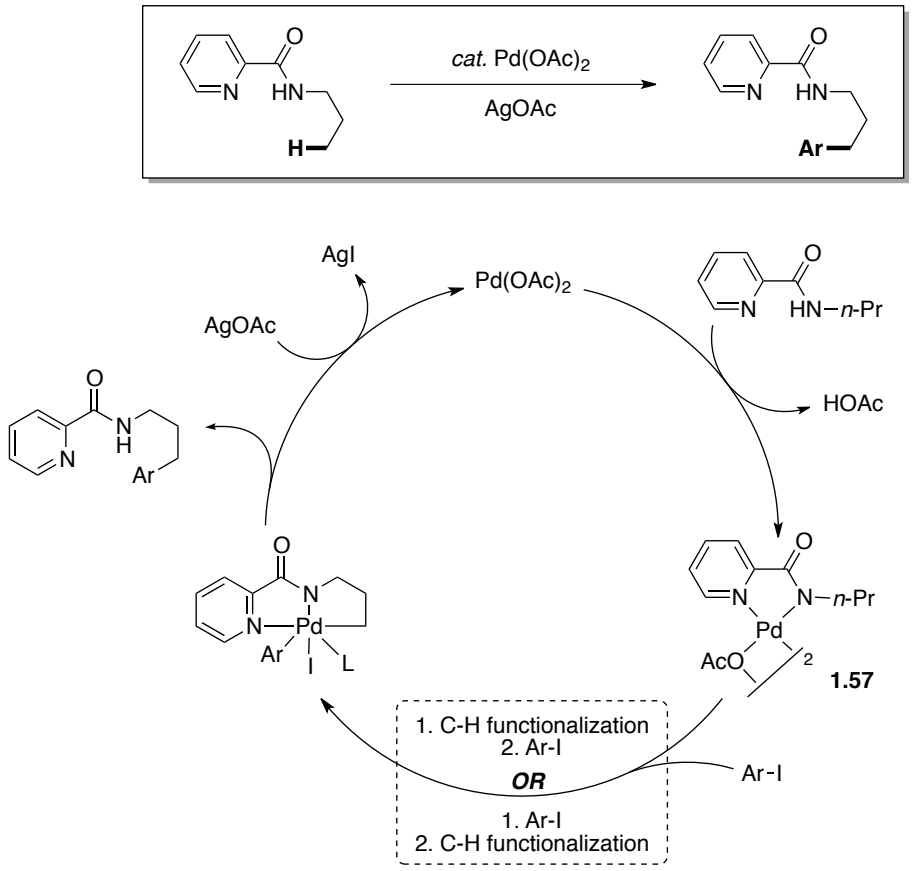
As evidenced by the literature overview in Section 1.2, significant advances in the field of Pd-catalyzed alkane arylation have been limited until the last decade. This may be due to the lack of knowledge related to the mechanism of these transformations, particularly with respect to C-H bond cleavage. In the following sections, recent mechanistic studies on these processes will be presented, including computational, kinetic and stoichiometric experiments. First, the mechanism of auxiliary-directed Pd(II)-catalyzed arylation of primary and secondary C(sp^3)-H bonds will be discussed in Section 1.3.1. In Section 1.3.2, evidence suggesting a common mechanism in "proximity-enabled" Pd(0)-catalyzed intramolecular alkane arylation will be displayed.

1.3.1 Mechanism of Auxiliary-Assisted Pd(II)-Catalyzed Alkane Arylation

Section 1.2.1.3 highlighted the parameters and scope of auxiliary-directed alkane arylation, pioneered by Daugulis and co-workers. In their seminal report, a Pd(II)/Pd(IV) catalytic cycle was proposed (Scheme 1.18).[24] While indirect evidence for cyclopalladated intermediate **1.57** had been obtained,[48] uncertainty remained as to the order of events between C(sp^3)-H bond functionalization and aryl iodide coupling.

[48] An analogous intermediate to **1.57** (where *n*-Pr was replaced by Bn) was isolated and characterized by X-Ray crystallography. See ref 24.

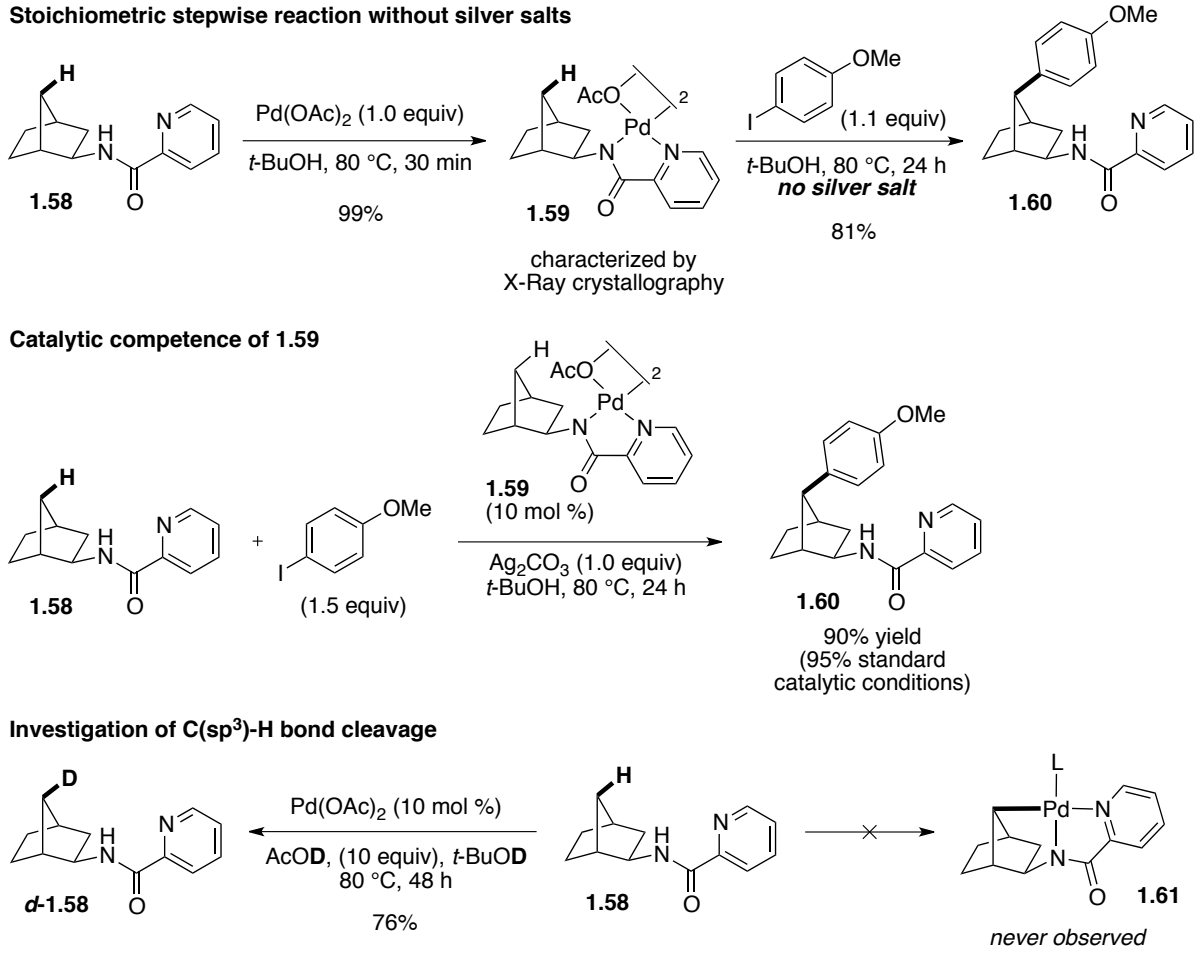
Scheme 1.18 First proposed mechanism for auxiliary-directed alkane arylation



In 2011, He and Chen further investigated the mechanism of picolinamide-directed C(sp^3)-H bond arylation (Scheme 1.19).[25d] Treatment of picolinamide derivative **1.58** with 1.0 equivalent of $Pd(OAc)_2$ in *t*-BuOH at 80 °C for 30 min yielded quantitative amounts of a yellow solid. X-Ray crystallography confirmed that the product was Pd dimer **1.59**. Dimer **1.59** was coupled with 1.1 equivalents of aryl iodide under standard reaction conditions, with the exception of 1.0 equivalent of Ag_2CO_3 additive, to provide compound **1.60** in 81% yield (compared to 95% for the standard catalytic reaction). Product formation from **1.59** in the absence of Ag_2CO_3 suggested that silver additives were not required for carbon-carbon bond formation and thus, may instead play a role in catalyst regeneration. Additional support for **1.59** as a relevant catalytic intermediate was obtained by evaluating its catalytic competence. Indeed, when 10 mol % **1.59** was used as a catalyst instead of $Pd(OAc)_2$, product **1.60** was generated in comparable yield to the standard conditions. In order to further evaluate the

mechanism of C(sp^3)-H bond cleavage, conversion of picolinamide **1.58** to C(sp^3)-H palladated intermediate **1.61** was attempted. Unfortunately, **1.61** was never observed. However, deuterium-labeling experiments provided insight into the order of events between C-H bond functionalization and aryl iodide coupling. Submitting **1.58** to 10 mol % $Pd(OAc)_2$ and 10 equivalents of AcOD in deuterated *t*-BuOD at 80 ºC for 48 hours led to 76% deuterium incorporation *in the absence of aryl iodide*. This result indicated that alkane palladation occurs in the absence of aryl iodide, suggesting that C(sp^3)-H functionalization occurs prior to aryl iodide coupling in the catalytic cycle.

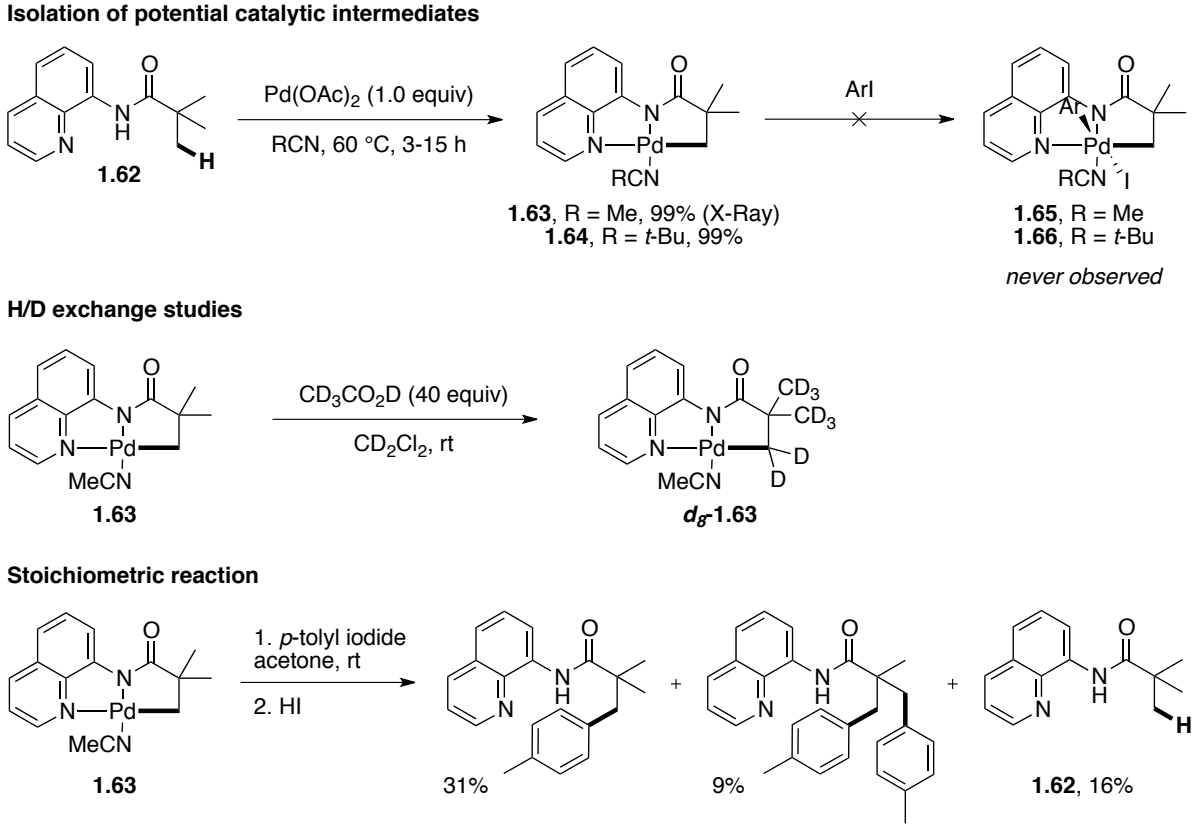
Scheme 1.19 Mechanistic studies for picolinamide-directed alkane arylation



While He and Chen were unable to isolate palladated intermediate **1.61**, Shabashov and Daugulis found that treatment of 8-aminoquinoline pivalamide (**1.62**) with 1.0 equivalent

of $Pd(OAc)_2$ in nitrile solvents, afforded the desired palladacycles **1.63** and **1.64** as yellow-green crystals in 99% yield (Scheme 1.20).[25c] Unfortunately, conversion of **1.63**/**1.64** to the postulated Pd(IV) intermediate **1.65**/**1.66** was not successful. Nevertheless, access to Pd(II)-intermediate **1.63** enabled the further investigation of C(sp^3)-H bond cleavage in these transformations. Compound **1.63** was treated with 40 equivalents of CD_3CO_2D and the rate of H/D exchange was monitored by ^1H NMR. Within minutes, complete conversion to ***d*$_8$-1.63** was observed, indicating that Pd-catalyzed C(sp^3)-H bond cleavage is a fast, reversible process at this temperature and on this time scale. Finally, the relevance of **1.63** as a catalytic intermediate was demonstrated by its successful stoichiometric coupling with 5.0 equivalents of *p*-tolyl iodide in acetone at room temperature. Subsequent removal of Pd salts by addition of HI revealed a mixture of mono- and diarylated products, correlating with previous catalytic results. Product formation in the absence of a silver salt supports He and Chen's conclusion that the latter is likely responsible for catalyst regeneration.

Scheme 1.20 Mechanistic studies for 8-aminoquinoline-directed alkane arylation



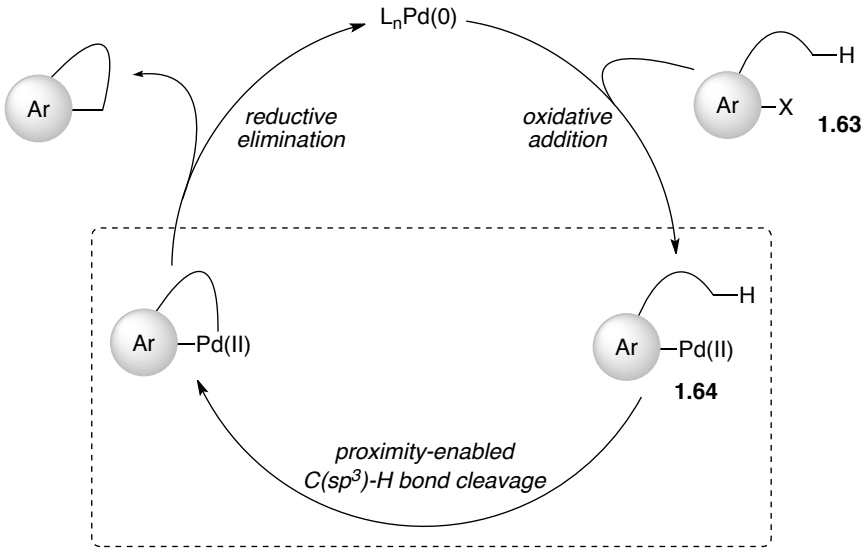
The results of both mechanistic studies lend support to Daugulis' original mechanistic proposal for auxiliary-directed Pd(II)-catalyzed alkane arylation (Scheme 1.18). Evidence strongly suggests that C(sp^3)-H bond functionalization occurs prior to reaction with the aryl iodide component. Direct evidence for Pd(IV)-intermediates in the catalytic cycle remains elusive and the potential formation of Pd(III)-species has been recognized.[23] More pertinent to the upcoming discussion in Section 1.3.2, very little attention has been focused on the mechanism of Pd-catalyzed C(sp^3)-H bond cleavage thus far.

1.3.2 Mechanism of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Oxidative Addition-Induced Alkane Arylation

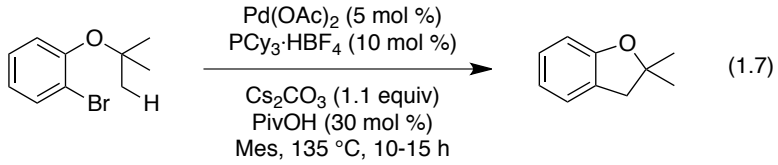
The general catalytic cycle for intramolecular oxidative addition-induced alkane arylation is depicted in Scheme 1.21. Oxidative addition of aryl halide **1.63** to the Pd(0)-catalyst produces Pd(II)-intermediate **1.64**, which can undergo C(sp^3)-H bond cleavage with subsequent reductive elimination to yield the desired product. Recent reports by Fagnou[39] as well as Clot and Baudoin[38c,49] have led to a better understanding of the mechanism of C(sp^3)-H bond cleavage. Based on density functional theory (DFT) calculations (*vide infra)*, a concerted metalation-deprotonation (CMD) pathway has been proposed, similar to arylations at C(sp^2)-H bonds.[50]

[49] Kefalidis, C. E.; Baudoin, O.; Clot, E. *Dalton Trans.* **2010**, *39*, 10528-10535.
[50] For selected reviews on C-H bond cleavage via a CMD pathway, see: (a) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727-2734; (b) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820-5831; (c) Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749-823; (d) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118-1126; (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315-1345.

Scheme 1.21 General catalytic cycle for Pd(0)-catalyzed oxidative addition-induced alkane arylation

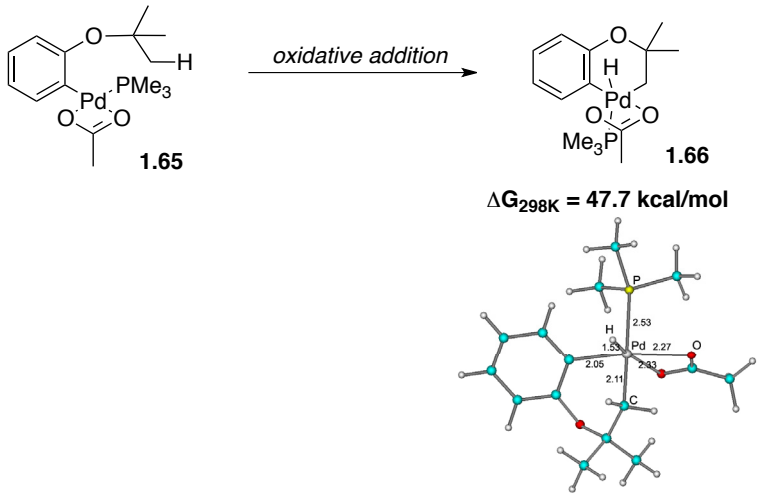


In their 2007 report, Fagnou and coworkers examined C-H bond cleavage in the context of dihydrobenzofuran synthesis (eq 1.7) using DFT calculations at the B3LYP/DZVP level of theory.[39] The relevance of a Pd(IV) pathway, involving oxidative addition of the C-H bond to Pd(II)-intermediate **1.65**, was first examined and quickly eliminated due to the high energy associated with Pd(IV) alkyl-hydride **1.66** (Scheme 1.22).



(1.7)

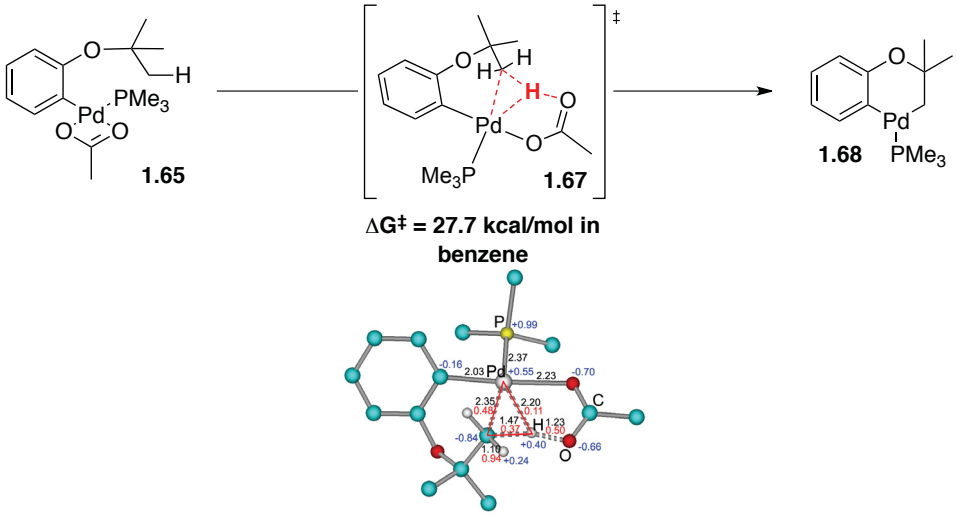
Scheme 1.22 Energy and structure of the potential Pd(IV) alkyl-hydride intermediate



However, direct C-H bond cleavage from Pd(II)-intermediate **1.65** via transition state (TS) **1.67** to yield palladacycle **1.68** was determined to be much more energetically favourable (Scheme 1.23). Indeed, TS **1.67**, corresponding to a concerted metalation-deprotonation, was located at $\Delta G^{\ddagger}$ = 27.7 kcal/mol in benzene. Of note, **1.67** featured a three-center two-electron agostic interaction between the Pd(II) center and the C(sp^3)-H bond being cleaved, leading to a significant weakening of the latter.[51] The pivalic acid additive was found to be intimately involved in this transition state, acting as an intramolecular base for proton abstraction. It should be noted that the phosphine ligand (PCy_3) and the pivalate base were modeled as PMe_3 and acetate, respectively, as was common in C-H functionalization calculations. Since this communication, evidence has appeared to indicate that the use of simplified phosphines and bases can lead to distorted transition states, which may not provide a complete account of the parameters that guide C-H bond cleavage.[49]

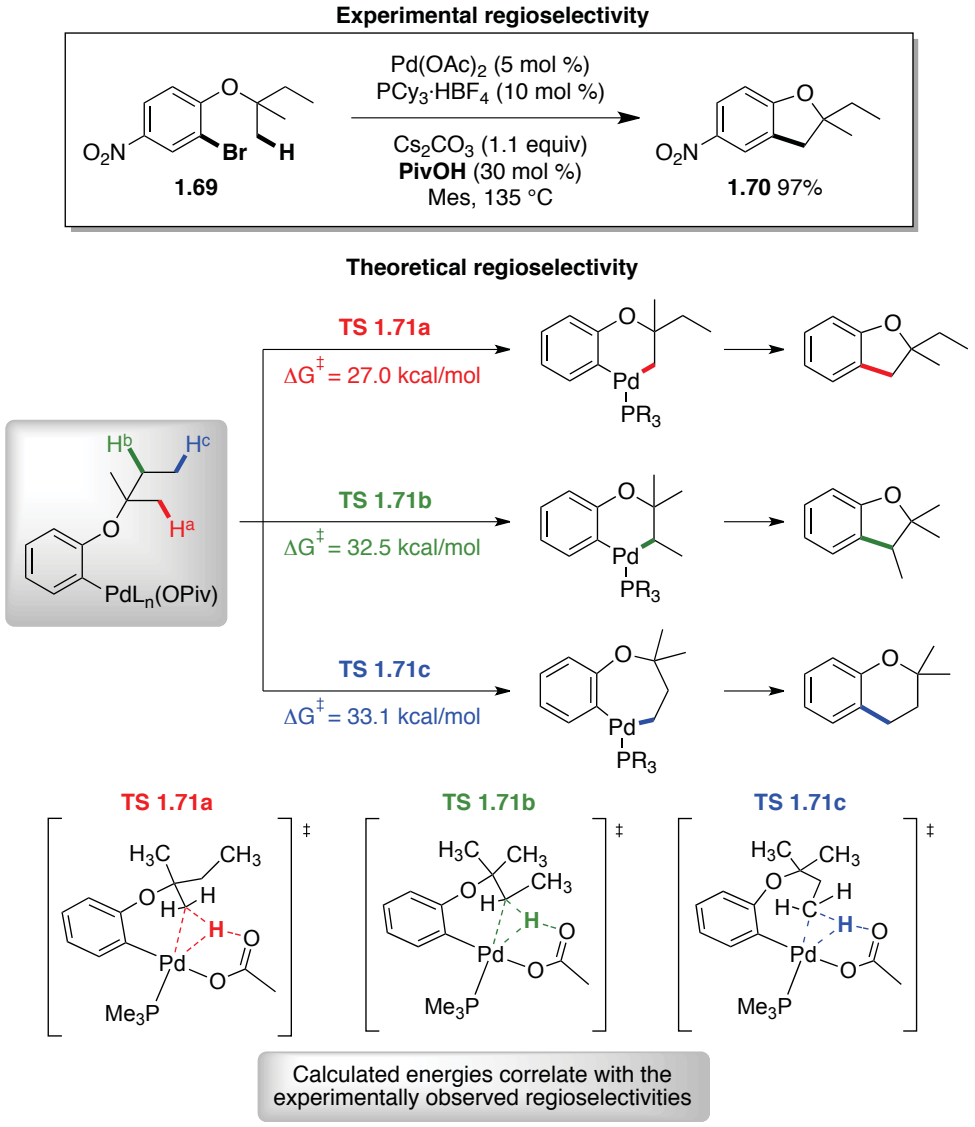
[51] For a review on agostic interactions in transition metal compounds, see: Brookhart, M.; Green, M. L. H.; Parkin, G. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 6908-6914.

Scheme 1.23 Concerted metalation-deprotonation transition state for C-H bond cleavage



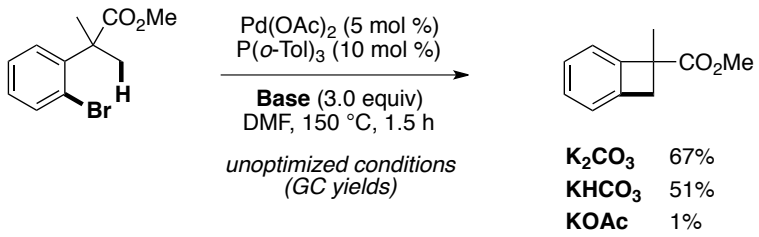
To provide additional support for this mechanism, the correlation between experimental and theoretical results for regioselective alkane arylation via the CMD pathway was studied (Scheme 1.24). As was highlighted in Section 1.2.2.1, these reactions demonstrated complete regioselectivity for arylation of primary aliphatic C-H bonds. For example, aryl bromide **1.69** furnished dihydrobenzofuran **1.70** in 97% yield. When the selectivity for arylation at **H^a** over **H^b** and **H^c** was examined theoretically, the CMD pathway predicted a clear energetic preference for primary C(sp^3)-**H^a** bond cleavage. Arylation at methylene C-**H^b** was 5.5 kcal/mol higher in energy while functionalization of the more remote methyl group (**H^c**) was the least favoured (+6.1 kcal/mol). This excellent correlation between theoretical results and experimental observations provides further credibility to the proposed CMD transition state for C(sp^3)-H bond cleavage.

Scheme 1.24 Correlation between experimental and theoretical regioselectivity



Clot and Baudoin have performed an in-depth computational study on the mechanism of benzocyclobutene formation *via* Pd(0)-catalyzed alkane arylation.[38c,49] DFT calculations at the B3PW91 level of theory were employed to investigate the elemental steps of the catalytic cycle: oxidative addition, anionic ligand exchange (bromide for base), C(sp^3)-H bond cleavage and reductive elimination. Special attention was focused on the influence of the base throughout these steps. It should be noted that, experimentally, K_2CO_3 proved optimal, while $KHCO_3$ led to diminished yields and KOAc provided less than 5% of the desired product (Scheme 1.25).

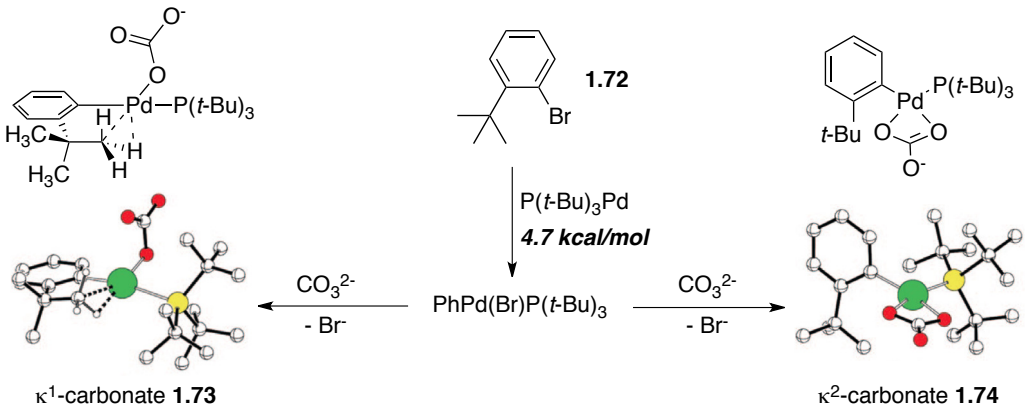
Scheme 1.25 Influence of the base on benzocyclobutene formation



2-Bromo-*tert*-butylbenzene **1.72** was chosen as a model substrate as it reacted experimentally in 46% yield and lacked functional groups that could affect the reaction mechanism. Oxidative addition of **1.72** to Pd(0) was found to be very facile, with an activation barrier of 4.7 kcal/mol (Scheme 1.26). Bromide ligand exchange was significantly easier for carbonate than bicarbonate or acetate, affording two potential new catalytic intermediates: κ^1-carbonate **1.73** and κ^2-carbonate **1.74**. Intermediate **1.73** features a stabilizing agostic interaction with an aliphatic C-H bond of the *tert*-butyl substituent. κ^2-Carbonate **1.74** is reminiscent of intermediate **1.65** (κ^2-acetate) from Fagnou's work (Scheme 1.23). It should be noted that these calculations do not address the lack of solubility of carbonate bases under these conditions. Indeed, previous reports of C(sp^2)-H arylation reactions have demonstrated that alkali metal carbonate bases are sparingly soluble in DMA at temperatures greater than 100 ºC.[52] In these cases, an inner-sphere *acetate-promoted* C-H bond cleavage has been invoked, with the *$Pd(OAc)_2$ precatalyst acting as the source of base*.[34]

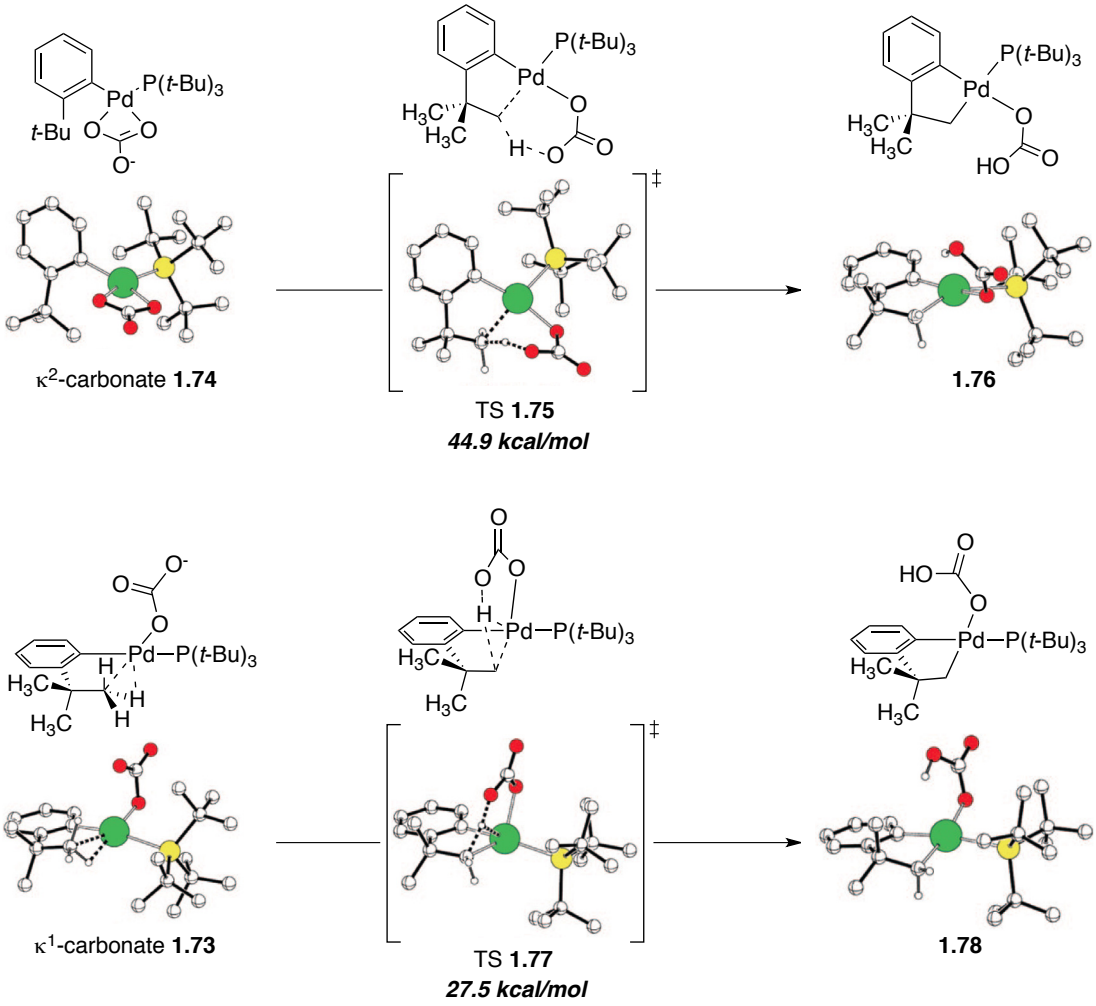
[52] Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581-590.

Scheme 1.26 Lowest energy pathways for oxidative addition and ligand exchange



C(sp^3)-H bond cleavage from κ^2-carbonate intermediate **1.74** appeared to proceed via a concerted metalation-deprotonation transition state **1.75** similar to the one proposed by Fagnou (**1.67**, Scheme 1.27). The carbonate ligand enabled intramolecular proton abstraction to generate cyclopalladated intermediate **1.76**. However, the activation barrier for TS **1.75** (44.9 kcal/mol) was found to be much greater than those previously reported for CMD transition states.[50] When cyclopalladation of κ^1-carbonate **1.73** was explored, CMD transition state **1.77** of significantly lower energy (27.5 kcal/mol) was uncovered. In this TS, proton transfer to the uncoordinated oxygen of the carbonate ligand occurs in the plane perpendicular to Ph-Pd-P(*t*-Bu)$_3$.

Scheme 1.27 Transition states for C-H bond cleavage from **1.71** and **1.72**



Finally, C(sp^2)-C(sp^3) bond formation via reductive elimination from intermediate **1.78** was found to be more facile than C(sp^3)-H palladation (TS energy = 22.5 kcal/mol) despite the formation of a strained 4-membered ring benzocyclobutene product.

The reports of Baudoin/Clot and Fagnou both support a rate-limiting C(sp^3)-H bond cleavage in Pd(0)-catalyzed alkane arylation. Similar intramolecular base-assisted CMD transition states, featuring agostic Pd···C-H interactions, were found in both cases. However, while Fagnou reported C-H bond cleavage from κ^2-acetate intermediate **1.65**, Baudoin/Clot found that palladation from κ^1-carbonate intermediate **1.73** proceeded via a lower energy pathway. While these results correlate with experimental outcomes and provide initial

insight into the mechanism of C(sp^3)-H bond cleavage, crucial reaction properties (for example solubility) are not taken into account in these calculations.

1.4 Perspectives

Enormous progress in the field of alkane arylation is apparent by the numerous strategies and methods that have been developed in recent years. Pd(II)-catalyzed processes enable efficient *intermolecular* C(sp^3)-H arylation. High levels of regioselectivity are typically obtained due to the use of directing groups. While significant progress is being made towards the application of removable auxiliaries as directing groups, the use of organometallic reagents as the source of arene and/or the addition of stoichiometric amounts of oxidant for catalyst turnover remains a limitation.

Our group has investigated the use of Pd(0) catalysis in alkane arylation. As previously mentioned, the ability to use inexpensive, easily prepared aryl bromides and chlorides as coupling partners, in addition to the general functional group tolerance of Pd(0) catalysis, makes it an attractive alternative to Pd(II) catalysis. Currently, examples of Pd(0)-catalyzed C(sp^3)-H arylation are almost exclusively limited to *intramolecular* reactions at *methyl groups*. These limitations are most likely due to our poor mechanistic understanding, which is based on theoretical investigations. Thus, experimental mechanistic studies are warranted to provide opportunities for the design of improved catalytic systems. Ultimately these will lead to new directions in alkane arylation, including highly selective intermolecular and/or enantioselective reactions.

2 Intramolecular Alkane Arylation from Aryl Chlorides

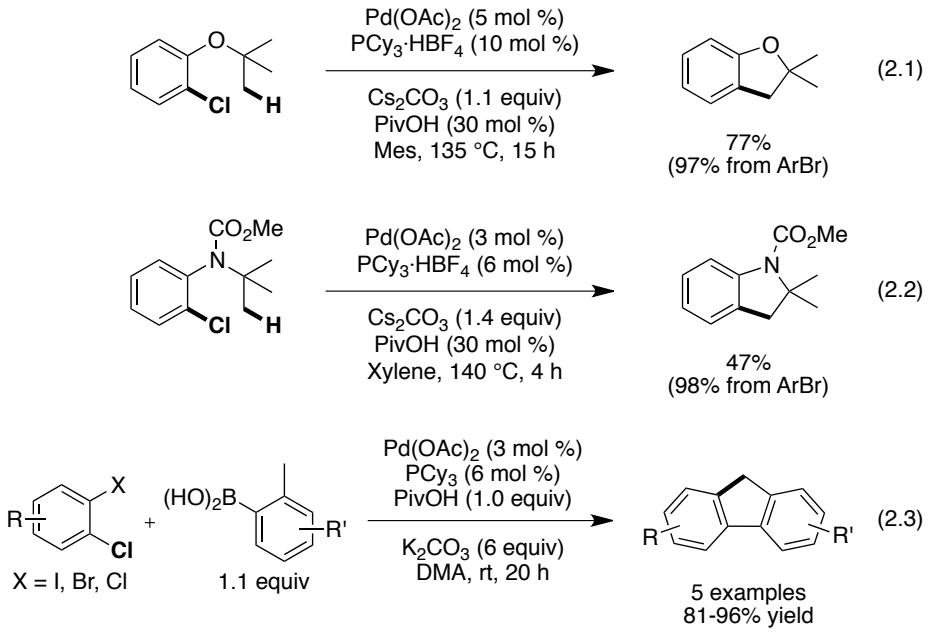
2.1 Background

Recent efforts in the context of Pd(0)-catalyzed intramolecular C(sp^3)-H arylation have enabled the synthesis of a broad scope of carbocycles and heterocycles (Section 1.2.2.1). Aryl halides remain the preferred source of arene coupling partner under this catalytic manifold since the C-X bond enables the necessary change in catalyst oxidation state, from Pd(0) to Pd(II), for C-H bond functionalization to occur. Literature reports have almost exclusively employed aryl iodides or bromides as coupling partners, and the limited use of aryl chlorides is unexpected considering their use in traditional cross-coupling reactions.[53] This may be attributed to the greater strength of the C-Cl bond, rendering oxidative addition less facile,[54] in combination with the challenge in functionalizing C(sp^3)-H bonds.[4k,11] Of note, a similar trend has been observed in C(sp^2)-H bond functionalization reactions.[10] This may be due to efforts in catalyst development that have centered around facilitating the C-H bond functionalization step of the catalytic cycle, neglecting more established oxidative addition and reductive elimination processes.

Previous examples of intramolecular Pd(0)-catalyzed alkane arylation from aryl chlorides are almost solely limited to those found in equations 2.1-2.3. In their initial communications, Fagnou[39] as well as Fujii and Ohno[40] reported single examples of heterocycle formation (dihydrobenzofuran and indoline, respectively) from the

[53] For a review on the use of aryl chlorides in palladium-catalyzed coupling reactions, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176-4211.
[54] Bond dissociation energies for Ph-X: Cl = 95.5 kcal/mol; Br = 80.4 kcal/mol; I = 65.0 kcal/mol. Luo, Y. R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, FL, 2003; Chapter 5.

corresponding aryl chloride starting materials (eqs 2.1 and 2.2). Hu and coworkers also reported the use of aryl chloride coupling partners with their second-generation conditions for the domino cross-coupling/benzylic C-H arylation of dihaloarenes with boronic acid derivatives (eq 2.3).[46d]



The greater number of commercially available aryl chlorides (and their lower cost) make these coupling partners attractive alternatives to aryl iodides and bromides for future reaction development. In this chapter, the expanded scope of palladium-catalyzed intramolecular alkane functionalization from aryl chlorides will be described. DFT calculations revealing additional knowledge on the parameters for regioselective C(sp^3)-H bond functionalization will also be presented. Experimental and theoretical portions of this work were performed in collaboration with the Baudoin group (University Claude Bernard Lyon 1, France) and Clot group (University Montpellier 2, France), respectively. Section 2.2.1 represents work done at the University of Ottawa while the computational results in Section 2.2.2 were obtained by Christos E. Kefalidis and Eric Clot. Portions of this Chapter have been reproduced with permission from Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716. Copyright 2010 American Chemical Society.

2.2 Results and Discussion

2.2.1 Reaction Development and Scope

Prior to this work, our group had developed reaction conditions for the formation of 2,2-dialkyldihydrobenzofurans from aryl bromides via C(sp^3)-H bond arylation (Scheme 1.14).[39] Given the relevance of this motif in biological[55] and medicinal[56] compounds (Figure 2.1), the use of aryl chlorides for its formation was investigated.

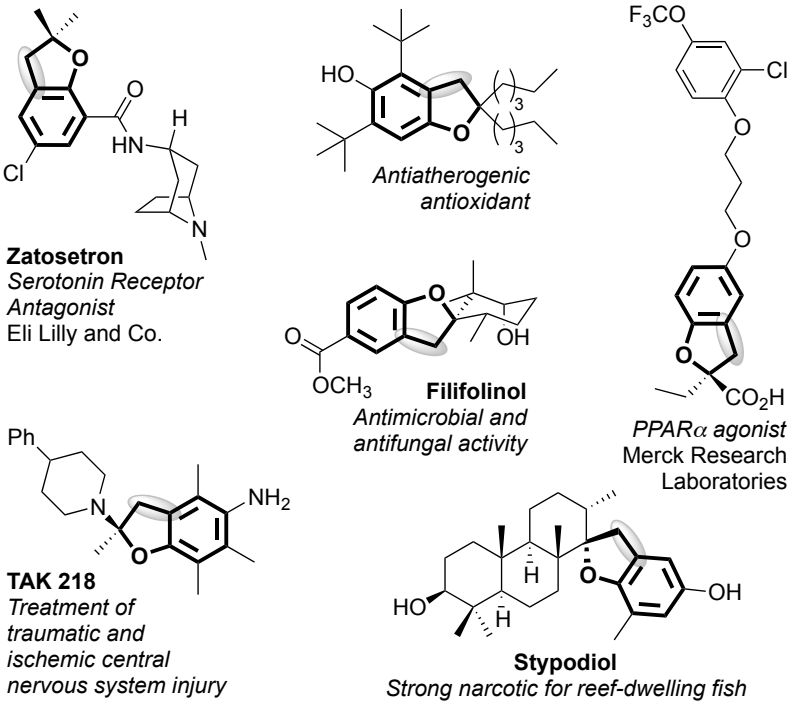


Figure 2.1 Biologically active and medicinally relevant compounds containing the 2,2-dialkyldihydrobenzofuran motif

[55] (a) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1981**, *46*, 22-27. (b) Torres, R.; Villarroel, L.; Urzua, A.; Delle Monache, F.; Delle Monache, G.; Gacs-Baitz, E. *Phytochemistry* **1994**, *36*, 249-250.

[56] (a) Cohen, M. L.; Bloomquist, W.; Gidda, J. S.; Lacefield, W. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 350-355. (b) Ohkawa, S.; Fukatsu, K.; Miki, S.; Hashimoto, T.; Sakamoto, J.; Doi, T.; Nagai, Y.; Aono, T. *J. Med. Chem.* **1997**, *40*, 559-573. (c) Tamura, K.; Kato, Y.; Ishikawa, A.; Kato, Y.; Himori, M.; Yoshida, M.; Takashima, Y.; Suzuki, T.; Kawabe, Y.; Cynshi, O.; Kodama, T.; Niki, E.; Shimizu, M. *J. Med. Chem.* **2003**, *46*, 3083-3093. (d) Shi, G. Q.; Dropinski, J. F.; Zhang, Y.; Santini, C.; Sahoo, S. P.; Berger, J. P.; MacNaul, K. L.; Zhou, G.; Agrawal, A.; Alvaro, R.; Cai, T.-q.; Hernandez, M.; Wright, S. D.; Moller, D. E.; Heck, J. V.; Meinke, P. T. *J. Med. Chem.* **2005**, *48*, 5589-5599.

When aryl chloride **2.1**, possessing an *ortho tert*-butoxy substituent, was subjected to $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Cs_2CO_3 (1.1 equivalents) and PivOH (30 mol %) in mesitylene at 140 °C for 16 hours, the desired product **2.2** was generated in 77% yield (eq 2.1). Reaction optimization revealed that the conditions originally reported for alkane arylation from aryl bromides were also optimal for the use of aryl chlorides. Once again, a pronounced effect was observed with respect to the use of pivalic acid as an additive (Figure 2.2).[39,46d] In the absence of pivalic acid, product formation was not observed. A screen of catalytic or stoichiometric quantities of the additive revealed optimal results when 0.30 equivalents were employed.

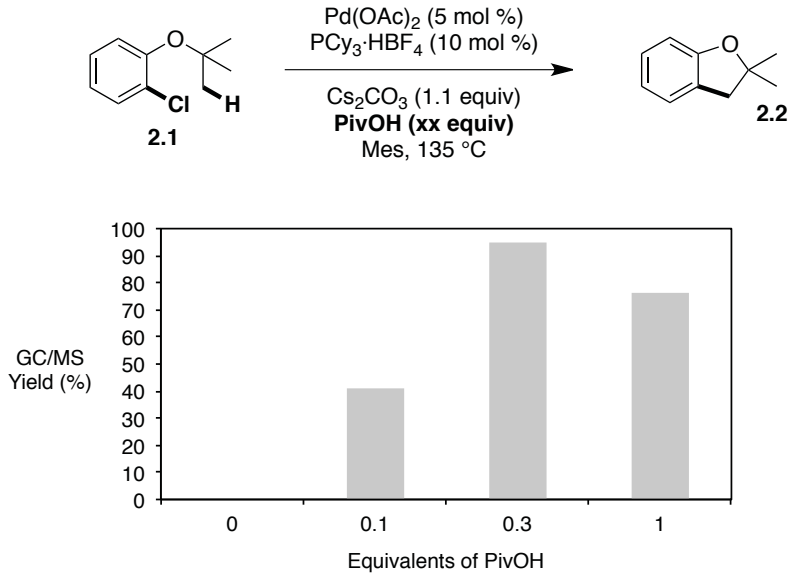
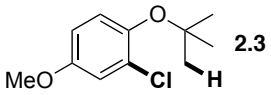
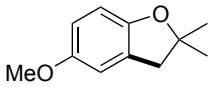
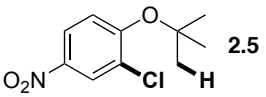
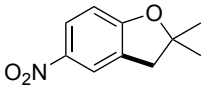
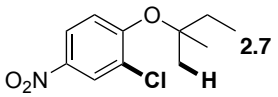
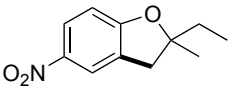
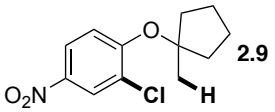
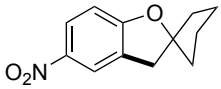
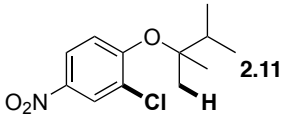
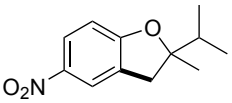
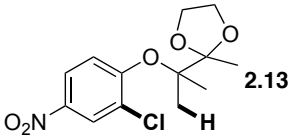
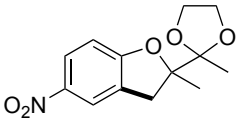
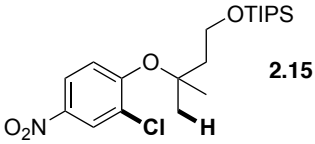
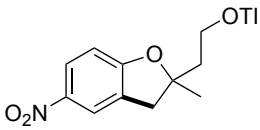
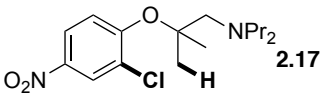
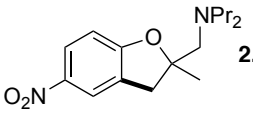


Figure 2.2 Effect of pivalic acid equivalents on the yield of **2.2**

The scope of this intramolecular C(sp^3)-H arylation from aryl chlorides is outlined in Table 2.1. Electron-donating (entry 1) and -withdrawing (entry 2) groups on the aromatic ring were well tolerated and generated the corresponding dimethyldihydrobenzofurans **2.4** and **2.6** in high yields (96% and 88% respectively). The reactions were highly regioselective, affording exclusively the products of ring closure at methyl C-H bonds over analogous methylene (**2.8** and **2.10**) or methyne (**2.12**) positions (entries 3-5). Additionally,

five-membered ring closure occurred preferentially over six-membered ring formation in substrates containing multiple methyl substituents (entries 3 and 5).

Table 2.1 Scope of dihydrobenzofurans synthesized by intramolecular C(sp^3)-H arylation[a]

Entry	Starting Material	Product	Yield (%)
1	 **2.3**	 **2.4**	96
2	 **2.5**	 **2.6**	88
3	 **2.7**	 **2.8**	84
4	 **2.9**	 **2.10**	64
5	 **2.11**	 **2.12**	77
6	 **2.13**	 **2.14**	95
7	 **2.15**	 **2.16**	87
8	 **2.17**	 **2.18**	55

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PCy_3{\cdot}HBF_4$ (10 mol %), Cs_2CO_3 (1.1 equiv), PivOH (30 mol %) and the starting material were heated to 140 °C in mesitylene for 16 hours.

The compatibility of this method with various functional groups was also investigated with aryl chlorides **2.13**, **2.15**, and **2.17**. The reaction of protected ketone **2.13** led to product

2.14 in 95% yield (Table 2.1, entry 6). Silyl-protected alcohols also reacted nicely, as exemplified by the formation of **2.16** in 87% yield from aryl chloride **2.15** (entry 7). Finally, a Lewis-basic tertiary amine was tolerated under the reaction conditions, albeit leading to the dihydrobenzofuran **2.18** in only 55% yield (entry 8).[57] Of note is the absence of product resulting from arylation at the more "activated" methylene C-H bond adjacent to the nitrogen heteroatom.[58]

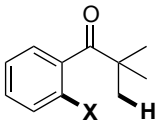
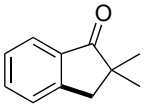
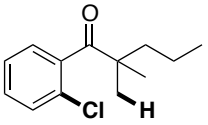
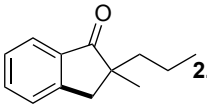
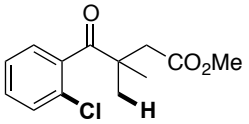
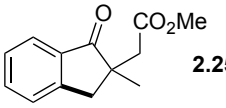
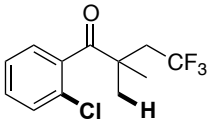
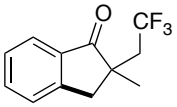
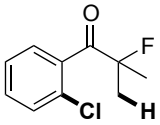
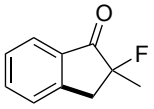
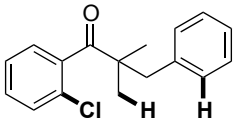
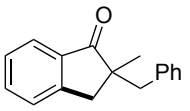
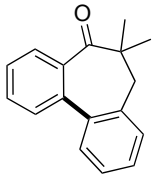
We next sought to extend this methodology to new substrate classes containing other challenging functional groups, which remained unexplored in Pd(0)-catalyzed alkane arylation. Accordingly, (*o*-chloro)ketophenones were chosen due to the potential unproductive coordination of the carbonyl group to Pd(II), rendering C(sp^3)-H bond cleavage impossible. When these substrates were submitted to the conditions previously developed for dihydrobenzofuran synthesis (Table 2.1), the desired indanones were obtained in good to excellent yields (Table 2.2). Enhanced reactivity was observed with this substrate class and the catalyst loading was decreased to 2 mol % without affecting the product yield (Table 2.2, entry 1). This could be explained by the activation of the C-Cl bond toward oxidative addition by the presence of an *ortho* electron-withdrawing group. Aryl bromides were found to react under these conditions, as demonstrated by the formation of **2.21** from **2.20** in 98% yield (entry 2). The reaction of chloride **2.22**, bearing a *n*-propyl substituent, also furnished indanone **2.23** selectively but in a moderate 50% yield (entry 3). In the presence of an acidic C(sp^3)-H bond, known to readily undergo Pd(0)-catalyzed α-arylation,[13] this catalyst system favours reactivity at the less activated but more sterically accessible methyl C-H bond (entry 4). Substrate **2.26**, containing a trifluoromethyl functional group, reacted smoothly and regioselectively to afford **2.27** in 89% yield (entry 5). The arylation of **2.28**, containing a fluorine atom adjacent to the keto group, produced fluorinated indanone **2.29** in a moderate 47% yield (entry 6). Aryl chloride **2.30** demonstrates the preference for methyl C-H bond arylation over functionalization of the typically more reactive benzylic C(sp^3)-H and aryl C(sp^2)-H bonds (entry 7).[4] Indeed, indanone **2.31a** was isolated as the major product in 65% yield, together with the direct C(sp^2)-H arylation product **2.31b** in 32% yield, while no

[57] The diminished yield for **2.18** was due to isolation problems. Under these conditions, complete conversion of **2.17** is observed and **2.18** is generated in 85% ^{1}H NMR yield.
[58] For a review on transformations at C(sp^3)-H bonds alpha to nitrogen in heterocycles, see: Campos, K. *Chem. Soc. Rev.* **2007**, *36*, 1069-1084.

product resulting from arylation at the benzylic C(sp^3)-H bond was detected. These results (Table 2.2, entries 4, 5, and 7), combined with those for amine **2.17** (Table 2.1, entry 8) as well as with previous data,[38c,39] appear to indicate that steric interactions contribute significantly to reaction site selectivity. These may override electronic influences at the methylene C(sp^3)-H bond known to promote reactivity, such as the α-heteroatom effect[59] in **2.17** and acidity in **2.24**, **2.26**, and **2.30**.

[59] For selected reviews on the α-heteroatom effect, see: (a) Murahashi, S.-I.; Takaya, H. *Acc. Chem. Res.* **2000**, *33*, 225-233. (b) Murahashi, S.-I. In *Handbook of C-H Transformations*; Dyker, G.; Wiley-VCH: Weinheim, 2005; Vol. 2, pp 319-326.

Table 2.2 Scope of indanones synthesized by intramolecular C(sp^3)-H arylation[a]

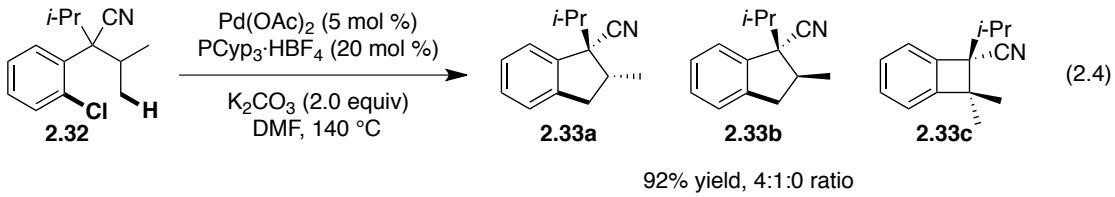
Entry	Starting Material	Product	Yield (%)
1	 X = Cl **2.19**	 **2.21**	93[b]
2	X = Br **2.20**		98
3	 **2.22**	 **2.23**	50
4	 **2.24**	 **2.25**	77
5	 **2.26**	 **2.27**	89
6	 **2.28**	 **2.29**	47
7	 **2.30**	 **2.31a**	65
		 **2.31b**	32

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Cs_2CO_3 (1.1 equiv), PivOH (30 mol %) and the starting material were heated to 140 °C in mesitylene for 16 hours. [b] 2 mol% $Pd(OAc)_2$

2.2.2 Mechanistic Insight

In collaboration with Kefalidis and Clot, the parameters of *regioselective* intramolecular C(sp^3)-H functionalization were examined in greater detail. DFT calculations, performed at the B3PW91 level of theory, were used to examine different mechanistic pathways in substrates where regioselective C(sp^3)-H bond cleavage occurs. Calculations were performed on substrate **2.32**, which was studied experimentally in the portion of this work performed by the Baudoin group (eq 2.4). Using a catalyst based on

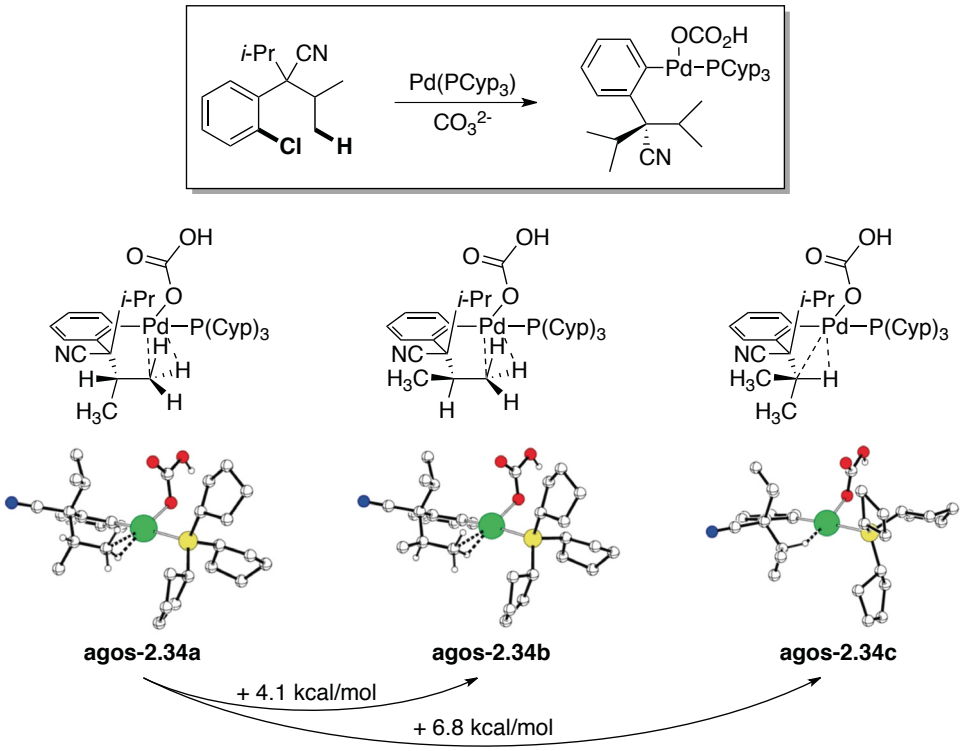
$Pd(OAc)_2$ and $PCyp_3 \cdot HBF_4$, indanes **2.33a** and **2.33b** were generated in 92% yield and 4:1 dr. No benzocyclobutene **2.33c** formation, from arylation of the tertiary C-H bond, was observed in this case.



(2.4)

Based on previous calculations (Section 1.3.2),[38c] Kefalidis and Clot examined $C(sp^3)$-H bond cleavage, via a concerted metalation-deprotonation transition state, leading to products **2.33a-c**. Following oxidative addition of the C-Cl bond to Pd(0) and ligand exchange from chloride to carbonate, three potential catalytic intermediates featuring an agostic Pd···C-H interaction can be located: **agos-2.34a**, **agos-2.34b** and **agos-2.34c**. These intermediates are the catalytic precursors to **2.33a**, **2.33b** and **2.33c** respectively. **Agos-2.34a** is 4.1 kcal/mol and 6.8 kcal/mol more stable than **agos-2.34b** and **agos-2.34c**, respectively, due to a shorter Pd···C bond distance (Scheme 2.1).

Scheme 2.1 Formation of catalytic intermediates containing an agostic Pd···C-H interaction

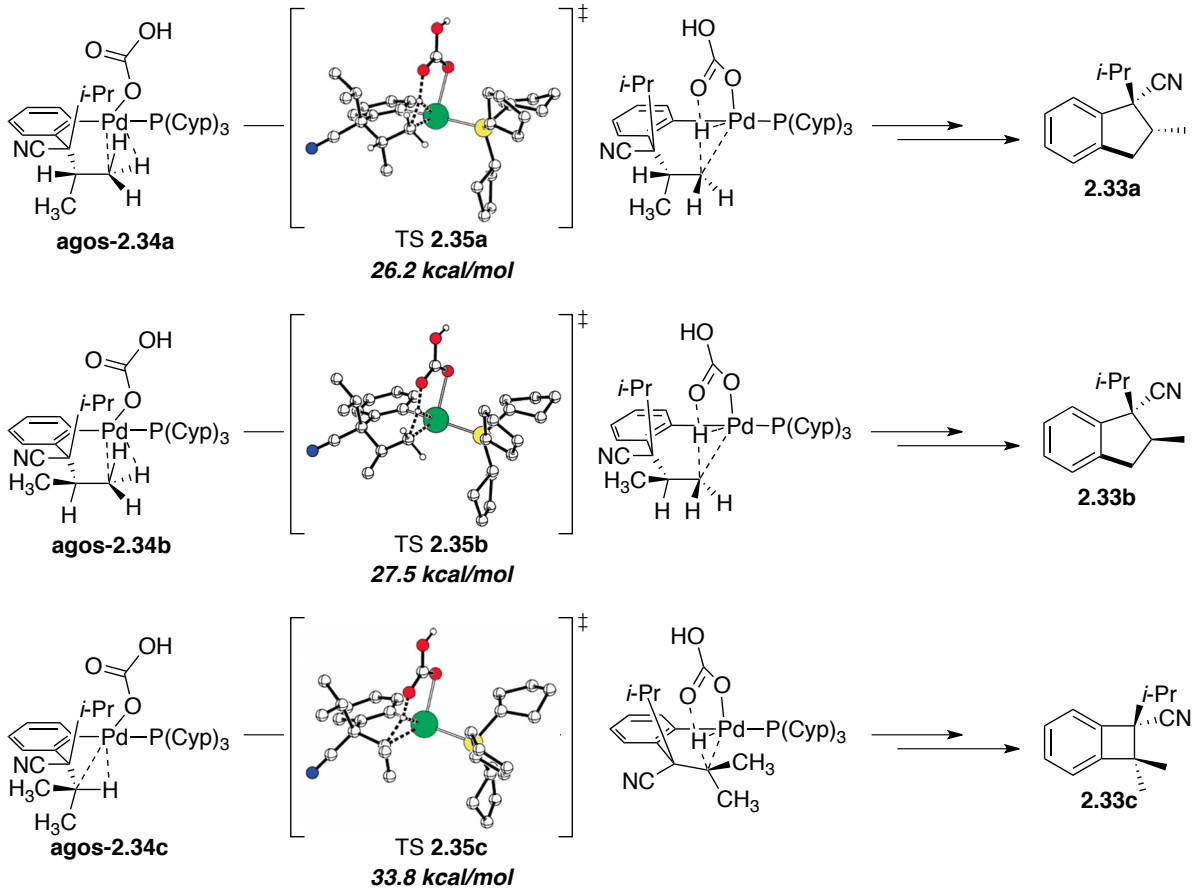


Of note, the agostic C(sp^3)-H bond in **agos-2.34a** and **agos-2.34b** is located *trans* to the κ^1-coordinated base. This *trans* geometry is incompatible with the classic scenario where the creation of an agostic interaction weakens the C-H bond to be cleaved. However, Macgregor, Whittlesey et al. have recently demonstrated that an agostic interaction can promote the deprotonation of a geminal C(sp^3)-H bond.[60] Along these lines, intermediates **agos-2.34a** and **agos-2.34b** are particularly adapted to inner-sphere deprotonation of a geminal C(sp^3)-H bond via CMD transition states **2.35a** and **2.35b** (Scheme 2.2). However, intermediate **agos-2.34c**, which does not have a geminal C-H bond, must first break the agostic interaction prior to C(sp^3)-H bond cleavage via CMD transition state **2.35c**. Transition state **2.35c** is therefore significantly higher in energy than transition states **2.35a** and **2.35b** (33.8 kcal/mol compared to 26.2 kcal/mol and 27.5 kcal/mol, respectively), supporting the clear experimental preference for arylation at primary over tertiary aliphatic C-H bonds. The more facile C-H bond cleavage in TS **2.35a**, compared to TS **2.35b**, is due

[60] Häller, L. J. L.; Page, M. J.; Macgregor, S. A.; Mahon, M. F.; Whittlesey, M. K. *J. Am. Chem. Soc.* **2009**, *131*, 4604-4605.

to the stronger Pd···C interaction in **agos-2.35a**, which enhances the acidity of the geminal hydrogen atom to be transferred.

Scheme 2.2 Transition states for C(sp^3)-H bond cleavage from **agos-2.34a-c**



2.3 Conclusions and Perspectives

In this chapter, our efforts towards the development of a general palladium-catalyzed intramolecular C(sp^3)-H arylation using aryl chlorides were presented. The importance of employing a catalytic amount of pivalic acid in these reactions was demonstrated, with 30 mol % proving optimal. Using this method, a variety of dihydrobenzofurans and indanones were prepared in average to excellent yields. The source of regioselectivity for arylation at primary C(sp^3)-H bonds was studied using DFT calculations, in collaboration

with Kefalidis and Clot. Aliphatic C-H bond cleavage appeared to be rate-determining. Regioselectivity results from the creation of a Pd···C-H agostic interaction, which increases the acidity of the geminal C-H bond that is cleaved via a CMD transition state.

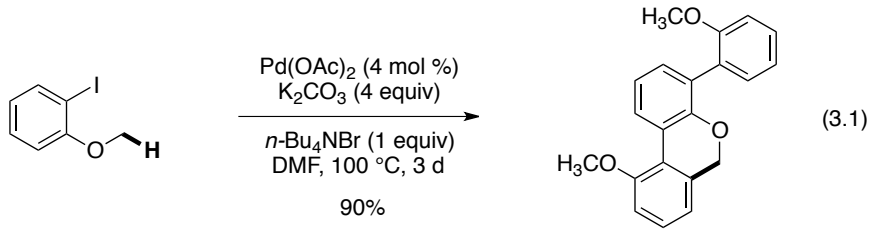
As a field, alkane arylation has witnessed significant growth over the last five years. The development of conditions enabling the use of a wide range of aryl electrophiles, including triflates, mesylates and tosylates, will be crucial to the long-term application of this reactivity in industrial settings. Theoretical mechanistic studies have started to provide insight into the parameters that guide C(sp^3)-H bond cleavage, which should enable the future design of optimal substrates and catalysts to effect these transformations.

3 Alkane Arylation Adjacent to Amides and Sulfonamides

3.1 Background

3.1.1 Alkane Arylation Adjacent to Heteroatoms – Reactivity and Challenges

Pd(0)-catalyzed arylation at aliphatic C-H bonds adjacent to a heteroatom has been poorly investigated despite the general perception of these positions as "activated" towards transition metal catalysis due to electronic effects.[58] Pioneering work by Dyker revealed that C(sp^3)-H bond arylation adjacent to an oxygen atom could be catalyzed by $Pd(OAc)_2$ (eq 3.1).[35] This methodology was subsequently employed by Suau and coworkers for the synthesis of 4,5-dioxoaporphine alkaloids.[61]



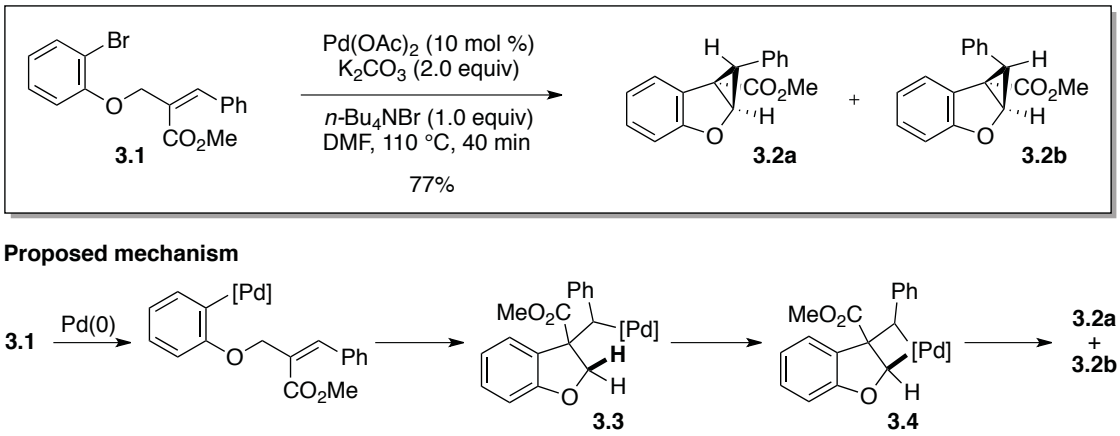
(3.1)

In 2008, Kim et al. reported a similar, intriguing Pd(0)-catalyzed arylation of C(sp^3)-H bonds adjacent to an oxygen atom (Scheme 3.1).[62] The proposed mechanism is initiated by oxidative addition and subsequent intramolecular 1,2-migratory insertion to yield palladated intermediate **3.3**. Due to the absence of β-hydrogens, proximity-enabled aliphatic C-H bond cleavage occurs, affording 4-membered palladacycle **3.4**. Reductive elimination

[61] Suau, R.; López-Romero, J. M.; Rico, R. *Tetrahedron Lett.* **1996**, *37*, 9357-9360.
[62] Kim, H. S.; Gowrisankar, S.; Kim, S. H.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 3858-3861.

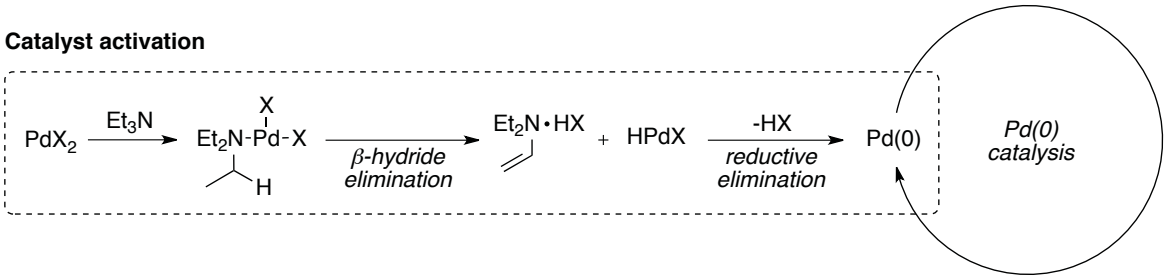
provides the observed products **3.2a** and **3.2b**. Of note, this reaction also represents a rare example of alkane arylation at secondary C-H bonds.

Scheme 3.1 Pd(0)-catalyzed alkane arylation adjacent to an oxygen atom



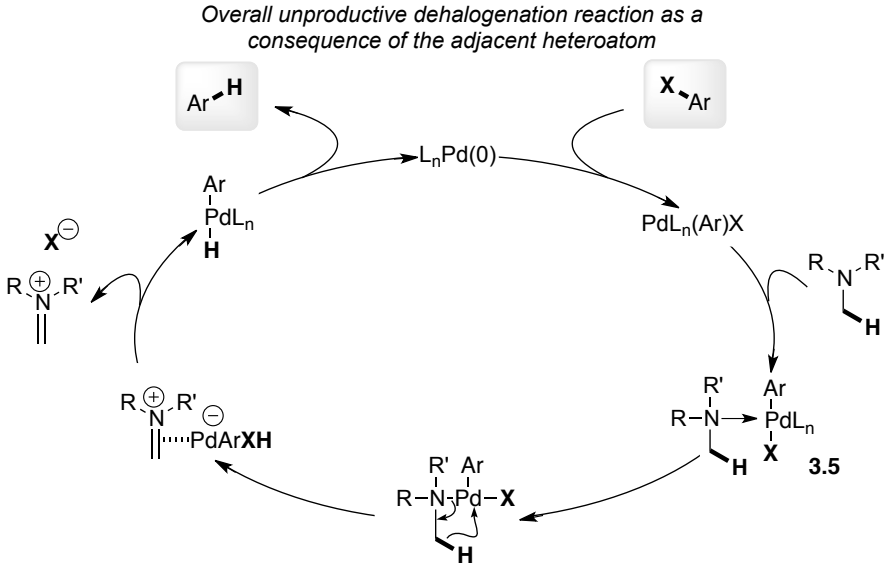
Besides these examples, little progress has been observed in this area. It should also be noted that no examples of Pd(0)-catalyzed arylations at C(sp^3)-H bonds adjacent to nitrogen had been reported at the time of this work. The apparent modest developments in this area of C(sp^3)-H bond functionalization can be attributed to the α-heteroatom effect.[59] Lewis-basic heteroatoms, for example nitrogen, tend to bind Pd(II) species in solution, which favours subsequent *β*-hydride elimination. The resulting Pd-hydride can undergo reductive elimination to generate Pd(0). This process has been exploited as a strategy for the generation of Pd(0) from air stable Pd(II) precatalysts in traditional cross-coupling reactions (Scheme 3.2).

Scheme 3.2 Generation of Pd(0) from air stable Pd(II) precatalysts using triethylamine



While a useful tool for the generation of active Pd(0)-catalysts, this same reactivity represents a significant hurdle in Pd(0)-catalyzed transformations of aryl halides, where oxidative addition is the initial step in the catalytic cycle. Amine binding to Pd(II) intermediate **3.5**, resulting from oxidative addition, leads to the overall unproductive dehalogenation of the aryl halide starting material (Scheme 3.3). This undesired transformation has been previously documented in the development of palladium-catalyzed aryl amination reactions as well as other palladium-catalyzed cross-coupling processes[63]

Scheme 3.3 Pd-catalyzed reduction of aryl halides due to the α-heteroatom effect



3.1.2 Mechanistic Aspects of C(sp^3)-H Bond Cleavage in Alkane Arylation

Previous theoretical reports by our group,[39] as well as the groups of Baudoin and Clot,[38c,49] have provided insight on the mechanism of Pd(0)-catalyzed alkane arylation (Section 1.3.2). A concerted metalation-deprotonation (CMD) pathway for C(sp^3)-H bond cleavage has been proposed, similar to direct arylation reactions at C(sp^2)-H bonds.[50] These calculations also highlight the critical role of the basic additives in the CMD transition state,

[63] (a) Brenda, M.; Knebelkamp, A.; Greiner, A.; Heitz, W. *Synlett* **1991**, 809-810; (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348-1350; (c) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626-3633.

typically in the form of carbonate or carboxylate derivatives. While computational results correlate with catalytic reaction outcomes, limited experimental studies have been carried out to directly probe the mechanism of these transformations. Furthermore, these theoretical calculations heavily rely on the assumption of a Pd(0)/Pd(II) catalytic cycle being operative, with $C(sp^3)$-H bond cleavage occurring at a Pd(II) intermediate. At the time of this work, no direct experimental evidence on the mechanism of Pd(0)-catalyzed alkane arylation had been reported. Most significantly, the crucial role(s) of carbonate and/or carboxylate bases in these transformations was very poorly understood.[64]

In this Chapter, the development and scope of Pd(0)-catalyzed alkane arylation adjacent to a nitrogen atom in amides and sulfonamides will be presented. The isolation and characterization of a catalytically active Pd(II) intermediate and the direct observation of $C(sp^3)$-$C(sp^2)$ bond formation from this intermediate will be discussed. The role of both pivalate and carbonate bases in this transformation will be evaluated using stoichiometric organometallic reactions and DFT calculations. Finally, kinetic studies will complete the mechanistic investigation, providing insight into the factors that govern catalysis and a clearer picture of the complete catalytic cycle. A portion of the work on the scope of alkane arylation adjacent to sulfonamides (Table 3.5) was done in collaboration with a summer student, Benjamin Chung. The DFT calculations presented in Section 3.2.3 were performed by Dr. Serge I. Gorelsky. Portions of this Chapter have been reproduced with permission from Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705. Copyright 2010 American Chemical Society.

[64] Previous reports on Pd(0)-catalyzed $C(sp^2)$-H arylation *employing a pivalic acid cocatalyst* propose that pivalate i) lowers the energetic barrier of C-H bond cleavage via an inner-sphere CMD mechanism, and ii) acts as a proton shuttle between the arene and the insoluble stoichiometric carbonate base (proton sink). See ref 50e and references therein.

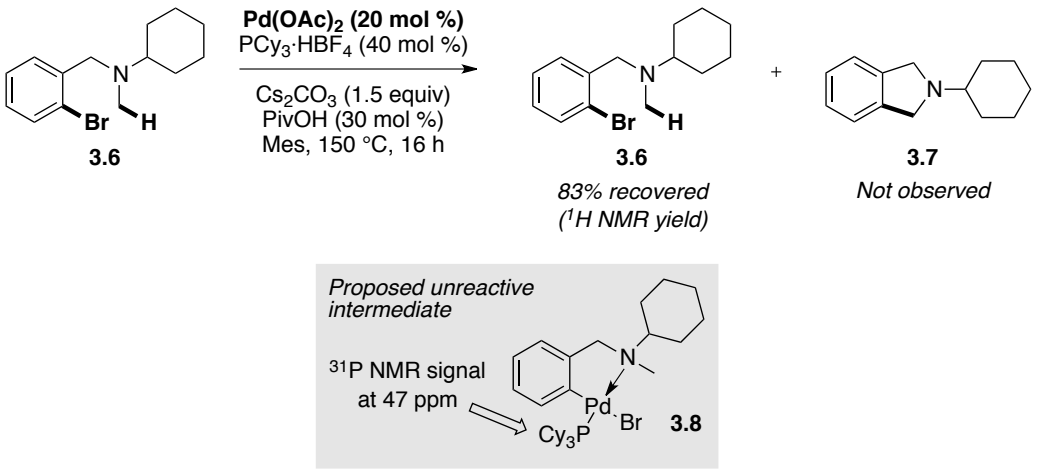
3.2 Results and Discussion

3.2.1 Reaction Development and Scope

3.2.1.1 Initial Discovery of the Desired Reactivity

Our efforts towards the development of conditions for alkane arylation adjacent to a nitrogen heteroatom began by evaluating the cyclization of amine **3.6** using reaction conditions previously reported for the synthesis of dihydrobenzofurans via C(sp^3)-H functionalization.[39,65] In the presence of 5 mol % $Pd(OAc)_2$, 10 mol % $PCy_3 \cdot HBF_4$, 1.1 equivalents of Cs_2CO_3 and 30 mol % PivOH in mesitylene at 150 °C for 16 hours, product **3.7**, resulting from C(sp^3)-H arylation, was not detected by GC-MS. Increasing the catalyst loading to 20 mol % did not improve the reaction outcome, and starting amine **3.6** was recovered in 83% yield (Scheme 3.4). The proportional decrease in starting material recovery with higher catalyst loadings, in combination with the absence of product formation, suggests that unreactive intermediate **3.8** is generated under these conditions. A ^{31}P NMR spectrum of the crude reaction mixture reveals a signal at 47 ppm, correlating with previous literature reports for similar complexes.[66]

Scheme 3.4 Initial investigation of C(sp^3)-H bond arylation adjacent to an amine

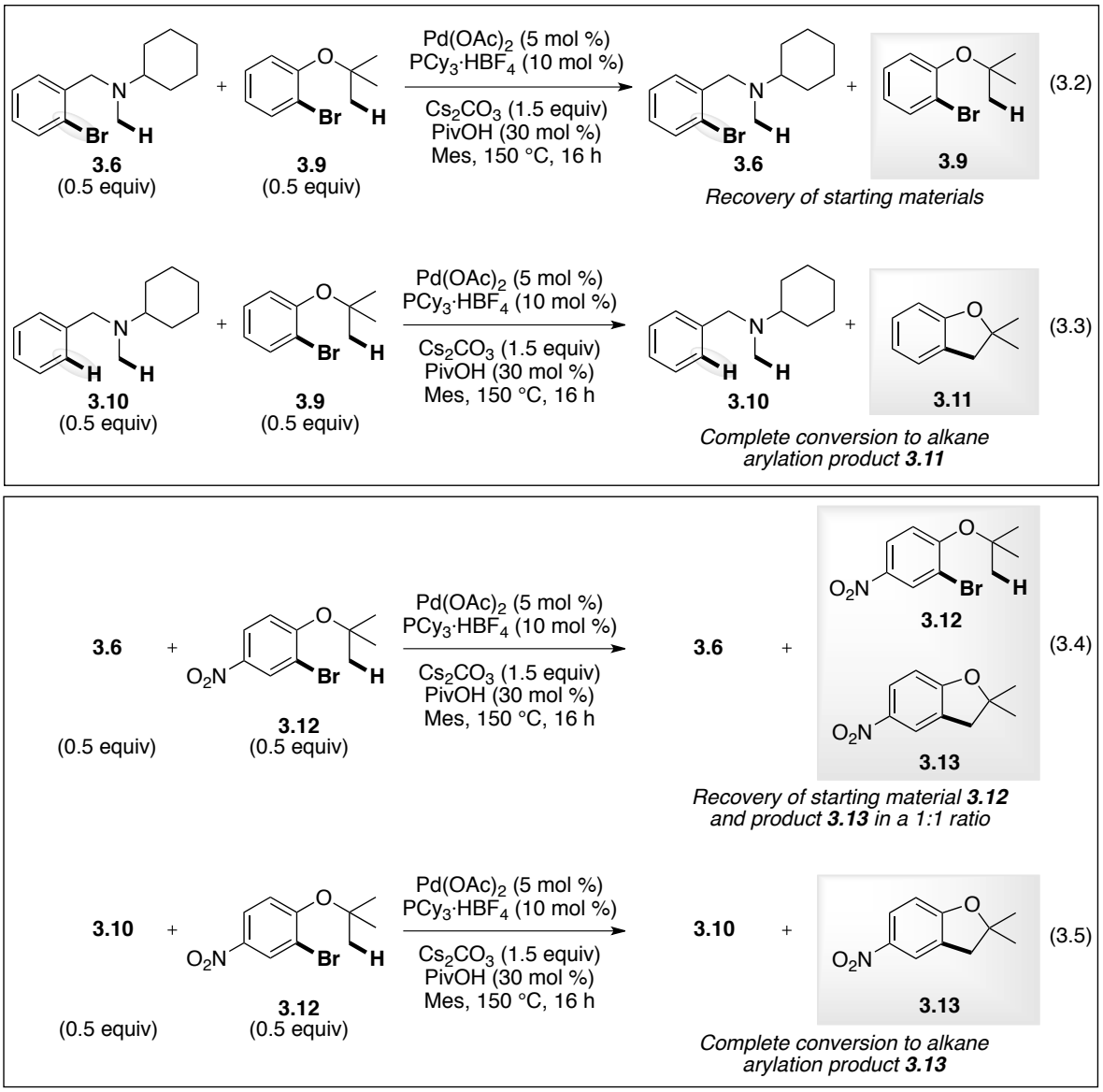


[65] Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.

[66] A signal at 45 ppm (s) has been observed for the corresponding *N*-(2-bromobenzyl)-*N*-dimethylamine derived complex. See: Bedford, R. B.; Cazin, C. S. J.; Coles, S. J.; Gelbrich, T.; Horton, P. N.; Hursthouse, M. B.; Light, M. E. *Organometallics* **2003**, *22*, 987-999.

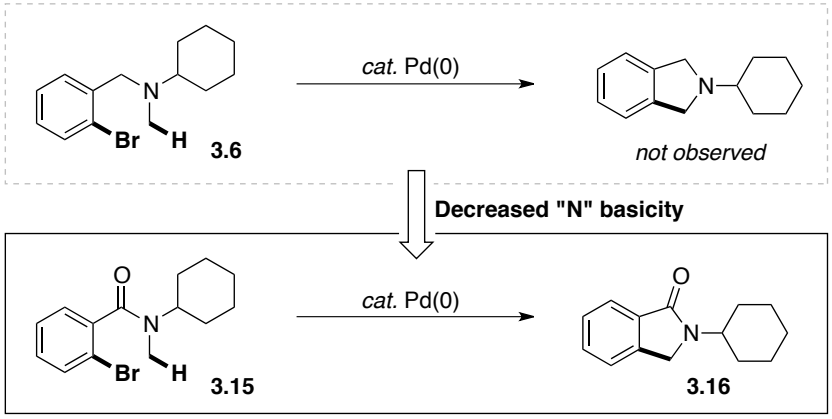
Next, the lack of reactivity observed with amine **3.6** due to potential catalyst poisoning was further examined. One-pot reactions were performed with either amine **3.6** or **3.10** in the presence of ether **3.9** in a 1:1 ratio (Scheme 3.5). Ether **3.9** was chosen as a probe for catalyst availability as it is a highly reactive substrate towards alkane arylation under these reaction conditions, typically yielding dihydrobenzofuran **3.11** in greater than 95% yield.[39] Cyclization of ether **3.9** in the presence of **3.6** led to recovery of the starting material (eq 3.2), however reactivity was completely restored in the presence of amine **3.10** (eq 3.3). This observation supports the hypothesis of catalyst sequestration in the first reaction through the formation of intermediate **3.8**, where the nitrogen lone pair of the substrate coordinates to the Pd(II) center and inhibits C(sp^3)-H bond cleavage. Similar experiments were performed with ether **3.12**, containing an electron-withdrawing group on the arene, in the presence of amines **3.6** or **3.10** (eqs 3.4 and 3.5, respectively). Once again, the same conclusion was obtained as to the formation of the unreactive palladacycle **3.8**. Nonetheless, in this situation some dihydrobenzofuran **3.13** is obtained in the presence of amine **3.6** (eq 3.4), highlighting the greater ease of oxidative addition of electron-deficient aryl bromides to Pd(0).

Scheme 3.5 Catalyst sequestration studies



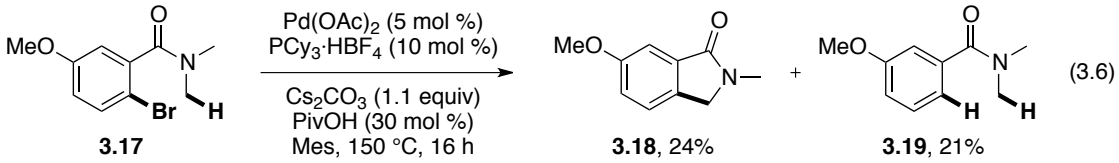
Based on these results, we hypothesized that a less Lewis-basic nitrogen atom could avoid the undesired formation of palladacycle **3.8** and therefore enable product formation. To this effect, amide **3.15** was chosen as a substrate for alkane arylation adjacent to a heteroatom. After careful reaction optimization (*vide infra*), the desired product **3.16** was obtained (Scheme 3.6).

Scheme 3.6 Effect of nitrogen Lewis-basicity on the reaction outcome



3.2.1.2 Reaction Optimization

The first successful result for arylation of aliphatic C-H bonds adjacent to a nitrogen atom was obtained when amide **3.17** was subjected to a catalyst system based on $Pd(OAc)_2$/ $PCy_3 \cdot HBF_4$ in the presence of Cs_2CO_3/PivOH (eq 3.6). The desired product **3.18** was obtained in 24% yield in combination with 21% reduced starting material **3.19**. The remainder of the mass balance was unreacted starting material. Subsequent attempts at reaction optimization revealed that this transformation was highly irreproducible. Oxygen must be rigorously excluded for successful product formation.[67]

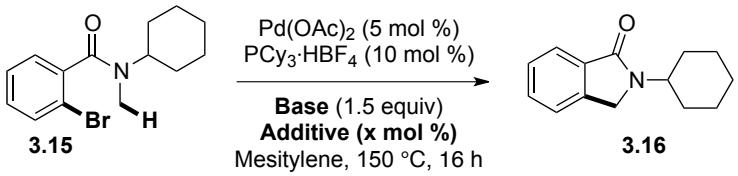


Over the course of our studies, we found that the base had a significant influence on the outcome of the reaction. Similar to previous reports, both the carbonate and the pivalate additives appear to play an important role (Table 3.1).[39,46d,64] When the reaction was carried out in the presence of a stoichiometric amount of Cs_2CO_3, an insoluble base under the reaction conditions, 15% conversion to product was observed (entry 1). Changing the base

[67] See supporting information for the detailed reaction protocol.

to the more soluble CsOPiv led to 6% conversion (entry 2). However, when a stoichiometric quantity of a carbonate base in combination with a catalytic or stoichiometric amount of pivalate were used, complete conversion of starting material was obtained and the desired product was isolated in yields greater than 83% (entries 4-5). In comparison, the use of cesium carbonate as the stoichiometric base in conjunction with a catalytic amount of acetic acid leads to a significantly decreased product yield (entry 3). The rationale for the difference in catalytic activity between pivalate or acetate additives remains elusive at this time. However, the significant decrease in yield when acetic acid is used instead of pivalic acid as an additive in Pd(0)-catalyzed transformations at C-H bonds has been previously observed.[50e]

Table 3.1 Effect of the base and the additive on the alkane arylation of *N*-methylamide



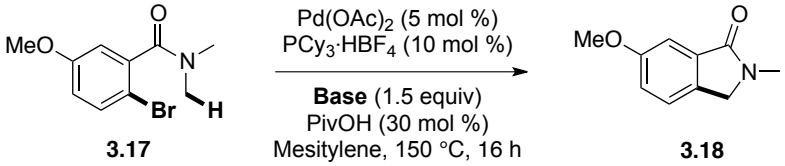
Entry	Base	Additive	Yield (%)[a]
1	Cs_2CO_3	none	14[b]
2	CsOPiv	none	6[b]
3	Cs_2CO_3	AcOH (30 mol%)	27[b]
4	Cs_2CO_3	PivOH (30 mol%)	83
5	Cs_2CO_3	CsOPiv (110 mol%)	88

[a] Isolated yields. [b] Determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

A further screen of alkali carbonates showed a surprising counterion effect on the outcome of the reaction (Table 3.2). While a reaction employing Na_2CO_3 provided no product (entry 1), a reaction with K_2CO_3 gave incomplete conversions and significant amounts of dehalogenated starting material **3.19** (entry 2). Rb_2CO_3 was found to be the optimal base for the cyclization of 2-bromoaryl amides. The use of this base was particularly successful, compared to the use of Cs_2CO_3, in cases where less sterically demanding substituents were present on the amide nitrogen, due to the minimized formation of

byproduct **3.19**. Indeed, lactam **3.18** was isolated in 56% yield when Rb_2CO_3 was chosen as the source of base compared to 48% with the use of Cs_2CO_3 (entries 3 and 4).

Table 3.2 Optimization of the source of alkali carbonate



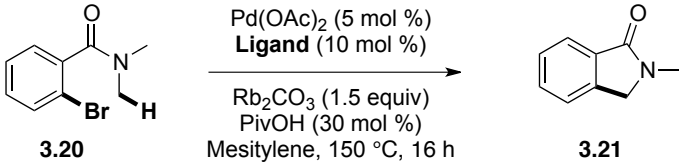
3.17 **3.18**

Entry	Base	Yield (%)[a]
1	Na_2CO_3	0[b]
2	K_2CO_3	31
3	Rb_2CO_3	56
4	Cs_2CO_3	48

[a] Isolated yields. [b] Determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

Finally, the formation of lactam **3.21** from amide **3.20** was studied using a variety of ligands possessing different steric and electronic properties (Table 3.3). While $PCy_3 \cdot HBF_4$ was found to be the optimal ligand based on product yield (entry 1), interesting steric and electronic trends were uncovered. The reaction appears to be very sensitive to the steric bulk of the ligand. Indeed, minimal product formation is observed in the presence of $P(t\text{-Bu})_3 \cdot HBF_4$ compared to 76% yield of **3.21** when $PCy_3 \cdot HBF_4$ is used (entries 1 and 2). A significant difference in yield was also observed between reactions employing electron-poor and electron-rich triarylphosphine ligands (entries 5 and 6). These results support the use of electron-rich ligands to promote alkane arylation, with trialkylphosphine ligands being optimal.

Table 3.3 Effect of the ligand on the alkane arylation of *N*-methylamides



3.20 **3.21**

Entry	Ligand	Yield (%)[a]
1	$PCy_3 \cdot HBF_4$	76[b]
2	$P(t\text{-Bu})_3 \cdot HBF_4$	5
3	$P(t\text{-Bu})_2Me \cdot HBF_4$	13
4	CyJohnPhos[c]	17
5	$P(p\text{-F-}C_6H_4)_3$	9
6	$P(p\text{-OMe-}C_6H_4)_3$	24

[a] Determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. [b] Isolated yields. [c] CyJohnPhos = 2-(Dicyclohexylphosphino)biphenyl.

3.2.1.3 Reaction Scope

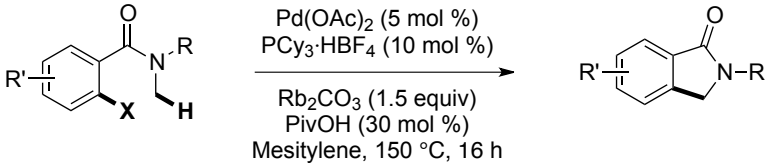
Illustrative examples of the scope of the reaction with respect to substitution on both the aliphatic and aromatic portions of the amide are shown in Table 3.4. Under the optimized conditions, amide **3.20** gives product **3.21** in 76% isolated yield (entry 2). An aryl chloride is also tolerated, as exemplified by the reaction of **3.22** (using Cs_2CO_3 as a base) to yield lactam **3.21** in 67% yield (entry 1). However, the reaction using an aryl iodide fails completely and only trace amounts of the desired product are observed (entry 3). It should be noted that diminished reactivity for C-H arylation reactions with aryl iodides has been previously observed.[68] This has been attributed to the catalyst poisoning effect of the resulting soluble iodide salts. In some cases, high yields can be restored by the use of silver salts as additives.[52] Unfortunately, the addition of Ag_2CO_3 or AgOTf to these alkane arylations did not improve the reaction outcome.

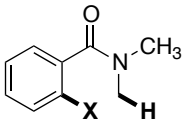
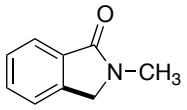
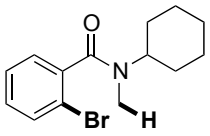
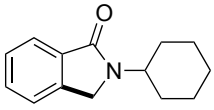
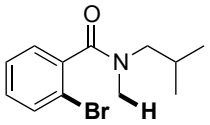
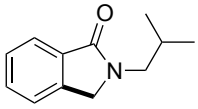
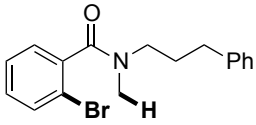
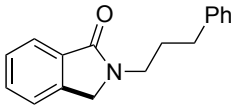
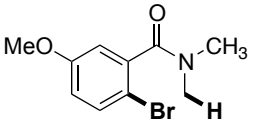
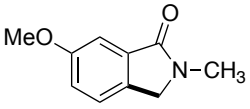
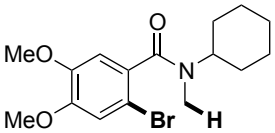
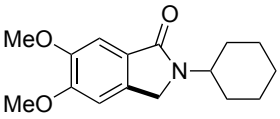
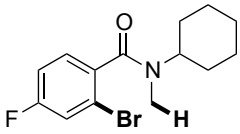
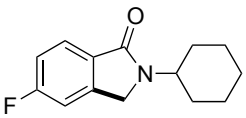
The alkane arylation of more sterically encumbered cyclohexyl and *iso*butyl substituted *N*-methylamides proceeds in good yields, affording products **3.16** and **3.25** in 83% and 68% yield respectively (entries 4 and 5). As with previous experimental and

[68] For selected examples, see: (a) Chabert, J. F. D.; Joucla, L.; David, E.; Lemaire, M. *Tetrahedron* **2004**, *60*, 3221-3230; (b) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826-1834. See also ref 52.

computational results, exclusive selectivity is observed for arylation at methyl over methylene or methyne C(sp^3)-H bonds (Sections 1.2.2.1 and Chapter 2).[38c,39,65] The reaction of **3.26**, possessing a remote phenyl substituent, gives rise to isoindoline **3.27** albeit in poor yield (entry 6). On the aromatic portion of the amide, the presence of an electron-donating group leads to slightly attenuated reactivity. For example, methoxy-substituted 2-bromoaryl amides **3.17** and **3.28** generate products **3.18** and **3.29** in 56% and 44% yield respectively (entries 7 and 8). Fluorinated arene **3.30** also reacts well, yielding product **3.31** in 70% (entry 9).

Table 3.4 Scope of the intramolecular C(sp^3)-H arylation of *N*-methylamides



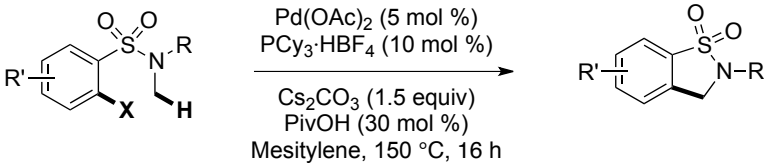
Entry	Starting Material		Product	Yield (%)[a]
1		X = Cl **3.22**	 **3.21**	67[b]
2		X = Br **3.20**		76
3		X = I **3.23**		Trace
4		**3.15**		**3.16** 83
5		**3.24**		**3.25** 68
6		**3.26**		**3.27** 37
7		**3.17**		**3.18** 56
8		**3.28**		**3.29** 44
9		**3.30**		**3.31** 70

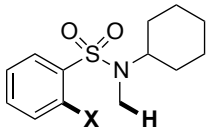
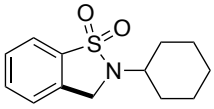
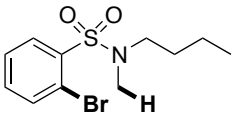
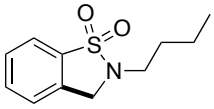
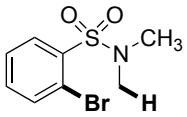
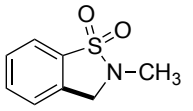
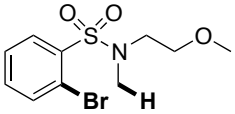
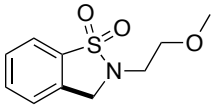
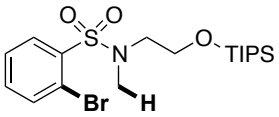
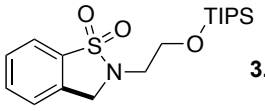
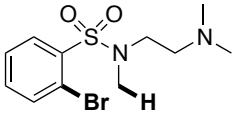
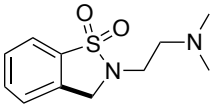
[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Rb_2CO_3 (1.5 equiv), PivOH (30 mol %) and the starting material were heated to 150 °C in mesitylene for 16 hours. Yields are of isolated product. [b] Cs_2CO_3 was used as the base.

Based on our initial hypothesis, the arylation of aliphatic C-H bonds adjacent to other electron-poor nitrogen-containing functional groups was also investigated. Sulfonamides were found to be compatible substrates for this transformation when Cs_2CO_3 was used as a

base (Table 3.5). Indeed, aryl bromide **3.32** and chloride **3.31** provide product **3.33** in 62% and 67% yield respectively (entries 1 and 2). Other simple alkane substituents on the sulfonamide are tolerated under the reaction conditions as exemplified by *n*-butyl-substituted sulfonamide **3.34** and dimethylsulfonamide **3.36** (entries 3 and 4). The presence of functional groups such as an ether (entry 5) and a TIPS-protected alcohol (entry 6) does not hinder product formation as **3.39** and **3.41** are obtained in moderate yields (59% and 47% respectively). Finally, Lewis-basic functional groups, such as amines, are well tolerated as exemplified by the formation of product **3.43** in 71% yield (entry 7).

Table 3.5 Scope of the intramolecular C(sp^3)-H arylation of *N*-methylsulfonamides



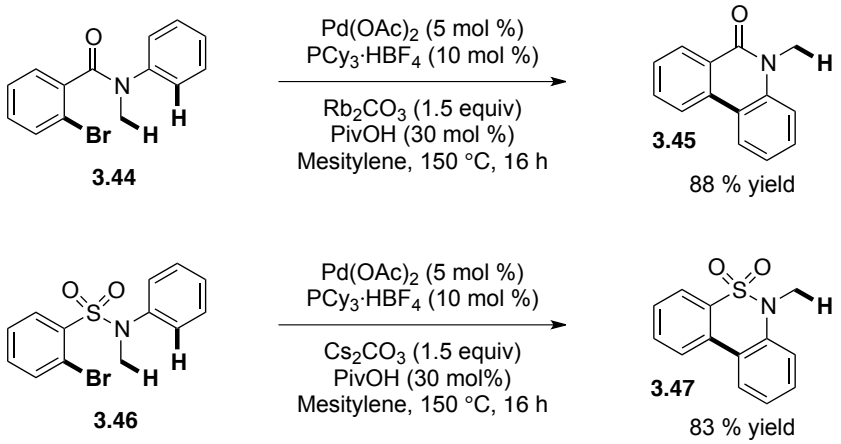
Entry	Starting Material		Product	Yield (%)[a]
1		X = Cl **3.31**	 **3.33**	67
2		X = Br **3.32**		62
3		**3.34**	 **3.35**	82
4		**3.36**	 **3.37**	52
5		**3.38**	 **3.39**	59
6		**3.40**	 **3.41**	47
7		**3.42**	 **3.43**	71

[a] Conditions: $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Cs_2CO_3 (1.5 equiv), PivOH (30 mol %) and the starting material were heated to 150 °C in mesitylene for 16 hours. Yields are of isolated product.

We next designed an intramolecular competition reaction to probe the preference of our optimized catalyst for reactivity at sp^2 vs. sp^3 C-H bonds. Not surprisingly, when 2-bromo-*N*-methyl-*N*-phenylbenzamide **3.44** was exposed to the standard reaction conditions for arylation at aliphatic positions, exclusive selectivity for reaction at the arene C-H bond was observed, with product **3.45** being obtained in 88% yield (Scheme 3.7). A similar result

was obtained for the corresponding sulfonamide **3.46**, which exclusively gave the product of direct arylation (**3.47**) in 83% yield. The complete selectivity for C(sp^2)-H arylation, despite the formation of a 7-membered palladacycle in this reaction pathway, compared to alkane arylation *via* a 6-membered palladacycle, is dictated by more facile catalyst-substrate interactions through the π-system of the arene.[4,10]

Scheme 3.7 Intramolecular competition between sp^2 and sp^3 C-H arylation



3.2.2 Mechanistic Studies

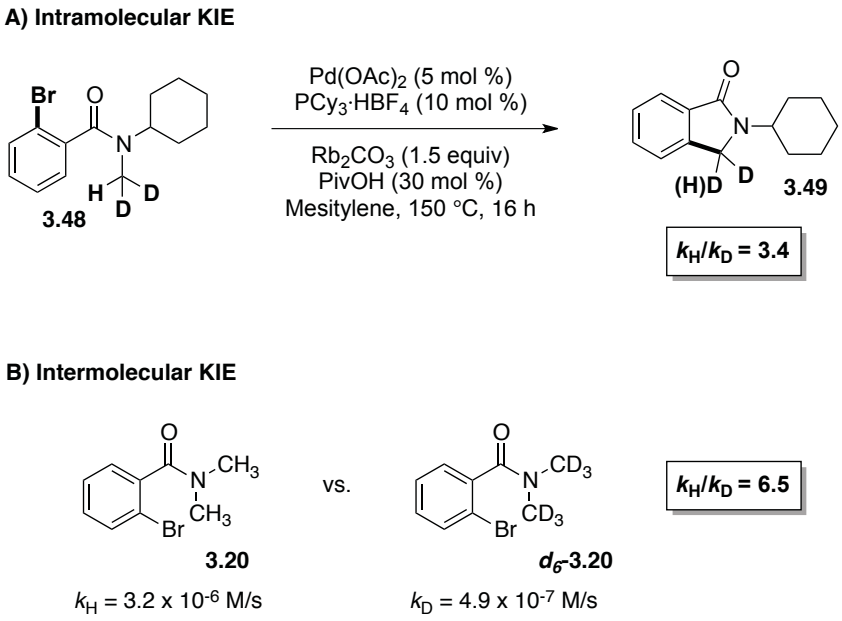
As has been previously highlighted in Sections 1.3.2, 2.2.2 and 3.1.2, little direct experimental evidence pertaining to the mechanism of C-H bond cleavage in Pd(0)-alkane arylation has been obtained. Such mechanistic knowledge is required to facilitate further reaction development and catalyst design in this expanding area of research. To this effect, both mechanistic and kinetic experiments were devised to further our awareness of the parameters that guide reactivity in arylation reactions at aliphatic positions adjacent to heteroatoms. These results will be presented in the upcoming pages.

3.2.2.1 Kinetic Isotope Effect

An intramolecular kinetic isotope effect (KIE) study was conducted with substrate **3.48** (Scheme 3.8A). This amide was chosen to observe the preference of the catalyst for

C-H(D) bond cleavage without the bias of potential amide rotamers.[69] The k_H/k_D value of 3.4 is indicative of a kinetically significant (although not necessarily rate-limiting) C-H bond-cleaving reaction step. To determine the importance of C-H bond cleavage in the overall reaction rate, an intermolecular KIE experiment was also carried out (Scheme 3.8B). A side-by-side comparison of reaction rates for 2-bromo-*N,N*-dimethylbenzamide **3.20** and d_6-2-bromo-*N,N*-dimethylbenzamide ***d*$_6$-3.20** led to a k_H/k_D value of 6.5 indicating that the C-H(D) bond is cleaved during the rate determining step of the reaction.[70,71]

Scheme 3.8 Kinetic isotope effect experiments



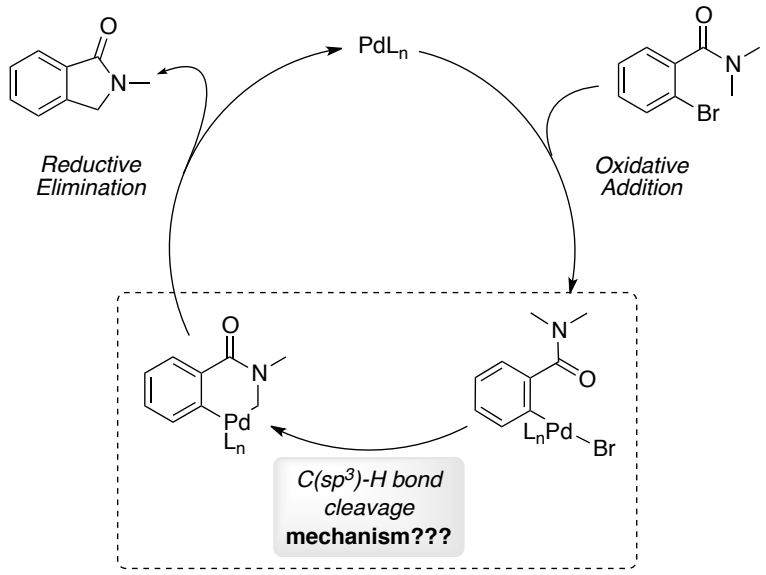
3.2.2.2 Isolation and Characterization of a Catalytically Relevant Pd(II) Intermediate

The proposed catalytic cycle for alkane arylation adjacent to amides and sulfonamides can be simplified to three steps: (1) oxidative addition of the aryl bromide to the Pd(0) catalyst, (2) C(sp^3)-H bond cleavage and (3) reductive elimination of the desired product from the Pd(II) intermediate to regenerate the Pd(0) species (Scheme 3.9).

[69] Signals for both amide conformations do not coalesce even at 120 ºC on the ^{1}H NMR time scale.
[70] The larger KIE value for intermolecular vs intramolecular competitions is atypical and is not fully understood at this time although errors on side-by-side intermolecular competitions are intrinsically larger due to the nature of the experiment. In any case, the conclusion of a rate-limiting C-H bond-cleaving event remains.
[71] See supporting information for further details on kinetic experiments.

Oxidative addition of aryl halides to Pd(0)-phosphine complexes as well as reductive elimination from Pd(II) complexes to form carbon-carbon bonds are well documented reactions whose mechanisms have been extensively studied experimentally.[72,73] However, little experimental work has been done concerning the mechanism of C-H bond cleavage at aliphatic positions as well as the role of the bases involved in this elementary reaction step.

Scheme 3.9 Simplified proposed catalytic cycle



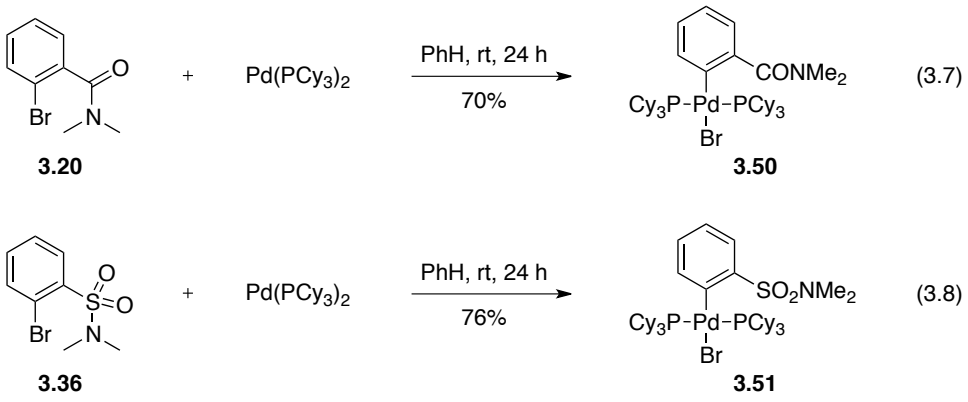
In order to directly examine this catalytic step, Pd(II) intermediate **3.50** resulting from oxidative insertion of 2-bromo-*N,N*-dimethylbenzamide **3.20** to $L_nPd(0)$ was prepared. Reaction of 1.5 equivalents of **3.20** with $Pd(PCy_3)_2$ in benzene at room temperature for 24 hours led to the isolation of air-stable Pd(II) complex **3.50** in 70% yield (eq 3.7).[74]

[72] For selected mechanistic studies on oxidative addition of Pd(0) to aryl halides, see: (a) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276-2282; (b) Hartwig, J. F.; Frédéric, P. *J. Am. Chem. Soc.* **1995**, *117*, 5373-5374; (c) Amatore, C.; Bucaille, A.; Fuxa, A.; Jutand, A.; Meyer, G.; Ntepe, A. N. *Chem. Eur. J.* **2001**, *7*, 2134-2142; (d) Amatore, C.; Jutand, A.; Thuilliez, A. *J. Organomet. Chem.* **2002**, *643-644*, 416-423; (e) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944-6945; (f) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 5842-5843; (g) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141-8154 and references therein.

[73] For selected mechanistic studies on reductive elimination for C-C bond formation, see: (a) Culkin, D. A.; Hartwig, J. F. *Organometallics* **2004**, *23*, 3398-3416; (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974-10983.

[74] Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184-1194.

Similarly, the Pd(II) intermediate **3.51**, resulting from oxidative insertion of $Pd(PCy_3)_2$ to 2-bromo-*N,N*-dimethylbenzenesulfonamide **3.36**, was also prepared in 76% yield (eq 3.8). The structure of **3.50** was confirmed by X-ray crystallography and revealed a four-coordinate square planar complex containing two *trans* PCy_3 ligands (Figure 3.1). No significant interactions between the amide moiety and the Pd(II) center are present in the structure as the distances between Pd(1) and O(1) or N(1) are 3.09 Å and 4.50 Å respectively.



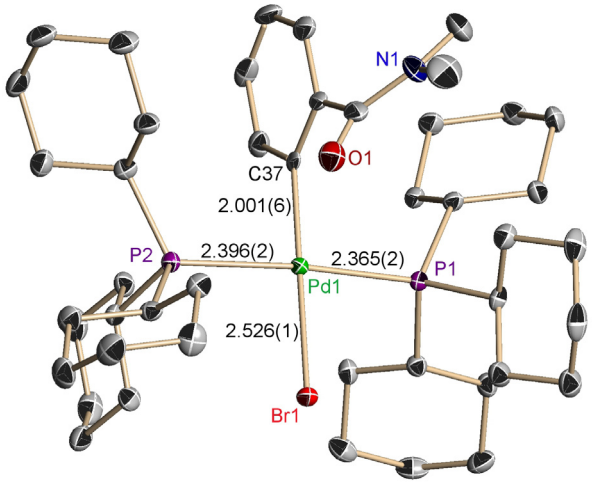
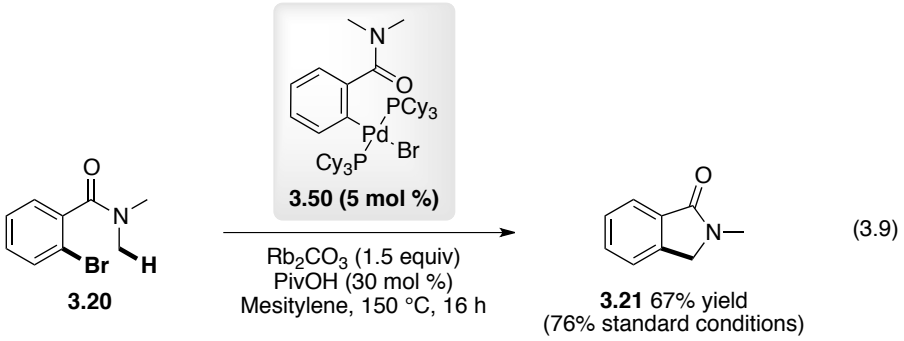


Figure 3.1 ORTEP plot of $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50**. All H atoms have been omitted for clarity. Anisotropic displacement ellipsoids are shown at the 50% probability level. Selected bond lengths (Å) are indicated on the diagram.

Prior to probing the mechanism of $C(sp^3)$-H bond cleavage with $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50**, its relevance as a catalytic intermediate was first

established to shed any potential doubt that it may represent an off-cycle unreactive catalytic species. To this effect, 2-bromo-*N,N*-dimethylbenzamide **3.20** was subjected to the standard reaction conditions, replacing $Pd(OAc)_2$ (5 mol %) and $PCy_3 \cdot HBF_4$ (10 mol %) with $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50** (5 mol %). The product of alkane arylation **3.21** was obtained in 67% yield, compared to 76% under the standard reaction conditions, supporting that **3.50** is a catalyst precursor for the reaction (eq 3.9).



(3.9)

3.2.2.3 Comparative Reaction Kinetics for Different Catalyst Systems

The kinetic competence of $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50**, as well as other palladium catalyst systems, for product formation was evaluated by following the reaction kinetics. The appearance of product over time was monitored by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.[71] Comparable rates of product formation were observed using 3 catalyst systems (Figure 3.2): the standard catalyst combination of $Pd(OAc)_2$ (5 mol %) and $PCy_3 \cdot HBF_4$ (10 mol %) (Conditions A), $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50** (5 mol %) (Conditions B), and the commercially available Pd(0) catalyst $Pd(PCy_3)_2$ (5 mol %) (Conditions C). These comparable rates indicate the absence of a catalyst initiation period to generate Pd(0) from $Pd(OAc)_2$ under the standard reaction conditions (Conditions A) since rates of catalysis are comparable to those when Pd(0) systems are used (Conditions C). Moreover, these results demonstrate the ability of $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50** to rapidly generate the active catalytic species for the C-H bond-cleaving reaction step. A control reaction using $Pd(PCy_3)_2$ in the absence of a pivalate source (Conditions D) emphasizes once again the crucial role of this base for catalysis to occur.

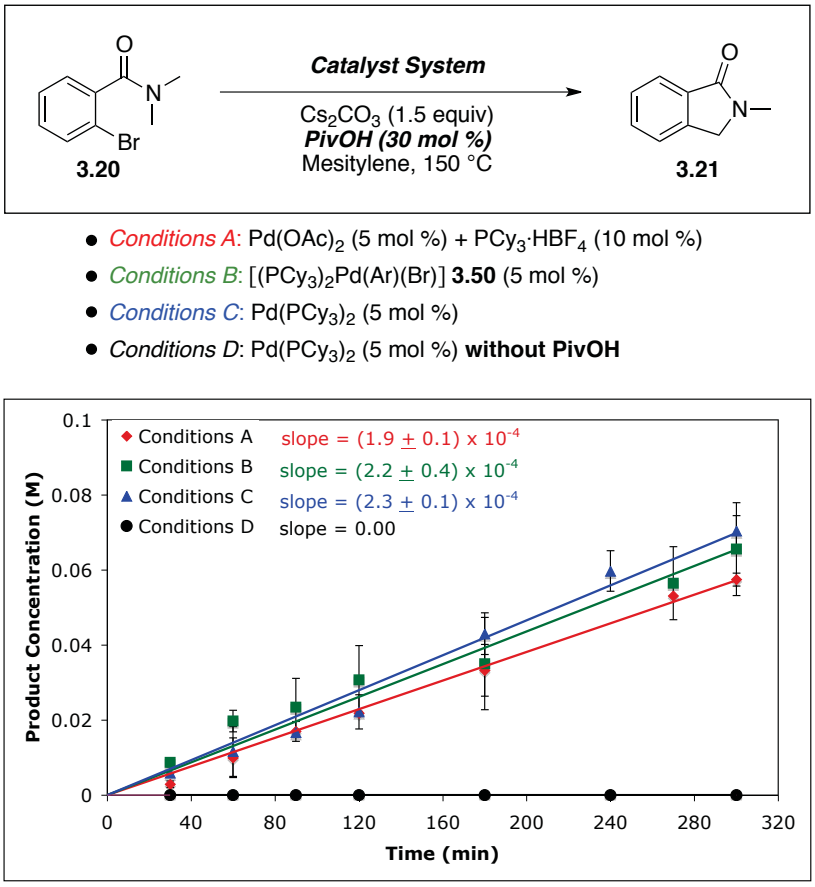
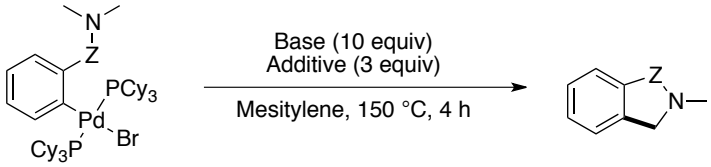


Figure 3.2 Initial formation of product **3.21** over time under different catalytic conditions: $Pd(OAc)_2$ (5 mol %) + $PCy_3{\cdot}HBF_4$ (10 mol %) (Conditions A, ♦), $[(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)]$ **3.50** (5 mol %) (Conditions B, ■), $Pd(PCy_3)_2$ (5 mol %) (Conditions, C ▲) and $Pd(PCy_3)_2$ (5 mol %) without pivalic acid (Conditions D, ●). The data points for product concentrations are the average of two runs and were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

*3.2.2.4 Stoichiometric Mechanistic Studies with $[(PCy_3)_2Pd(Ar)(Br)]$ **3.50** and **3.51***

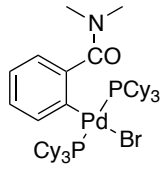
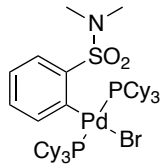
In order to evaluate the role of both the pivalate and carbonate bases in the previously proposed concerted metalation-deprotonation pathway for C(sp^3)-H bond cleavage,[38c,39,65] stoichiometric studies with $[(PCy_3)_2Pd(Ar)(Br)]$ **3.50** and **3.51** were carried out. These complexes were chosen since they allow us to directly probe the C-H bond-cleaving step. The results of these stoichiometric studies, performed in mesitylene at 150 °C for 4 hours with various bases and additives, are highlighted in Table 3.6.

Table 3.6 Stoichiometric studies with complexes **3.50** and **3.51** to probe the role of pivalate and carbonate bases in C(sp^3)-H bond cleavage



3.50 (Z = CO)
3.51 (Z = SO_2)

3.21 (Z = CO)
3.37 (Z = SO_2)

Entry		Base	Additive	Yield (%)[a]
1		none	none	0
2		Cs_2CO_3	none	0
3		CsOPiv	none	28
4		Cs_2CO_3	CsOPiv	96
5		none	none	0
6		Cs_2CO_3	none	7
7		CsOPiv	none	35
8		Cs_2CO_3	CsOPiv	80

[a] Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

In the absence of both forms of base (entries 1 and 5) as well as with the use of a strong carbonate base (entries 2 and 6), minimal or no product formation is observed. The absence of reactivity in the latter reactions is not surprising based on the very poor solubility of carbonate in mesitylene even at these temperatures. The stoichiometric reaction of complex **3.50** and **3.51** with CsOPiv generates products **3.21** and **3.37** in low yields (28% and 35% respectively) (entries 3 and 7). These results correlate with those reported in catalytic studies (Table 3.1). However, the modest reactivity observed with CsOPiv in the presence of *stoichiometric* palladium leads us to further examine our working hypothesis for the combined use of catalytic pivalate and stoichiometric carbonate in these reactions.[64,75] The use of both bases in *catalytic* transformations at C-H bonds that proceed *via* a CMD transition state has been rationalized by the requirement for a soluble basic species responsible for deprotonation (pivalate) and an insoluble proton sink responsible for

[75] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496-16497.

sequestration of H^+ and pivalate regeneration (carbonate). The latter should therefore not be required for product formation under *stoichiometric* conditions. Finally, the reaction of $[(PCy_3)_2Pd(Ar)(Br)]$ **3.50** and **3.51** with Cs_2CO_3 (10.0 equiv) and CsOPiv (3.0 equiv) in mesitylene at 150 °C for 4 hours gave 96% and 80% yield of alkane arylation products **3.21** and **3.37** respectively (entries 4 and 8).[76] These results not only support the required combination of carbonate and pivalate for productive reactions (see Table 3.1), but also underline the complexity of the role(s) played by these species in the CMD pathway.

3.2.3 Computational Studies

To gain additional insight into the role of pivalate in C-H bond cleavage, the isolation and characterization of a Pd(II) intermediate of general structure $[(PCy_3)_nPd(Ar)(OPiv)]$ and its evaluation as a catalytically and kinetically competent species should be investigated. Unfortunately all attempts at synthesizing, isolating and characterizing this potential catalytic intermediate were unsuccessful, leading us to examine its role through the use of computational studies.

3.2.3.1 Pivalate as a Promoter of Phosphine Dissociation

KIE experiments and mechanistic data support a turnover-limiting $C(sp^3)$-H bond cleavage *via* a base-enabled CMD transition state (*vide supra*). DFT calculations were performed to determine the ground state energies of various potential Pd(II) intermediates and CMD transition states (Figures 3.3 and 3.4).[77] Intermediates **III** and **IV**, resulting from PMe_3 dissociation from **II** and amide coordination through either the oxygen or nitrogen atom, are respectively 1.7 and 4.8 kcal/mol higher in energy than structure **II**. In structure **IV**, the nitrogen lone pair is no longer in conjugation with the amide carbonyl due to its coordination to Pd(II). κ^2-Acetate complex **I** is 0.6 kcal/mol lower in energy than structure **II**. Therefore, prior to the rate-limiting CMD process (Figure 3.5), the thermodynamic equilibrium shifts towards intermediate **I**, a direct precursor to the inner-sphere pivalate

[76] A ten-fold amount of carbonate and pivalate were used to mimic the relative base:palladium ratios that are found under the standard catalytic conditions. See supporting information for further experimental details.

[77] PCy_3 was modeled as PMe_3 and pivalate as acetate to minimize computational costs. It should be noted that after this work was performed, Baudoin Clot have published an account demonstrating that the use of simplified phosphines and bases in DFT calculations for $C(sp^3)$-H functionalization can lead to distorted transition states. See ref 49.

(acetate for computational purposes)-enabled CMD TS.[78] The free energy of the CMD transition state **TS-I** is 29.1 kcal/mol, which is slightly higher than the free energy of the corresponding transition state for intramolecular alkane arylation in the synthesis of dihydrobenzofurans (27.0 kcal/mol).[39] Similar to previous reports,[38c,39] a three-centre two-electron agostic interaction was found at the transition state between the Pd(II) center and the C-H σ-bond being cleaved (Figure 3.5).

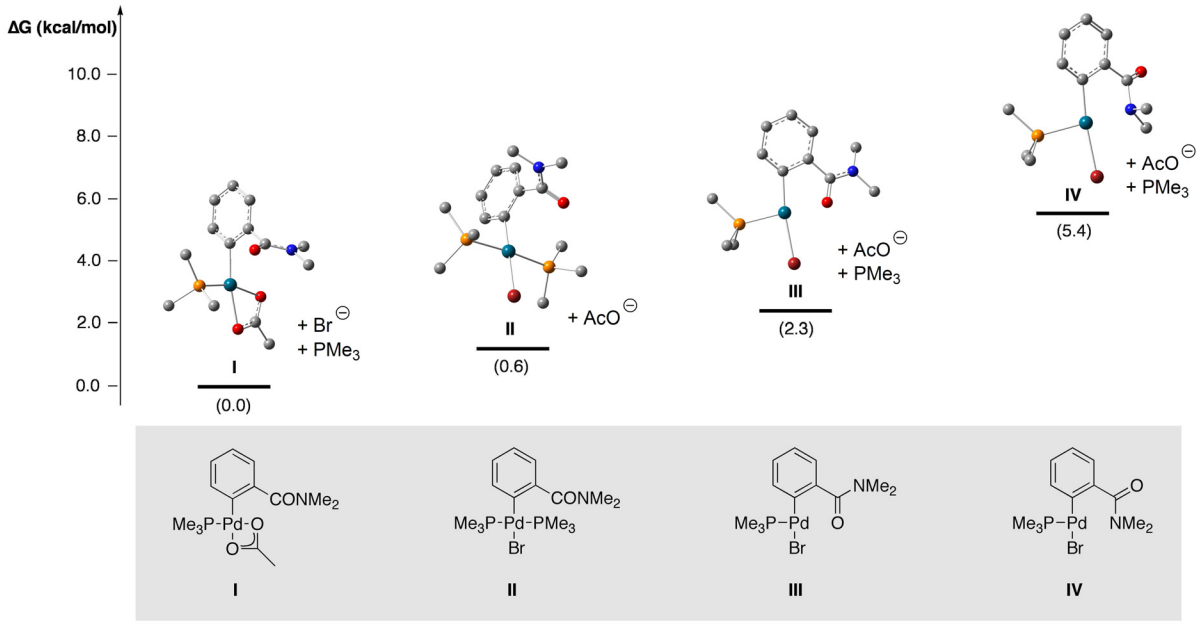


Figure 3.3 Gibbs free energies (at 298 K in toluene) of potential Pd(II) intermediates prior to the CMD transition state for C(sp^3)-H bond cleavage. Hydrogen atoms have been omitted for clarity.

To lend additional support to the hypothesis that pivalate plays a crucial role in promoting phosphine dissociation from Pd(II), and therefore increasing the concentration of reactive intermediate **I**, stoichiometric reactions were performed with Pd(II)-intermediate **3.51**. Side-by-side reactions of complex **3.51** *with and without CsOPiv* in mesitylene at 120 °C were carried out to observe the effect of added CsOPiv on the concentration of free PCy_3 in solution. The reaction outcome was monitored by ^{31}P NMR (Figure 3.4). In the

[78] This discussion does not take into consideration the generation of **I** (or **III**/**IV**) from **II**. It should be noted that since KIE studies revealed that C(sp^3)-H bond cleavage is involved in the rate-determining step of the catalytic cycle (Section 2.1), any transition states (or other intermediates) to generate **I** or **III**/**IV** from **II** will be lower in energy and therefore not significant in the overall rate expression.

absence of CsOPiv, starting material **3.51** remains almost exclusively the sole product in solution (Figure 3.4a). Trace amounts of PCy_3 and proposed intermediate **3.52** could be detected. When the same experiment is performed in the presence of CsOPiv (6 equivalents), very little starting complex **3.51** remains after 20 minutes at 120 °C. Instead, a significant amount of free PCy_3 can be detected with the simultaneous appearance of a second signal at 43.7 ppm, which is proposed to correspond to κ^2-pivalate complex **3.53** (Figure 3.4b).[79] The relative concentrations of Pd(II) intermediates observed under these different reaction conditions support the results of DFT calculations in Figure 3.3 and provide additional evidence for the role of pivalate as a promoter of phosphine dissociation.

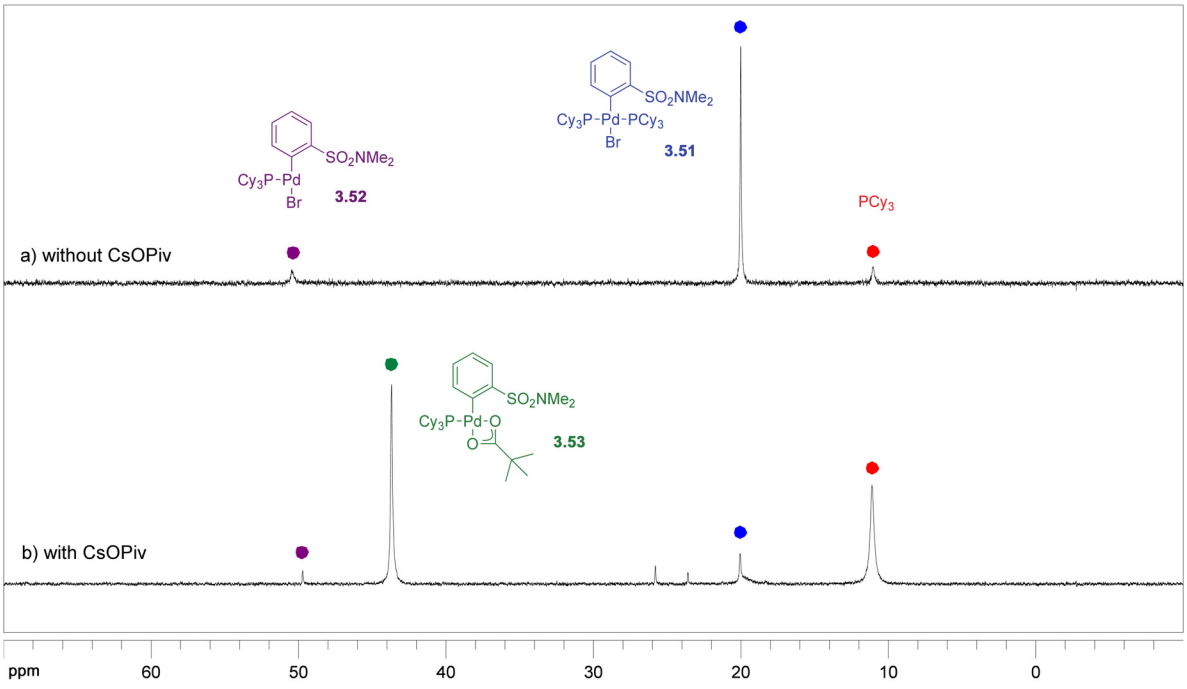


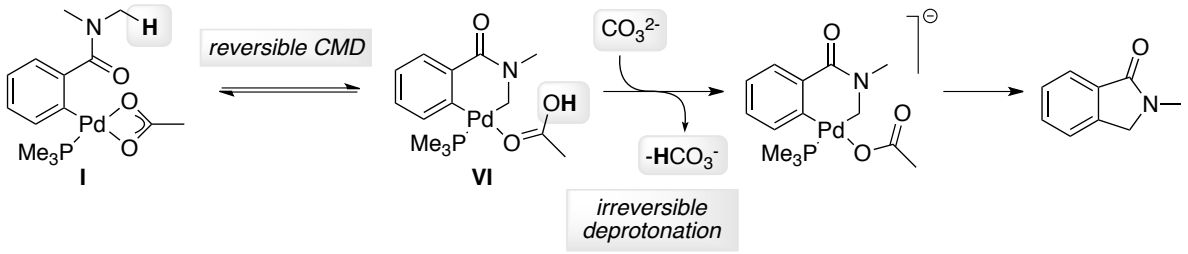
Figure 3.4 Observation of PCy_3 dissociation from Pd(II)-intermediate **3.51** (a) in the absence of CsOPiv and (b) in the presence of 6 equivalents of CsOPiv. Complex **3.51** and CsOPiv (if added) were stirred in mesitylene at 120 °C for 20 minutes after which time ^{31}P NMR spectra were collected at 60 °C.

[79] Attempts to isolate and/or characterize the intermediate corresponding to this new phosphorus signal were unsuccessful.

3.2.3.2 The Role of Carbonate in Product Formation

As previously discussed, stoichiometric reactions revealed a lack of reactivity in the presence of only Cs_2CO_3 or CsOPiv as a source of base compared to near quantitative product yields when both were added to the reaction mixture (Table 3.6). These results appear to indicate that both carbonate and pivalate play an active role in C-H bond cleavage. This apparent synergy has been investigated through the use of DFT calculations which reveal a highly *reactant-biased* potential energy surface for the C(sp^3)-H bond cleaving step (Figure 3.5). The κ^1-pivalic (acetic) acid complex **VI**, resulting from pivalate (acetate)-enabled CMD transition state **TS-I**, is a highly energetic ground state structure (ΔG = 18.2 kcal/mol relative to the reactant complex **I**). Unless the pivalic (acetic) acid ligand is quickly deprotonated, **VI** can readily revert to the reactant complex **I**. Carbonate, or other bases, may be required as a driving force for the reaction, by sequestering H^+ and pushing intermediate **VI** towards the desired product (Scheme 3.10). These conclusions are consistent with the experimental observation of low product yields in stoichiometric studies employing pivalate exclusively as the base (Table 3.6, entries 3 and 7).

Scheme 3.10 Proposed role of carbonate as the driving force for irreversible C(sp^3)-H bond cleavage



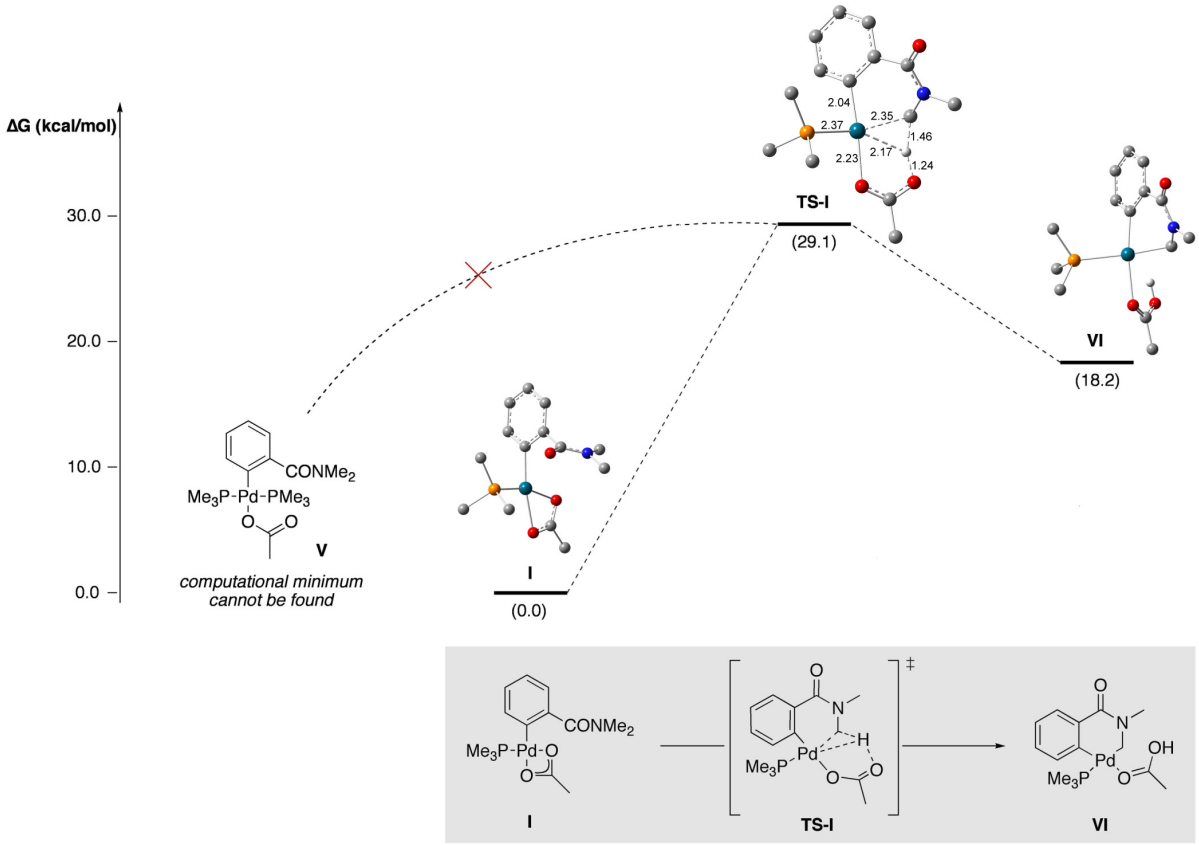


Figure 3.5 Gibbs free energies (at 298 K in toluene) of the formation of κ^1-acetic acid complex **VI** from intermediate **I** *via* CMD transition state **TS-I** featuring an agostic Pd(II)···C-H interaction. Selected bond distances (Å) are indicated. Hydrogen atoms that do not participate in the CMD process have been omitted for clarity.

Further computational studies revealed that pivalate (acetate) also plays a crucial role in blocking potential catalysis inhibition by excess phosphine in the reaction medium. A computational minimum for a bisphosphine κ^1-acetate complex **V** was not found when the CMD transition state (**TS-I**) is collapsed back to starting material. Instead, the structure invariably reverts to κ^2-acetate intermediate **I** (Figure 3.5). This suggests that **V** is not a relevant intermediate in the catalytic cycle.

These results, combined with previous experimental studies (see Section 3.2.2), highlight the importance of *both* basic species in Pd(0)-catalyzed arylations at C(sp^3)-H bonds. *Not only does the pivalate act as the base which enables C-H bond cleavage, but it also increases the concentration of Pd(II) reactive intermediate **I** prior to the CMD reaction*

*step while also preventing reaction inhibition by excess free phosphine in solution. The carbonate base in this system may also have a more active role in C(sp^3)-H bond cleavage than previously believed, by favoring product formation through the irreversible deprotonation of the post-CMD catalytic intermediate **VI**.*

3.2.3.3 Effect of Nitrogen Basicity in C(sp^3)-H Bond Cleavage

Catalyst sequestration studies (Scheme 3.5) and ^{31}P NMR experiments (Scheme 3.4) suggest the formation of a problematic intermediate **3.8**, featuring nitrogen coordination to the Pd(II) center, as an explanation for the observed lack of reactivity with more Lewis-basic nitrogen-containing substrates. While the generation of intermediate **3.8** effectively blocks product formation, we wondered whether the change in electron density on the heteroatom affected other aspects of C-H bond cleavage. To this effect, DFT calculations were performed to investigate the alkane arylation of 2'-bromobenzyl-*N*,*N*-dimethylamine (Figure 3.6).

When the potential energy surfaces for C(sp^3)-H bond cleavage in amine and amide substrates are compared, the explanation for the lack of reactivity with amine derivatives becomes apparent. In amide derivatives, κ^2-acetate complex **I** is the direct precursor to CMD transition state **TS-I**, which is 29.1 kcal/mol uphill from this intermediate (Figure 3.5). However, in amine derivatives, κ^2-acetate complex **VII** is not the most stable ground state structure; κ^1-acetate complex **VIII** is 8.1 kcal/mol lower in energy and is the precursor to CMD transition state **TS-VIII** (Figure 3.6). This increase in the ground state stability of the intermediate prior to C-H bond cleavage leads to a significantly higher energy barrier for this transition state (38.4 kcal/mol). A second CMD transition state **TS-VII** for C(sp^3)-H bond cleavage from κ^2-acetate complex **VII** can also be found and is 38.8 kcal/mol higher in energy than the most stable ground state structure **VIII**. **TS-VII** and **TS-VIII** differ in the orientation of the lone pair and the substituents on the nitrogen atom.

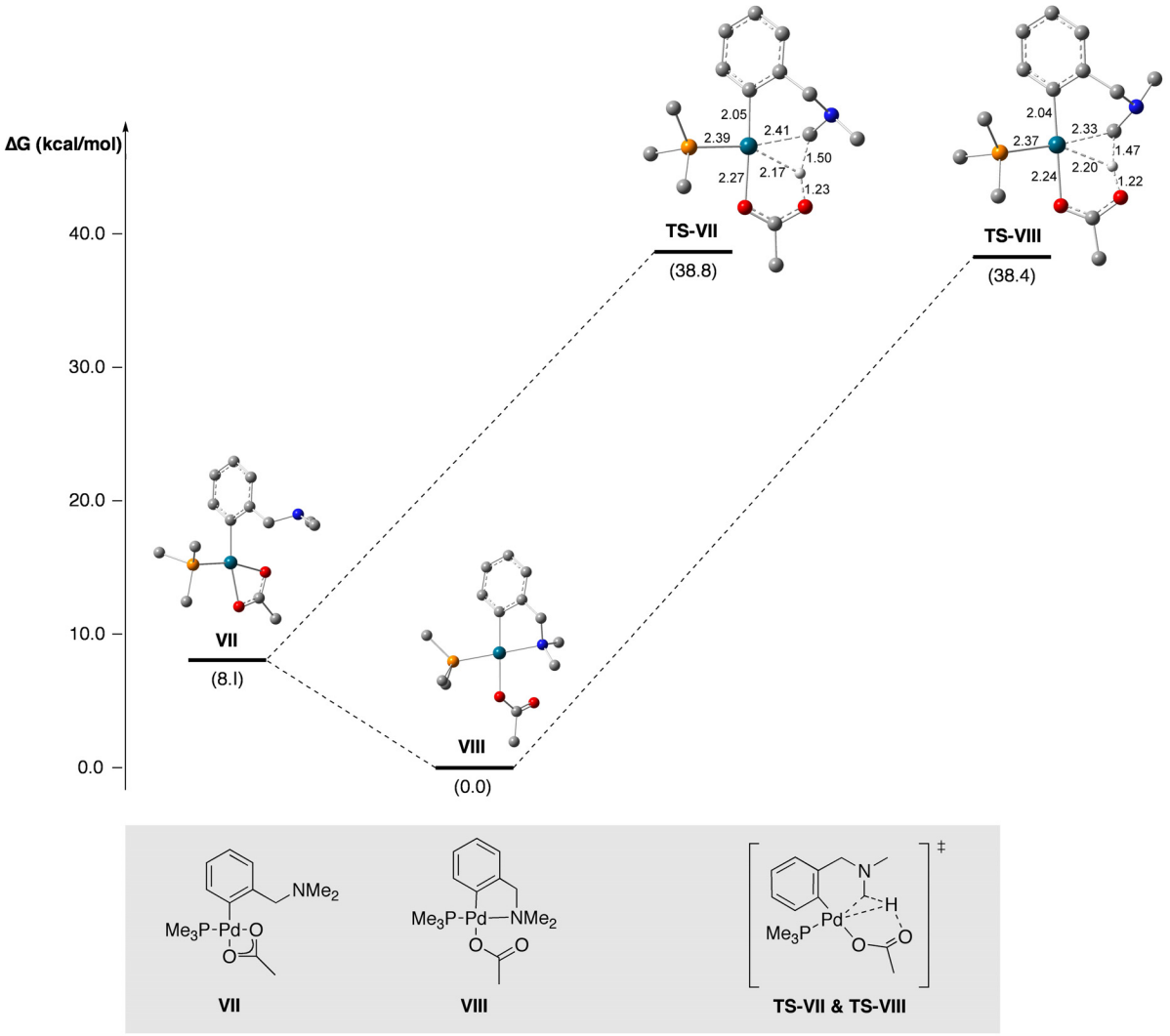


Figure 3.6 Gibbs free energies (at 298 K in toluene) of potential Pd(II) intermediates prior to the CMD transition state **TS-VIII** in the arylation of a C(sp^3)-H bond adjacent to an amine. Selected bond distances (Å) in the CMD transition state are indicated. Hydrogen atoms that do not participate in the CMD process have been omitted for clarity.

These two possible CMD transition states (**TS-VII** and **TS-VIII)** exhibit similar features to **TS-I** (Figures 3.5 and 3.6). **TS-VII** and **TS-VIII** feature a three-centre two-electron agostic interaction between the Pd(II) atom and the C-H σ bond being cleaved. Similar bond lengths are observed for the atoms that participate in the concerted metalation-deprotonation process, indicating that the degree of bond formation/bond cleavage in all three transition states is comparable and that increased nitrogen atom basicity does not affect the nature of the transition state for C(sp^3)-H bond cleavage.

Combined with experimental observations (Schemes 3.4 and 3.5), the results of this DFT study support the conclusion that the electron density on the nitrogen atom does not affect C(sp^3)-H bond cleavage, or the properties of the C-H bond, but rather leads to more stable palladium-substrate interactions, rendering the energy barrier for C-H bond cleavage too high.

3.2.4 Kinetic Experiments to Determine Reagent Orders

Efforts in future catalyst and reaction design are best focused on accelerating the turnover-limiting step of the catalytic cycle. To establish the reaction rate expression, kinetic studies were performed to determine the order in each component in the reaction of 2-bromo-*N*,*N*-dimethylbenzamide **3.20**.[71] Initial rates were determined for reactions where the concentrations in starting material (Figure 3.7), palladium (Figure 3.8), ligand (Figure 3.9) and pivalate (Figure 3.10) were modified independently.

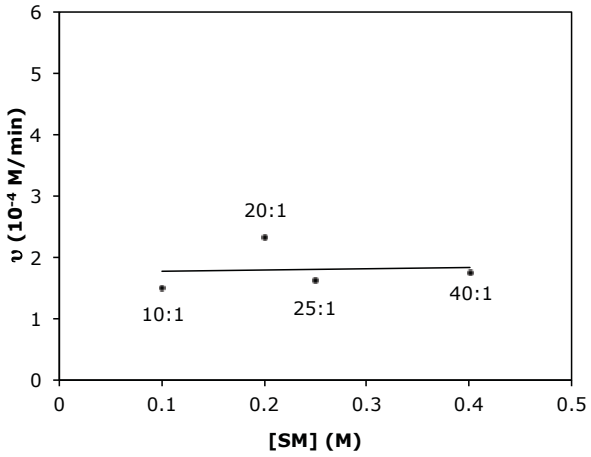


Figure 3.7 Dependence of the initial rate on the concentration of 2-bromo-*N,N*-dimethylbenzamide **3.20** (SM) (0.10-0.40 M). Conditions: [$Pd(PCy_3)_2$] = 1.0 x 10^{-2} M and [PivOH] = 6.0 x 10^{-2} M in 2.9 mL of mesitylene with 0.872 mmol of Cs_2CO_3 at 150 °C. Yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Data labels represent **3.20**:palladium ratios.

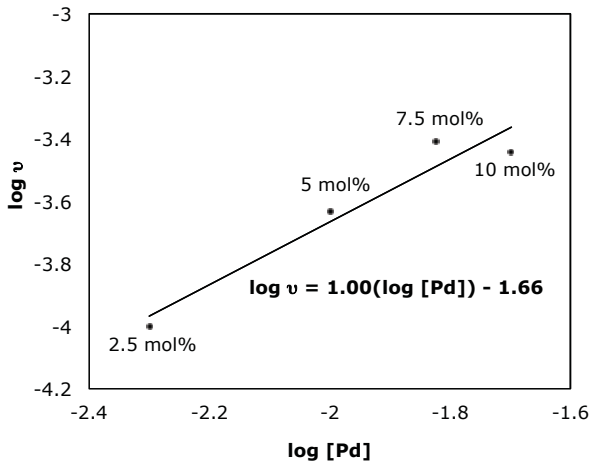


Figure 3.8 Dependence of the logarithm of the initial rate on the logarithm of the concentration of $Pd(PCy_3)_2$ (5.0×10^{-3} – 2.0×10^{-2} M). Conditions: [2-bromo-*N,N*-dimethylbenzamide **3.20**] = 0.20 M and [PivOH] = 6.0×10^{-2} M in 2.9 mL of mesitylene with 0.872 mmol of Cs_2CO_3 at 150 °C. Yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Data labels represent the catalyst loading.

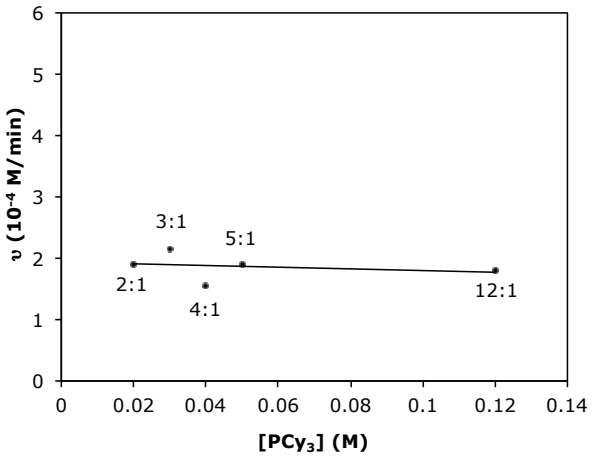


Figure 3.9 Dependence of the initial rate on the concentration of $PCy_3 \cdot HBF_4$ (2.0×10^{-2} – 1.2×10^{-1} M). Conditions: [2-bromo-*N,N*-dimethylbenzamide **3.20**] = 0.20 M, $[Pd(OAc)_2] = 1.0 \times 10^{-2}$ M and [PivOH] = 6.0×10^{-2} M in 2.9 mL of mesitylene with 0.872-1.16 mmol of Cs_2CO_3 at 150 °C. Yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Data labels represent phosphine:palladium ratios.

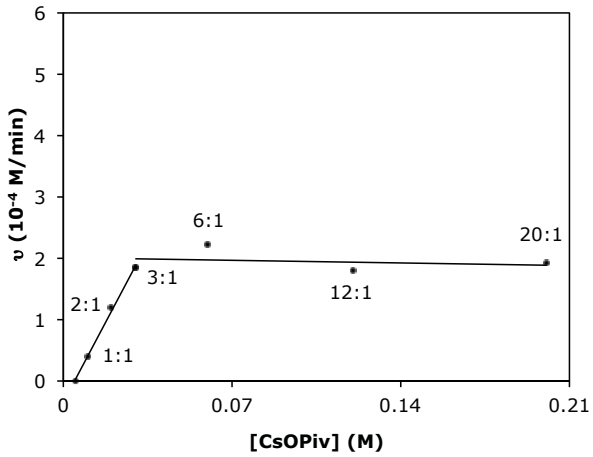


Figure 3.10 Dependence of the initial rate on the concentration of CsOPiv (5.0 x 10^{-3} – 2.0 x 10^{-1} M). Conditions: [2-bromo-*N,N*-dimethylbenzamide **3.20**] = 0.20 M and [$Pd(PCy_3)_2$] = 1.0 x 10^{-2} M in 2.9 mL of mesitylene with 0.872 mmol of Cs_2CO_3 at 150 °C. Yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Data labels represent pivalate:palladium ratios.

Plotting the initial rate against the concentration of 2-bromo-*N,N*-dimethylbenzamide **3.20** reveals that the reaction is zeroth-order in substrate (Figure 3.7), indicating that oxidative addition is not rate-determining. A plot of the logarithm of initial rates versus the logarithm of the concentration in palladium reveals a slope of 1.00 for catalyst loadings of 2.5, 5, 7.5 and 10 mol % (Figure 3.8). $Pd(PCy_3)_2$ was used as the palladium source instead of $Pd(OAc)_2$ to avoid any potential rate effects due to the presence of additional acetate ions in solution.[34] The slope of 1.00 is indicative of a first-order rate dependence in catalyst loading. Next, the effect of excess phosphine on the rate was examined. The plot of initial rates versus the concentration of phosphine demonstrates that PCy_3:Pd ratios in excess of 2:1, i.e. the standard catalytic conditions, do not inhibit catalysis (Figure 3.9).[80] This correlates with computational results suggesting that pivalate coordination to Pd(II) may prevent inhibition of the CMD step through phosphine coordination to Pd(II) (see Section 3.2.3).

Finally, the effect of pivalate concentrations on initial rates was also examined. A linear increase in initial rate is observed for 0.5:1, 1:1, 2:1 and 3:1 pivalate:palladium ratios

[80] A 1:1 palladium:ligand ratio led to diminished product yield, although the kinetic profile of this reaction was not monitored.

(Figure 3.10). The dependence of the initial rate on the concentration of pivalate changes from first to zeroth-order, revealing saturation kinetics, when pivalate:palladium ratios exceed 3:1. Figure 3.10 also reveals an optimal rate acceleration around 30 mol% pivalate additive (6:1 pivalate:palladium), further validating the selection of this amount of pivalic acid additive during reaction development (Section 3.2.1).

From this kinetic data, the rate expression for the formation of isoindolinones by alkane arylation under standard catalytic conditions can be expressed as:

$$\text{rate} = k\,[\text{Pd}][\text{PivO}^-]^n$$

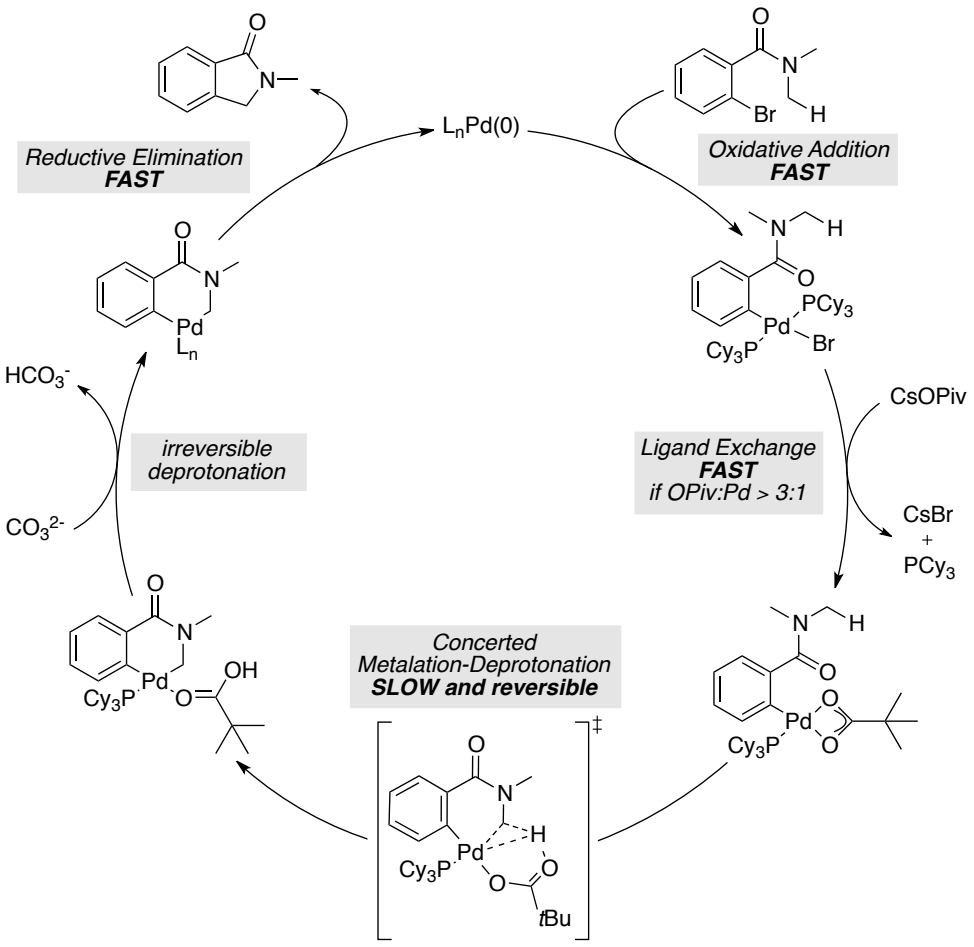
$n = 1$ when $\text{PivO}^-:\text{Pd} < 3:1$

$n = 0$ when $\text{PivO}^-:\text{Pd} > 3:1$.

3.2.5 Catalytic Cycle

Based on these mechanistic, kinetic and computational results, a clearer picture of the catalytic cycle for arylation at C(sp^3)-H bonds emerges (Scheme 3.11). Oxidative addition of the aryl halide to Pd(0) occurs rapidly under the reaction conditions, affording a Pd(II) intermediate. This species may undergo a rapid ligand exchange, replacing the halide by a pivalate ion generated *in situ* from the reaction of pivalic acid with carbonate. Kinetic studies reveal the importance of the concentration of pivalate on this elementary reaction step. Indeed, PivO^-:Pd ratios greater than 3:1 are required for saturation of palladium in this ligand. Computational and experimental results further support the formation of a κ^2-pivalate Pd(II) intermediate as the direct precursor to the CMD reaction step, which is enabled by the pivalate ligand. The post-CMD intermediate is deprotonated by the carbonate base which acts as the driving force of the reaction by making C(sp^3)-H bond cleavage irreversible. The cycle is completed by rapid reductive elimination of the desired product with regeneration of the Pd(0) catalyst.

Scheme 3.11 Proposed catalytic cycle



3.3 Conclusions and Perspectives

The development and scope of the Pd(0)-catalyzed intramolecular alkane arylation adjacent to amides and sulfonamides was presented in this Chapter. Tuning the Lewis basicity of the nitrogen atom proved to be crucial for the desired transformation. Mechanistic studies confirmed that C(sp^3)-H bond cleavage is the rate-limiting step of the catalytic cycle. The isolation of a Pd(II) intermediate has allowed, for the first time, a direct evaluation of the C-H bond cleaving step in Pd(0)-catalyzed C-C bond formation at nonacidic aliphatic C-H bonds. This event appears to occur through a CMD pathway, featuring cooperative assistance by both pivalate and carbonate bases. Computational

studies further elucidated a second crucial role for the pivalate additive as a promoter of phosphine dissociation prior to the CMD transition state.

Overall, these mechanistic studies highlight the importance of basic additives in catalytic transformations at C-H bonds. The notion of multiple roles for a single additive at the metal center should influence future reaction development in this field. Additionally, the intimate involvement of the pivalate base at the transition state for C-H bond cleavage suggests that chiral carboxylate additives should facilitate enantioselective C-H arylation reactions (see Chapter 5). Indeed, an elegant study has just appeared highlighting the cooperative interactions between chiral phosphine ligands and bulky carboxylate additives in asymmetric alkane arylation.[81] These encouraging results demonstrate the importance of mechanistic understanding for future reaction design. However, despite our improved understanding of these transformations, questions remain. Notably, the mechanism of catalyst activation is currently unknown. The high catalyst loadings often observed in C-H arylation reactions may be due to incomplete formation of the active catalytic species under the reaction conditions. Pd-precatalysts that have been recently developed for challenging cross-coupling reactions, as well as methods for catalyst activation, should be investigated in C-H arylation chemistry.[82,83]

[81] Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238-2242.
[82] For selected examples, see: (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686-6687; (b) Kinzel, T.; Zhang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 14073-14075.
[83] For a recent application of a modified version of the precatalyst in ref 82b in the direct C(sp^2)-H arylation of thiophene derivatives, see: Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658-668.

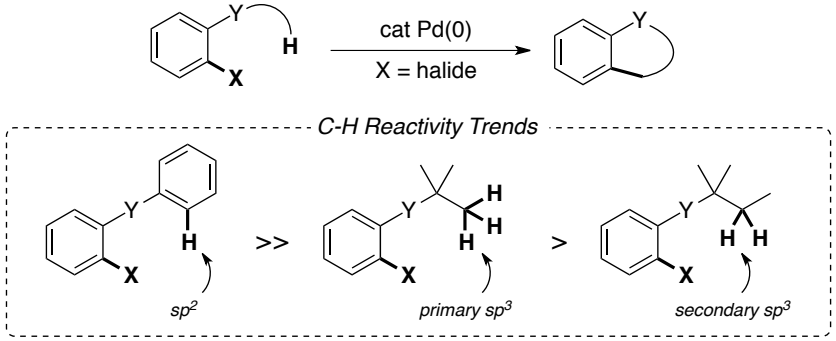
4 Arylation at Cyclopropane C(sp^3)-H Bonds

4.1 Background

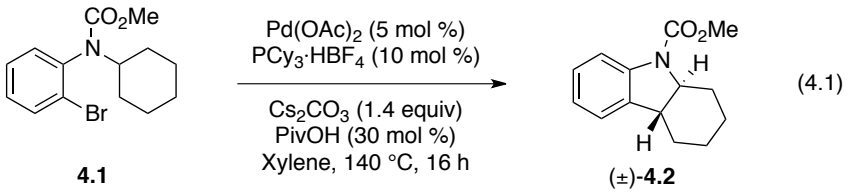
4.1.1 Pd(0)-Catalyzed Alkane Arylation at Secondary C-H Bonds

Efforts in the area of Pd(0)-catalyzed alkane arylation have led to an increase in reports of various methods for carbocycle and heterocycle synthesis over the past decade. While these transformations are still considered more challenging than the arylation of C(sp^2)-H bonds, mechanistic studies have provided insight, enabling future reaction development.[11] Common to these previous reports is the high level of chemoselectivity for arylation at primary C(sp^3)-H bonds over secondary or tertiary positions (Scheme 4.1). The nature of this selectivity has been investigated in part by recent theoretical studies (Section 2.2.2).[65] Examples of methylene arylation under Pd(0)-catalysis are limited to rare examples in a couple of communications.

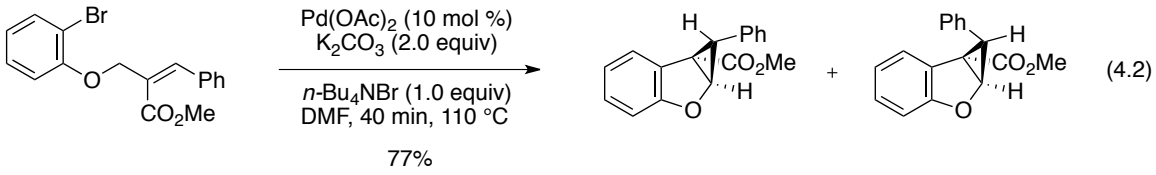
Scheme 4.1 Pd(0)-catalyzed intramolecular C-C bond formation involving C-H bonds of varying hybridization



In their 2008 report on the preparation of indoline derivatives via intramolecular alkane arylation, Fujii, Ohno and coworkers described an interesting case of methylene arylation.[40] Treatment of aniline **4.1** with a catalyst based on $Pd(OAc)_2/PCy_3$ afforded *trans*-fused tricyclic indoline **4.2** in 76% yield. Compared to the equivalent arylation of a methyl group (Scheme 1.15), this reaction required only slightly higher catalyst loadings (5 mol % compared to 3 mol %) and longer reaction times (16 hours compared to 2 hours). Of note, the presence of β-hydrogen atoms was not problematic for the desired transformation. In 2011-2012, the Kündig and Cramer groups investigated this example of secondary C(sp^3)-H arylation in the context of asymmetric Pd(0)-catalyzed alkane arylation (see Chapter 5).[44,81]



The second example of Pd(0)-catalyzed methylene arylation was reported by Kim and coworkers, also in 2008 (eq 4.2).[62] This reaction was discussed in Section 3.1.1 in the context of alkane arylation adjacent to a heteroatom. This transformation occurs via an "intercepted" intramolecular Heck reaction, where proximity-enabled methylene C-H bond cleavage occurs instead of β-hydride elimination due to the absence of a β-hydrogen atom.

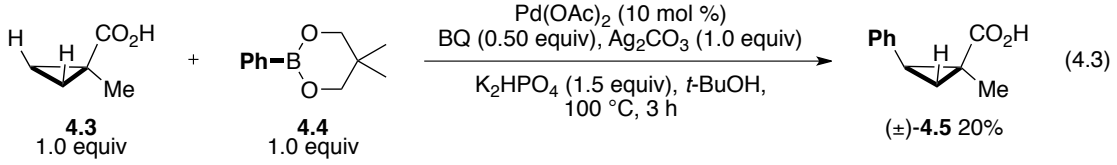


4.1.2 Pd(II)-Catalyzed Arylation at Cyclopropane C(sp^3)-H Bonds

Contrary to the lack of examples of secondary C(sp^3)-H arylation under Pd(0) catalysis, there is a considerable number of reports on Pd(II)-catalyzed methylene arylation.

These reports will not be extensively described in the following section (see Section 1.2.1 for a brief overview), however a discussion of Pd(II)-catalyzed arylations at C(sp^3)-H bonds in cyclopropanes is warranted based on the topic of this Chapter. The Yu group has been at the forefront of this field since their first report of cyclopropane C-H iodination in 2005.[84] Since then, publications have surfaced for cyclopropane alkylation, alkenylation, arylation and carbonylation via C-H functionalization.[85,86]

The first report of cyclopropane C-H arylation appeared in 2007.[18] Yu and coworkers found that cyclopropane **4.3** could be coupled with phenylboronate **4.4** under carboxylate-directed Pd(II)-catalysis to afford arylated product **4.5** (eq 4.3). While the yield of the reaction was quite poor (20%), this transformation represented a marked divergence from typical regioselectivities since the methyl group remained unfunctionalized under these conditions.



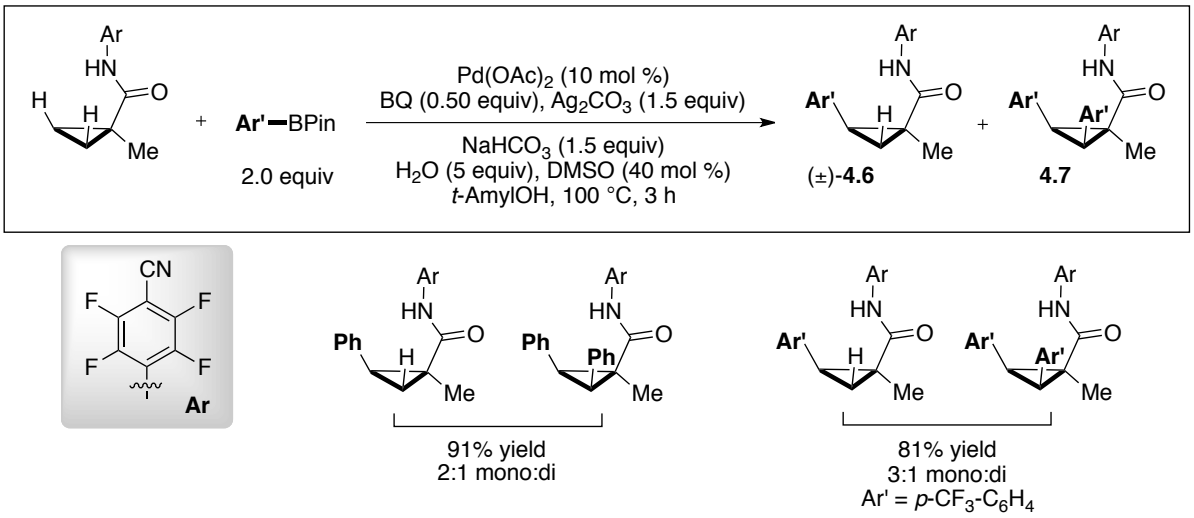
(4.3)

With the discovery of *N*-arylamides as improved directing groups for Pd(II)-catalyzed C(sp^3)-H bond functionalization, [87] cyclopropane arylation was reinvestigated.[85e] Optimization studies revealed that *N*-(2,3,5,6-tetrafluoro-benzonitrile)amide was the optimal directing group for this transformation (Scheme 4.2). The use of arylboronic acid pinacol esters (2.0 equivalents) as the source of arene in conjunction with $NaHCO_3$ as the base also proved crucial for successful product formation.

[84] Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112–2115.
[85] For examples of Pd(II)-catalyzed cyclopropane C–H bond functionalization, see: (a) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680–3681; (b) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378–17380; (c) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541–6544; (d) Kubota, A.; Sanford, M. S. *Synthesis* **2011**, 2579–2589; (e) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 19598-19601. See also refs 18, 19, 84.
[86] For an example of Ru-catalyzed carbonylation of a cyclopropane C–H bond, see: Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070–8073.
[87] For selected references, see: (a) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275-1277; (b) Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *Chem. Lett.* **2011**, *40*, 1004-1006. See also refs 29 and 85a,b.

Using these second-generation conditions, cyclopropane C(sp^3)-H arylation occurred in significantly higher yields albeit with mixtures of mono- (**4.6**) and diarylated products (**4.7**).

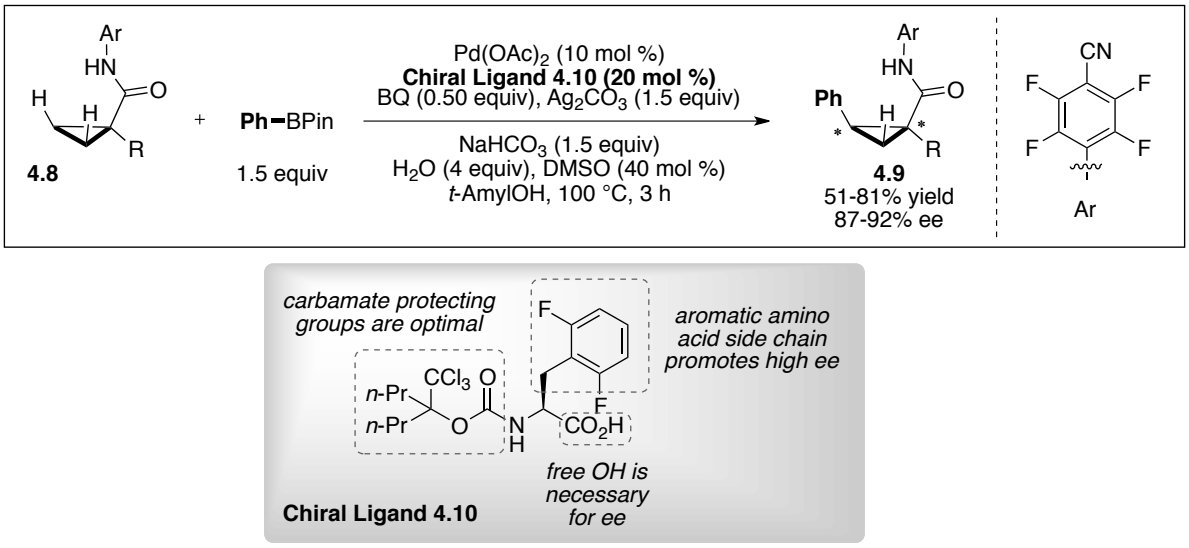
Scheme 4.2 Cyclopropane C(sp^3)-H arylation using an *N*-arylamide directing group



Based on these promising results, Yu and coworkers explored the development of an asymmetric variant of this reaction. Amino acid derivatives were evaluated as chiral ligands based on their previously successful application in Pd(II)-catalyzed enantioselective C(sp^2)-H olefination and alkylation reactions.[88] A significant amount of optimization was required to determine the optimal ligand structure. It should be noted that the authors observed a proportional increase in selectivity for monoarylation as enantiomeric excesses increased. Carbamate protecting groups on the amine component of the amino acid provided optimal yields and ees. Important increases in enantioselectivity were also observed when amino acids with aromatic side chains were employed. Finally, the carboxylic acid moiety appeared to be crucial for enantioinduction, since the installation of a protecting group on this functional group led to completely racemic product. Thus, employing optimal chiral ligand **4.10**, various amides **4.8** underwent asymmetric C(sp^3)-H functionalization to generate phenyl-substituted cyclopropanes **4.9** in good to excellent yields with high levels of ee (Scheme 4.3).

[88] (a) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882-4886; (b) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460-461.

Scheme 4.3 Asymmetric C(sp^3)-H arylation employing chiral amino acid ligands

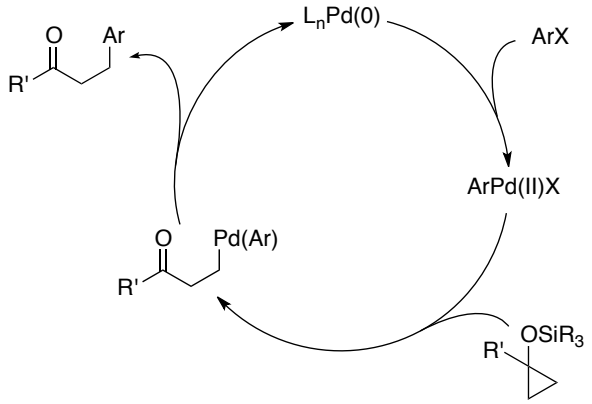


4.1.3 Pd(0)-Catalyzed Reactions with Cyclopropanes

Prior to this work, Pd(0)-catalyzed cyclopropane C(sp^3)-H functionalization, initiated by oxidative addition of an aryl-halide to Pd(0), had not been reported. Typically, the inherent reactivity of cyclopropane rings towards electrophilic Pd(II) intermediates leads to ring opened products rather than C(sp^3)-H bond cleavage. This strategy has been extensively employed to generate palladium homoenolates, which can be exploited for cross-coupling reactions (Scheme 4.4).[89]

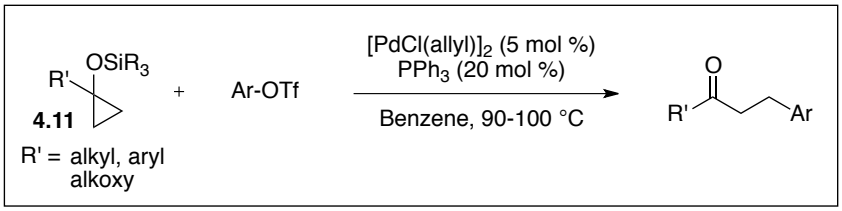
[89] For initial reports, see: (a) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296-3298; (b) Aoki, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1988**, *29*, 1541-1542; (c) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 6541-6544; (d) Aoki, S.; Nakamura, E. *Synlett* **1990**, 741-742; (e) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809-2821; (f) Kan, S.-K.; Yamaguchi, T.; Ho, P.-S.; Kim, W.-Y.; Yoon, S.-K. *Tetrahedron Lett.* **1997**, *38*, 1947-1950.

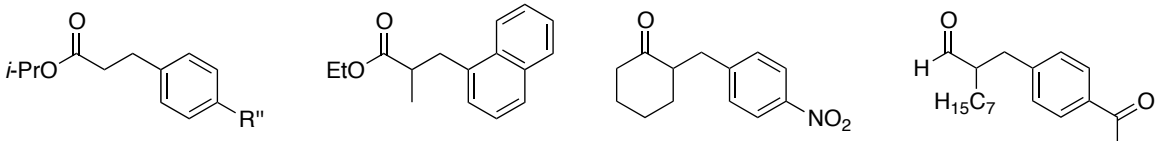
Scheme 4.4 Pd-catalyzed cyclopropane ring-opening and cross-coupling



In 1988, Nakamura, Kuwajima and coworkers reported a palladium-catalyzed protocol for the arylation of siloxycyclopropanes.[89a] Treatment of cyclopropanes of general structure **4.11** with $[PdCl(allyl)]_2$ (5 mol %) and PPh_3 (10 mol %) in benzene provided β-arylated esters, ketones or aldehydes (Scheme 4.5). The authors proposed a catalytic cycle similar to the one presented in Scheme 4.4. The intermediacy of a highly electrophilic cationic Pd(II) species was found to be of utmost importance to enable C-C bond cleavage. Indeed, the use of aryl halides led to unproductive reactions. Only aryl triflates (or aryl diazonium salts), which generate a cationic Pd(II) intermediate after oxidative addition, afforded the desired product. Good to excellent yields were obtained with electron-neutral or -deficient aryl triflates (**4.12**, **4.14**-**4.16**). Electron-rich aryl triflates were found to be incompatible coupling partners (**4.13**), providing further evidence that C-C bond cleavage occurs from an electrophilic Pd(II) species. It should be noted that cleavage of the least substituted C-C bond occurs preferentially, as evidenced by the exclusive formation of **4.14**-**4.16** from the corresponding 2-substituted siloxycyclopropanes.

Scheme 4.5 Pd-catalyzed conversion of siloxycyclopropanes to β-arylated esters, ketones or aldehydes





4.12, R'' = $C(O)CH_3$, 59%
4.13, R'' = OCH_3, 0%

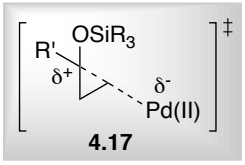
4.14, 87%

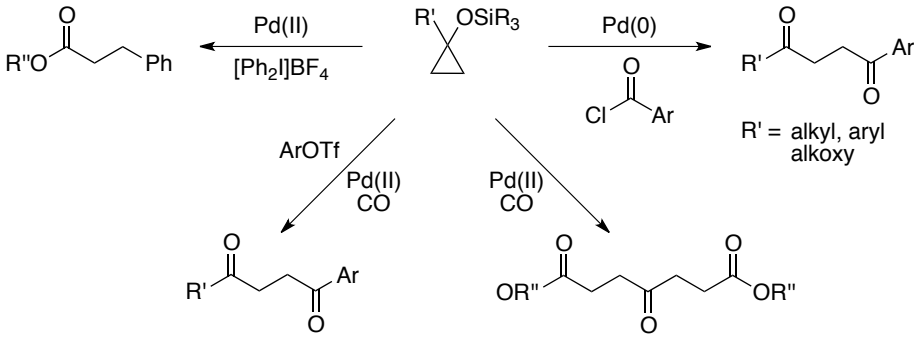
4.15, 68%

4.16, 65%

This initial report was followed by a series of publications on Pd-catalyzed transformations of siloxycyclopropanes, including acylations,[89c,e] carbonylative-dimerizations,[89b] carbonylative-arylations,[89d] and arylations using iodonium salts[89f] (Scheme 4.6). Theoretical and experimental studies supported the formation of a common Pd-homoenolate intermediate in these reactions, generated via transition state **4.17**.[89e]

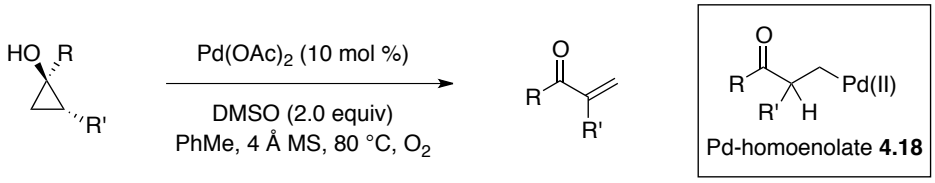
Scheme 4.6 Pd-catalyzed transformations of siloxycyclopropanes



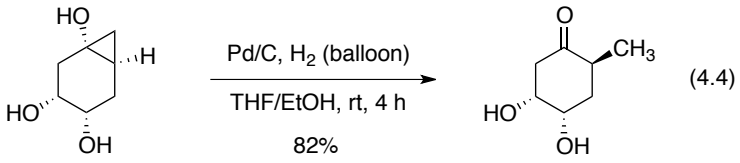


More recently, similar Pd-catalyzed cyclopropane ring-opening reactions have been reported from simple unprotected cyclopropanols. In 2000, Park and Cha disclosed a Pd(II)-catalyzed protocol for cyclopropane ring-opening with subsequent dehydrogenation, via β-hydride elimination from the Pd-homoenolate **4.18**, to generate α,β-unsaturated ketones.[90] Synthetically useful regioselectivities were obtained, with preferential bond cleavage occurring at the least substituted C-C bond (Scheme 4.7).

Scheme 4.7 Synthesis of α,β-unsaturated ketones via cyclopropanol ring-opening



Shan and O'Doherty later employed a similar strategy in their syntheses of carbasugar C1-phosphates and cyclitols.[91] Key to their success was the use of a Pd-catalyzed regioselective cyclopropanol ring-opening under hydrogenation conditions (eq 4.4).



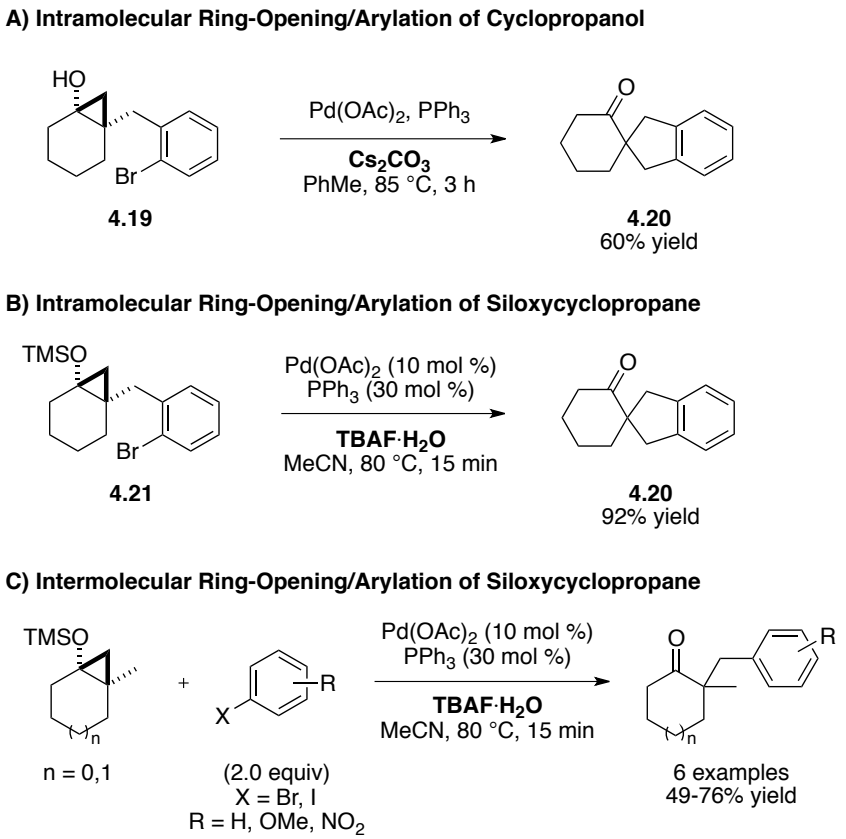
(4.4)

Based on the promising results of Cha and O'Doherty, Rosa and Orellana hypothesized that unprotected cyclopropanols could be used as precursors for Pd-homoenolates in Pd(0)-catalyzed cross-coupling processes,[92] similar to the pioneering work of Nakamura and Kuwajima.[89] Indeed, treatment of aryl bromide **4.19** with $Pd(OAc)_2$ and PPh_3 generated spirocycle **4.20** in 60% yield (Scheme 4.8A). However, cyclopropanol **4.19** appeared to decompose under the reaction conditions. Thus the use of TMS-protected

[90] Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147-149.
[91] (a) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3381-3384; (b) Shan, M.; O'Doherty, G. A. *Synthesis* **2008**, 3171-3179.
[92] Rosa, D.; Orellana, A. *Org. Lett.* **2011**, *13*, 110-113.

4.21, which can be deprotected *in situ*, was investigated. Reaction optimization revealed that by replacing the base (Cs_2CO_3) with a fluoride source (TBAF·H_2O), spirocycle **4.20** could be obtained in 92% yield after only 15 minutes (Scheme 4.8B). These conditions could also be applied to an intermolecular cross-coupling variant of this reaction (Scheme 4.8C). Of note, in contrast to previous reports, aryl bromides and iodides, as well as electron-rich arenes, are well tolerated under these conditions.

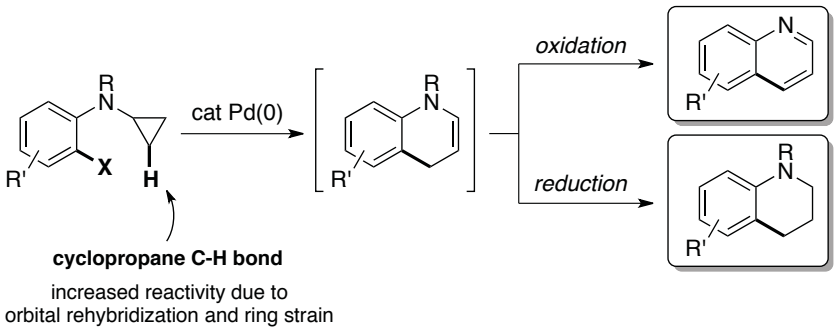
Scheme 4.8 Pd(0)-catalyzed ring-opening/arylation of cyclopropane derivatives



In this Chapter, the development and scope of a novel Pd(0)-catalyzed intramolecular arylation reaction at cyclopropane methylene C(sp^3)-H bonds will be described. This transformation generates 1,4-dihydroquinolines, via in situ ring-opening, which can be subsequently oxidized or reduced to the corresponding quinolines or 1,2,3,4-tetrahydroquinolines (Scheme 4.9). Evidence will also be presented to demonstrate that this transformation is mechanistically different from traditional Pd-catalyzed

cyclopropane ring-opening reactions, occurring via pivalate-assisted C(sp^3)-H bond cleavage.[93] It should be noted that this project was done in collaboration with Dr. Benoît Liégault, who performed the portion of this work related to the synthesis of chromenes (eq 4.6).

Scheme 4.9 Pd(0)-catalyzed arylation at secondary cyclopropane C-H bonds

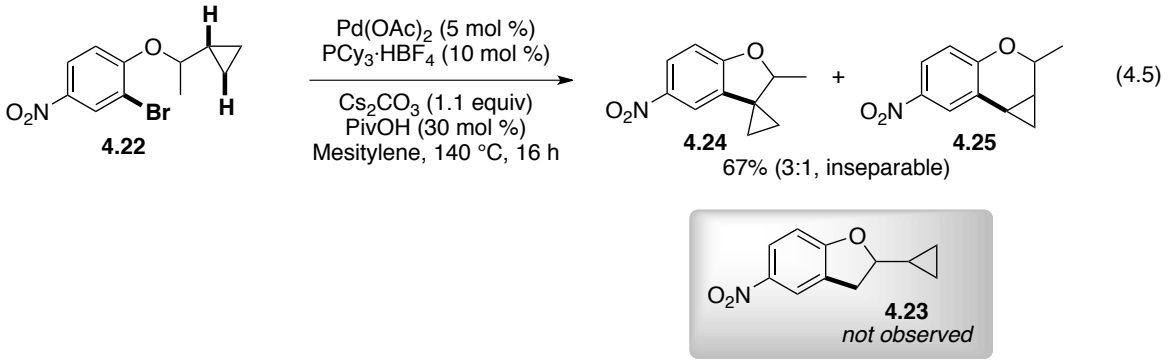


4.2 Result and Discussion

4.2.1 Reaction Development and Scope

Over the course of our investigation of dihydrobenzofuran synthesis via alkane arylation, we came across an intriguing result. Subjecting aryl bromide **4.22** to $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Cs_2CO_3 (1.1 equiv) and PivOH (30 mol %) in mesitylene at 140 ºC did not provide the expected product **4.23**. Instead, an inseparable mixture (3:1 ratio) of dihydrobenzofuran **4.24** and chroman **4.25** was obtained in 67% yield (eq 4.5).

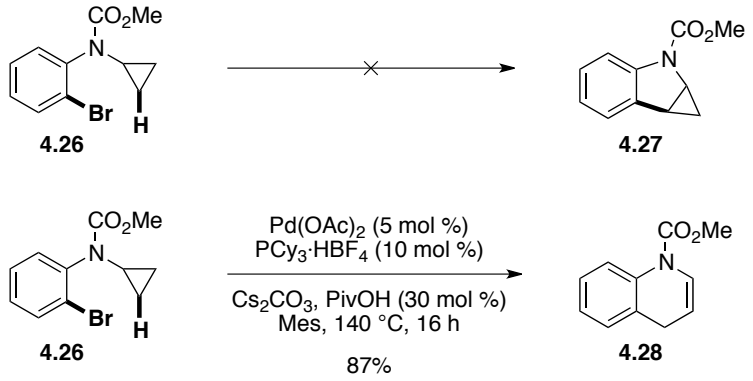
[93] Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244-248.



(4.5)

Unfortunately, a screen of the different reaction parameters did not improve the product yields or selectivities. Thus, we opted to examine the functionalization of aniline derivative **4.26**,[94] a substrate class that had previously demonstrated improved reactivity in alkane arylation.[40] Surprisingly, the desired indoline **4.27** was not observed when **4.26** was submitted to our standard reaction conditions. Instead, dihydroquinoline **4.28** was isolated in 87% yield.

Scheme 4.10 Initial investigations for reaction development



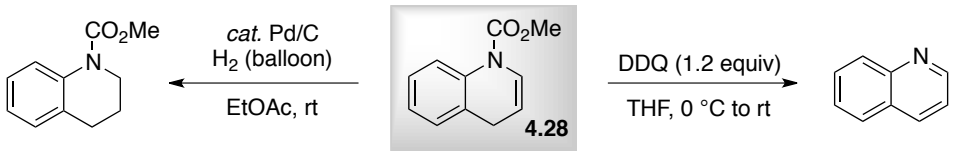
Hypothesizing that the high reaction temperature of 140 °C was promoting cyclopropane ring opening in **4.27**, we sought to find conditions for C(sp^3)-H arylation at lower temperatures. While alkane arylation from aryl chlorides (Chapter 2) and adjacent to heteroatoms (Chapter 3) requires temperatures of 135 °C or greater, we hoped that the

[94] See supporting information for the preparation of the cyclopropylaniline starting materials.

"sp^2"-character of cyclopropane C-H bonds may lower the energetic barrier for C-H bond cleavage in this system. Indeed, the use of stoichiometric K_3PO_4 with a catalytic amount of CsOPiv led to complete conversion of aryl bromide **4.26** at 90 °C. Unfortunately, dihydroquinoline **4.28** was once again obtained as the major product. Other base/additive combinations, such as Cs_2CO_3/PivOH, K_2CO_3/CsOPiv, KO*t*-Bu/CsOPiv and stoichiometric K_3PO_4 or CsOPiv, led to incomplete conversions (or no reaction at all) as well as significant amounts of dehalogenated starting material. In all cases, indoline **4.27** could not be detected. A ligand screen revealed that electron-rich trialkylphosphines provided optimal yields of **4.28**, with P(*t*-Bu)$_2$Me·HBF$_4$ proving slightly better than PCy$_3$·HBF$_4$ and PCyp$_3$·HBF$_4$. Less than 10% starting material conversion was observed with the very bulky P(*t*-Bu)$_3$·HBF$_4$. Finally, the reaction was most efficient in non-polar and high-boiling aromatic solvents, with slightly higher product yields obtained in mesitylene than toluene. Throughout this evaluation of reaction conditions, a divergence in selectivity for the formation of **4.27** over **4.28** was never observed.

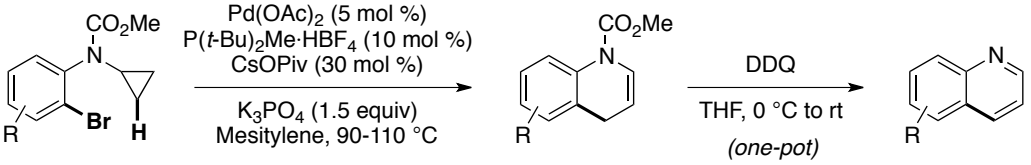
It should be noted that once isolated, **4.28** decomposes over time. We therefore opted to investigate the viability of conducting a subsequent same-pot oxidation (or reduction) protocol to obtain the corresponding quinoline (or tetrahydroquinoline) (Scheme 4.11). Upon further examination, we found that treatment of a diluted (THF) and cooled (0 °C) reaction mixture with DDQ (1.2 equivalents) led to optimal product yields with minimal byproduct formation. On the other hand, the crude mixture containing **4.28** could be subjected to catalytic amounts of Pd/C under vigorous stirring and an atmosphere of H_2 to generate the corresponding tetrahydroquinoline.

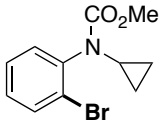
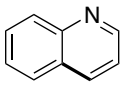
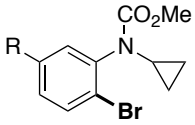
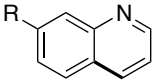
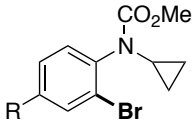
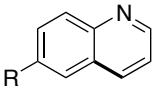
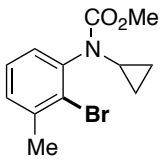
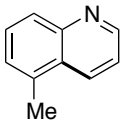
Scheme 4.11 Conditions for same-pot conversion of dihydroquinoline to quinoline or tetrahydroquinoline



With these conditions in hand, the scope of Pd(0)-catalyzed cyclopropane C(sp^3)-H arylation was investigated. The transformation of 2-bromoaniline derivatives to quinolines is demonstrated in Table 4.1. Electron-rich (entry 4), electron-poor (entries 5-8) and electron-neutral (entries 2,3 and 9) substituents are all well tolerated, generating the corresponding quinolines in good to excellent yields. Substitution of the arene ring at positions *ortho*, *meta* and *para* to the C-Br bond is tolerated. Steric hindrance does not appear to impede oxidative addition to the Pd(0) catalyst as demonstrated by the formation of quinoline **4.43** in 87% yield from aryl bromide **4.42** (entry 9). It should be noted that the methylcarbamate protecting group can be replaced by a benzylcarbamate (Cbz), albeit at a minor cost in yield (entries 2 and 3).

Table 4.1 Quinoline synthesis from aryl bromides

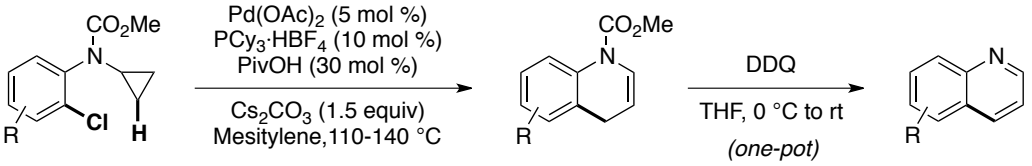


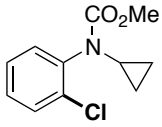
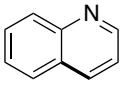
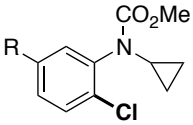
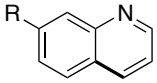
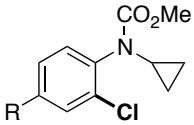
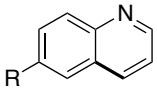
entry	aryl bromide		quinoline		R	yield[a]
1		**4.26**		**4.29**	/	87%
2		**4.30a**		**4.31**	Me	67%
3[b]		**4.30b**		**4.31**	Me	59%
4		**4.32**		**4.33**	OMe	91%
5		**4.34**		**4.35**	CF_3	78%
6		**4.36**		**4.37**	F	73%
7		**4.38**		**4.39**	NO_2	61%
8		**4.40**		**4.41**	CN	65%
9		**4.42**		**4.43**	/	87%

[a] Isolated yields. [b] *N*-Protecting group "CO_2Me" was replaced by "CBz".

The use of aryl chloride coupling partners for the Pd(0)-catalyzed alkane arylation of cyclopropanes was also examined. Reevaluation of the reaction conditions revealed that the use of $PCy_3{\cdot}HBF_4$ (10 mol %) as the ligand and Cs_2CO_3 with catalytic PivOH as the base/additive combination, enabled the preparation of other diversely substituted quinolines after a slight increase in reaction temperature (Table 4.2). Electron-donating and -withdrawing substituents are well tolerated, as exemplified by the formation of quinolines **4.46**, **4.48** and **4.50** (entries 2-4).

Table 4.2 Quinoline synthesis from aryl chlorides



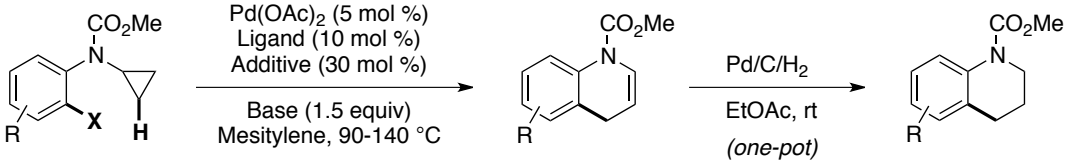
entry	aryl halide		quinoline		R	yield[a]
1		**4.44**		**4.29**	/	76%
2		**4.45**		**4.46**	OTIPS	85%
3		**4.47**		**4.48**	CF_3	52%
4		**4.49**		**4.50**	CO_2Me	82%

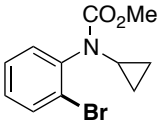
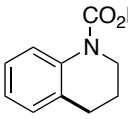
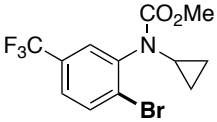
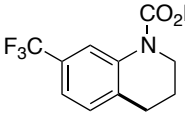
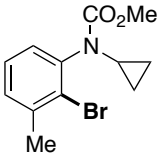
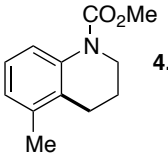
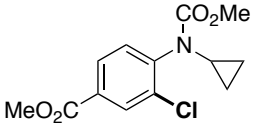
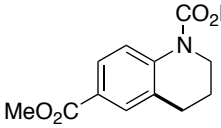
[a] Isolated yields.

Finally, the preparation of *N*-protected tetrahydroquinolines from aryl bromides and chlorides has been investigated (Table 4.3). This class of heterocycle can be prepared using the conditions previously developed for Pd-catalyzed cyclopropane C(sp^3)-H arylation (Tables 4.1-4.2) with a subsequent same-pot reduction using catalytic amounts of Pd/C under an atmosphere of H_2 (Table 4.3). Excellent yields are generally obtained with the exception of CF_3-substituted aryl bromide **4.34**, which proved more difficult to reduce (entry 2). Steric

hindrance adjacent to the C-Br bond is well tolerated, as demonstrated by the synthesis of tetrahydroquinoline **4.53** in 99% yield.

Table 4.3 Tetrahydroquinoline synthesis from aryl bromides and chlorides

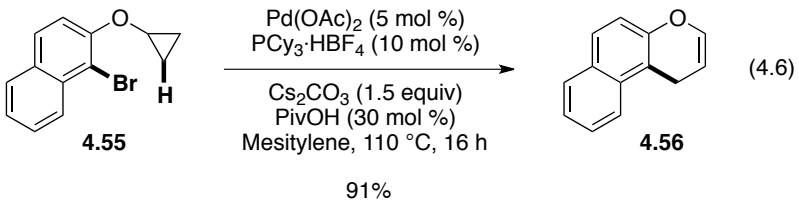


entry	aryl halide		tetrahydroquinoline		conditions[a]	yield[b]
1		**4.26**		**4.51**	A	82%
2		**4.34**		**4.52**	A	45%[c]
3		**4.42**		**4.53**	A	99%
4		**4.49**		**4.54**	B	95%

[a] **Conditions A**: $Pd(OAc)_2$ (5 mol %), $P(t\text{-}Bu)_2Me{\cdot}HBF_4$ (10 mol %), CsOPiv (30 mol %), K_3PO_4 (1.5 equiv), 90-110 °C, 16 h; **Conditions B**: $Pd(OAc)_2$ (5 mol %), $PCy_3{\cdot}HBF_4$ (10 mol %), PivOH (30 mol %), Cs_2CO_3 (1.5 equiv), 140 °C, 3 h. [b] Isolated yields. [c] The intermediate dihydroquinoline was also isolated in 53% yield.

Based on our first result for cyclopropane arylation (eq 4.5) and the successful synthesis of quinolines and tetrahydroquinolines using this method, we explored the functionalization of cyclopropyl ethers. Employing conditions B from Table 4.3 at 110 °C, ether **4.55** was converted to chromene **4.56** in excellent yield (eq 4.6). An evaluation of the reaction parameters did not reveal conditions where spontaneous cyclopropane ring-opening

could be avoided. It should be noted that other lower molecular weight chromenes could be prepared using this method, however they proved too volatile to isolate in acceptable yields.

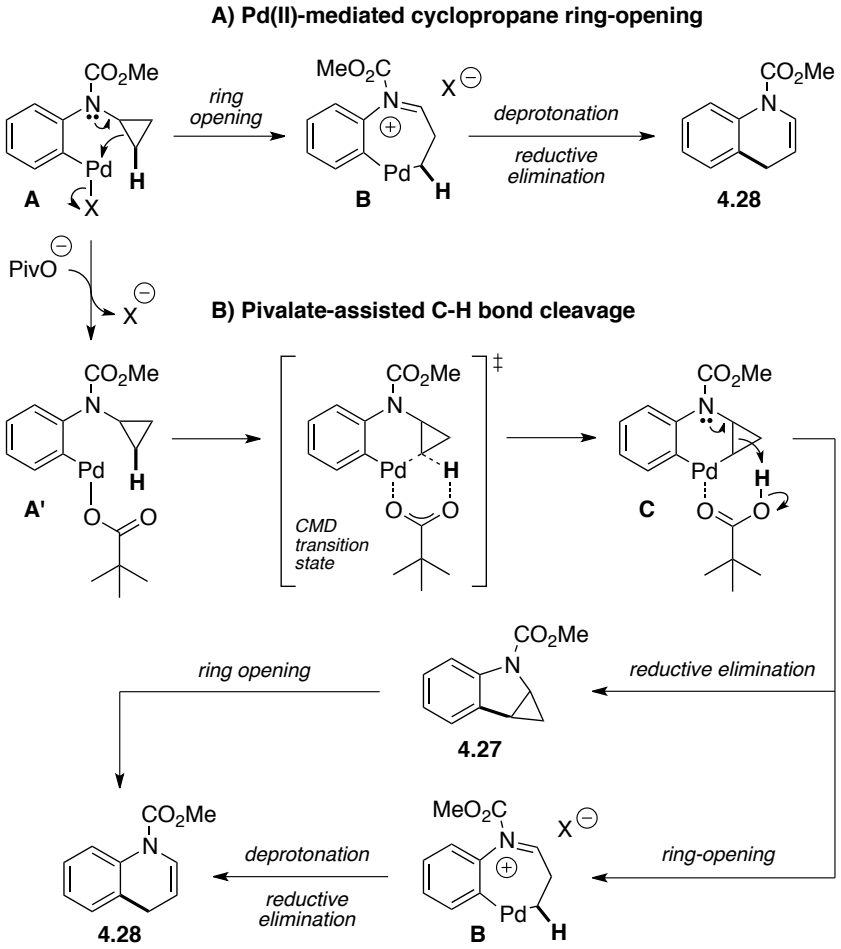


(4.6)

4.2.2 Mechanistic Insight

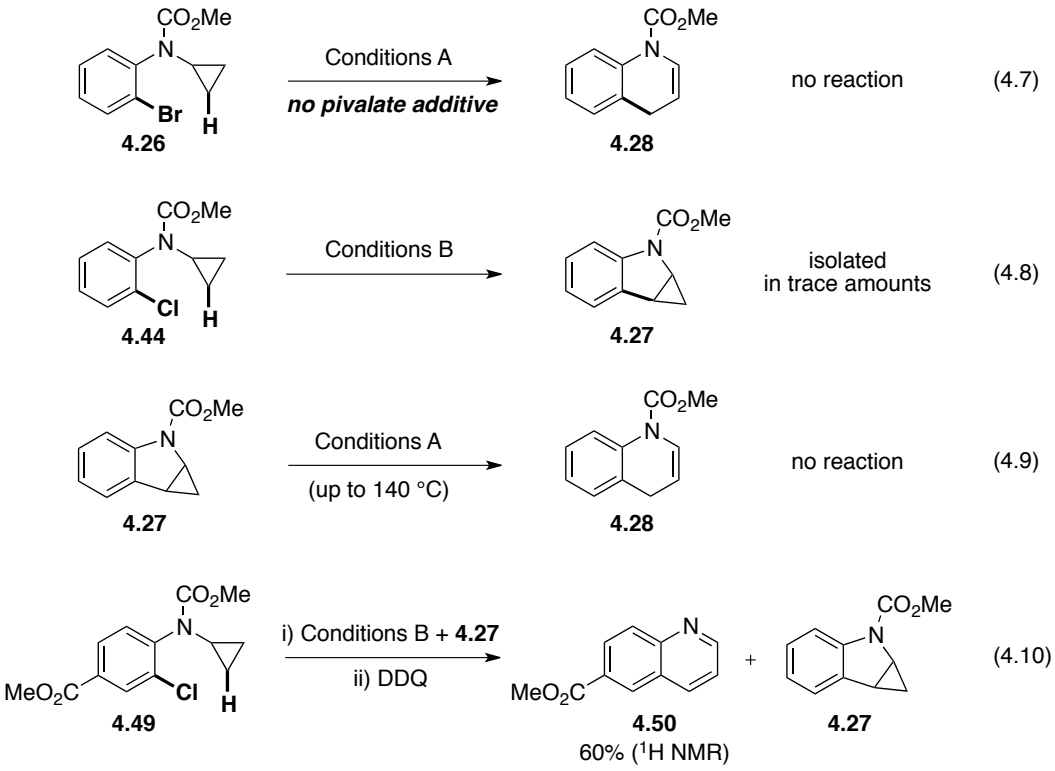
The formation of dihydroquinolines under these reaction conditions can be explained by two potential mechanisms (Scheme 4.12). Similar to the mechanisms presented in Section 4.1.3, following oxidative addition of the aryl halide to Pd(0), intermediate **A** could undergo cyclopropane ring-opening due to the proximity of an electrophilic Pd(II) center. Subsequent deprotonation and reductive elimination would generate the observed dihydroquinoline **4.28** (Scheme 4.12A). Alternatively, oxidative addition followed by anionic ligand exchange of bromide for pivalate would lead to the formation of intermediate **A'**. This Pd(II) species could undergo pivalate-assisted C(sp^3)-H bond cleavage, a process that has been well studied in the context of alkane arylation at primary C-H bonds.[50e] At this stage, palladacycle **C** could reductively eliminate indoline **4.27**, leading to dihydroquinoline **4.28** via *in situ* ring-opening. However, due to the high amount of ring strain in **C**, reductive elimination may be very challenging. Thus, generation of intermediate **B** via cyclopropane ring-opening with concomitant strain release, may be favoured (Scheme 4.12B). It should be noted that the intramolecular proton transfer in this latter pathway is reminiscent of the discussion in Section 3.2.3 on the reversibility of C(sp^3)-H bond cleavage via a CMD transition state.

Scheme 4.12 Potential mechanisms to explain dihydroquinoline formation



With these hypotheses in mind, we designed experiments to uncover the true mechanism of this transformation. Reaction optimization had revealed that the pivalate additive was crucial to obtaining optimal product yields. Indeed, performing a standard reaction for the alkane arylation of cyclopropylaniline **4.26** *in the absence of a source of pivalate*, leads to no desired dihydroquinoline product **4.28** (eq 4.7). The crucial importance of a pivalate source is difficult to explain according to pathway A (Scheme 4.12). However, the use of carboxylate additive is well precedented in Pd(0)-catalyzed C-H bond arylation and is consistent with C(sp^3)-H bond cleavage occurring via a CMD transition state (Scheme 4.12B).[50d,e] In a separate experiment, trace amounts of tetrahydrocyclopropa[b]indole **4.27** were isolated (eq 4.8), which led us to investigate its role as a reaction intermediate (Scheme 4.12B). Compound **4.27** was independently prepared via a Simmons-Smith

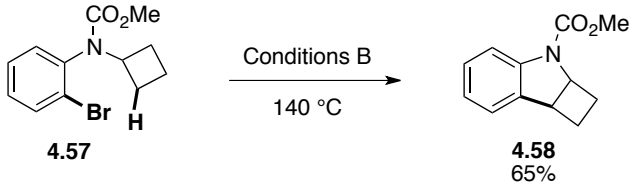
cyclopropanation of the corresponding *N*-protected indole.[95] When submitted to the typical reaction conditions, **4.27** proved to be very stable and cyclopropane ring-opening was not observed (eq 4.9). To exclude cyclopropane ring-opening by a catalytic species, **4.27** was added to a standard reaction employing aryl chlorides **4.49**. While quinoline **4.50** was obtained in 60% yield (^{1}H NMR), indoline **4.27** remained intact (eq 4.10). These results suggest that dihydroquinoline formation occurs through a three-step sequence (Scheme 4.12B): i) pivalate-promoted methylene C–H bond cleavage, ii) cyclopropane C–C bond cleavage/ring-opening and, iii) deprotonation and reductive elimination.



While these results are suggestive for mechanistic scenario B in Scheme 4.12, we sought additional evidence to lend support to this conclusion. The Pd(0)-catalyzed arylation of cyclobutane **4.57** was evaluated since this process would generate a palladacycle analogous to **C** (Scheme 4.12) but containing less ring strain. We therefore hoped that this intermediate may be less prone to ring-open prior to reductive elimination. Under standard

[95] For a review on the Simmons-Smith reaction, see: Charrette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1-415.

reaction conditions (Conditions B, 140 °C), indoline **4.58** was isolated in 65% yield (eq 4.11). Combined with our initial observation of successful cyclopropane C-H arylation in ether **4.22** (eq 4.5), this provides *direct evidence for methylene C–H bond functionalization* under these catalytic conditions.



4.57 **4.58** 65% (4.11)

4.3 Conclusions and Perspectives

In this Chapter, our efforts towards the development of a cyclopropane C-H arylation protocol have been presented. Mechanistic evidence suggests that the products obtained are the result of cyclopropane ring-opening *after* C-H bond cleavage and *prior* to reductive elimination. While these transformations support the possibility of developing alkane arylation reactions at methylene positions, significant strides towards more reactive catalysts must be made before this type of reactivity may be observed in more general aliphatic systems. Indeed, cyclopropane C-H bonds may be considered more activated towards transition metal catalysis based on their "sp^2"-character than regular aliphatic C-H bonds. This characteristic should be exploited as a stepping-stone towards the long-term goal of developing *intermolecular* Pd(0)-catalyzed alkane arylation reactions.

5 Enantioselective Alkane Arylation

5.1 Background

In the last decade, significant advances have been made in the field of transition metal-catalyzed methods for the functionalization of unactivated aliphatic C-H bonds. Accordingly, several of the parameters that guide this reactivity have been established, leading to the application of this strategy in natural product synthesis.[26] However, due to the high energetic cost of C-H bond cleavage, aspects of selectivity (chemo-, regio- and stereoselectivity) remain very challenging. In this section, several groups' efforts towards the development of diastereoselective or enantioselective C(sp^3)-H bond functionalization will be described.[96]

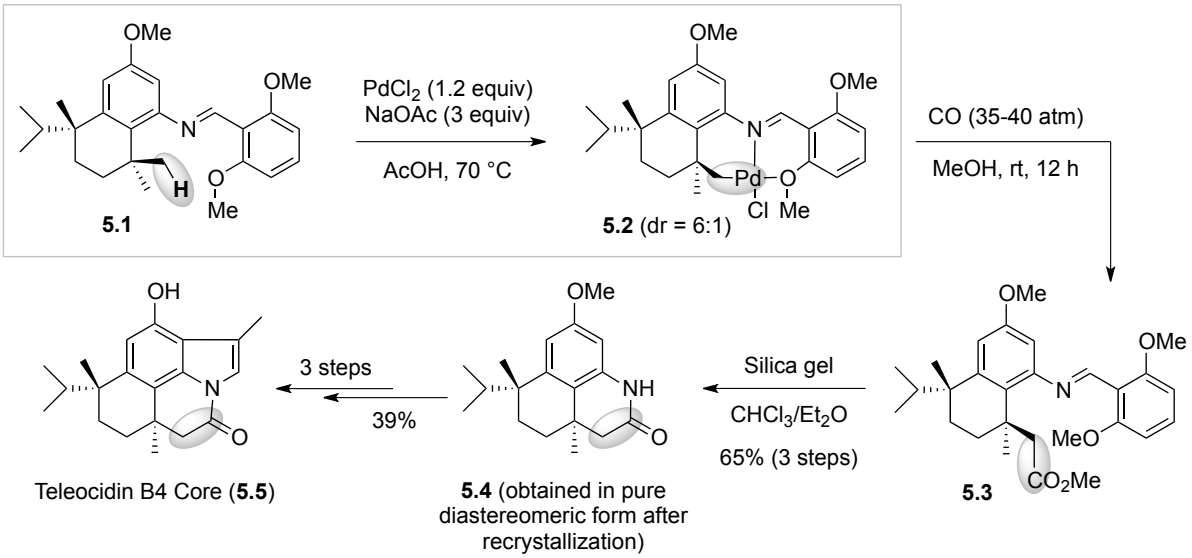
5.1.1 Pd(II)-Mediated/Catalyzed Diastereoselective C(sp^3)-H Functionalization

In 2002, Sames et al. reported an early example of Pd(II)-mediated, auxiliary-directed, diastereoselective C(sp^3)-H bond cleavage in their synthesis of the core of teleocidin B4 (Scheme 5.1).[97] The authors found that upon treatment of intermediate **5.1** with $PdCl_2$ in the presence of NaOAc, **5.2** could be obtained as a 6:1 mixture of diastereomers. The stereochemical outcome of this transformation is guided by the preference for the isopropyl group to occupy the pseudo-equatorial position, predisposing the *anti* methyl group to react with palladium due to its accessibility (pseudo-equatorial as well). Methoxycarbonylation of **5.2** by addition of CO (35-40 atm) and methanol yielded **5.3**, which was directly converted to lactam **5.4** *via* acidic hydrolysis of the chelating auxiliary.

[96] For a review on diastereoselective and enantioselective transition metal-catalyzed C-H functionalization reactions, see: Giri, R; Shi, B.-F; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242-3272.
[97] Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856-11857.

After recrystallization and three additional synthetic operations, the core of teleocidin B4 (**5.5**) was obtained.

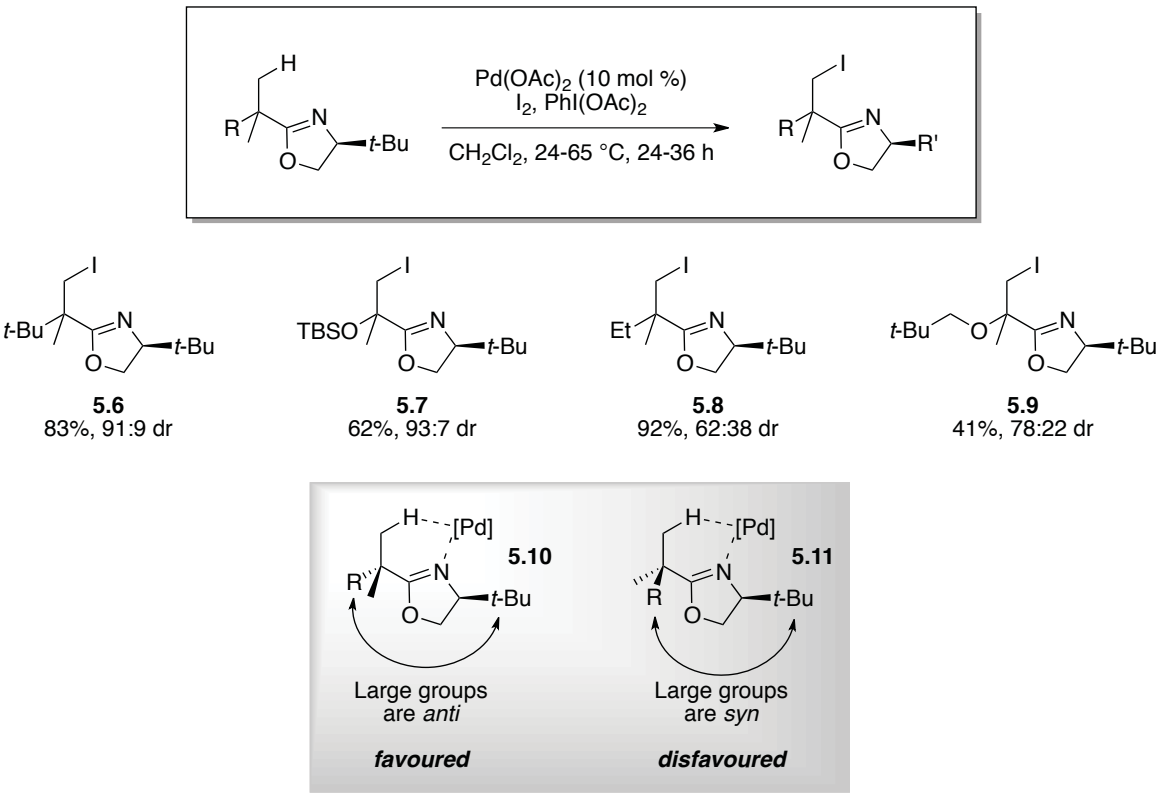
Scheme 5.1 Synthesis of the core of teleocidin B4 employing a diastereoselective Pd(II)-mediated C-H functionalization



Yu and co-workers have reported diastereoselective C(sp^3)-H iodination and acetoxylation reactions employing catalytic amounts of Pd(II) salts (Scheme 5.2).[84,98] The use of a chiral oxazoline auxiliary to direct the catalyst enabled C-H bond cleavage in moderate to excellent levels of diastereoselectivity. Of note, these catalytic conditions are very mild, with most reactions occurring at room temperature. Significantly higher levels of diastereoselectivity were obtained in the presence of bulky R groups *alpha* to the C(sp^3)-H bond. For example, **5.6** and **5.7** are obtained in 91:9 and 93:7 dr, respectively, while **5.8** and **5.9** are only obtained in 62:38 and 78:22 dr. The authors suggested that selective C(sp^3)-H bond cleavage occurs due to unfavourable interactions between the larger substituent (R) and the side-chain of the chiral auxiliary in *syn* conformer **5.11**. *Anti* conformer **5.10** is preferred and thus, diastereoselective C(sp^3)-H functionalization can occur.

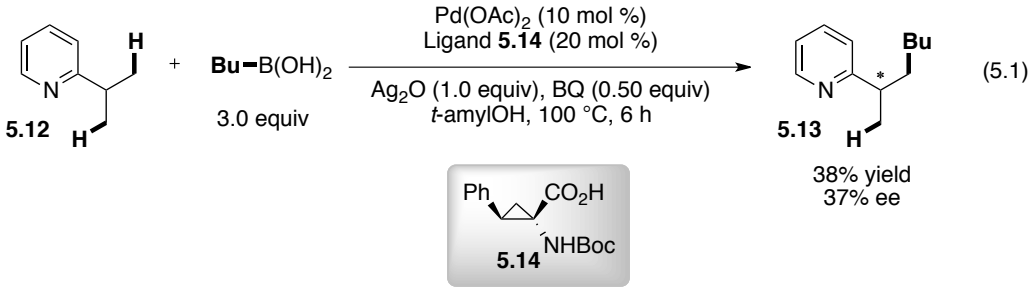
[98] (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420-7424; (b) Giri, R.; Chen, X.; Hao, X.-S.; Li, J.-J.; Liang, J.; Fan, Z.-P.; Yu, J.-Q. *Tetrahedron: Asymmetry* **2005**, *16*, 3502-3505.

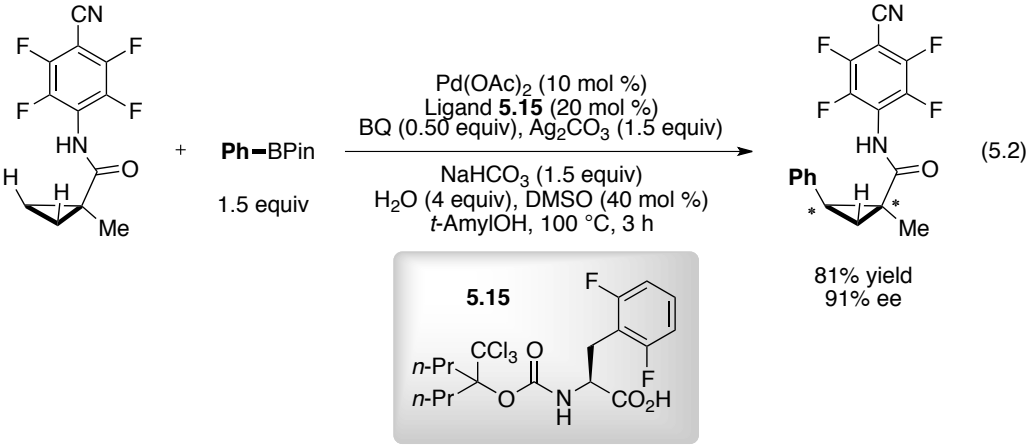
Scheme 5.2 Diastereoselective Pd(II)-catalyzed iodination of methyl groups



5.1.2 Enantioselective C(sp^3)-H Bond Functionalization

In 2008, Yu and coworkers reported the first example of Pd-catalyzed enantioselective C(sp^3)-H bond functionalization (eq 5.1).[88a] A catalyst based on $Pd(OAc)_2$ (10 mol %) and monoprotected amino acid **5.14** as a chiral ligand (20 mol %) enabled the selective pyridine-directed alkylation of a prochiral methyl group in **5.12**. Thus, derivative **5.13** was obtained in 38% yield with moderate, but promising, levels of enantiomeric excess (37%). The use of amino acids as chiral ligands for Pd(II)-catalyzed enantioselective alkane arylation was explored in greater detail by the Yu group in 2011 (eq 5.2).[85e] Excellent levels of enantioselectivity could be obtained after extensive ligand optimization. Their observations and results were highlighted in Section 4.1.2 (Scheme 4.3).



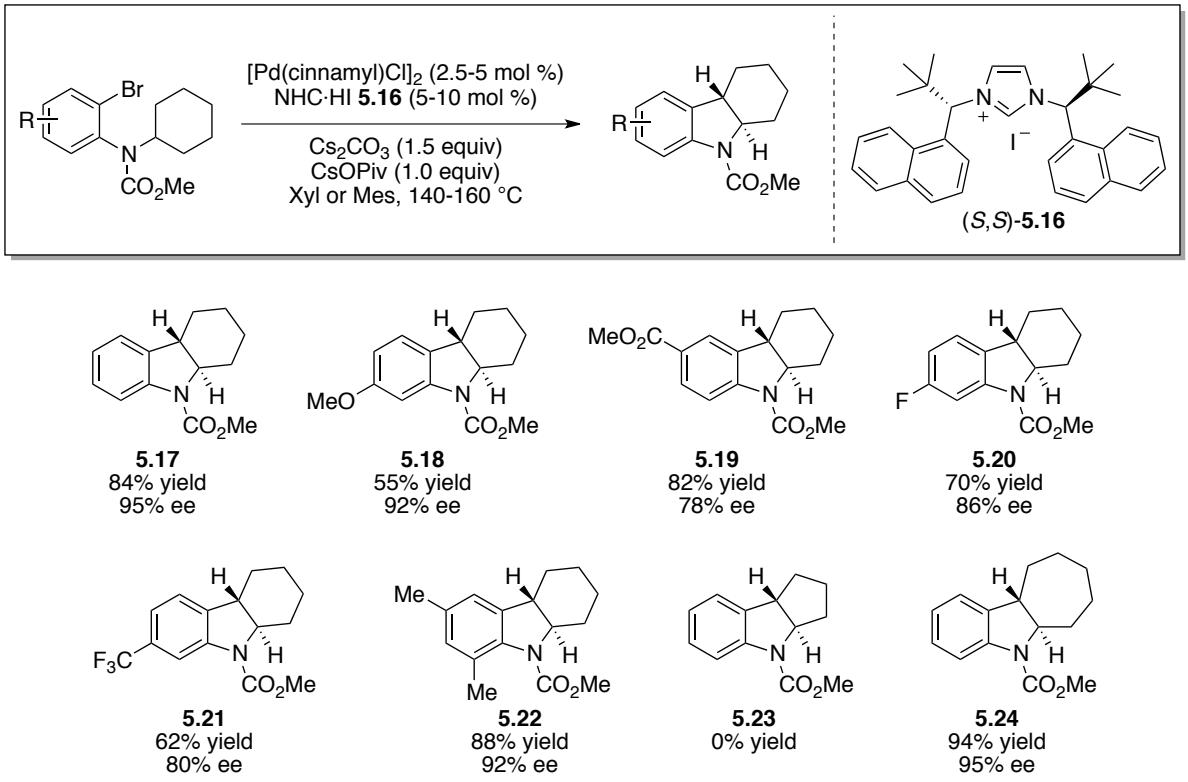


Examples of Pd(0)-catalyzed enantioselective alkane arylation have remained elusive until very recently. In 2011, two significant contributions from the groups of Kündig and Kagan appeared in the literature.[44] Interestingly, different strategies for asymmetric induction were employed in both cases. Kündig et al. investigated the use of chiral NHC ligands to induce a challenging enantioselective arylation at a secondary C(sp^3)-H bond (see Section 4.1 for a discussion on methylene C-H functionalization).[44a] It should be noted that examples of palladium-catalyzed asymmetric transformations employing chiral NHC ligands are limited.[99] Reaction optimization, especially with respect to the structure of the NHC, revealed that a catalyst based on [Pd(cinnamyl)Cl]$_2$ and NHC **5.16** led to optimal yields and enantioselectivities of *trans*-fused indolines (Scheme 5.3). In the absence of a source of pivalate, only trace amounts of product were observed, highlighting once again the crucial role of this additive in C(sp^3)-H arylation reactions. The scope of the reaction was first examined with respect to substitution on the arene ring. Electron-neutral and -donating groups typically led to higher levels of enantioselectivity, as exemplified by the formation of

[99] Gade, L. H.; Bellemin-Laponnaz, S. *Top. Organomet. Chem.* **2007**, *21*, 117-157.

indolines **5.18** and **5.22** in 92% ee. The presence of electron-withdrawing groups was also tolerated, albeit at a slight cost in enantiomeric excess (**5.19-5.21**). Methylene C(sp^3)-H arylation of a cyclopentyl ring was unsuccessful (**5.23**), however functionalization of a cycloheptyl ring provided the corresponding indoline **5.24** in 94% yield and 95% ee.

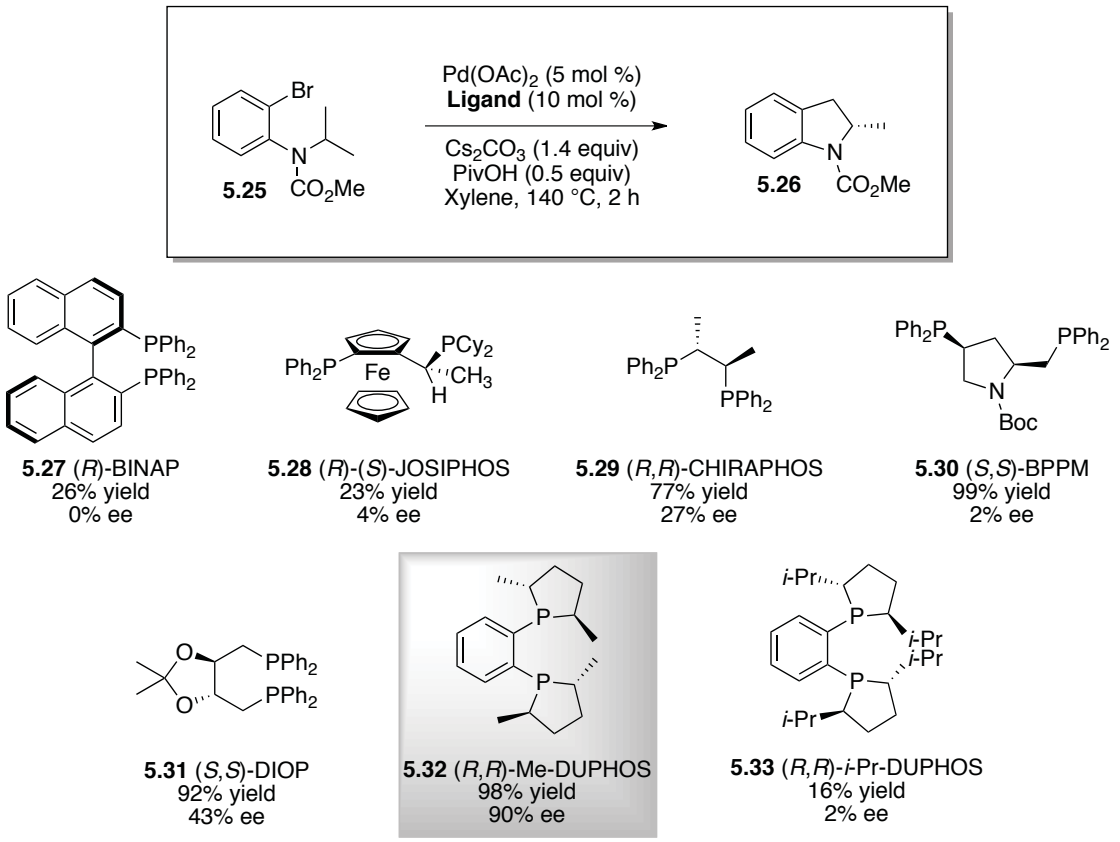
Scheme 5.3 Asymmetric synthesis of *trans*-fused indolines



Kagan et al. have developed a similar method for the synthesis of enantioenriched 2-methylindolines.[44b] Towards this goal, the use of commercially available, chiral bidentate phosphines as a source of chiral information was investigated (Scheme 5.4). Test reactions with 2-bromoaniline derivative **5.25** revealed that a catalyst system based on 5 mol % $Pd(OAc)_2$ and 10 mol % (*R*,*R*)-Me-DUPHOS **5.32** enabled the formation of indoline **5.26** in 98% isolated yield with 90% ee. The bulkier ligand (*R*,*R*)-*i*-Pr-DUPHOS **5.33** led to a significantly diminished product yield and the nearly complete loss of enantioselectivity. Chiral ligands containing di- or triaryl phosphine motifs (**5.27-5.31**) were less effective. Employing (*R*,*R*)-Me-DUPHOS **5.32**, a 2-iodoaniline, analogous to **5.25**, was converted to

2-methylindoline **5.26** in 82% yield and 90% ee. Unfortunately, aryl chlorides did not react under the current optimal conditions.

Scheme 5.4 Chiral ligand screen for the synthesis of 2-methylindolines via enantioselective alkane arylation



In this Chapter, our efforts towards the development of an intramolecular enantioselective Pd(0)-catalyzed alkane arylation reaction will be described.[100] Different strategies towards this goal will be highlighted, including the use of i) chiral acids as additives instead of pivalic acid and ii) chiral phosphines as ligands for palladium. It should be noted that this work was performed in 2008. At that time, no examples of Pd(0)-catalyzed enantioselective C(sp^3)-H arylation had appeared in the literature.

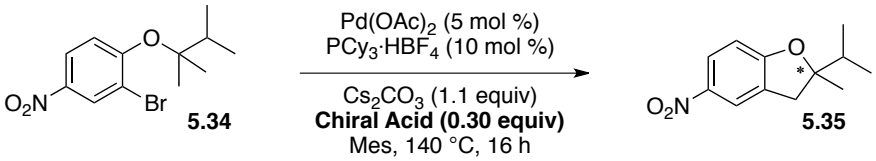
[100] Rousseaux, S.; Fagnou, K. *Unpublished results*.

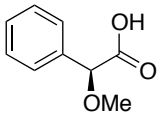
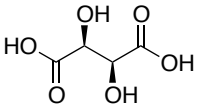
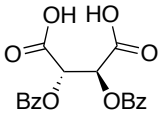
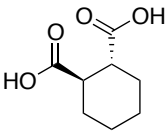
5.2 Reaction Development

At the outset of this work, the mechanistic understanding of Pd(0)-catalyzed alkane arylation was limited to the preliminary theoretical studies performed by our group (Section 1.3.2).[39] The pivalic acid additive was found to play a crucial role as the anionic ligand that facilitates inner-sphere C(sp^3)-H bond cleavage. Thus, we hypothesized that enantioselectivity could be induced by replacing pivalic acid by a chiral carboxylic acid (Table 5.1). The transformation of aryl bromide **5.34** to dihydrobenzofuran **5.35** was chosen as a test reaction, since under standard catalytic conditions, **5.35** is produced in 90% yield.[39] Unfortunately, while several acids favoured formation of the desired product in moderate to excellent yield, enantiomeric excess was never observed (entries 1-4). Limited conversion was achieved when amino acids were tested as a source of carboxylate (entries 5-6). Based on the report by Yu and coworkers (eq 5.1) that appeared during this study,[88a] monoprotected L-Boc-valine was tested for the preparation of enantioenriched **5.35**. Once again, poor yield (20%) and no enantiomeric excess was obtained.

Recent results obtained by our group in the context of Pd(0)-catalyzed direct C(sp^2)-H arylation may provide insight for the lack of enantioinduction in these reactions. The failure of these chiral carboxylic acids to provide even trace amounts of ee may indicate that they are not ligated to palladium during catalysis. Instead, the acetate from the Pd(II)-precatalyst, which has been demonstrated to have a non-innocent role in C-H arylation reactions where an external source of carboxylate (pivalate) is not added, may be preferentially bound to the palladium centre.[34] In light of these results, other Pd-precatalysts, which do not contain carboxylate counterions, should be explored in combination with hindered chiral carboxylates that may mimic the steric bulk of pivalate.

Table 5.1 Evaluation of chiral carboxylic acids as additives for enantioselective alkane arylation

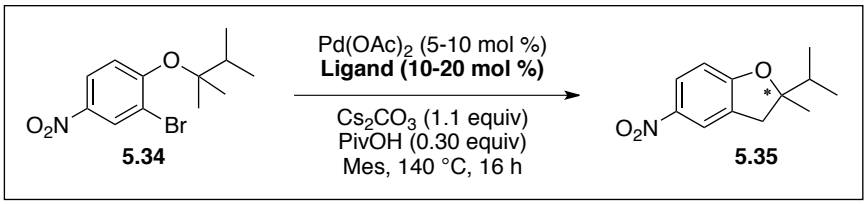


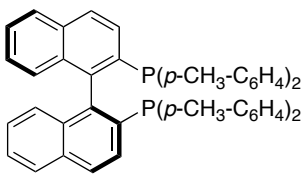
Entry	Acid	Yield[a]	ee[b]
1		74%	0%
2		49%	0%
3		96%	0%
4		26%	0%
5	L-leucine	<5%	0%
6	L-proline	<5%	0%
7	L-Boc-valine	20%	0%

[a] Determined by GC-MS. [b] Determined by HPLC.

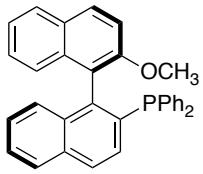
The lack of success with the use of chiral carboxylic additives in alkane arylation prompted us to explore more traditional routes to enantioselective Pd(0)-catalysis. Thus, we explored replacing the standard ligand (PCy_3) by a chiral phosphine ligand. Selected examples of the chiral phosphines that were examined are shown in Scheme 5.5. (*S*)-TolBINAP **5.36** and (*R*)-(*R*)-TANIAPHOS2 **5.43** provided promising levels of enantioinduction, 57% and 23% ee respectively, although with very minimal product yield. Alternatively, (*R*)-MOP **5.37** and (*R*)-(*R*)-WALPHOS1 **5.41** afforded the desired product in moderate yield with limited to no enantiomeric excess. (*S*)-TolBINAP **5.36** was selected for further investigations.

Scheme 5.5 Evaluation of chiral phosphines for enantioselective alkane arylation

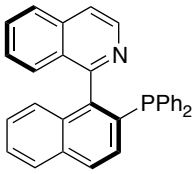




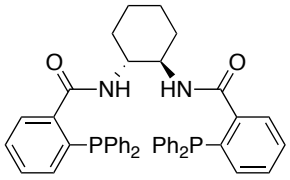
5.36 (*S*)-TolBINAP
7% yield
57% ee



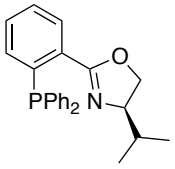
5.37 (*R*)-MOP
32% yield
0% ee



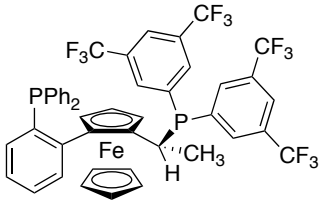
5.38 (*S*)-QUINAP
15% yield
3% ee



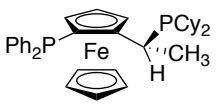
5.39 (*R,R*)-DACH Phenyl Trost
0% yield
0% ee



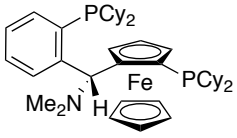
5.40 (*R*)-(*i*-Pr)PHOX
8% yield
10% ee



5.41 (*R*)-(*R*)-WALPHOS1
43% yield
7% ee



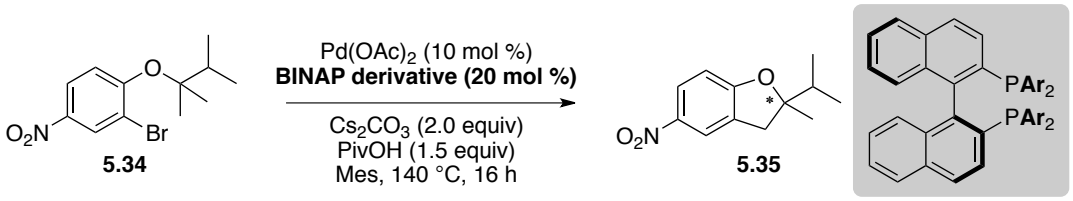
5.28 (*R*)-(*S*)-JOSIPHOS
<5% yield
11% ee



5.42 (*R*)-(*R*)-TANIAPHOS2
<5% yield
23% ee

Several reaction parameters were examined including palladium sources, the use of additives for catalyst activation and base/carboxylate equivalents and ratios. Slightly improved, and more importantly reproducible, results were obtained when 2.0 equivalents of Cs_2CO_3 were employed in combination with 1.5 equivalents of a source of pivalate (either PivOH or CsOPiv). The use of other Pd-precatalysts, including Pd_2dba_3 and $[Pd(allyl)Cl]_2$, did not significantly improve the yield or enantiomeric excess of **5.35**. Hypothesizing that generation of the active L*Pd(0) species from Pd(II)-precatalysts may be problematic, additives (Et_3N and $PhB(OH)_2$) that are known to facilitate reduction of Pd(II) to Pd(0) were evaluated. Once again, no improvement was observed and **5.35** was obtained in up to 10% yield and 54% ee. Finally, we further examined the structure of ligand **5.36** (Table 5.2). While (*S*)-BINAP and (*S*)-TolBINAP afforded **5.35** in 6-7% yield and 57% ee (entries 1 and 2), (*S*)-XylBINAP led to a four-fold increase in yield (26%) albeit at a significant cost in ee (32%) (entry 3).

Table 5.2 Enantioselective dihydrobenzofuran synthesis employing chiral BINAP derivatives

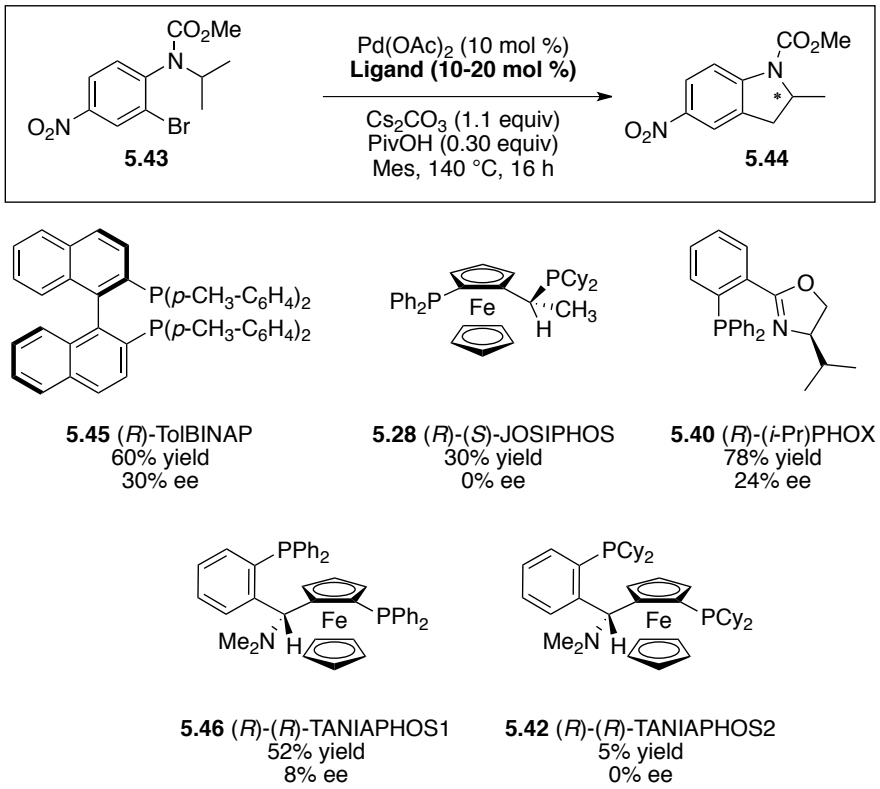


Entry	Aryl (Ar)	Yield[a]	ee[b]
1	BINAP	6%	57%
2	TolBINAP	7%	57%
3	XylBINAP	26%	32%

[a] Determined by GC-MS. [b] Determined by HPLC.

In 2008, Fujii and Ohno published the synthesis of indoline derivatives via Pd(0)-catalyzed C(sp^3)-H arylation.[40] Compared to our analogous dihydrobenzofuran synthesis, enhanced reactivity was observed for this substrate class. Indeed, methylene C(sp^3)-H bonds and methyl groups with neighbouring β-hydrogens underwent alkane arylation in good yields (Scheme 1.15). These intriguing results led us to investigate the use of these substrates for the development of enantioselective alkane arylation reactions. Treatment of 2-bromoaniline derivative **5.43** with $Pd(OAc)_2$ (5 mol %), $PCy_3 \cdot HBF_4$ (10 mol %), Cs_2CO_3 (1.1 equivalents) and PivOH (30 mol %) in mesitylene at 140 °C afforded indoline **5.44** in 80% yield. Having ascertained the desired reactivity, enantioselective intramolecular alkane arylation of **5.43** was explored using chiral phosphines (Scheme 5.6). Amongst the screened ligands, (*R*)-TolBINAP **5.45** and (*R*)-(*i*-Pr)PHOX **5.40** gave optimal yield and ee combinations.

Scheme 5.6 Enantioselective alkane arylation for the synthesis of indolines

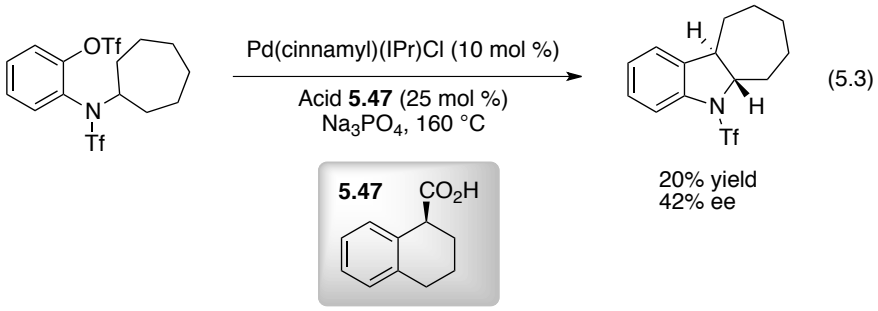


5.3 Conclusions and Perspectives

The results discussed within this Chapter, in addition to the recent studies of Kündig and Kagan,[44] demonstrate that Pd(0)-catalyzed intramolecular alkane arylation can occur with high levels of enantioselectivity in the presence of chiral ligands. Interestingly, the preparation of indolines via C(sp^3)-H arylation appears better suited to the application of asymmetric catalysis than the analogous formation of dihydrobenzofurans. While our study failed to produce a highly enantioselective catalyst system, (*R*)-TolBINAP **5.45** and (*R*)-(*i*-Pr)PHOX **5.40** emerged as promising leads for further studies.

As was highlighted in Section 5.1.2, highly enantioselective Pd-catalyzed C(sp^3)-H arylation reactions have only recently (2011) begun to appear in the literature. While both chiral NHC and chiral phosphine ligands have been successfully applied to Pd(0)-catalysis, the use of chiral carboxylic acids as substitutes for the crucial pivalic acid additive could present an attractive, and intriguing, alternative. During the final stages of the preparation of

this thesis, Cramer and coworkers reported an elegant example of this concept (eq 5.3).[81] While only a moderate level of enantiomeric excess was observed, this reaction nicely illustrates the application of knowledge acquired through mechanistic studies to reaction development. Additionally, the authors found that cooperative ligand effects could be obtained by combining chiral phosphine ligands with chiral carboxylic acids, leading to higher levels of ee.



(5.3)

6 Dearomatization of Phenols – Introduction

For decades, the dearomatization of aromatic compounds has been widely recognized as a powerful tool for the generation of high levels of molecular complexity from simple planar chemical feedstocks.[101] The numerous applications of this strategy in natural product synthesis are indicative of its power, robustness and practicality.[102] Examples of dearomatization, via either oxidation or reduction, are found in nature and these processes have been invoked in numerous natural product biosyntheses.[103] In this Chapter, selected applications of "classic" methods for arene dearomatization and their use in total synthesis will be briefly highlighted. The bulk of the discussion will focus on the dearomatization/functionalization of *phenol and its derivatives*.

6.1 Classic Methods for the Dearomatization of Arenes

6.1.1 Birch reduction(-alkylation)

Since its discovery over 50 years ago, the Birch reduction has been extensively used as a powerful tool for the reduction of arene rings to the corresponding alicyclic compounds.[104] In the presence of an alcohol, treatment of arenes with Li, Na or K dissolved in liquid

[101] For selected reviews, see: (a) Mander, L. N. *Synlett* **1991**, 134-144; (b) Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273-282; (c) Kündig, E. P.; Pape, A. *Top. Organomet. Chem.* **2004**, *7*, 71-94; (d) Harman, W. D. *Top. Organomet. Chem.* **2004**, *7*, 95-127; (e) Quideau, S.; Pouységu, L.; Deffieux, D. *Curr. Org. Chem.* **2004**, *8*, 113-148; (f) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, *4*, 467-495.

[102] For recent reviews on the use of dearomatization protocols in natural product synthesis, see: (a) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235-2261; (b) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068-4093.

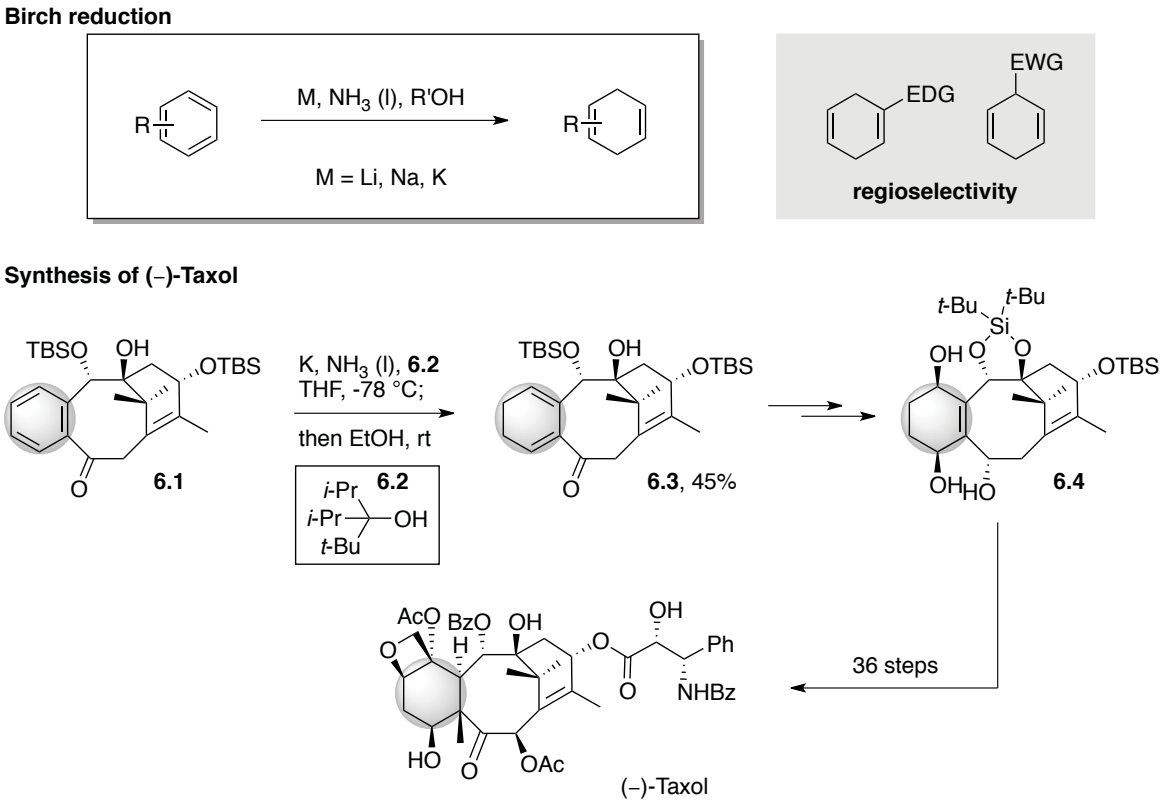
[103] For a review, see: Quideau, S. in *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH, Weinheim, 2002; pp.539-573.

[104] For selected reviews, see: (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1-334; (b) Birch, A. J. *Pure Appl. Chem.* **1996**, *68*, 553-556; (c) Rao, G. S. R. S. *Pure Appl. Chem.* **2003**, *75*, 1443-1451.

ammonia generates 1,4-cyclohexadienes (or dearomatized heterocycles). This process occurs with predictable regioselectivity, which is highly dependent on the nature of the substitutents (i.e., electron-donating or -withdrawing groups). Birch reductions have been employed as a synthetic strategy for the preparation of numerous natural products, including the Kuwajima group's synthesis of (–)-Taxol in 2000 (Scheme 6.1).[105] During the course of their synthesis, these authors found that subjecting advanced intermediate **6.1** to standard Birch conditions (K, NH_3 and *t*-BuOH) did not afford the desired product **6.3**. Instead, a side-product resulting from reduction of the ketone to the corresponding alcohol was obtained in 88% yield. Hypothesizing that replacing *t*-BuOH with a more hindered alcohol would favour protonation of the more sterically accessible arene ring, intermediate **6.1** was submitted to a Birch reduction in the presence of alcohol **6.2** and the desired cyclohexadiene **6.3** was obtained in 45% yield. Subsequent manipulations converted **6.3** into diol **6.4** which was further elaborated to (–)-Taxol.

[105] Kusama, H.; Hara, R.; Kawahara, S.; Nishimor, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811-3820.

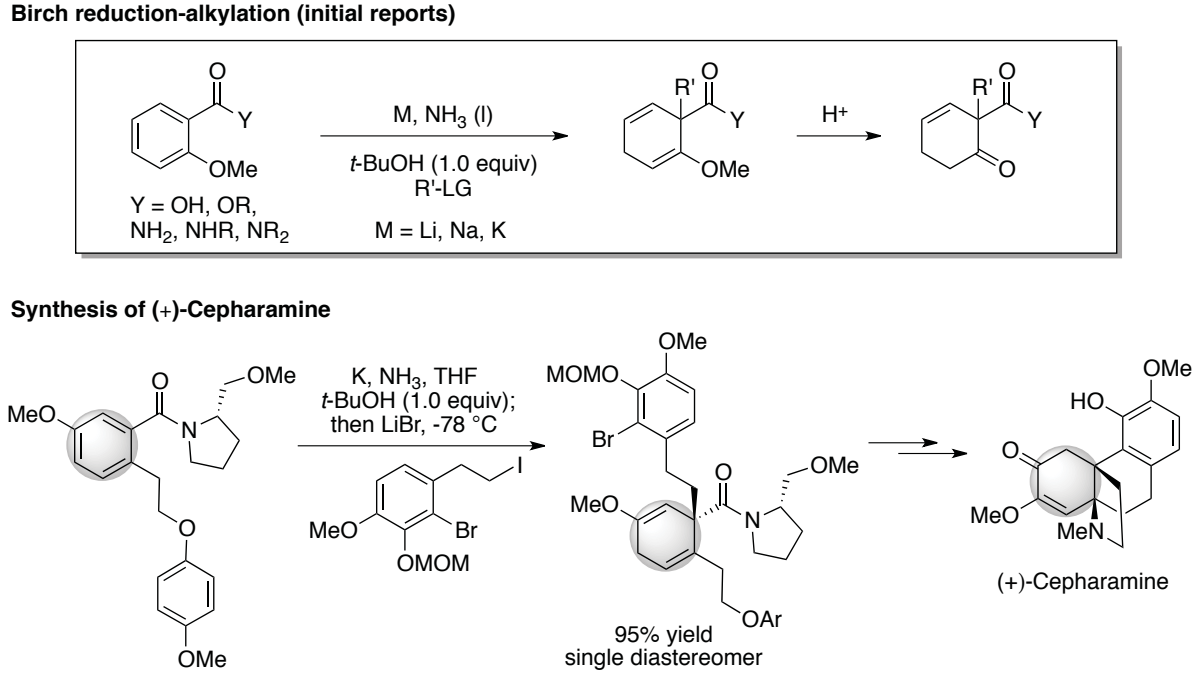
Scheme 6.1 Birch reduction and its application in the total synthesis of (–)-Taxol



The carbanion generated upon treatment of an arene with an alkali metal dissolved in liquid ammonia can also be trapped by an alkyl electrophile as an alternative to simple protonation (Scheme 6.2). This process, known as a Birch reduction-alkylation, has been well studied and applied to the synthesis of numerous natural products.[104a] Diastereoselective variants of this transformation which employ chiral auxiliaries have also been developed.[106] The Schultz group has actively participated in this field since their first report of diastereoselective Birch reduction-alkylation in 1984.[107] Since then, they have employed this strategy for the preparation of natural products, including (+)-cepharamine (Scheme 6.2).[108]

[106] For selected reviews, see: (a) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207-213; (b) Schultz, A. G. *Chem. Commun.* **1999**, 1263-1271.
[107] Schultz, A. G.; Sundararaman, P. *Tetrahedron Lett.* **1984**, *25*, 4591-4594.
[108] Schultz, A. G.; Wang, A. *J. Am. Chem. Soc.* **1998**, *120*, 8259-8260.

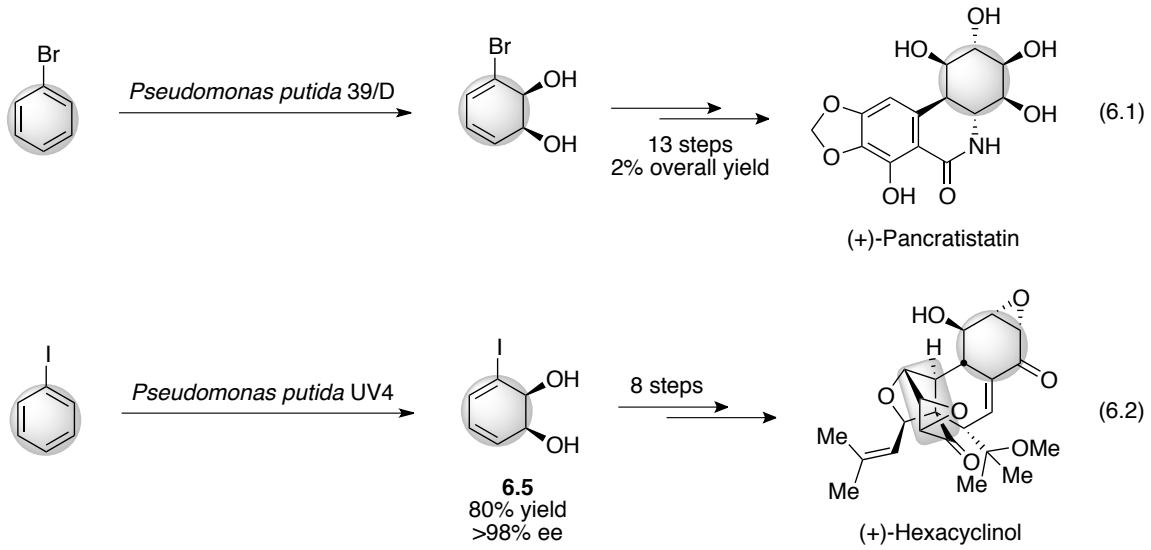
Scheme 6.2 Birch reduction-alkylation and its application in the total synthesis of (+)-Cepharamine



6.1.2 Chemoenzymatic Dihydroxylation

Recognizing the simplicity and efficiency of enzymatic processes, synthetic organic chemists have explored the use of biocatalysis in arene dearomatization.[109] Mutant strains of *Pseudomonas putida* have been examined in the context of dearomatizing-dihydroxylation of monosubstituted benzenes. The resulting diols, obtained with excellent levels of enantiomeric excess, have been extensively used as starting materials in the synthesis of complex alkaloids and carbohydrates. Indeed, Hudlicky and coworkers employed this strategy towards the first enantioselective synthesis of (+)-pancrastistatin (eq 6.1).[110] More recently, enzymatic dihydroxylation was used by Banwell and coworkers to prepare (+)-hexacyclinol.[111] Treatment of iodobenzene with *Pseudomonas putida* UV4 provided diol **6.5** in 80% yield and greater than 98% ee. Compound **6.5** was further transformed and subsequently dimerized to afford the desired natural product (eq 6.2).

[109] For a recent review, see: Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685-703.
[110] Tian, X.; Hudlicky, T.; Königsberger, K. *J. Am. Chem. Soc.* **1995**, *117*, 3643-3644.
[111] Pinkerton, D. M.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2009**, *11*, 4290-4293.

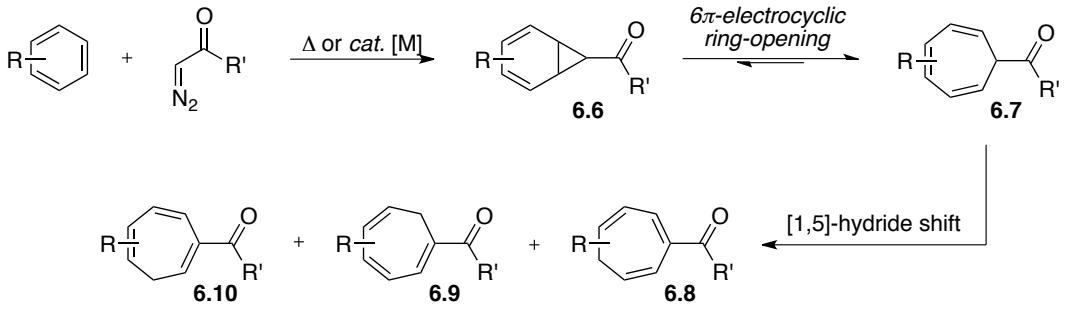


6.1.3 Büchner Reaction

The Büchner reaction, discovered over a century ago, represents an important method for the synthesis of seven-membered rings.[112] The reaction of benzene derivatives with α-diazocarbonyl compounds generates norcaradiene intermediates of general structure **6.6** which readily undergo 6π-electrocyclic ring-opening. Under thermal conditions, **6.7** can isomerize to a mixture of cycloheptatrienes **6.8**-**6.10** via [1,5]-hydride shift (Scheme 6.3). Typically, the equilibrium favours cycloheptatriene formation, however steric and electronic effects have been shown to push the equilibrium towards norcaradiene **6.6**. It should also be noted that these transformations are generally not observed with electron-deficient arenes, since arene cyclopropanation becomes too challenging.

[112] For a recent review, see: Reisman, S. E.; Nani, R. R.; Levin, S. *Synlett* **2011**, 2437-2442 and references therein.

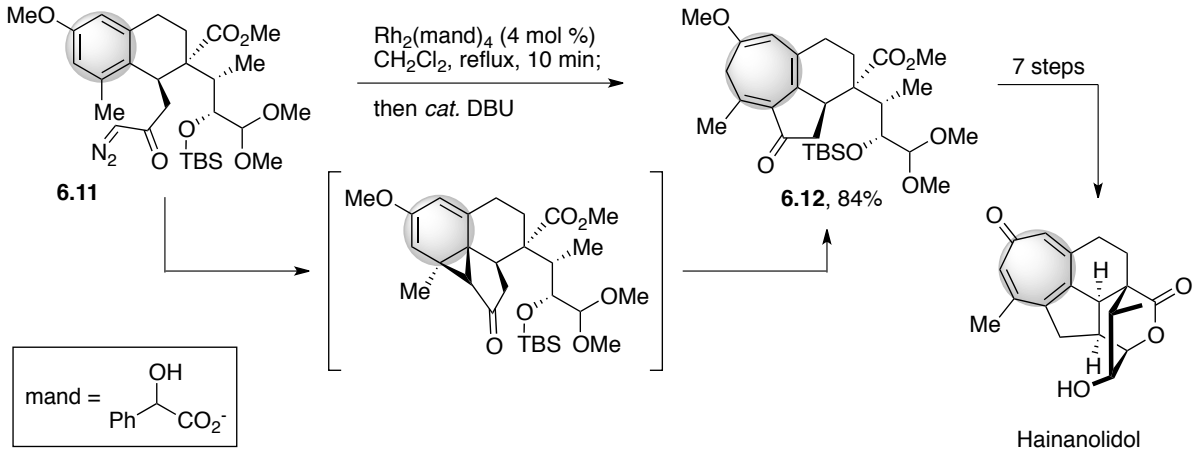
Scheme 6.3 Büchner reaction



Recent efforts in transition metal-catalyzed Büchner reactions have led to improved yields and selectivities, which has translated to the application of this methodology in natural product synthesis. Several research groups have employed this strategy to prepare the bicyclo[5.3.0]decane core of complex molecules. In 1998, Mander et al. investigated the use of an arene cyclopropanation in their total synthesis of hainanolidol (Scheme 6.4).[113] Treatment of intermediate **6.11** with 4 mol % rhodium mandelate in dichloromethane at reflux for 10 minutes yielded an unstable cycloheptatriene intermediate, which was rapidly isomerized to cycloheptatriene **6.12** upon addition of a catalytic amount of DBU. Hainanolidol was finally obtained after seven additional synthetic transformations. Despite the use of 8 mol % rhodium to effect the key transformation and the need for several protecting groups, this synthesis represented one of the first to highlight the powerful potential for the use of the Buchner reaction in complex settings.

[113] Frey, B.; Well, A. P.; Rogers, D. H.; Mander, L. N. *J. Am. Chem. Soc.* **1998**, *120*, 1914-1915.

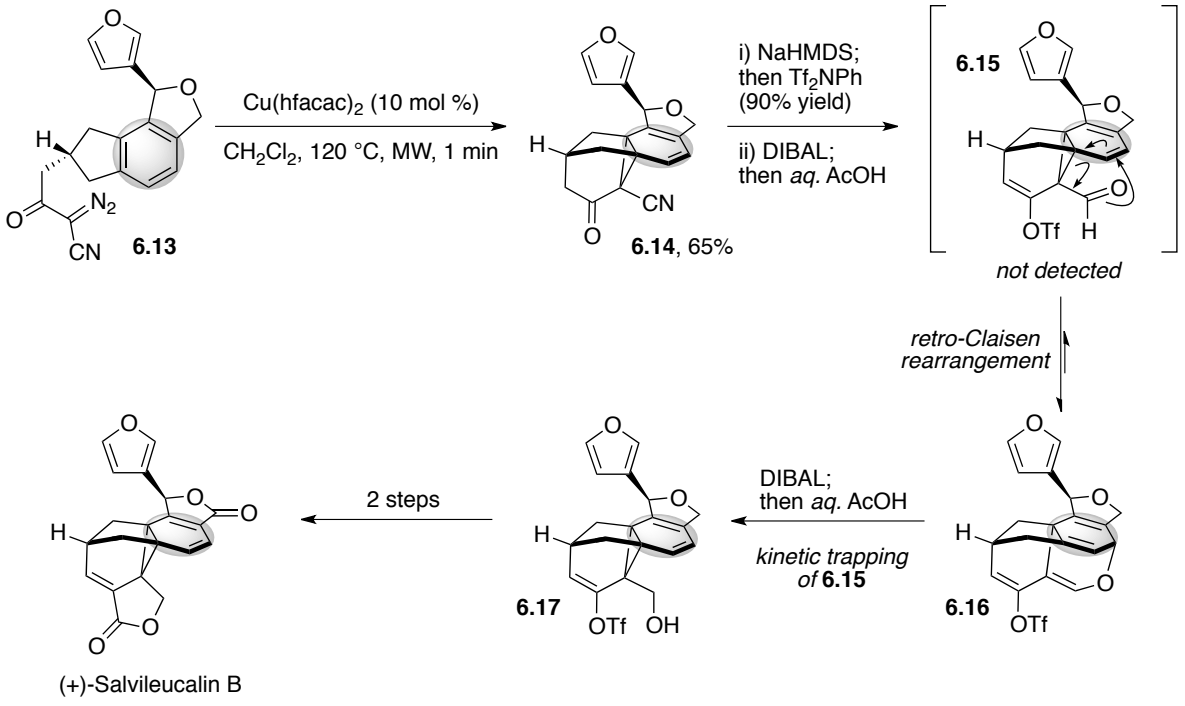
Scheme 6.4 Total synthesis of hainanolidol based on a Büchner reaction



As previously mentioned, steric and electronic effects can favour the formation of a norcaradiene intermediate, rather than the ring-opened cycloheptatriene product (Scheme 6.3). While examples of arene cyclopropanation without ring-opening are less prominent, reports have begun to highlight some of the factors that govern this selectivity. Notably, the choice of catalyst appears to be very important: copper catalysts generate norcaradienes in lower yields but significantly improved selectivities compared to rhodium catalysts. Reisman and coworkers have employed a copper-catalyzed intramolecular Büchner reaction in their recent synthesis of salvileucalin B (Scheme 6.5).[114] Subjecting intermediate **6.13** to 10 mol % $Cu(hfacac)_2$ in dichloromethane provided norcaradiene **6.14** in 65% yield. The use of this catalyst was found to be crucial to favour arene cyclopropanation over cyclopentanone formation via C-H insertion. Dearomatized intermediate **6.14** was converted to (+)-salvileucalin B after a few additional synthetic steps. Interestingly, norcaradiene **6.15** rapidly underwent a retro-Claisen rearrangement to generate unstable intermediate **6.16**. Due to the reversible nature of this transformation, the reaction mixture containing **6.16** could be treated with DIBAL, leading to the kinetic trapping of **6.15** as alcohol **6.17**. Subsequent palladium-catalyzed carbonylation/lactam formation and selective oxidation yielded the desired natural product.

[114] (a) Levin, S.; Nani, R. N.; Reisman, S. E. *Org. Lett.* **2010**, *12*, 780-783; (b) Levin, S.; Nani, R. N.; Reisman, S. E. *J. Am. Chem. Soc.* **2011**, *133*, 774-776.

Scheme 6.5 Synthesis of (+)-salvileucalin B via an intramolecular Büchner reaction



6.2 Dearomatization of Phenol and its Derivatives

The dearomatization of phenol, and its derivatives, has been an area of extensive investigation in recent decades.[101f,102] This can be explained in part due to the fact that this process has been invoked in the biosynthesis of various natural products.[103] Figure 6.1 highlights some of these targets, which have been prepared by synthetic organic chemists, employing phenol dearomatization strategies.[102] Typically, the desired products contain the alicyclic core generated during the dearomatizing-step. However, phenol dearomatization has also been used to generate transient, highly reactive species, which undergo subsequent transformations that may lead to rearomatization (for example, (–)-diazonamide A[115]).

[115] Burgett, A. W. G.; Li, Q.; Wei, Q.; Harran, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4961-4966.

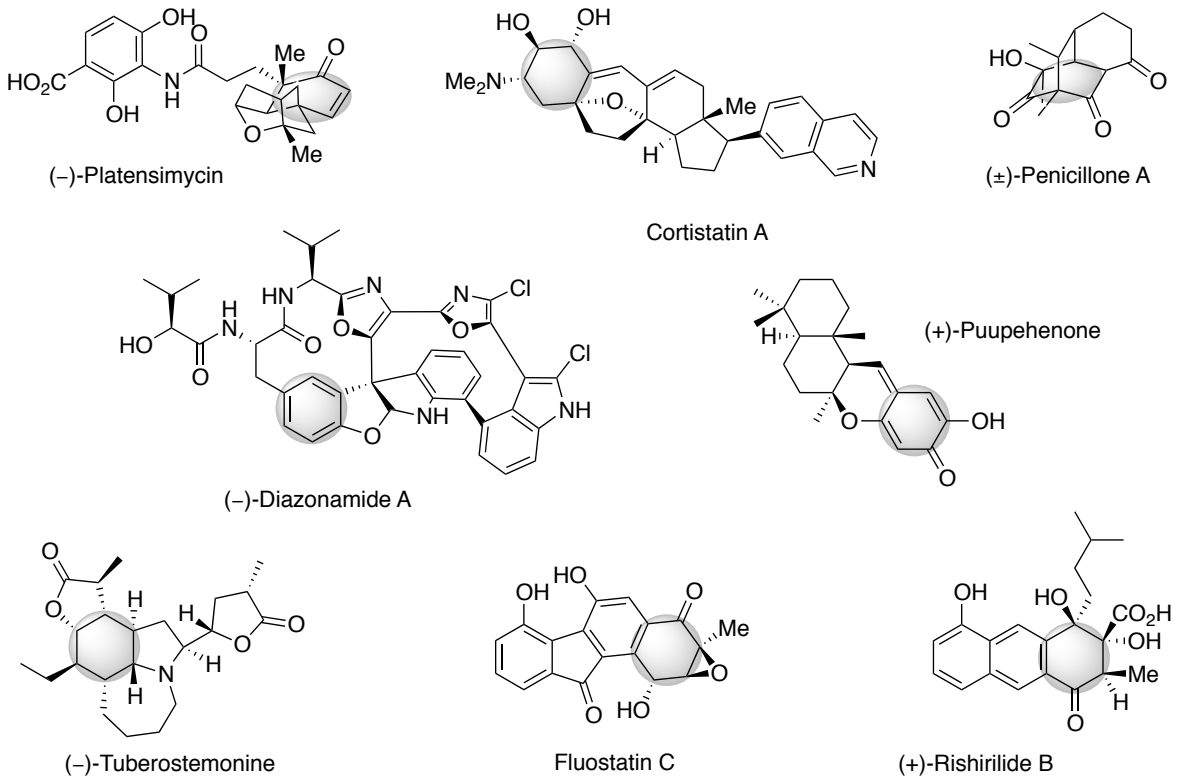
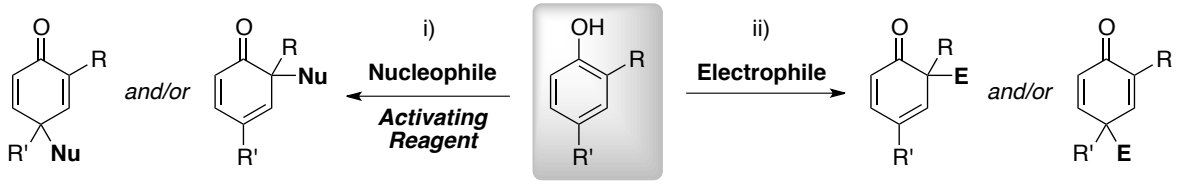


Figure 6.1 Natural products that have been synthetized using phenol dearomatization strategies

While several methods have been developed in this expanding area of research, an exhaustive overview of these will not be possible in the context of this Chapter. Instead, two principal approaches will be highlighted based on their mechanism and the general strategy employed: i) activation of the phenol as an electrophile, which subsequently reacts with nucleophiles, and ii) alkylation of nucleophilic phenol derivatives by electrophiles (Scheme 6.6). In both cases, functionalization occurs either ortho or para to the hydroxyl functional group for dearomatization to occur.

Scheme 6.6 Activation modes for phenol dearomatization

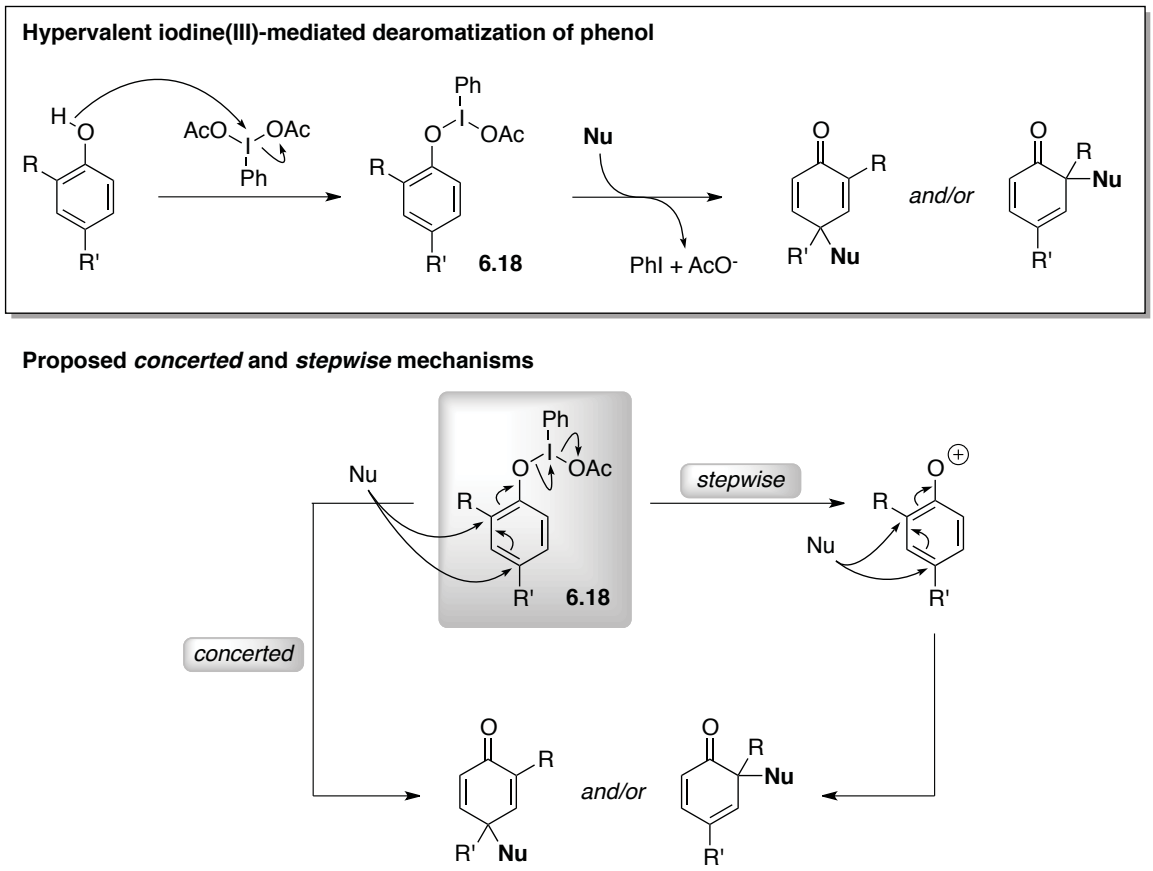


6.2.1 **Dearomatization by Addition of External Oxidants**

Currently, one of the most frequently employed methods for the dearomatization of phenols is the use of external oxidants, such as hypervalent iodine(III) reagents, to activate the arene towards nucleophilic attack (Scheme 6.7).[116] Phenyliodonium(III) diacetate (PIDA) and non-nucleophilic phenyliodonium(III) bis(trifluoroacetate) (PIFA) have emerged as the optimal reagents for these transformations. Regioselectivity for C-2 (*ortho*) vs C-4 (*para*) nucleophilic addition is typically dictated by steric effects. However, the presence of an electron-donating group has been shown to alter the position of attack to the more hindered site due to the stabilization of the developing positive charge. The mechanism of these transformations has remained rather elusive until very recently. Both concerted and stepwise mechanisms have been proposed for arene oxidation/nucleophilic attack as depicted in Scheme 6.7. Recent results in the development of chiral hypervalent iodine(III) reagents for enantioselective phenol dearomatization (*vide infra*) favour a concerted mechanism.

[116] For recent reviews on the chemistry of hypervalent iodine, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656-3665; (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299-5358; (c) Zhdankin, V. V. *ARKIVOC* **2009**, 1-62; (d) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185-1197.

Scheme 6.7 Hypervalent iodine(III)-mediated dearomatization of phenol

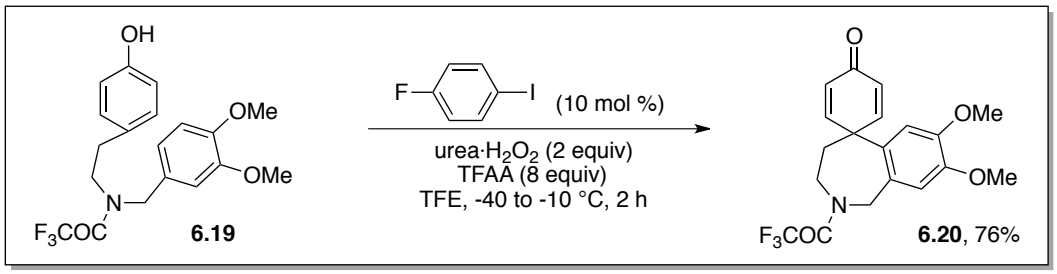


While a powerful tool for the dearomatization of phenols, the use of stoichiometric amounts of hypervalent iodine reagent represents a drawback. The ability to use the hypervalent iodine reagent in catalytic quantities, in combination with a less-expensive stoichiometric terminal oxidant, provides significant advantages.[117] Along these lines, Kita and coworkers have recently developed a carbon-carbon bond-forming protocol for the dearomatization of phenols, employing simple iodoarenes and a reoxidation system based on H_2O_2/trifluoroacetic anhydride.[118] Reaction optimization revealed that treatment of phenol derivatives with 10 mol % 4-fluoroiodobenzene, 2 equivalents of urea·H_2O_2 and 8 equivalents of trifluoroacetic anhydride (TFAA) in 2,2,2-trifluoroethanol (TFE) provided cyclohexadienones in moderate to excellent yields (Scheme 6.8). The combination of H_2O_2

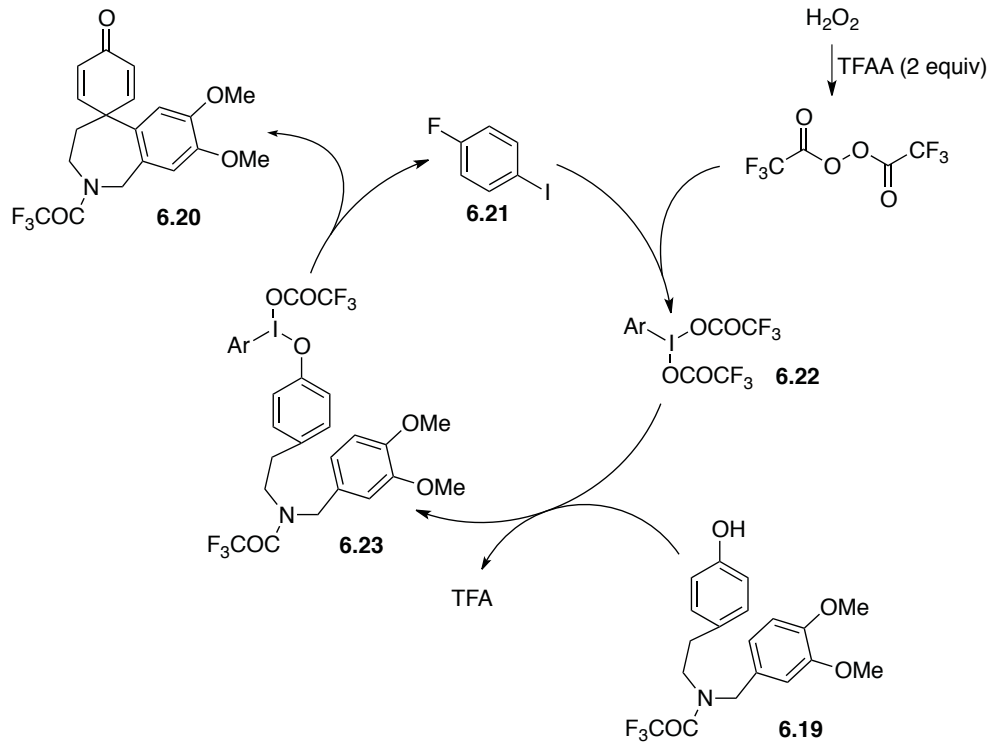
[117] For a review, see: Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402-4404. See also ref 116d.
[118] Dohi, T.; Minamitsuji, Y.; Maruyama, A.; Hirose, S.; Kita, Y. *Org. Lett.* **2008**, *10*, 3559-3562.

and TFAA was proposed to generate bis(trifluoroacetyl) peroxide *in situ*, which is responsible for the oxidation of iodoarene **6.21** to hypervalent iodine(III) species **6.22**. Reaction of phenol **6.19** with the latter leads to the desired product **6.20** in 76% yield, via hypervalent iodine(III) intermediate **6.23**.

Scheme 6.8 *In situ* generation of a catalytic hypervalent iodine(III) reagent for the dearomatization of phenol derivatives

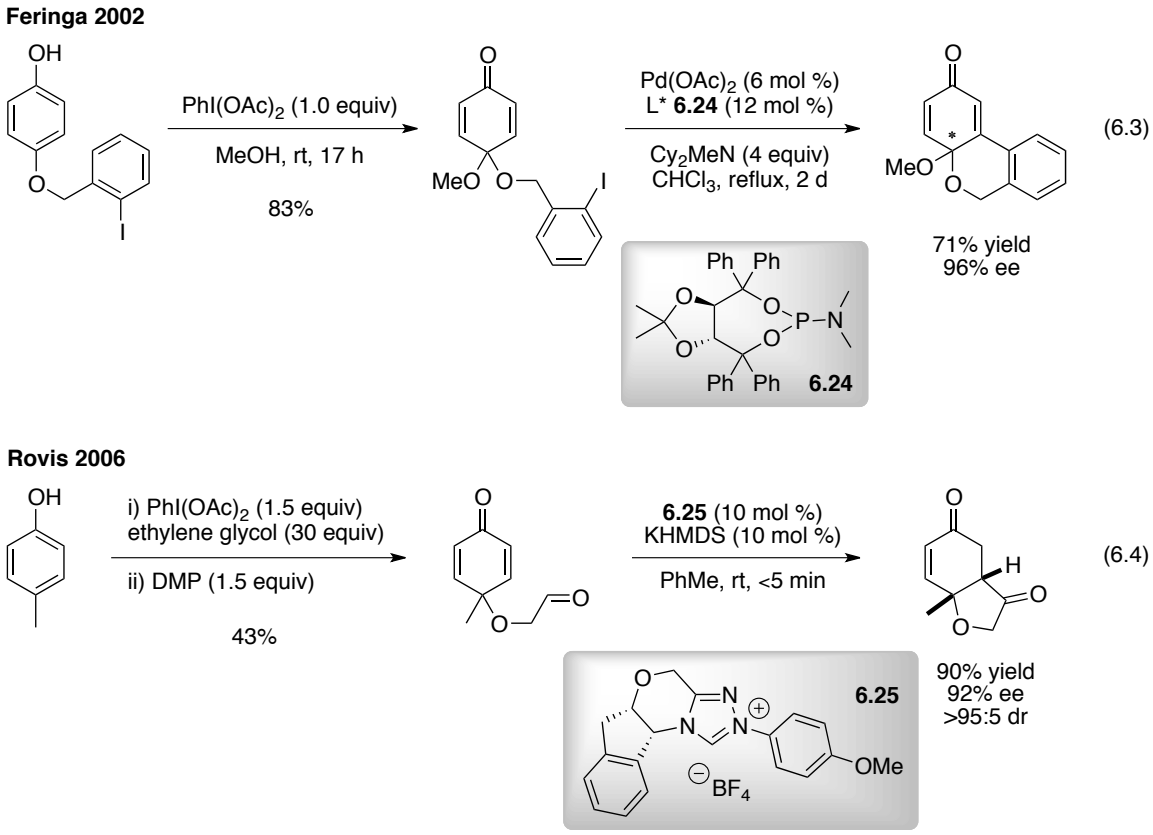


Proposed mechanism

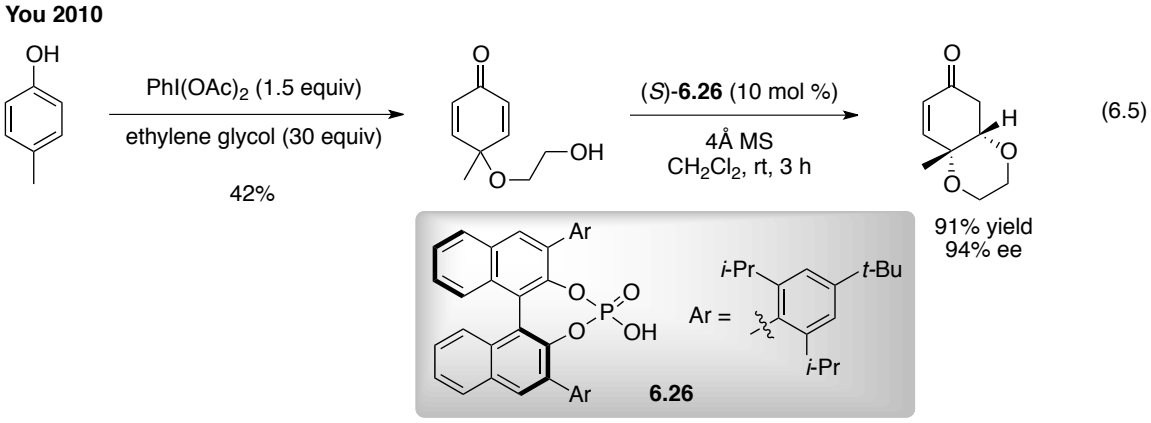


Hypervalent iodine(III)-mediated dearomatization processes generate quaternary sp^3-hybridized centres, providing an opportunity for the formation of enantioenriched products. Initial strategies towards this goal have been based on the desymmetrization of the

cyclohexadienenone intermediates that are initially generated. Several transformations have been employed to this effect, including (but not limited to) asymmetric Heck reactions (eq 6.3),[119] organocatalyzed Stetter reactions (eq 6.4)[120] and Michael additions (eq 6.5).[121] Of note, the source of chirality in these transformations is highly varied: chiral ligands for palladium catalysis (eq 6.3), enantioenriched organocatalysts (eq 6.4) and chiral Brønsted acid catalysts (eq 6.5). The breadth of these transformations, and the high levels of enantiomeric excess that are achieved, further highlight the synthetic importance of cyclohexadienones obtained through the dearomatization of phenols.

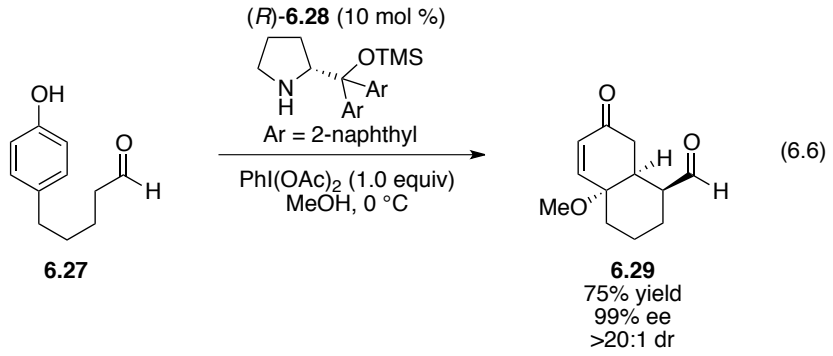


[119] Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184-185.
[120] (a) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552-2553; (b) Liu, Q.; Rovis, T. *Org. Proc. Res. Dev.* **2007**, *11*, 598-604.
[121] (a) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028-16029; (b) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056-4057; (c) Gu, Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 5192-5195; (d) Gu, Q.; You, S.-L. *Chem. Sci.* **2011**, *2*, 1519-1522.



(6.5)

In 2008, Gaunt and coworkers reported a *one step* catalytic enantioselective dearomatization strategy based on a domino process involving oxidative dearomatization and enantioselective desymmetrizing Mannich reaction (eq 6.6).[122] In this case, instead of converting the cyclohexadienone intermediate to an enantioenriched product in a stepwise manner, an organocatalyst was directly added to the oxidative dearomatization protocol. The authors found that subjecting phenol **6.27** to 1.0 equivalent of $PhI(OAc)_2$ and 10 mol % organocatalyst **6.28** in methanol as a solvent/nucleophile afforded product **6.29** in 75% yield, 99% ee and >20:1 dr.



(6.6)

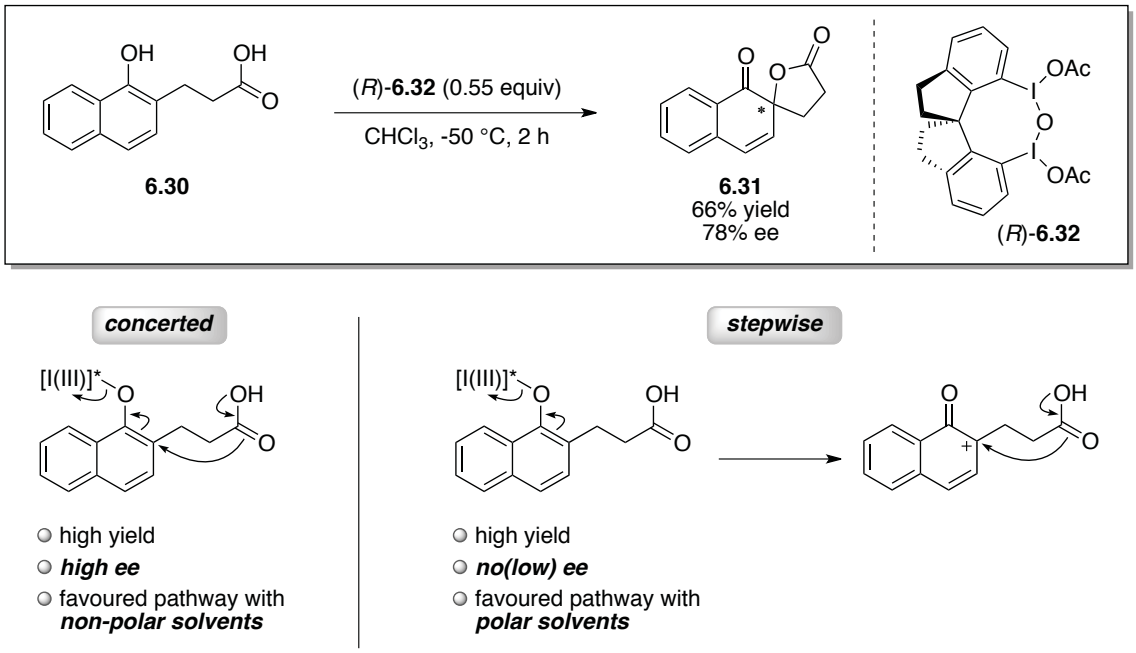
In 2008, Kita and coworkers reported an enantioselective dearomatization of phenol based on chiral hypervalent iodine(III) reagents.[123,124] Compound (*R*)-**6.32**, containing a

[122] Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404-405.
[123] Dohi, T.; Maruyama, A.; Takenaga, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S. B.; Kita, Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 3787-3790.

rigid 1,1'-spirobiindance backbone, was found to react with naphthol **6.30**, producing spirolactone **6.31** in 66% yield and 78% ee (Scheme 6.9). In addition to being the first example of an enantioselective dearomatization of phenol, this report also had significant implications for the mechanism of iodine(III)-mediated oxidative dearomatization. As previously mentioned, concerted and stepwise mechanisms have been proposed for these transformations (Scheme 6.7). The ability of a chiral hypervalent iodine(III) reagent to induce enantioselective dearomatization strongly supports a concerted pathway where nucleophilic attack of the phenol occurs with concomitant elimination of iodoarene (Scheme 6.9). Additionally, reaction optimization revealed that solvent polarity had a significant impact on the levels of enantioselectivity. Indeed, while non-polar solvents yielded spirolactone **6.31** with good levels of enantiomeric excess, more polar solvents such as acetonitrile and HFIP led to significant drops in ee values while maintaining good product yields. These latter observations suggest that the mechanism of dearomatization may also be more cationic (stepwise) in nature when stabilization of the developing positive charge is possible. These results highlight that the mechanism of oxidative dearomatization is highly dependent on the nature of the substrate and the reaction conditions, which should be strongly taken into consideration for new reaction development and the application of these methods in natural product synthesis.

[124] For additional examples of chiral hypervalent iodine(III)-mediate enantioselective dearomatization of phenol derivatives, see: (a) up to 50% ee: Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 4605-4609; (b) up to 77% ee: Boppisetti, J. K.; Birman, V. B. *Org. Lett.* **2009**, *11*, 1221-1223; (c) up to 92% ee: Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2175-2177.

Scheme 6.9 Enantioselective dearomatization of a naphthol derivative mediated by a chiral hypervalent iodine(III) reagent



6.2.2 Alkylative Dearomatization of Phenols

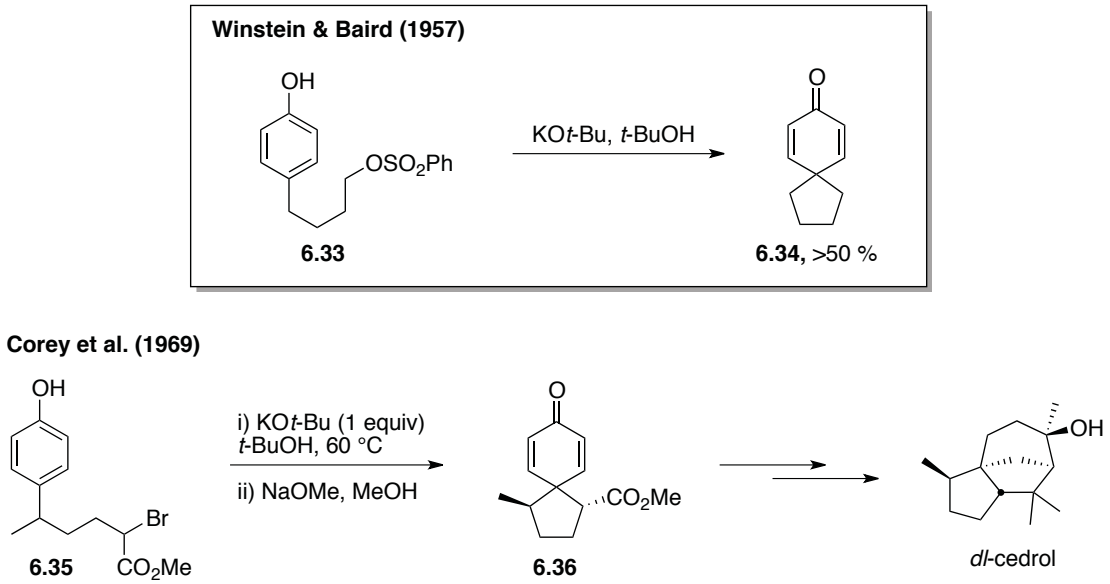
Phenols are inherently nucleophilic and thus readily react with electrophiles to provide *O*-, *C2*- and/or *C4*-functionalized products. In this context, the electrophilic alkylation of appropriately substituted phenols can lead to dearomatized products. While intramolecular reactions are usually required for dearomatization to be favoured over S_EAr reactions (Friedel-Crafts chemistry), some examples of intermolecular processes have been reported. Typically, the phenol (or its protected derivative) is activated as the more nucleophilic phenolate by addition of strong base (or *in situ* removal of a protecting group). While numerous groups have contributed to this field, only selected examples of this alkylation/dearomatization strategy will be highlighted in the upcoming section, with a particular focus on their application in natural product synthesis.

In 1957, Winstein and Baird published the seminal report for the formation of spirocyclohexadienone **6.34** upon treatment of phenol **6.33** with a slight excess of KO*t*-Bu in dry *tert*-butanol (Scheme 6.10).[125] A little over a decade later, Corey and coworkers

[125] Winstein, S.; Baird, R. *J. Am. Chem. Soc.* **1957**, *79*, 756-757.

employed these conditions to achieve the synthesis of *dl*-cedrol.[126] Reaction of phenol **6.35** with KO*t*-Bu in dry *t*-BuOH afforded a near 1:1 mixture of *cis* and *trans* spirocyclohexadienone products. This non-ideal mixture could be exclusively converted to the more stable *trans* product upon addition of a solution of sodium methoxide in methanol. Key intermediate **6.36** was subsequently further elaborated into two natural products: *dl*-cedrene and *dl*-cedrol.

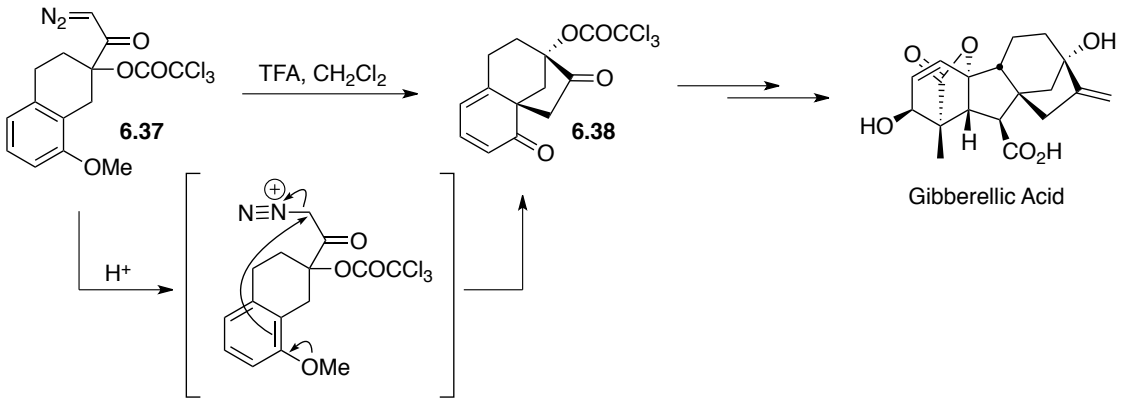
Scheme 6.10 Initial reports of phenol dearomatization via *para*-alkylation



Mander and coworkers have investigated the use of substrates containing α-diazoketone motifs in the same type of transformation.[101a] Subjecting anisole derivative **6.37** to a solution of trifluoroacetic acid (TFA) in dichloromethane generated the corresponding α-diazonium intermediate, which underwent intramolecular nucleophilic displacement to generate cyclohexadiene **6.38**. Intermediate **6.38** was subsequently converted to gibberellic acid (Scheme 6.11).[127]

[126] Corey, E. J.; Girotra, N. N.; Mathew, C. T. *J. Am. Chem. Soc.* **1969**, *91*, 1557-1559.
[127] (a) Blair, I. A.; Ellis, A.; Johnson, D. W.; Mander, L. N. *Aust. J. Chem.* **1978**, *31*, 405-409; (b) Cossey, A. L.; Mander, L. N. *Tetrahedron Lett.* **1979**, *20*, 969-972; (c) Lombardo, L.; Mander, L. N.; Turner, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 6626-6628.

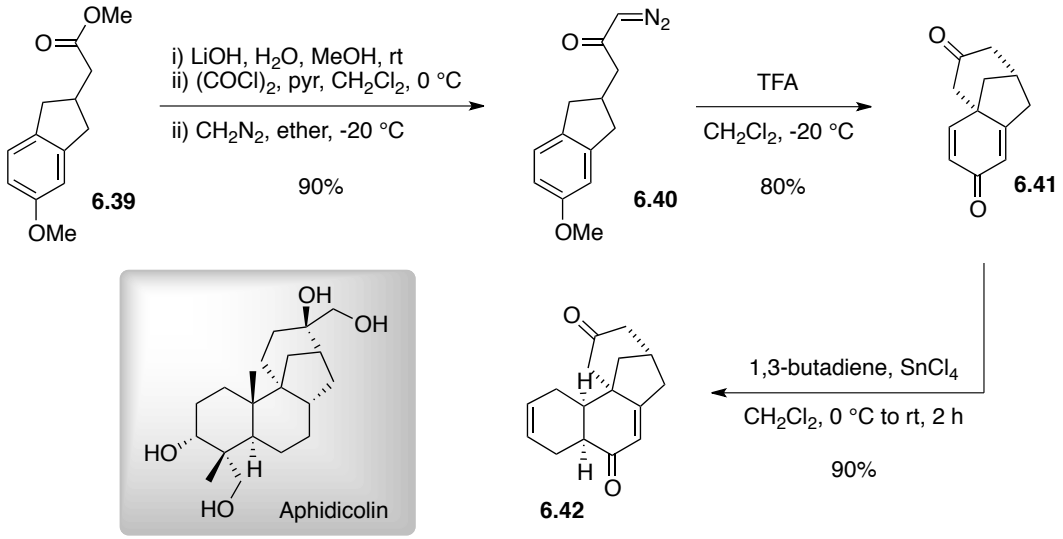
Scheme 6.11 Synthesis of gibberellic acid via *ortho*-alkylation/dearomatization



Nicolaou and Zipkin further illustrated the synthetic utility of *para*-alkylation/dearomatization in their synthesis of the core of aphidicolin (Scheme 6.12).[128] Based on the Mander group's procedure, intermediate **6.39** was converted to the corresponding α-diazoketone **6.40**. Addition of **6.40** to a solution of trifluoroacetic acid in dichloromethane at -20 °C generated **6.41** in 80% yield after 5 minutes. Cyclohexadienone **6.41** was elaborated into **6.42**, which contains the final ring in the skeleton of the natural product, via a stereoselective Diels-Alder reaction. This last transformation further demonstrates the value/potential of the products of phenol dearomatization reactions, which generate good dienophiles.

[128] Nicolaou, K. C.; Zipkin, R. E. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 785-786.

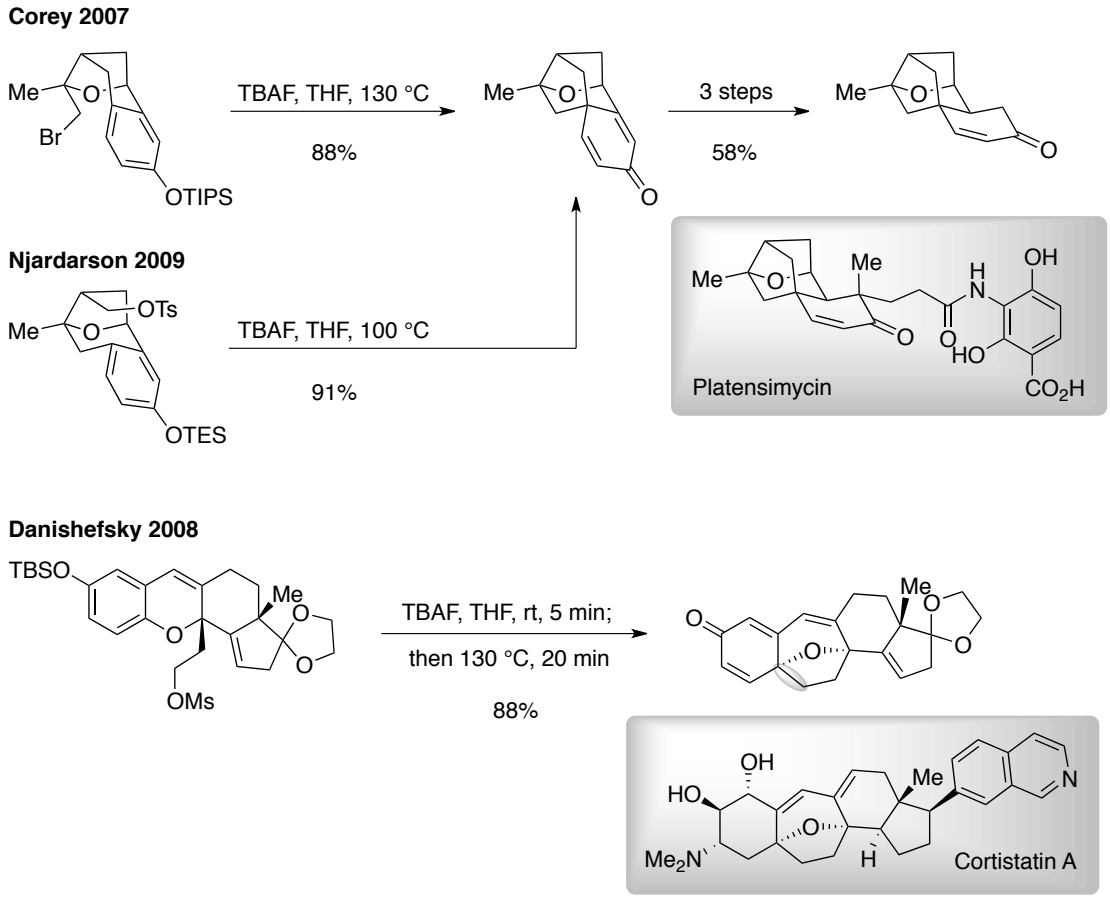
Scheme 6.12 Synthesis of the core of aphidicolin via *para*-alkylation/dearomatization and Diels-Alder reaction



Phenol dearomatization through intramolecular alkylation reactions is still employed as a key strategy for the synthesis of complex natural products (Scheme 6.13). Indeed, this method has been utilized to generate the tetracyclic core, and the key quaternary stereocenter, of platensimycin by the groups of Corey and Njardarson.[129] Dai and Danishefsky have also prepared the pentacyclic core of cortistatin A along these lines.[130] In all cases, fluoride promoted desilylation initiates the dearomatization process.

[129] (a) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921-4923; (b) McGrath, N. A.; Bartlett, E. S.; Sittihan, S.; Njardarson, J. T. *Angew. Chem., Int. Ed.* **2009**, *48*, 8543-8546.
[130] Dai, M.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610-6612.

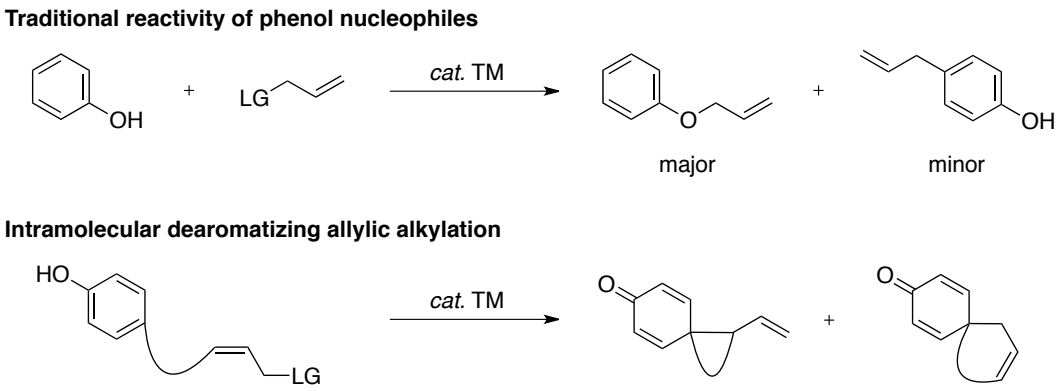
Scheme 6.13 Recent total synthesis employing phenol alkylation/dearomatization



Transition metal-catalyzed allylic alkylation has also been investigated in the context of phenol dearomatization.[131] It should be noted that typically, phenols are *O*-alkylated in these reactions rather than *C*-alkylated. However, in the context of intramolecular allylic alkylation, *C*-alkylation with concomitant dearomatization is possible (Scheme 6.14).

[131] For selected reviews, see: (a) Trost, B. M. *Chem. Rev.* **1996**, *96*, 395-422; (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2944; (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258-297.

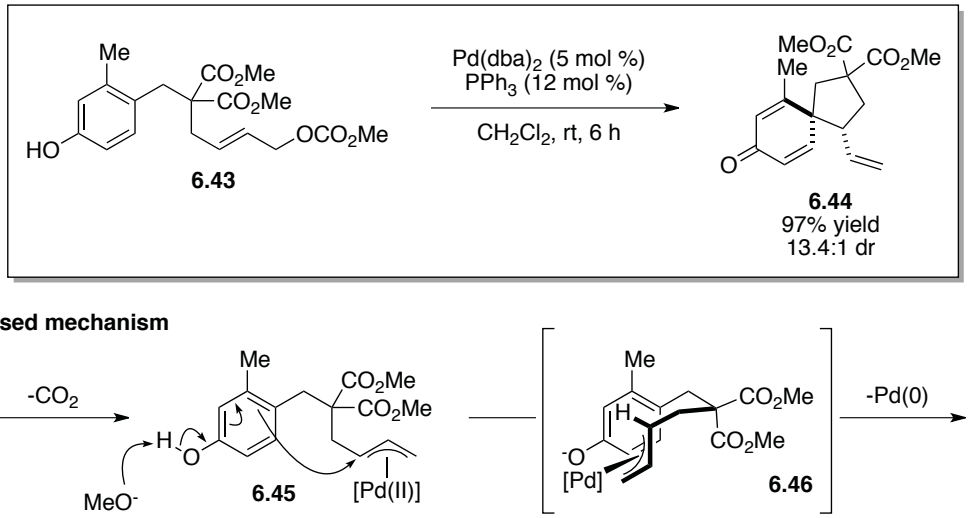
Scheme 6.14 Transition metal-catalyzed allylic alkylation of phenol



In 2010, Hamada and coworkers reported a Pd(0)-catalyzed intramolecular allylic alkylation protocol for the preparation of spirocyclohexadienones from phenol derivatives (Scheme 6.15).[132] An evaluation of palladium sources, ligands and solvents revealed that the use of 5 mol % $Pd(dba)_2$, 12 mol % PPh_3 in dichloromethane at room temperature cleanly converted **6.43** to **6.44** in 97% yield and 13.4:1 dr. Preliminary results, for example the lack of reaction with anisole derivatives, led the authors to propose the mechanism in Scheme 6.15. Oxidative addition generates π-allyl-Pd(II) intermediate **6.45**, which can be deprotonated by the equivalent of methoxide generated in the process. Carbon-carbon bond formation is proposed to occur via chair-like conformation **6.46** to yield the desired product.

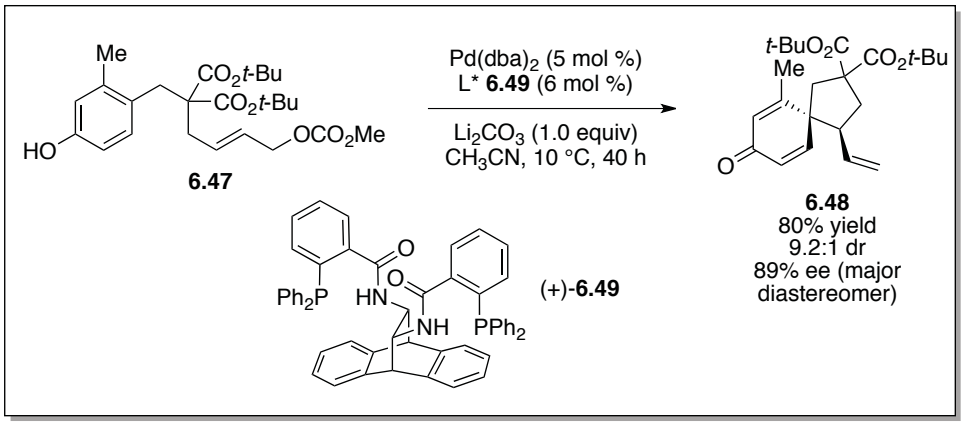
[132] Nemoto, T.; Ishige, Y.; Yoshida, M.; Kohno, Y.; Kanematsu, M.; Hamada, Y. *Org. Lett.* **2010**, *12*, 5020-5023.

Scheme 6.15 Pd(0)-catalyzed intramolecular allylic alkylation/dearomatization



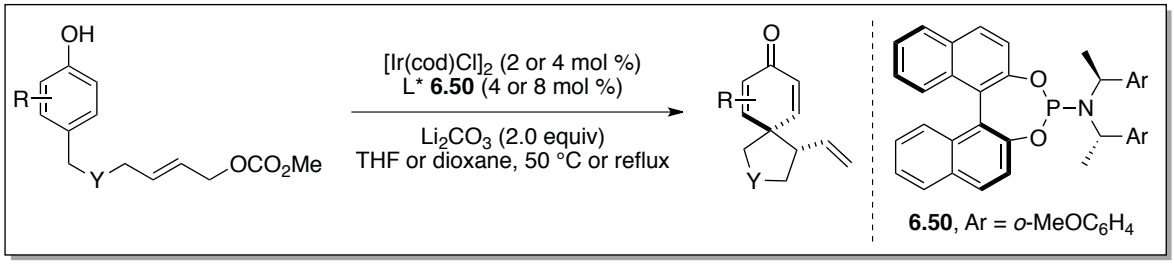
The involvement of the catalyst at the carbon-carbon bond-forming step in this process offers the opportunity for asymmetric catalysis. Indeed, several chiral phosphine ligands have been developed for asymmetric Pd(0)-catalyzed allylic alkylations.[131] For this dearomatization protocol, preliminary results revealed that the use of chiral ligand (+)-**6.49** in combination with $Pd(dba)_2$ and Li_2CO_3 in acetonitrile at 10 °C generated spirocyclohexadienone (*S*,*S*)-**6.48** in 80% yield (9.2:1 dr) with 89% ee of the major diastereomer.

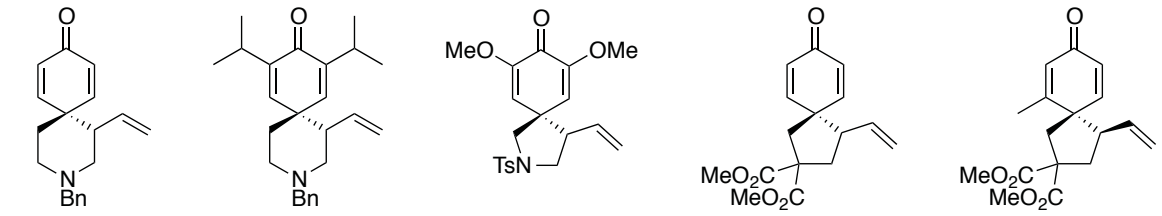
Scheme 6.16 Enantioselective Pd(0)-catalyzed allylic alkylation/dearomatization



Shortly after the Hamada group report, You and coworkers published an Ir-catalyzed asymmetric allylic alkylation/dearomatization of phenols.[133] Compared to the previous palladium-catalyzed protocol, the authors determined that a catalyst system based on $[Ir(cod)Cl]_2$ and chiral phosphoramidite **6.50** provided a broader scope of spirocyclohexadienones in good to excellent yields and high levels of enantiomeric excess (85-97% ee) (Scheme 6.17). For example, unlike the Hamada report, six-membered rings could be generated with this protocol (**6.51** and **6.52**). Nitrogen atoms (**6.51**-**6.53**) and geminal ester groups (**6.54** and **6.55**) were tolerated in the tether as well as substitution on the phenol ring (**6.52**, **6.53** and **6.55**). The reaction was also found to be diastereoselective (**6.55**), most likely proceeding via a mechanism similar to the one proposed by Hamada. It should be noted that while the You protocol offers advantages with respect to scope and ee, it is operationally more challenging than the Hamada process. Indeed, the transformation involves two manipulations: the active iridium catalyst is first generated and isolated prior to the addition of substrate, base and solvent.

Scheme 6.17 Ir-catalyzed asymmetric allylic alkylation/dearomatization

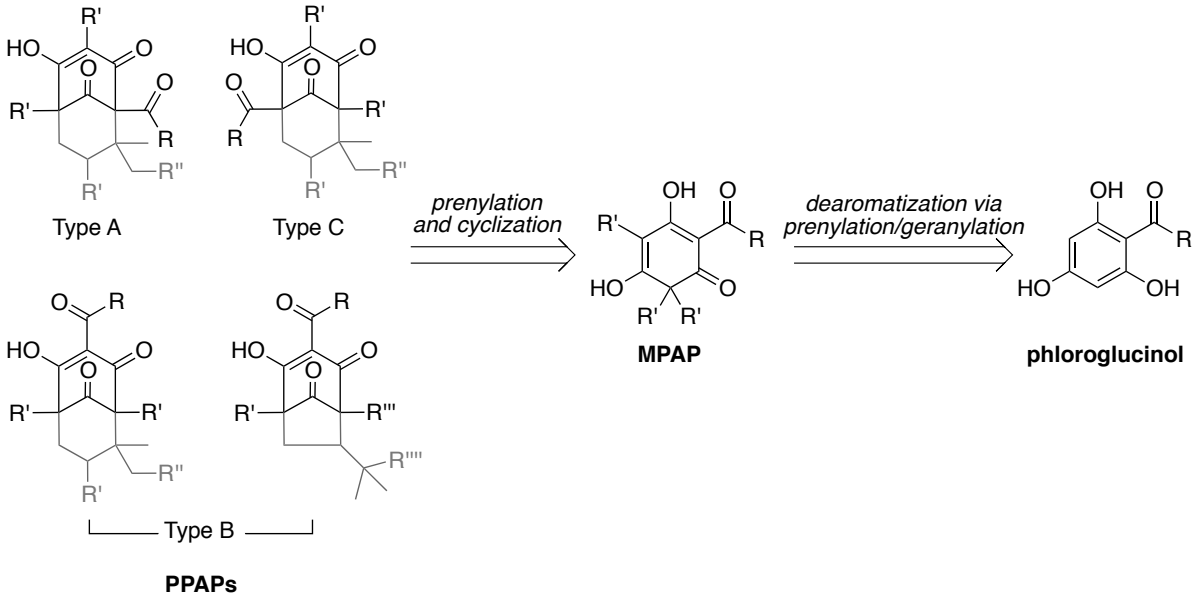




[133] Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455-4458.

The polycyclic polyprenylated acylphloroglucinol (PPAP) family of natural products has been proposed to biosynthetically originate from monocyclic polyprenylated acylphloroglucinols (MPAPs), which arise from the enzyme-catalyzed dearomatization via prenylation (or geranylation) of phloroglucinol (Scheme 6.18).[134]

Scheme 6.18 Proposed biosynthesis of the polycyclic polyprenylated acylphloroglucinol (PPAP) family



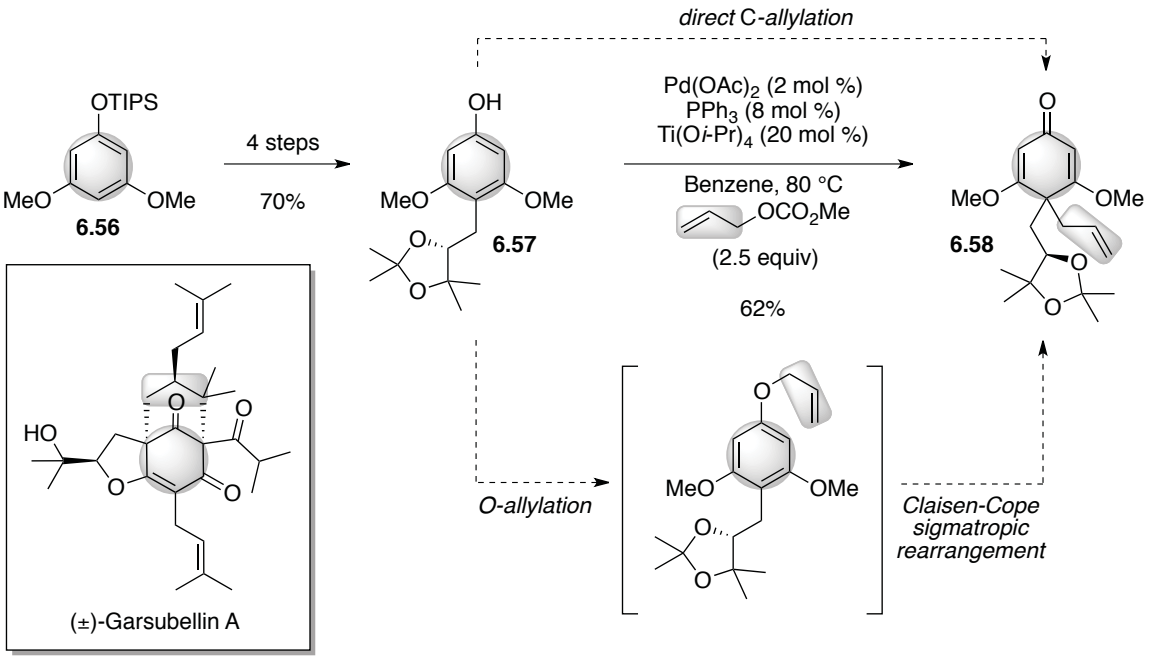
Based on this proposed biosynthesis, several groups have prepared members of the PPAP class of natural products via the dearomatization of phenolic derivatives.[135] For example, Siegel and Danishefsky accomplished the total synthesis of (±)-garsubellin A in 2006 employing a Pd-catalyzed allylic alkylation/dearomatization process (Scheme 6.19).[135a] Protected phloroglucinol **6.56** was selectively converted to alkylated phloroglucinol derivative **6.57**. Subjecting **6.57** to 2 mol % $Pd(OAc)_2$, 8 mol % PPh_3 and 20 mol % $Ti(O\textit{i}\text{-}Pr)_4$ in the presence of allyl methyl carbonate yielded dearomatized intermediate **6.58** in 62% yield. Compound **6.58** could be further elaborated into the natural product. This

[134] (a) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963-3986; (b) Dakanali, M.; Theodorakis, E. A. in *Biomimetic Organic Synthesis, Volume 1*; Poupon, E. and Nay, B., Eds.; Wiley-VCH: Weinheim, 2011.

[135] For selected examples, see: (a) Siegel, D. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 1048-1049; (b) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682-12683; (c) Couladouros, E. A.; Dakanali, M.; Demadis, K. D.; Vidali, V. P. *Org. Lett.* **2009**, *11*, 4430-4433; (d) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. B. *Org. Lett.* **2010**, *12*, 3532-3535; (e) Zhang, Q.; Mitasev, B.; Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2010**, *132*, 14212-14215.

allylic alkylation/dearomatization may proceed via direct *para C*-allylation, similar to the processes described by Hamada and You.[132,133] However, as previously mentioned, phenols typically undergo intermolecular *O*-allylation (Scheme 6.14). Thus, a pathway based on *O*-allylation and subsequent Claisen-Cope sigmatropic rearrangement cannot be excluded for the formation of cyclohexadienone **6.58**.[136] The authors suggest that the driving force for the generation of **6.58** is the stabilization imparted by the doubly vinylogous carbonate moiety.

Scheme 6.19 Total synthesis of (±)-garsubellin A via intermolecular Pd-catalyzed allylic alkylation/dearomatization



6.3 Perspectives

The dearomatization of phenol and its derivatives has been long considered an interesting, highly applicable, yet challenging process in organic chemistry. Several strategies have been developed to achieve this goal and this field remains in constant evolution. The discussion in this Chapter has focused on two main concepts for phenol

[136] Although beyond the scope of the discussion in this Chapter, it should be noted that Claisen rearrangements have been previously employed as a strategy for phenol dearomatization. See ref 102b for a discussion on the application of this dearomatization technique in natural product synthesis.

dearomatization: i) activation/oxidation by the addition of hypervalent iodine(III) reagents, and ii) *ipso*-alkylation of substituted phenols. The current application of these two strategies in natural product synthesis further highlights the importance of these developments as a general tool in organic chemistry. However, limited methods for the *asymmetric* dearomatization of phenolic derivatives currently exist. Developments in this area are desirable to provide new opportunities for the total synthesis of enantiomerically enriched natural product.

7 Pd(0)-Catalyzed Arylative Dearomatization of Phenols

7.1 Background

7.1.1 Arylative Dearomatization of Phenol

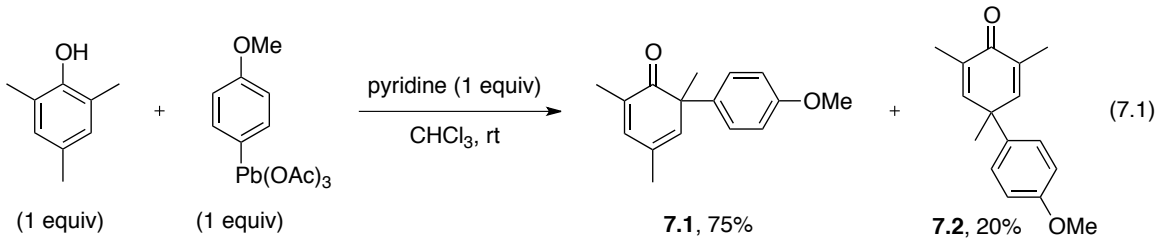
Despite the numerous carbon-carbon bond forming methods for the dearomatization of phenols, protocols which lead to $C(sp^2)$-$C(sp^3)$ bond formation (phenol alkenylation or arylation) remain limited.[137] Early reports first demonstrated that highly substituted phenols reacted with *p*-block arylating agents, such as aryllead(IV) and arylbismuth(V) compounds, to yield cyclohexadienone mixtures via arylative dearomatization.[138,139] In 1976, Sternhell and coworkers revealed that the reaction of equimolar amounts of mesitol, 4-methoxyphenyllead(IV) triacetate and pyridine in chloroform at room temperature produced a 3.75:1 mixture of *ortho*-arylated **7.1** and *para*-arylated **7.2** cyclohexadienones (eq 7.1). An evaluation of the reaction scope revealed that only electron-neutral and electron-rich substituents were tolerated on the phenol ring. Additionally, heavily substituted phenol derivatives participated more efficiently in the desired dearomatization process compared to mono and di-substituted phenols. The latter were often recovered from the

[137] For selected examples of alkenylative dearomatization of phenolic derivatives, see: (a) Appel, T. R.; Yehia, N. A. M.; Baumeister, U.; Hartung, H.; Kluge, R.; Ströhl, D.; Fanghänel, E. *Eur. J. Org. Chem.* **2003**, 47-53; (b) Larock, R. C.; Zhang, X. *J. Am. Chem. Soc.* **2005**, *127*, 12230-12231; (c) Tang, B.-X.; Yin, Q.; Tang, R.-Y.; Li, J.-H. *J. Org. Chem.* **2008**, *73*, 9008-9011; (d) Dohi, T.; Kato, D.; Hyodo, R.; Yamashita, D.; Shiro, M.; Kita, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3784-3787; (e) Leon, R.; Jawalekar, A.; Redert, T.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 1487-1490; (f) Dohi, T.; Nakae, T.; Ishikado, Y.; Kato, D.; Kita, Y. *Org. Biomol. Chem.* **2011**, *9*, 6899-6902.

[138] For an example of arylative dearomatization using aryllead(IV) reagents, see: Bell, H. C.; May, G. L.; Pinhey, J. T.; Sternhell, S. *Tetrahedron Lett.* **1976**, *47*, 4303-4306.

[139] For selected examples of arylative dearomatization using arylbismuth(V) reagents, see: (a) Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1981**, 503-504; (b) Barton, D. H. R.; Yadav-Bhatnagar, N.; Finet, J.-P.; Khamsi, J.; Motherwell, W. B.; Stanforth, S. P. *Tetrahedron* **1987**, *43*, 323-332.

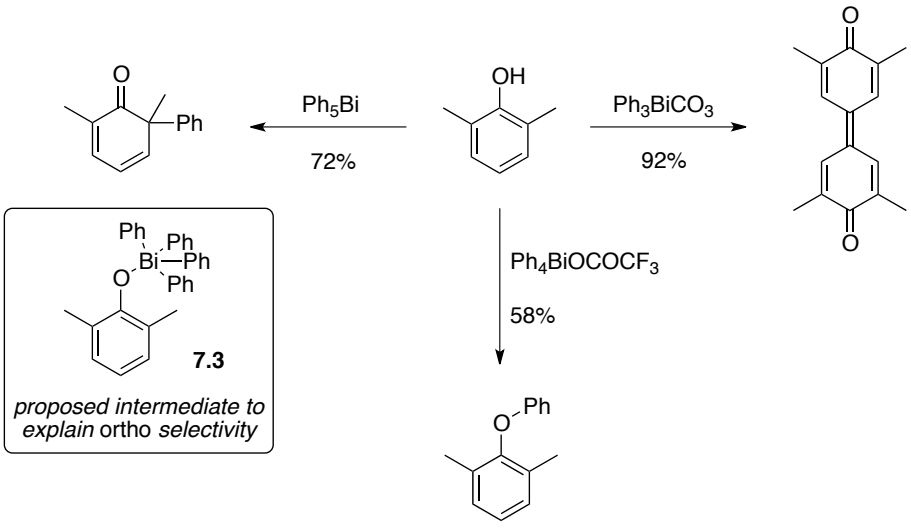
reaction mixture in greater than 50% yield. Other aryllead(IV) compounds also proved to be efficient dearomatizing agents, including 4-fluorophenyllead triacetate, phenyllead triacetate and 4-tolyllead triacetate.



(7.1)

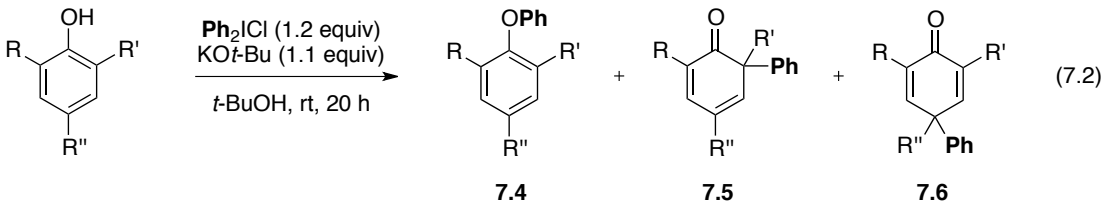
Barton and coworkers have investigated a similar arylative dearomatization employing arylbismuth(V) reagents.[139] The chemoselectivity of the process was found to be highly reagent (and substrate) dependent (Scheme 7.1).[140] For example, products of oxidative dimerization, *O*-arylation or *ortho*-arylative dearomatization were obtained in good yields using Ph_3BiCO_3, $Ph_4BiOCOCF_3$ and Ph_5Bi, respectively. Based on the *ortho*-selectivity for arylative dearomatization, **7.3** was proposed as a relevant intermediate from which intramolecular aryl group transfer could occur in a concerted fashion.[141]

Scheme 7.1 Arylation of phenol using arylbismuth(V) reagents

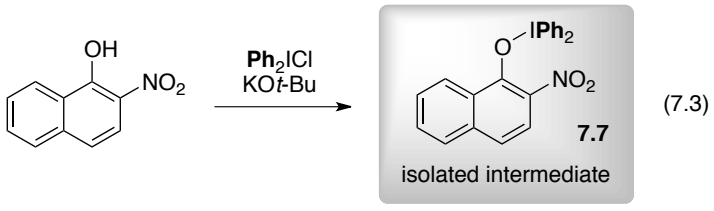


[140] See ref 139 and references therein.
[141] Barton, D. H. R.; Bhatnagar, N. Y.; Finet, J.-P.; Motherwell, W. B. *Tetrahedron* **1986**, *42*, 3111-3122.

In 2005, Ozanne-Beaudenon and Quideau reported a hypervalent iodine(III)-mediated phenylative dearomatization of phenols, as an alternative to the use of the toxic aryllead(IV)[138] and arylbismuth(V)[139] reagents previously described.[142] Treatment of substituted phenol and naphthol derivatives with 1.2 equivalents of Ph_2ICl and 1.1 equivalents of KO*t*-Bu in *t*-BuOH at room temperature for 20 hours was found to generate mixtures of *O*-phenylated **7.4** and *ortho C*-phenylated **7.5** products (eq 7.2). The product ratios were found to be highly dependent on the nature of the phenol substituents (steric and electronic effects), and in some cases, *para C*-phenylated **7.6** product was obtained.



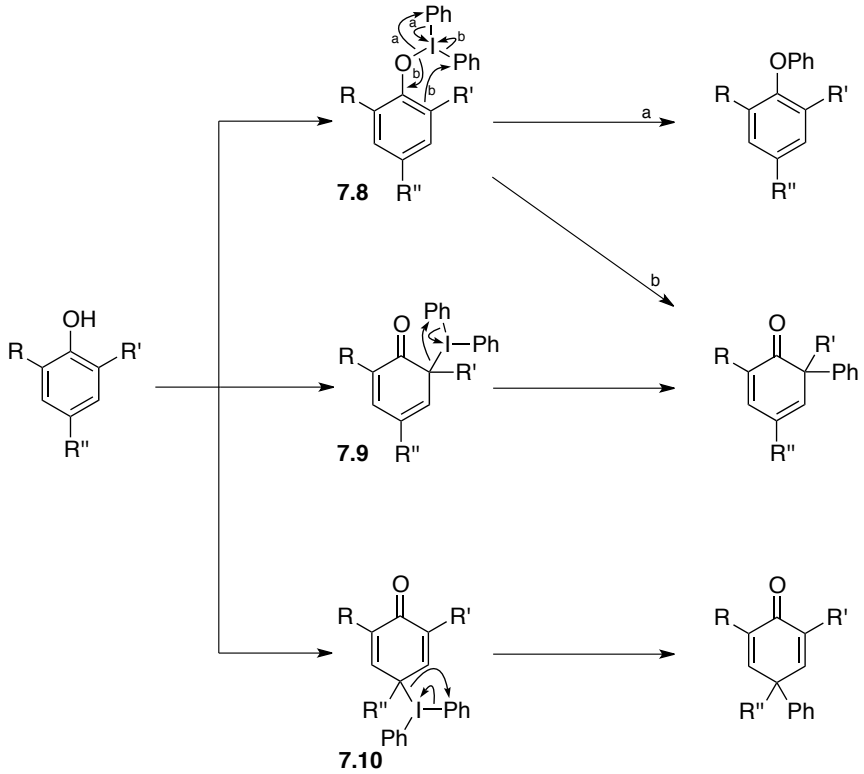
The mechanism of this transformation was examined both experimentally and computationally. The addition of 1,1-diphenylethylene, a radical trapping agent, did not affect the product yield, indicating that phenylation does not occur via radical intermediates. Additionally, the required use of a strong base and the isolation of intermediate **7.7** of general structure $ArOI(Ph)_2$ suggests that the reaction is initiated by deprotonation and chloride ligand displacement (eq 7.3).



[142] Ozanne-Beaudenon, A.; Quideau, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7065-7069.

The reaction selectivity, based on theoretical calculations, can be explained by the formation of intermediates **7.8**-**7.10**, which undergo ligand coupling to yield the observed products (Scheme 7.2). The relative ratios for formation of intermediates **7.8**-**7.10** are dictated by the magnitude of the HOMO coefficients at each position on the aromatic ring. Thus, the presence of *ortho* (or *para*) electron-donating groups increases the HOMO coefficient at the *ortho*-carbon and favours arylation at this position.

Scheme 7.2 Proposed ligand coupling mechanism for phenylative dearomatization

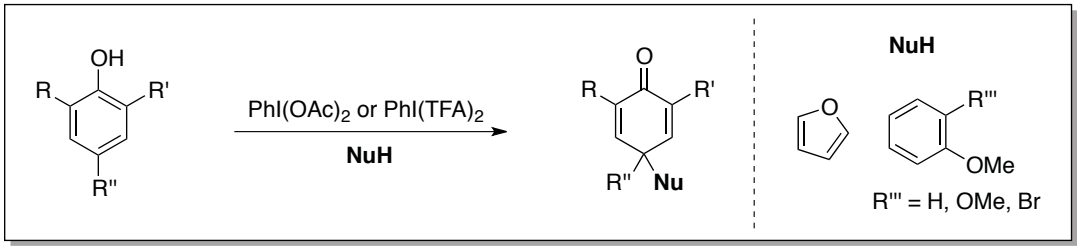


Strategies employing stoichiometric arylating agents for the dearomatization of phenols, while important and mechanistically interesting, are inherently wasteful. Indeed, the use of, sometimes toxic, arylating reagents in stoichiometric quantities produce significant amounts of metallic waste. Additionally, these reagents often contain several equivalents of the aryl group to be transferred (i.e. Ph_2ICl or Ph_5Bi) thus generating important losses of material, an important problem for the use of expensive or non-

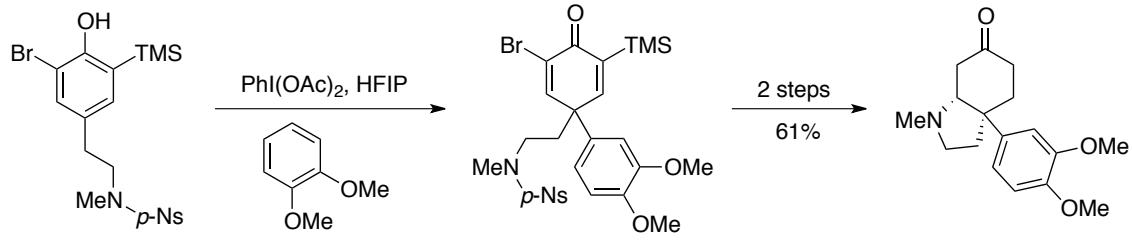
commercial arenes in these transformations. Finally, the product mixtures that are typically obtained further limit the synthetic utility of these reactions.

The oxidation of phenols, using stoichiometric amounts of hypervalent iodine(III) reagents (see Section 6.2.1), in the presence of nucleophilic arenes has also been employed as a strategy for arylative dearomatization. Canesi and coworkers have reported that nucleophilic arenes, such as anisole and furan derivatives, can be used for the dearomatization of 2,6-disubstituted phenol derivatives, initiated by $PhI(OAc)_2$ or $PhI(TFA)_2$ (Scheme 7.3).[143] Subsequently, they applied this method to the synthesis of mesembrine. While the yield of the key oxidative dearomatization was quite modest (18%), the cyclohexadienone intermediate **7.12** produced could be converted to the natural product in only 2 additional synthetic steps. This highlights the value of this method as a rapid means of constructing more complex structures from simple planar starting materials. Optimization of reaction conditions specifically for **7.11** may lead to improved yields of **7.12**.

Scheme 7.3 Hypervalent iondine(III)-mediated arylative dearomatization



Synthesis of mesembrine



7.11 **7.12**, 18% Mesembrine

While this method presents an attractive alternative to the use of stoichiometric arylating agents ($PhPb(OAc)_3$, Ph_5Bi or Ph_2ICl), the use of stoichiometric amounts of

[143] Guérard, K. C.; Sabot, C.; Beaulieu, M.-A.; Giroux, M.-A.; Canesi, S. *Tetrahedron* **2010**, *66*, 5893-5901.

hypervalent iodine(III) reagents remains a limitation. Additionally, this protocol is restricted to the use of very nucleophilic arenes. Thus, there remains a need to develop milder, preferentially catalytic, conditions to achieve the arylative dearomatization of phenols with high levels of chemoselectivity.

7.1.2 Transition Metal-Catalyzed Arylative Dearomatization

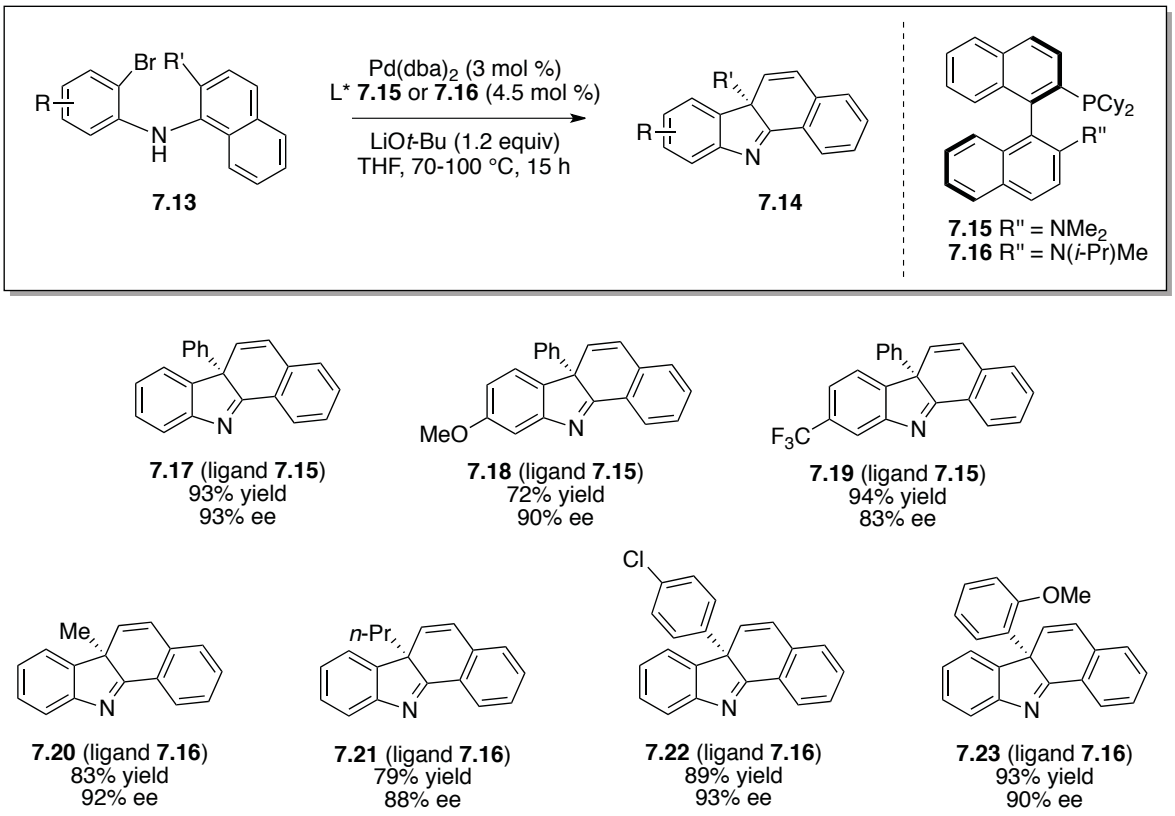
Few examples of catalytic methods for the dearomatization of arenes have been reported to date. However, recent success in Ir- and Pd-catalyzed dearomatization via allylic alkylation (Section 6.2.2) has prompted the investigation of Pd(0)-catalysis in intramolecular arylative dearomatization.[144] It should be noted that unlike allylic alkylation reactions, Pd(0)-catalyzed arylative dearomatizations are inherently more challenging since they involve a reductive elimination to form a quaternary center.

In 2009, Buchwald and coworkers developed a protocol for the asymmetric dearomatization of *N*-arylnaphthalenamine derivatives.[145] Employing a catalyst based on $Pd(dba)_2$ and chiral ligand **7.15** (KenPhos) or **7.16**, naphthalene derivatives **7.13** were converted to benzocarbazoles **7.14** in excellent yield with high levels of enantiomeric excess (Scheme 7.4). Both electron-rich and electron-deficient functional groups were tolerated on the aryl bromide portion of the starting material, as exemplified by the formation of **7.18** and **7.19** in 72% yield/90% ee and 94% yield/83% ee, respectively. Substitution on the naphthalene ring proved problematic when ligand **7.15** was used; under these conditions, high yields were maintained but product ee was significantly diminished. However, excellent levels of enantiomeric excess were restored with ligand **7.16**, which resembles **7.15** except for the replacement of the dimethylamino group by an (*iso*propyl)methylamino group.

[144] For examples of Pd(0)-catalyzed dearomatization via allylic alkylation, see: (a) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592-4593; (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315; (c) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381-2384; (d) Wu, Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418-11419; (e) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci.* **2012**, *3*, 205-208; (f) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680-1683. See also refs 132 and 133.

[145] García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676-6677.

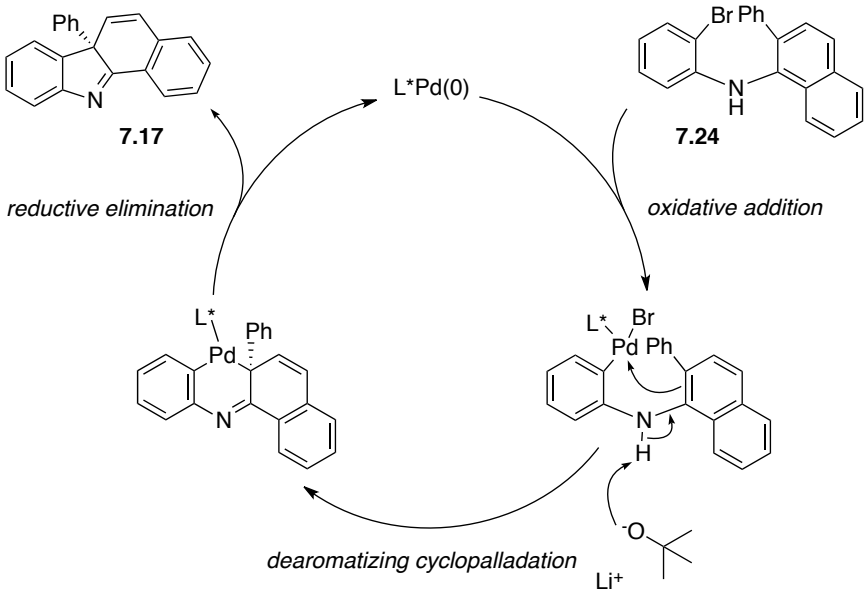
Scheme 7.4 Pd-catalyzed asymmetric arylative dearomatization of naphthalene derivatives



The proposed mechanism for this transformation is depicted in Scheme 7.5. The catalytic cycle is initiated by oxidative addition of aryl bromide **7.24** to the Pd(0) catalyst. Deprotonation enhances the nucleophilicity of the naphthyl derivative, which undergoes dearomatizing cyclopalladation with the electrophilic Pd(II) centre. Finally, reductive elimination provides the desired product **7.17** while regenerating the L*Pd(0) catalyst. Optimization studies revealed that the nature of the base was crucial. While LiHMDS, NaO*t*-Bu and NaHMDS also promoted dearomatization, albeit in diminished yields,

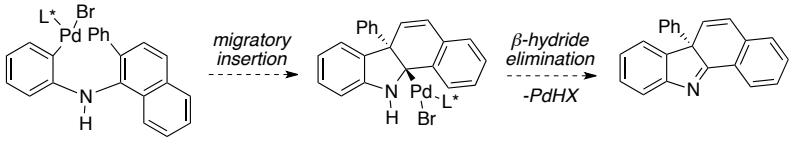
KHMDS and KO*t*-Bu were completely ineffective.[146] The reasons for this difference remain unclear.[147]

Scheme 7.5 Catalytic cycle for the dearomatization of naphthalene derivatives



Shortly after the Buchwald report, Bedford and coworkers disclosed similar processes for the intramolecular dearomatization of xylene and indole derivatives.[148] The authors found that treating precursors **7.25** or **7.27** with 5 mol % $Pd(OAc)_2$, 14 mol % SIPr (1,3-bis(2,6-diisopropylphenyl)imidazolidene) and an excess of NaO*t*-Bu in toluene at 100 ºC generated dearomatized products **7.26** and **7.28**. In the case of xylene derivatives **7.25**, a substituent at the 4-position was found to be crucial in order to isolate the desired

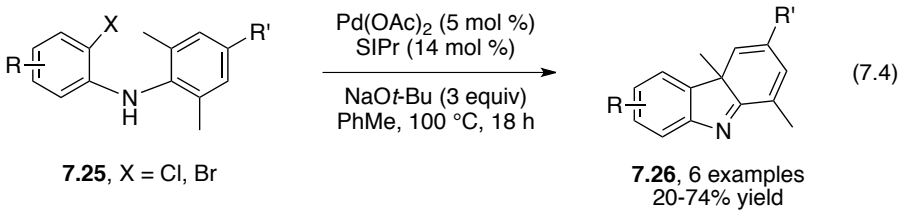
[146] The dependence of the reaction on the nature of the base suggested that the reaction does not proceed via a Heck-type pathway, where the base is required to deprotonate "PdHX".



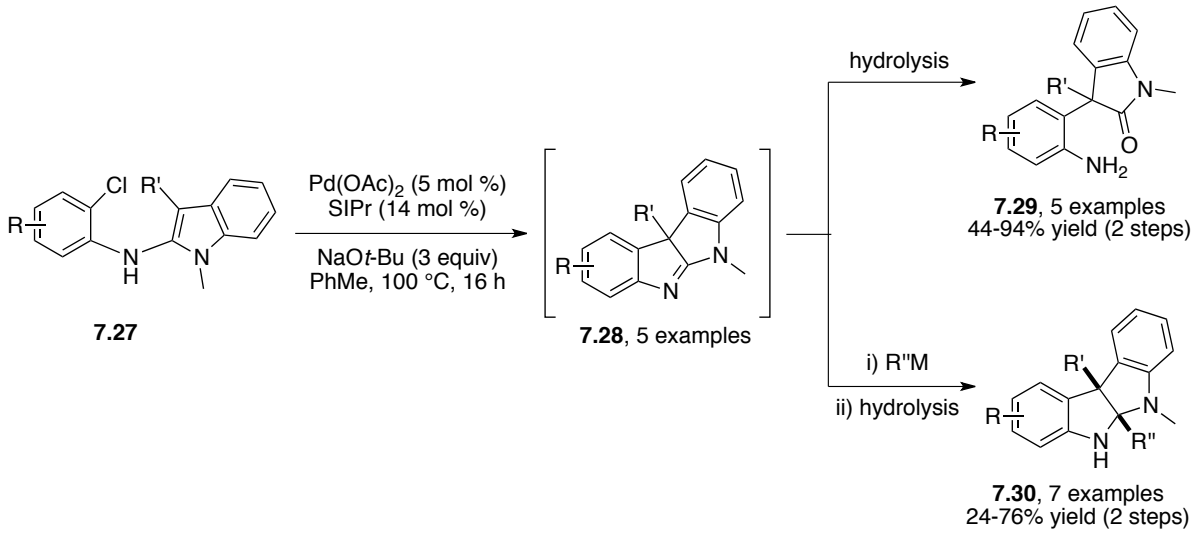
[147] It should be noted that intriguing results have been previously observed for the use of KO*t*-Bu in cross-coupling reactions. For example, KO*t*-Bu has been demonstrated to mediate the direct $C(sp^2)$-H arylation of pyridine and pyrazine derivatives with aryl iodides via a radical mechanism. Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673-4676.

[148] (a) Bedford, R. B.; Butts, C. P.; Haddow, M. F.; Osborne, R.; Sankey, R. F. *Chem. Commun.* **2009**, 4832-4834; (b) Bedford, R. B.; Fey, N.; Haddow, M. F.; Sankey, R. F. *Chem. Commun.* **2011**, *47*, 3649-3751.

product (eq 7.4). The intramolecular dearomatization of indoles **7.27** yielded highly unstable products **7.28**, which were directly converted to the corresponding 3,3-disubstituted oxindoles **7.29** or tetrahydroindolo[2,3-b]indoles **7.30** (Scheme 7.6). Similar to the observations of Buchwald and coworkers, the nature of the base was found to be very important for good product yields. The use of NaOAc, K_3PO_4 and Cy_2NMe led to starting material recovery as well as products of decomposition. Based on these observations, the authors also proposed a base-initiated dearomatization mechanism over a Heck-type pathway (Scheme 7.5).[146]



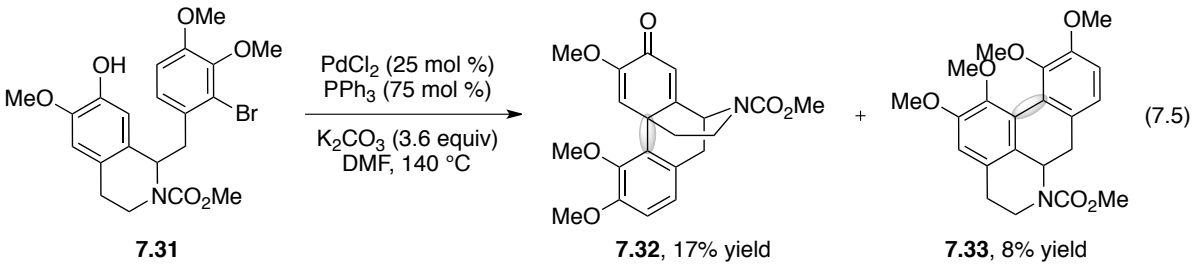
Scheme 7.6 Pd-catalyzed intramolecular dearomatization of indole derivatives



Concerning *transition-metal catalyzed arylative dearomatization of phenols*, a single example has been reported in the context of the synthesis of the skeleton of salutaridine.[149] Wiegand and Schäfer found that upon subjecting advanced synthetic intermediate **7.31** to

[149] Wiegand, S.; Schäfer, H. J. *Tetrahedron* **1995**, *51*, 5341-5350.

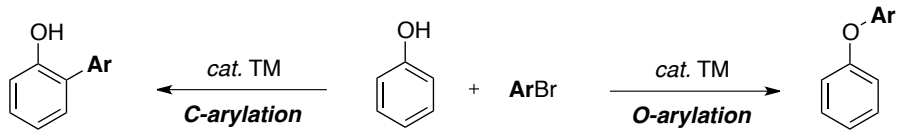
25 mol % $PdCl_2$, 75 mol % PPh_3 and 3.6 equivalents of K_2CO_3 in DMF at 140 ºC, spirocyclohexadienone **7.32** could be obtained in 17% yield along with 8% yield of aporphine **7.33** (eq 7.5).



7.31 **7.32**, 17% yield **7.33**, 8% yield

The limited developments in this type of reactivity for phenol derivatives may be explained by their propensity to form diaryl ethers via *O*-arylation and biaryls via direct *C*-arylation under transition-metal catalysis (Scheme 7.7).[150,151]

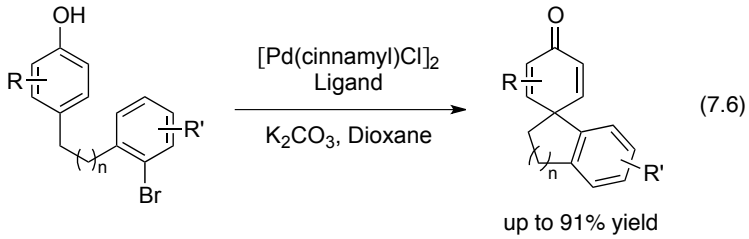
Scheme 7.7 Traditional transition metal-catalyzed arylation reactions of phenol



In this Chapter, efforts towards the development of a Pd(0)-catalyzed protocol for the dearomatization of phenols will be described (eq 7.6). This transformation provides spirocyclic compounds, an important motif in natural products and material science.[152] The development of an asymmetric version of this reaction will also be presented. It should be noted that the work presented in this Chapter was conducted in the laboratory of Prof. Stephen L. Buchwald at the Massachusetts Institute of Technology, in collaboration with

[150] For a review on the synthesis of diaryl ethers, see: Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271-2285.
[151] For selected examples of phenol C-arylation, see: (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2-3; (b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740-1742; (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112-114; (d) Oi, S.; Watanabe, S.; Fukita, S.; Inoue, Y. *Tetrahedron Lett.* **2003**, *44*, 8665-8668; (e) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Cerón, D.; Prashar, S. *Chem. Commun.* **2008**, 990-992.
[152] For a review on the synthesis of spirocyclic compounds, see: Kotha, S.; Deb, A. C.; Lahiri, K.; Manivanna, E. *Synthesis* **2009**, 165-193.

Dr. Jorge García-Fortanet, who was responsible for the initial reaction discovery as well as a portion of the reaction development and scope. Portions of this Chapter have been reproduced with permission from Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282-9285. Copyright 2011 American Chemical Society.



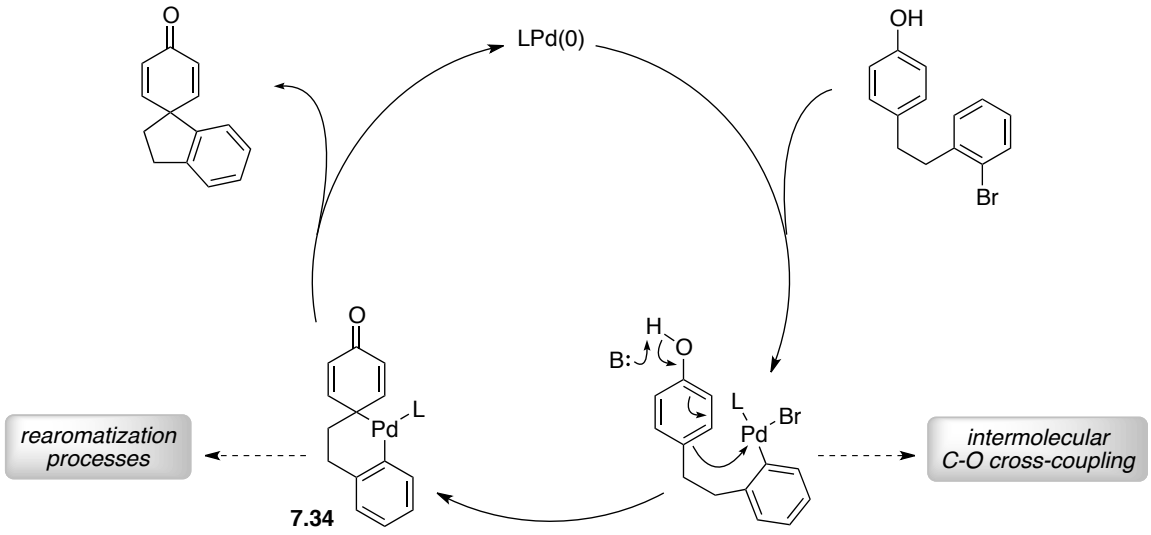
(7.6)

7.2 Results and Discussion

7.2.1 Reaction Development and Scope

Based on the Buchwald group's previous results for the Pd-catalyzed dearomatization of naphthalene derivatives, we envisaged a similar catalytic cycle for the equivalent transformation of phenol derivatives (Scheme 7.8). At the outset of our studies, we were aware that the success of our proposed dearomatization strategy relied on the ability to avoid diaryl ether formation arising from a competitive intermolecular C-O cross-coupling reaction and to favor product reductive elimination from palladacycle **7.34** over rearomatization processes.

Scheme 7.8 Proposed Pd-catalyzed dearomatization of phenol derivatives



With this in mind, we initially investigated catalyst systems that are inefficient for C–O cross-coupling and effective for C–C bond forming processes. Using $Pd(dba)_2$ (3 mol %), XPhos (4.5 mol %) and KO*t*-Bu (1.5 equivalents) in THF at 100 ºC, the desired product **7.36** was obtained in 6% yield from phenol **7.35** (Table 7.1, entry 1). An evaluation of bases revealed a significant increase in yield to 23% when K_3PO_4 was employed (entry 2). A further improvement to 34% was obtained with K_2CO_3 (entry 3).[153] Switching to $[Pd(cinnamyl)Cl]_2$ as the palladium source led to an additional augmentation in yield to 48%, indicating that the dibenzilideneacetone ligand from the $Pd(dba)_2$ precatalyst may be slightly inhibiting catalysis (entry 4). Finally, a significant jump in product yield to 77% was obtained by performing the reaction at 120 ºC in 1,4-dioxane (entry 5). An evaluation of biarylphosphine ligands revealed **7.37** to be optimal, providing **7.36** in 93% GC yield (entries 5-8).[154] The nature of the improved yields when **7.37** is employed is not completely understood at this time. However, based on previous studies on biarylphosphine ligands, certain trends have emerged.[155] First, bulky substituents on the lower aryl ring favour the

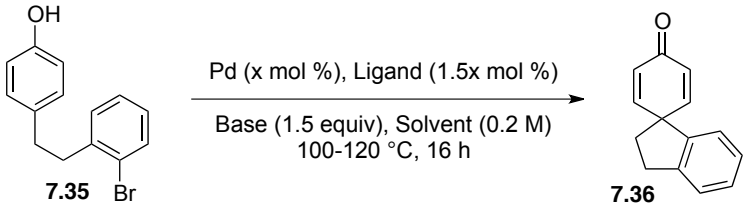
[153] The use of Li_2CO_3, Na_2CO_3 and Cs_2CO_3 did not promote the desired transformation. These results are in contrast to our previous work on the dearomatization of naphthalene derivatives, where sodium and lithium bases were more effective than potassium bases. These intriguing counterion effects are currently not understood and warrant additional studies.

[154] Other alkyl- and aryl-phosphines were also evaluated, however biarylphosphines provided significantly better yields of **7.36**.

[155] See ref 31a and references therein.

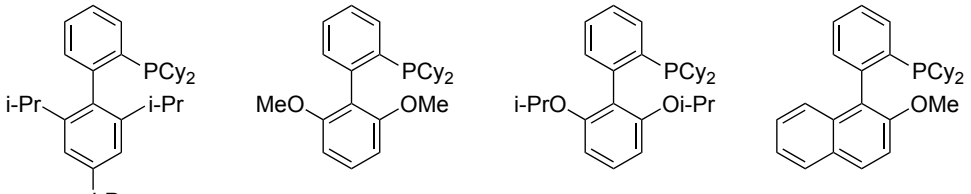
formation of $L_1Pd(0)$ over $L_2Pd(0)$ complexes in solution. Faster rates of oxidative addition and transmetalation are observed at $L_1Pd(0)$ due to its smaller size. Thus, ligand **7.37** may provide the optimal steric bulk to favour formation of $L_1Pd(0)$ while still facilitating transmetalation. Additionally, the methoxy-substituents on the lower ring of SPhos has been previously demonstrated to play a crucial role in stabilizing the oxidative addition complex $L_1Pd(Ar)X$, via a Pd···O interaction, in Suzuki-Miyaura cross-coupling reactions where transmetalation is rate determining. Thus, the methoxy group in **7.37** may be effectively increasing the concentration of oxidative addition complex, thus enabling the slow dearomatization ("transmetalation") step to occur.

Table 7.1 Optimization of the reaction conditions[a]



7.35 **7.36**

Entry	Pd (mol %)	Ligand	Base	Solvent	T (°C)	GC Yield (%)[b]
1	$Pd(dba)_2$ (3)	XPhos	KOt-Bu	THF	100	6
2	$Pd(dba)_2$ (3)	XPhos	K_3PO_4	THF	100	23
3	$Pd(dba)_2$ (3)	XPhos	K_2CO_3	THF	100	34
4	$[Pd(cinnamyl)Cl]_2$ (1.5)	XPhos	K_2CO_3	THF	100	48
5	$[Pd(cinnamyl)Cl]_2$ (1)	XPhos	K_2CO_3	Dioxane	120	77
6	$[Pd(cinnamyl)Cl]_2$ (1)	SPhos	K_2CO_3	Dioxane	120	43
7	$[Pd(cinnamyl)Cl]_2$ (1)	RuPhos	K_2CO_3	Dioxane	120	50
8	$[Pd(cinnamyl)Cl]_2$ (1)	**7.37**	K_2CO_3	Dioxane	120	93



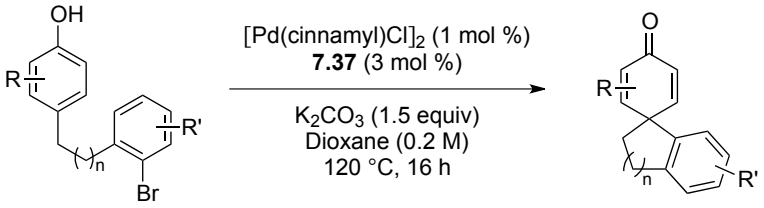
XPhos SPhos RuPhos **7.37**

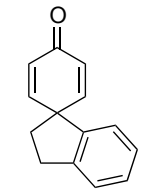
[a] Reaction conditions: Pd source (x mol %), ligand (1:1.5 Pd:Ligand ratio), base (1.5 equiv) and **7.35** (0.1 mmol) in solvent (0.2 M) at indicated temperature for 16 hours. [b] GC yield using dodecane as an internal standard.

Illustrative examples of the scope of this dearomatization protocol with respect to substitution on the phenol and benzene rings, as well as to the length of the tether are shown in Table 7.2. Submitting **7.35** to $[Pd(cinnamyl)Cl]_2$ (1 mol %), ligand **7.37** (3 mol %) and K_2CO_3 (1.5 equiv) in dioxane at 120 ºC for 16 hours provided **7.36** in 81% isolated yield. This transformation could also be performed on a 10 mmol scale, yielding **7.36** in 91%. Substitution at the position *ortho* to the hydroxyl group was well tolerated, as exemplified by **7.38** and **7.39,** which were obtained in 91% and 90% yield, respectively. Also, substrates bearing substituents *ortho* to the carbon undergoing rehybridization were compatible, providing the corresponding cyclohexadienones **7.40**, **7.41** and **7.42** in good yields. It should be noted that due to the importance of its nucleophilic character in the reaction, substitution on the phenol ring is at present limited to electron-neutral or -donating groups. With respect to the aryl bromide reaction component, electron-neutral (**7.43, 7.49**) and -donating (**7.44**) groups are well tolerated. Substrates with electron-withdrawing substituents proved to be more challenging and required either higher dilutions (**7.46**) or increased catalyst loadings (**7.47**) (*vide infra*). Chlorine-containing products **7.45** and **7.48** were obtained in good yields, providing a useful synthetic handle for further functionalization of the spirocyclohexadienone product. The carbon tether between both aromatic rings could be lengthened by one carbon without affecting product formation, as seen with tetralin derivative **7.50,** which was isolated in 84% yield. Unfortunately, increasing the tether to a four-carbon chain, or including a heteroatom in the tether, completely shutdown the reaction. No dearomatized products were obtained in these latter cases. Surprisingly, products of direct $C(sp^2)$-H arylation were never observed under these reaction conditions, despite their close similarity to previously reported conditions for Pd(0)-catalyzed intramolecular C-H arylation of phenolic derivatives.[156] It is possible that the use of $[Pd(cinnamyl)Cl]_2$ as a precatalyst is directly linked to this result. Indeed, carboxylate anions are thought to be crucial for C-H arylation to occur.[50e] These additives are often inadvertently incorporated to the reaction mixture through the use of a $Pd(OAc)_2$ precatalyst.[34]

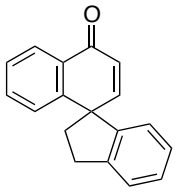
[156] For selected examples of Pd(0)-catalyzed intramolecular direct $C(sp^2)$-H arylation of phenolic derivatives, see: Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186-9187. See also refs 52 and 151a.

Table 7.2 Scope of the arylative dearomatization of phenols

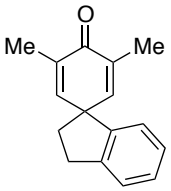




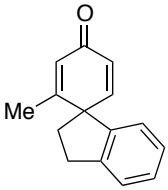
7.36, 81% (91%)[c]



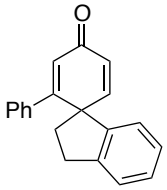
7.38, 91%



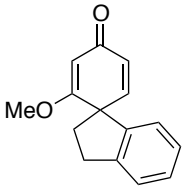
7.39, 90%



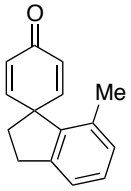
7.40, 79%



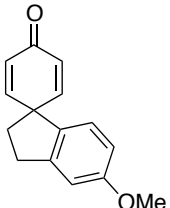
7.41, 75%



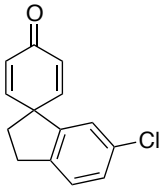
7.42, 73%



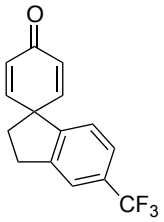
7.43, 83%



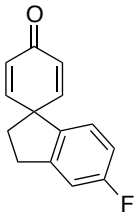
7.44, 89%



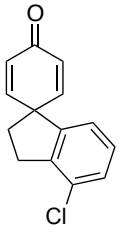
7.45, 74%



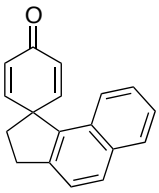
7.46, 44%[d]



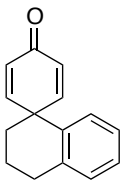
7.47, 74%[e]



7.48, 74%[e]



7.49, 51%[f]



7.50, 84%

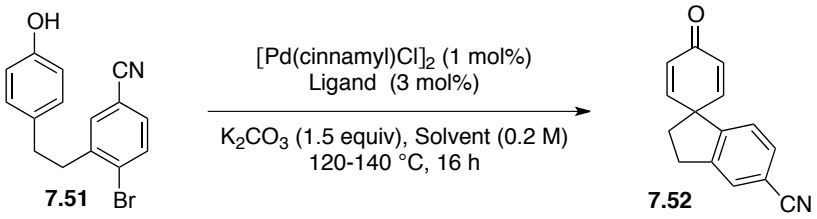
[a] Reaction conditions: $[Pd(cinnamyl)Cl]_2$ (1 mol %), **7.37** (3 mol %), K_2CO_3 (1.5 equiv) and phenol (1.00 mmol) in 1,4-dioxane (5 mL) at 120 °C for 16 hours. [b] Isolated yields (average of two runs). [c] Reaction performed on 10 mmol scale. [d] Concentration = 0.05 M. [e] $[Pd(cinnamyl)Cl]_2$ (2 mol %), **7.37** (6 mol %). [f] $[Pd(cinnamyl)Cl]_2$ (2.5 mol %), **7.37** (7.5 mol %).

7.2.2 Use of Electron-Deficient Aryl Bromide Coupling Partners

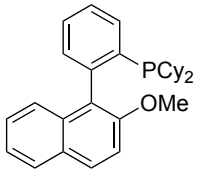
Surprisingly, electron-deficient aryl bromide components proved highly problematic under the optimized reaction conditions. While the standard reaction conditions could be slightly modified for certain substrates (Table 7.2, **7.46**), we sought to develop more general conditions for these electron-poor arenes. Phenol **7.51** was chosen for this purpose. Under the first-generation standard conditions (Table 7.3, entry 1), no spirocyclohexadienone **7.52**

could be observed and phenol **7.51** was recovered. Due to previous observations supporting the importance of the source of base (Table 7.1, entries 1-3),[153] our investigation began with a base screen. Unfortunately the desired product was never observed. An evaluation of biarylphosphine ligands revealed that SPhos and RuPhos provided limited amounts of **7.52** in dioxane at 120 ºC (entries 4 and 5). Changing the solvent to the less polar toluene improved the yield to 15% (entry 6). Increasing the reaction temperature to 140 ºC (in mesitylene) did not lead to an additional boost in yield (entry 7). While other reaction parameters were also evaluated (catalyst source, catalyst activation methods, catalyst loadings), the yield of **7.52** was never improved beyond 15%.

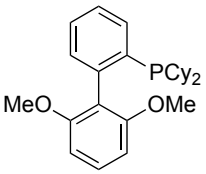
Table 7.3 Evaluation of reaction parameters for electron-deficient substrates



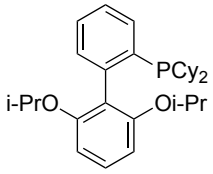
Entry	Ligand	Solvent	T (°C)	^{1}HNMR Yield (%)[b]
1	**7.37**	Dioxane	120	0
2	XPhos	Dioxane	120	0
3	BrettPhos	Dioxane	120	0
4	SPhos	Dioxane	120	4
5	RuPhos	Dioxane	120	6
6	RuPhos	Toluene	120	15
7	RuPhos	Mesitylene	140	15



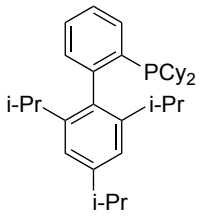
7.37



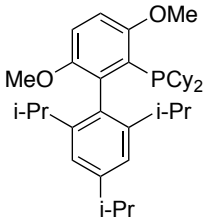
SPhos



RuPhos



XPhos

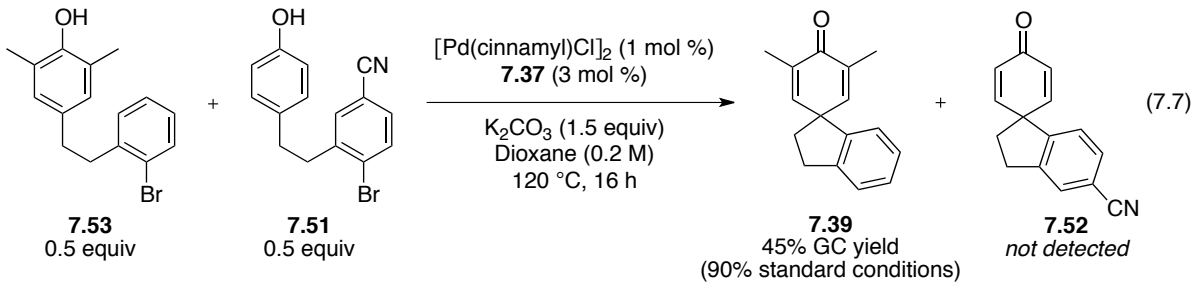


BrettPhos

[a] Reaction conditions: $[Pd(cinnamyl)Cl]_2$ (1 mol %), Ligand (3 mol %), K_2CO_3 (1.5 equiv) and phenol (0.10 mmol) in solvent (0.2 M) at the indicated temperature for 16 hours. [b] ^{1}H NMR yield using fluorene as an internal standard.

The dearomatization of **7.51** still remains a challenge. Hypothesizing that either the starting material, a catalytic intermediate or the product of this reaction may be poisoning the catalyst, a one-pot reaction was run under the standard catalytic conditions in the presence of phenols **7.53** and **7.51** (eq 7.7). Cyclohexadienone **7.39** was obtained in 45% GC yield (compared to 90% isolated yield for a standard catalytic reaction) and cyclohexadienone **7.52** was not detected. This result suggests that a catalytic derivative of **7.51** inhibits catalysis,

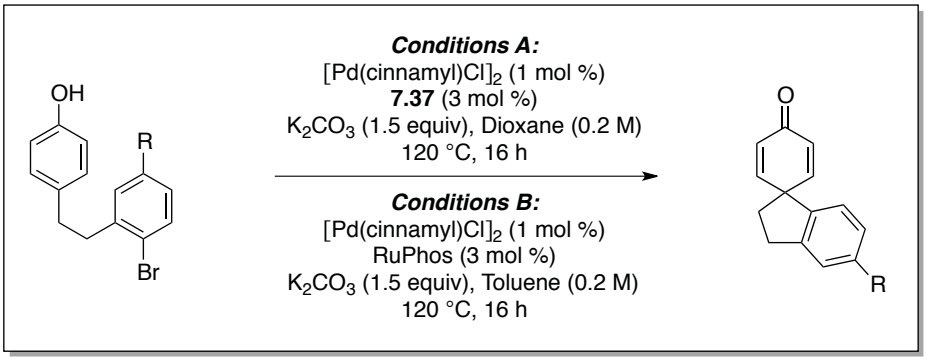
possibly by trapping a Pd(II) species (catalyst sink), leading to a gradual depletion of the active Pd(0) species and inferior yields of **7.39**. Additional experiments to better understand these results unfortunately did not provide any further insight.

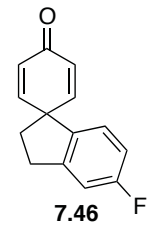


(7.7)

Nevertheless, the second-generation conditions were evaluated using other electron-deficient substrates that had been challenging substrates under the first-generation conditions (Table 7.2, **7.46** and **7.47**). Using the standard first-generation conditions (Conditions A), cyclohexadienones **7.46** and **7.47** were obtained in 32% and 23% GC yield, respectively (Scheme 7.9). Changing the ligand to RuPhos and the solvent to toluene (second-generation conditions, Conditions B), the yield of **7.46** was significantly improved (80%). The yield of product **7.47** was also improved albeit less drastically (36%). Of note, Conditions A are still optimal for electron-neutral reaction partners, as evidenced by the formation of **7.39** in 90% yield (Conditions A) vs 37% yield (Conditions B). While these results are encouraging, further work is required to better understand the poor reactivity of electron-deficient aryl bromides in order to design improved catalyst systems for these transformations.

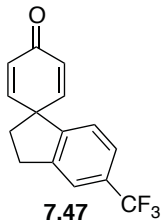
Scheme 7.9 First-generation vs second-generation conditions for arylative dearomatization of electron-deficient substrates





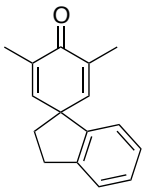
7.46

Conditions A: 32%
Conditions B: 80%



7.47

Conditions A: 23%
Conditions B: 36%

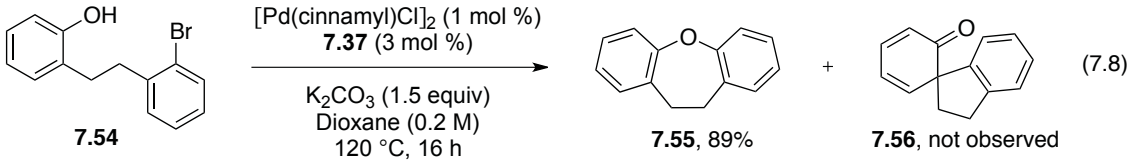


7.39

Conditions A: 90%
Conditions B: 37%

7.2.3 Ortho-Arylative Dearomatization

The dearomatization of *ortho*-substituted phenol **7.54** was examined (eq 7.8). Despite the use of optimal conditions for Pd(0)-catalyzed arylative dearomatization, diaryl ether **7.55**, resulting from an intramolecular C–O cross-coupling, was preferentially formed over the spirocyclohexa-2,4-dienone product **7.56**. This result is not surprising and highlights the challenge in favouring dearomatization over other well-established Pd(0)-catalyzed transformations.



7.54

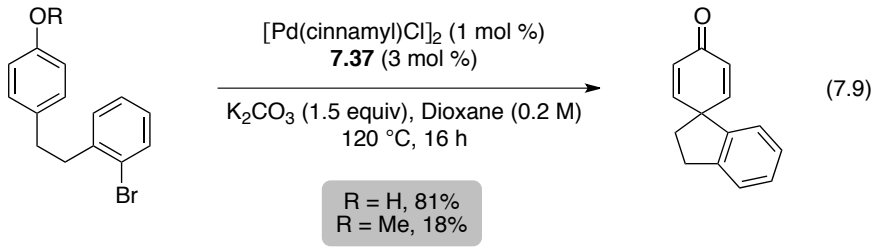
7.55, 89%

7.56, not observed

(7.8)

7.2.4 Mechanistic Insight

Initial studies have revealed that the presence of a free hydroxyl group is essential for the observed reactivity. When an anisole derivative was submitted to the standard reaction conditions, little product was observed (eq 7.9). Surprisingly, product resulting from direct C(sp^2)-H arylation was once again not observed. These results lend further support to the mechanistic scenario previously proposed by Bedford and coworkers[148] as well as by our group (Scheme 7.5);[145] dearomatization occurs via a base-initiated "S_EAr-type" reaction between the electron-rich arene (phenol) and the electrophilic Pd(II) species (Scheme 7.8).[146]



(7.9)

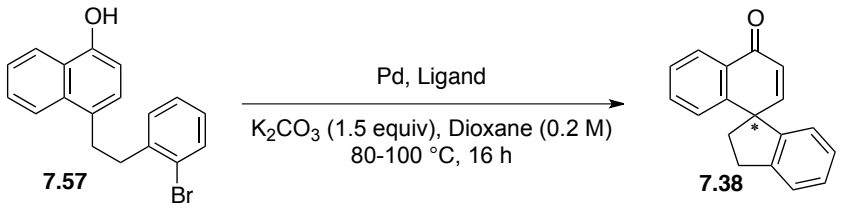
7.2.5 Asymmetric Pd(0)-Catalyzed Arylative Dearomatization of Phenols

We next focused our attention on the development of an asymmetric version of this reaction, the products of which would be cyclohexadienones bearing an enantioenriched all-carbon quaternary stereocenter.[157] Despite the importance of this motif in natural product synthesis, few asymmetric methods for their preparation exist.[158] An evaluation of chiral ligands revealed that a catalyst based on KenPhos (**7.15**)[159] enabled the formation of **7.38** in high yields and moderate levels of enantiomeric excess (31%) (Table 7.4, entry 1). A slightly improved ee and similar product yield were obtained when the reaction temperature was dropped by 20 ºC (entry 2). However, the reaction yields and levels of ee appeared to be highly irreproducible under these conditions (entries 1 and 2), leading us to investigate methods for catalyst activation that would ensure complete formation of the active L*Pd(0) complex. Thus, a water-mediated catalyst activation protocol was found to be optimal,

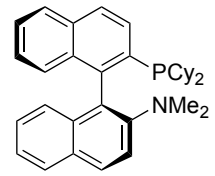
[157] For selected reviews, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388-401. (b) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369-396.
[158] Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383-1429.
[159] Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897-1900.

leading us to obtain good ee's in a reproducible manner (entries 3-6).[160,161] Indeed, **7.57** was converted to **7.38** in 91% GC yield with a moderate, but promising, 65% enantiomeric excess when treated with $Pd(OAc)_2$ (4 mol %), ligand **7.15** (12 mol %), H_2O (16 mol %) and K_2CO_3 (1.5 equivalents) in dioxane at 80 ºC (entry 4). Both yield and ee could be further improved to 99% and 91%, respectively, when ligand **7.58** was employed (entry 8); this ligand, bearing an additional element of chirality on the phosphorus atom, had been previously reported by our group in the enantioselective α-arylation and α-vinylation of oxindoles.[162,163]

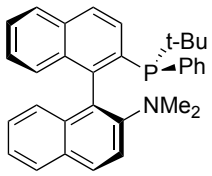
Table 7.4 Optimization of the asymmetric reaction conditions



Entry	Pd (mol%)	Ligand	Pd:L	T (°C)	Yield (%)[b]	ee (%)[c]	Procedure[d]
1	$[Pd(cinnamyl)Cl]_2$ (2)	**7.15**	1:1.5	120	88-97	31	one-pot
2	$[Pd(cinnamyl)Cl]_2$ (2)	**7.15**	1:1.5	100	77-95	40	one-pot
3	$Pd(OAc)_2$ (4)	**7.15**	1:3	100	99	61	water activation
4	$Pd(OAc)_2$ (4)	**7.15**	1:3	80	91	65	water activation
5	$Pd(OAc)_2$ (4)	**7.15**	1:2	100	73	47	water activation
6	$Pd(OAc)_2$ (4)	**7.15**	1:4	100	99	65	water activation
7	$Pd(OAc)_2$ (4)	**7.58**	1:3	100	99	78	water activation
8	$Pd(OAc)_2$ (4)	**7.58**	1:3	80	99	91	water activation



(*S*)-KenPhos (**7.15**)

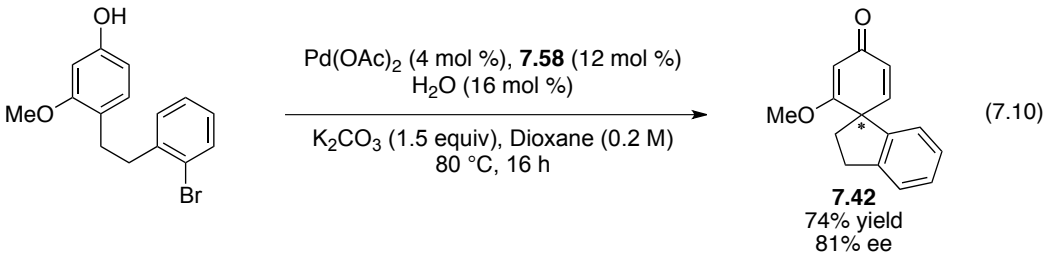


(*S,S*)-**7.58**

[a] Reaction conditions: Pd, ligand, base (1.5 equiv) and **7.57** (0.1 mmol) in solvent (0.2 M) at indicated temperature for 16 hours. [b] GC yield using dodecane as an internal standard. [c] Determined by HPLC. [d] See supporting information for general procedures.

[160] Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505-3508.
[161] See supporting information for additional details.
[162] Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900-9901.
[163] For the initial report of **7.58**, see: Hamada, T.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 999-1001.

The use of a catalyst based on ligand **7.58**, in combination with our water-mediated catalyst activation protocol, was also applicable to the asymmetric synthesis of **7.42**, obtained in 74% GC yield and 81% ee (eq 7.10). Unfortunately, this catalytic system was not effective for the asymmetric dearomatization of phenols bearing substituents adjacent to the C-Br bond (i.e. **7.43** and **7.49**). In these cases, the majority of the starting material was recovered, suggesting that these chiral ligands may be too bulky for oxidative addition and dearomatization ("transmetalation") to occur.



(7.10)

7.3 Conclusions and Perspectives

In this Chapter, our efforts towards the development of a Pd(0)-catalyzed arylative dearomatization of phenols were presented. Initial studies have demonstrated that the development of a highly enantioselective variant of this reaction is viable. While this method remains limited with respect to electron-deficient substitution on the arene rings involved, it highlights the advantages of employing transition metal-catalysis compared to traditional phenol oxidation/activation dearomatization processes (i.e. p-block arylating agents and hypervalent iodine(III) reagents). Not only are these processes less wasteful, but they also offer new opportunities for enantioinduction using asymmetric catalysis.

The development of catalytic and/or asymmetric methods for the dearomatization of phenols, or other arenes in general, has been an exciting and highly evolving area of research in the last decade. The numerous applications of these protocols in natural product synthesis is illustrative of its importance.[102] Significantly, the number of reports of *intramolecular* transition metal-catalyzed dearomatization reactions have grown very rapidly over the past

three years (at least 8 reports since 2009), with a particular focus on the development of asymmetric transformations. While the scope of electron-rich arenes that participate in these reactions continues to improve, the development of *enantioselective intermolecular* transition metal-catalyzed dearomatization reactions will be necessary for the long-term application of this methodology to the synthesis of complex, biologically active molecules.

8 Supporting Information

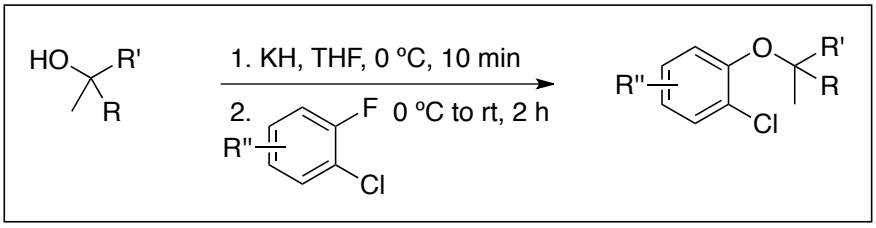
8.1 General Considerations

Reactions were set-up on the bench top and carried out under an argon atmosphere unless otherwise noted. HPLC Grade THF, Et_2O, benzene, toluene and CH_2Cl_2 were dried and purified *via* solvent purification system prior to their use. Mesitylene was stored over molecular sieves and used without further purification. DCE was purchased in Sure-Seal bottles and used without further purification. $Pd(OAc)_2$, $PCy_3{\cdot}HBF_4$, $P(t\text{-}Bu)_3{\cdot}HBF_4$, $P(t\text{-}Bu)_2{\cdot}HBF_4$, CyJohnPhos, $P(p\text{-}F\text{-}C_6H_4)_3$, $P(p\text{-}OMe\text{-}C_6H_4)_3$, K_2CO_3, Cs_2CO_3 and CsOPiv were stored in a dessicator and were weighed to air. Rb_2CO_3 was stored and weighed in a glovebox. K_3PO_4, NaOtBu and KOtBu were stored in a glovebox and small quantities were removed prior to their use. Cyclopropylamine was distilled and stored under argon. All other reagents and solvents were used without further purification.

^{1}H, ^{2}H, ^{13}C and ^{31}P NMR were recorded using 300 MHz, 400 MHz or 500 MHz spectrometers. Copies of these spectra can be found at the end of the supporting information. Spectra were calibrated according to residual solvent peaks ($CDCl_3$) or added TMS. ^{13}C NMR spectra were obtained with ^{1}H decoupling. For some starting materials, spectra were obtained at 55 °C (due to rotamers).

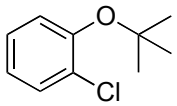
8.2 Intramolecular Alkane Arylation from Aryl Chlorides

8.2.1 Synthesis and Characterization of Ether Starting Materials



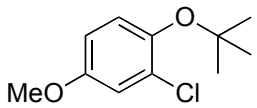
General Procedure A for the Preparation of Starting Materials

The desired alcohol (1.1 equiv) was added dropwise to a solution of KH (1.1 equiv) in THF (0.15 M) under argon at 0 ºC. The resulting mixture was stirred for 10 minutes after which the desired *ortho*-chloro-fluorobenzene was added and the flask was warmed to room temperature. The reaction was stirred for 2 hours (or until judged complete by TLC) and the crude product was extracted with CH_2Cl_2 (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



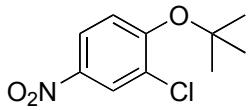
1-*tert*-Butoxy-2-chlorobenzene (2.1) A large excess of isobutene was added *via* cold finger to a solution of 2-chlorophenol (1.29 g, 10.0 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL, 1.0 M) under argon at -78 ºC. TfOH (60 μL, 0.80 mmol, 0.08 equiv) was then added dropwise and the solution was sittred at -78 ºC for 4 hours. Et_3N (0.20 mL) was added and the mixture was brought to room temperature. The crude reaction mixture was concentrated and purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 1.3 g of a clear oil in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.36 (dd, J = 8.0 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 6.71 (dd, J = 8.9, 3.1 Hz, 1H), 3.77 (s, 3H), 1.37 (s, 9H).
Exhibited spectral data identical to a previous report.[39]



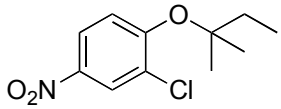
1-*tert*-Butoxy-2-chloro-4-methoxybenzene (2.3) A large excess of isobutene was added *via* cold finger to a solution of 2-chloro-4-methoxyphenol (1.60g, 10.0 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL, 1.0 M) under argon at -78 ºC. TfOH (60 μL, 0.80 mmol, 0.08 equiv) was then added dropwise and the solution was sittred at -78 ºC for 4 hours. Et_3N (0.20 mL) was added and the mixture was brought to room temperature. The crude reaction mixture was concentrated and purified by silica gel flash chromatography (2% Et_2O in petroleum ether) to afford 1.4 g of a clear oil in 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.02 (d, J = 8.9 Hz, 1H), 6.92 (d, J = 3.1 Hz, 1H), 6.71 (dd, J = 8.9, 3.1 Hz, 1H), 3.77 (s, 3H), 1.37 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 155.8, 145.6, 129.9, 125.6, 115.3, 113.0, 81.0, 55.8, 28.9. **HRMS** Calculated for $C_{11}H_{15}O_2Cl$ (M^+) 214.0761, Found 214.0738. **IR (ν_{max}/cm^{-1})** 3075, 2978, 2837, 1490, 1367, 1163, 1053, 861. **R_f** 0.33 (1% Et_2O in petroleum ether).



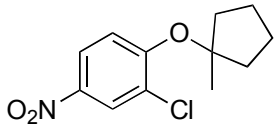
1-*tert*-Butoxy-2-chloro-4-nitrobenzene (2.5) *General procedure A for the preparation of starting materials* was followed using potassium *tert*-butoxide (352 mg, 3.13 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (500 mg, 2.85 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 470 mg of a clear oil in 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.28 (d, J = 2.8 Hz, 1H), 8.06 (dd, J = 9.1, 2.8 Hz, 1H), 7.20 (d, J = 9.1 Hz, 1H), 1.51 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.3, 142.3, 128.6, 126.1, 123.0, 121.1, 83.5, 29.0. **HRMS** Calculated for $C_{10}H_{12}NO_3Cl$ (M^+ - CH_3) 214.0271, Found 214.0268. **IR (ν_{max}/cm^{-1})** 3093, 2983, 2938, 1584, 1520, 1345, 1160, 730. **R_f** 0.33 (1% Et_2O in petroleum ether).



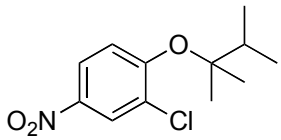
1-(*tert*-Pentyloxy)-2-chloro-4-nitrobenzene (2.7) *General procedure A for the preparation of starting materials* was followed using 2-methylbutan-2-ol (271 μL, 2.51 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (400 mg, 2.28 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3.5% Et_2O in petroleum ether) to afford 426 mg of a yellow oil in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.29 (d, J = 2.8 Hz, 1H), 8.07 (dd, J = 9.1, 2.8 Hz, 1H), 7.17 (d, J = 9.1 Hz, 1H), 1.85 (q, J = 7.5 Hz, 2H), 1.46 (s, 6H), 1.04 (t, J = 7.5 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.2, 141.9, 128.1, 126.1, 123.0, 120.1, 85.7, 35.1, 26.1, 8.5. **HRMS** Calculated for $C_{11}H_{17}NO_3Cl$ (M^+) 243.0662, Found 243.0602. **IR (ν_{max}/cm^{-1})** 3089, 2980, 2942, 1517, 1345, 1281, 744. **R_f** 0.37 (4% Et_2O in petroleum ether).



1-(1-Methylcyclopentyloxy)-2-chloro-4-nitrobenzene (2.9) *General procedure A for the preparation of starting materials* was followed using 1-methylcyclopentanol (314 mg, 3.13 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (500 mg, 2.85 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O in petroleum ether) to afford 405 mg of a pale yellow solid in 63% yield.

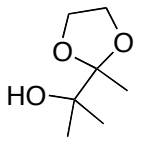
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.28 (d, J = 2.8 Hz, 1H), 8.08 (dd, J = 9.2, 2.8 Hz, 1H), 7.09 (d, J = 9.2 Hz, 1H), 2.31-2.23 (m, 2H), 1.86-1.76 (m, 4H), 1.74-1.68 (m, 2H), 1.62 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.1, 140.9, 126.4, 126.1, 123.2, 116.6, 92.2, 40.1, 24.9, 24.5. **HRMS** Calculated for $C_{12}H_{14}NO_3Cl$ (M^+ - CH_3) 240.0427, Found 240.0436. **IR (ν_{max}/cm^{-1})** 2967, 1584, 1343, 1282, 742. **R_f** 0.38 (4% Et_2O in petroleum ether). **Melting Point** 60-62 °C.



1-(2,3-Dimethylbutan-2-yloxy)-2-chloro-4-nitrobenzene (2.11) *General procedure A for the preparation of starting materials* was followed using 2,3-dimethylbutan-2-ol (1.12 mL, 9.02 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (1.44 g, 8.20 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 1.44 g of an orange oil in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.28 (d, J = 2.8 Hz, 1H), 8.05 (dd, J = 9.1, 2.8 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 2.15 (sept, J = 6.8 Hz, 1H), 1.42 (s, 6H), 1.05 (d, J = 6.8 Hz, 7H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.3, 141.8, 128.1, 126.2, 123.1, 119.9, 88.3, 38.5, 23.7, 17.7. **HRMS** Calculated for $C_{12}H_{16}NO_3Cl$ (M^+ - CH_3)

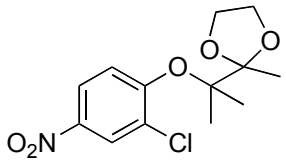
242.0584, Found 242.0589. **IR (ν_{max}/cm^{-1})** 2979, 2880, 1584, 1518, 1344, 1282, 1137, 735. **R_f** 0.36 (4% Et_2O in petroleum ether).



2-(2-Methyl-1,3-dioxolan-2-yl)propan-2-ol Synthesized according to a reported procedure,[164] using 3-hydroxy-3-methylbutan-2-one (1.05 mL, 9.80 mmol, 1.00 equiv), ethylene glycol (26.4 mL, 473.4 mmol, 48.3 equiv), *p*-toluenesulfonic acid (100 mg, 0.58 mmol, 0.060 equiv) and benzene (165 mL, 0.06 M). The product was obtained in 25% yield (354 mg).

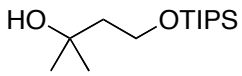
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 4.02 (s, 4H), 2.02 (s, 1H), 1.34 (s, 3H), 1.27 (s, 6H).

Commercially available - CAS#: 6322-38-9



1-(1-Methylcyclopentyloxy)-2-chloro-4-nitrobenzene (2.13) *General procedure A for the preparation of starting materials* was followed using 2-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (350 mg, 2.39 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (382 mg, 2.18 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (20% Et_2O in petroleum ether) to afford 238 mg of a green oil in 36% yield.

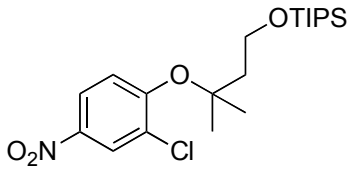
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.27 (d, J = 2.8 Hz, 1H), 8.06 (dd, J = 9.1, 2.8 Hz, 1H), 7.47 (d, J = 9.1 Hz, 1H), 4.10-3.99 (m, 5H), 1.50 (s, 3H), 1.45 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 157.7, 142.4, 128.6, 125.7, 122.7, 122.4, 111.8, 88.3, 65.4, 22.2, 19.8. **HRMS** Calculated for $C_{12}H_{13}NO_5Cl$ (M^+ - CH_3) 286.0482, Found 286.0460. **IR (ν_{max}/cm^{-1})** 3107, 2989, 2888, 1583, 1348, 1103, 752. **R_f** 0.30 (20% Et_2O in petroleum ether).



3-Hydroxy-3-methylbutoxytriisopropylsilane Synthesized according to a reported procedure, [165] using 3-methylbutane-1,3-diol (2.05 mL, 19.2 mmol, 1.00 equiv), triisopropylsilyl chloride (4.52 mL, 21.1 mmol, 1.10 equiv), imidazole (2.61 g, 38.4 mmol, 2.00 equiv) and dimethylformamide (19 mL, 1.0 M). The product was purified by silica gel flash chromatography (10% Et_2O in petroleum ether) to give 4.54 g of a clear oil in 91% yield.

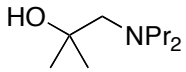
[164] Bernstein, S.; Heller, M.; Stolar, S. M. *J. Am. Chem. Soc.* **1954**, *76*, 5674-5678.
[165] Ogilvie, K. K.; Thompson, E. A.; Quilliam, M. A.; Westmore, J. B. *Tetrahedron Lett.* **1974**, *15*, 2865-2868.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 4.01 (t, J = 5.7 Hz, 2H), 1.72 (t, J = 5.7 Hz, 2H), 1.26 (s, 6H), 1.17-1.05 (m, 21H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 71.0, 61.6, 43.1, 29.4, 18.1, 11.8. **HRMS** Calculated for $C_{13}H_{29}O_2Si$ (M^+ - CH_3) 245.1937, Found 245.1922. **IR (ν_{max}/cm^{-1})** 3390, 2941, 2869, 1464, 1088. **R_f** 0.62 (40% Et_2O in petroleum ether).



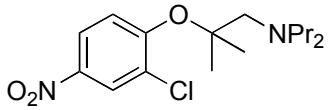
(3-(2-Chloro-4-nitrophenoxy)-3-methylbutoxy)triisopropylsilane (2.15) *General procedure A for the preparation of starting materials* was followed using 2-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (2.00 g, 7.68 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (1.23 g, 6.98 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 1.30 g of a green oil in 45% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.28 (d, J = 2.8 Hz, 1H), 8.07 (dd, J = 9.1, 2.8 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 3.96 (t, J = 6.9 Hz, 2H), 2.11 (t, J = 6.9 Hz, 2H), 1.51 (s, 6H), 1.14-1.02 (m, 21H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.1, 142.1, 128.4, 126.1, 123.1, 120.5, 84.7, 59.5, 45.3, 27.2, 18.2, 12.1. **HRMS** Calculated for $C_{17}H_{27}ClNO_4Si$ (M^+ - C_3H_7) 372.1398, Found 372.1403. **IR (ν_{max}/cm^{-1})** 2944, 2866, 1520, 1345, 1126, 747. **R_f** 0.35 (2% Et_2O in petroleum ether).



1-(Dipropylamino)-2-methylpropan-2-ol Synthesized according to a reported procedure,[166] using 2,2-dimethyloxirane (1.85 mL, 20.8 mmol, 1.00 equiv), dipropylamine (3.42 mL, 25.0 mmol, 1.20 equiv) and H_2O (8.0 mL, 2.6 M). The product was obtained as 1.95 g of a clear oil 55% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 3.49 (br, 1H), 2.51-2.47 (m, 4H), 2.39 (s, 2H), 1.52-1.43 (m, 4H), 1.15 (s, 6H), 0.88 (t, J = 7.4 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 69.1, 66.3, 58.5, 28.5, 20.8, 11.9. **HRMS** Calculated for $C_{10}H_{23}NO$ (M^+) 173.1780, Found 173.1758. **IR (ν_{max}/cm^{-1})** 3431, 2962, 2874, 1468, 1076. **R_f** 0.44 (40% Et_2O in petroleum ether).



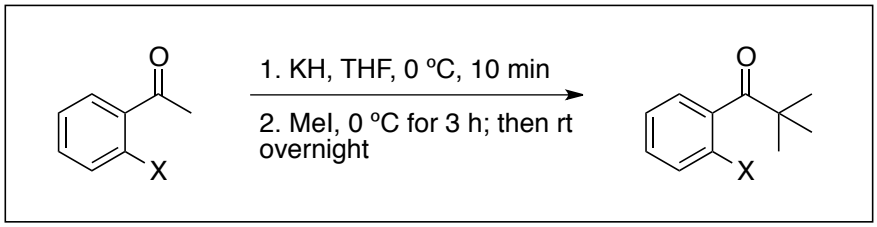
***N*-(2-(2-Chloro-4-nitrophenoxy)-2-methylpropyl)-*N*-propylpropan-1-amine (2.17)** *General procedure A for the preparation of starting materials* was followed using 1-(dipropylamino)2-methylpropan-2-ol (542 mg, 3.13 mmol, 1.10 equiv) and 2-chloro-1-fluoro-4-nitrobenzene (500 mg, 2.85 mmol, 1.00 equiv). The product was purified by silica

[166] Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649-3651.

gel flash chromatography (8% Et_2O in petroleum ether) to afford 528 mg of a yellow oil in 56% yield.

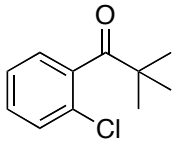
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.28 (d, J = 2.8 Hz, 1H), 8.06 (dd, J = 9.1, 2.8 Hz, 1H), 7.36 (d, J = 9.1 Hz, 1H), 2.72 (s, 2H), 2.56-2.51 (m, 4H), 1.52-1.40 (m, 10H), 0.87 (t, J = 7.3 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 158.4, 142.0, 128.0, 126.1, 122.9, 121.0, 87.2, 65.4, 57.8, 25.1, 20.3, 11.9. **HRMS** Calculated for $C_{14}H_{20}ClN_2O_3$ (M^+ - C_2H_5) 299.1162, Found 299.1126. **IR (ν_{max}/cm^{-1})** 3094, 2961, 2873, 1584, 1345, 1124, 748. **R_f** 0.35 (2% Et_3N and 6% Et_2O in petroleum ether).

8.2.2 Synthesis and Characterization of Ketone Starting Materials



General Procedure B for the Preparation of Starting Materials

The desired aryl halide (1.0 equiv) was added to a solution of KH (3.5 equiv) in THF (0.2 M) at 0 °C under argon. The resulting mixture was stirred for 10 minutes after which MeI was added (12 equiv). The solution was stirred at 0 °C for 3 hours before warming to room temperature and stirring overnight. The reaction was quenched with NH_4Cl sat., extracted, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

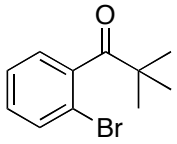


1-(2-Chlorophenyl)-2,2-dimethylpropanone (2.19) *General procedure B for the preparation of starting materials* was followed using 2'-chloroacetophenone (400 g, 2.59 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 214 mg of clear oil in 42% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.41-7.38 (m, 1H), 7.31 (ddd, J = 7.2, 7.2, 1.8 Hz, 1H), 7.27 (ddd, J = 7.2, 7.2, 1.5 Hz, 1H), 7.16-7.13 (m, 1H), 1.27 (s, 9H).

Exhibited spectral data identical to a previous report.[167]

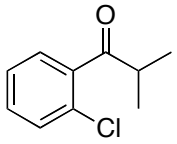
[167] Cahiez, G.; Luart, D.; Lecomte, F. *Org. Lett.* **2004**, *6*, 4395-4398.



1-(2-Bromophenyl)-2,2-dimethylpropanone (2.20) *General procedure B for the preparation of starting materials* was followed using 2'-bromoacetophenone (0.170 mL, 1.29 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient 100% petroleum ether to 2% Et_2O in petroleum ether) to afford 186 mg of a clear oil in 60% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.57 (ddd, J = 7.9, 1.2, 0.4 Hz, 1H), 7.32 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.26-7.20 (m, 1H), 7.13 (dd, J = 7.5, 1.8 Hz, 1H), 1.29 (s, 9H).

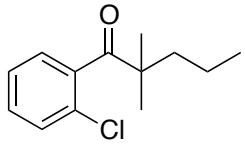
Exhibited spectral data identical to a previous report.[167]



1-(2-Chlorophenyl)-2-methylpropanone A flame dried flask containing magnesium (3.11 g, 128 mmol, 2.20 equiv) under argon was fitted with a condenser. Ether (4.0 ml) was added to the flask after which 2-bromopropane (14.3 g, 116 mmol, 2.00 equiv) was slowly added as a solution in ether (100 mL, 1.2 M), keeping the reaction at reflux. A solution of 2-chlorobenzonitrile (8.00 g, 58.2 mmol, 1.00 equiv) in benzene (100 mL, 0.58 M) was slowly added. The reaction was refluxed overnight. The solution was then cooled in an ice bath and the reaction was quenched by the dropwise addition of 10% H_2SO_4 (200 ml). The solution was heated to reflux for 48 hours to complete the hydrolysis after which the organic layer was separated and the aqueous phase was extracted with Et_2O (2 x 100 mL). The combined organic extracts were washed with 10% HCl, water and saturated $NaHCO_3$. The organic layer was dried with Na_2SO_4, filtered and concentrated. The crude product was purified by distillation to afford 7.60 g of a clear oil in 72% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.41-7.28 (m, 4H), 3.39-3.29 (m, 1H), 1.19-1.17 (m, 6H).

Exhibited spectral data identical to a previous report.[168]

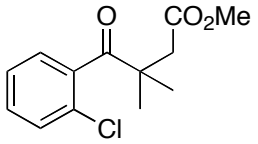


1-(2-Chlorophenyl)-2,2-dimethylpentanone (2.22) To a solution of 1-(2-chlorophenyl)-2-methylpropan-1-one (750 mg, 4.11 mmol, 1.00 equiv) in THF (14 mL, 0.3 M) was added lithium bis(trimethylsilyl)amide (1 M solution in THF) (5.3 mL, 5.3 mmol, 1.3 equiv). The reaction was stirred for 10 minutes before 1-iodopropane (0.80 mL, 8.2 mmol, 2.0 equiv) was added. The reaction was stirred at room temperature for 48 hours. The reaction was

[168] Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405-2407.

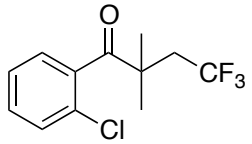
quenched with NH_4Cl sat. and extracted with ether (3 x 50 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on neutral aluminum oxide (10% toluene in petroleum ether) to afford 281 mg of a pale pink oil in 30% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.39-7.37 (m, 1H), 7.32-7.28 (m, 1H), 7.26-7.24 (m, 1H), 7.12-7.10 (m, 1H), 1.64-1.60 (m, 2H), 1.41-1.32 (m, 2H), 1.22 (s, 6H), 0.94 (t, J = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 211.3, 140.7, 130.1, 129.8, 129.7, 126.3, 126.1, 48.7, 42.2, 24.7, 17.9, 14.8. **HRMS** Calculated for $C_{13}H_{17}OCl$ (M^+ - C_3H_7) 181.0420, Found 181.0398. **IR (ν_{max}/cm^{-1})** 3066, 2962, 2873, 1696, 1471, 741. **R_f** 0.20 (10% toluene in petroleum ether).



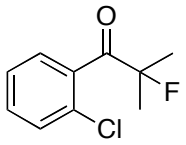
Methyl 4-(2-chlorophenyl)-3,3-dimethyl-4-oxobutanoate (2.24) To a solution of 1-(2-chlorophenyl)-2-methylpropan-1-one (450 mg, 2.46 mmol, 1.00 equiv) in THF (12 mL, 0.2 M) was added lithium bis(trimethylsilyl)amide (1 M solution in THF) (2.71 mL, 2.71 mmol, 1.10 equiv). The reaction was stirred for 10 minutes before methyl 2-iodoacetate (739 mg, 3.70 mmol, 1.50 equiv) was added. The reaction was stirred at room temperature overnight. The reaction was quenched with NH_4Cl sat. and extracted with ether (3 x 50 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel flash chromatography (15% Et_2O in petroleum ether) to afford 330 mg of a clear oil in 53% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.49-7.47 (m, 1H), 7.41-7.38 (m, 1H), 7.34-7.27 (m, 2H), 3.69 (s, 3H), 2.76 (s, 2H), 1.34 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 209.2, 172.1, 139.7, 130.1, 130.0, 129.6, 127.6, 126.3, 51.7, 47.0, 44.0, 25.6. **HRMS** Calculated for $C_{13}H_{15}ClO_3$ (M^+) 254.0710, Found 254.0701. **IR (ν_{max}/cm^{-1})** 3075, 2973, 1737, 1700, 1199, 743. **R_f** 0.27 (15% Et_2O in petroleum ether).



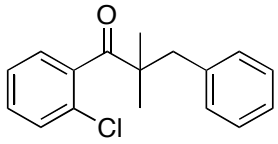
1-(2-Chlorophenyl)-4,4,4-trifluoro-2,2-dimethylbutanone (2.26) To a solution of 1-(2-chlorophenyl)-2-methylpropan-1-one (500 mg, 2.74 mmol, 1.00 equiv) in THF (9.1 mL, 0.3 M) was added potassium hydride (30% dispersion in mineral oil) (403 mg, 3.01 mmol, 1.10 equiv). The reaction was stirred for 10 minutes after which 1,1,1-trifluoro-2-iodoethane (0.40 mL, 4.1 mmol, 1.5 equiv) was added and the resulting mixture was heated to 80 °C and stirred for 48 hours. The reaction was quenched with NH_4Cl sat. and extracted with ether (3 x 50 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated. The product was purified by silica gel flash chromatography (gradient 10% toluene in petroleum ether to 1% Et_2O and 10% toluene in petroleum ether) to afford 103 mg of a clear oil in 14% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.42 (dd, J = 7.9, 1.2 Hz, 1H), 7.35 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 7.30 (ddd, J = 7.4, 7.4, 1.4 Hz, 1H), 7.18 (dd, J = 7.5, 1.7 Hz, 1H), 2.62 (q, J = 11.5 Hz, 2H), 1.38 (d, J = 1.0 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 208.1, 139.2, 130.4, 130.0, 129.7, 126.8, 126.6 (q, J = 276 Hz), 126.5, 46.0, 41.6 (q, J = 27 Hz), 25.1. **HRMS** Calculated for $C_{10}H_{10}ClO$ (M^+ - CH_2CF_3) 181.0420, Found 181.0339. **IR (ν_{max}/cm^{-1})** 3068, 2988, 1704, 1109, 742. **R_f** 0.27 (2% Et_2O in petroleum ether).



1-(2-Chlorophenyl)-2-fluoro-2-methylpropanone (2.28) To a solution of 1-(2-chlorophenyl)-2-methylpropan-1-one (400 mg, 2.19 mmol, 1.00 equiv) in MeOH (22 mL, 0.1 M) was added Selectfluor (1.55 g, 4.38 mmol, 2.00 equiv). The reaction was heated at reflux for 24 hours after which the mixture was cooled to room temperature, extracted with Et_2O (x3), dried with $MgSO_4$ and concentrated. The crude product was purified by silica gel flash chromatography (10% toluene in petroleum ether) to afford 310 mg of a pale yellow oil in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.44-7.26 (m, 4H), 1.70 (s, 3H), 1.65 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 205.7 (d, J = 31.0 Hz), 137.6 (d, J = 2.1 Hz), 131.2, 130.7 (d, J = 1.4 Hz), 130.1, 127.9 (d, J = 4.5 Hz) 126.4, 99.0 (d, J = 180.3 Hz), 25.2 (d, J = 23.9 Hz). **HRMS** Calculated for $C_{10}H_{10}ClOF$ (M^+) 200.0404, Found 200.0391. **IR (ν_{max}/cm^{-1})** 3073, 2989, 1716, 1436, 1195, 741. **R_f** 0.24 (10% toluene in petroleum ether).

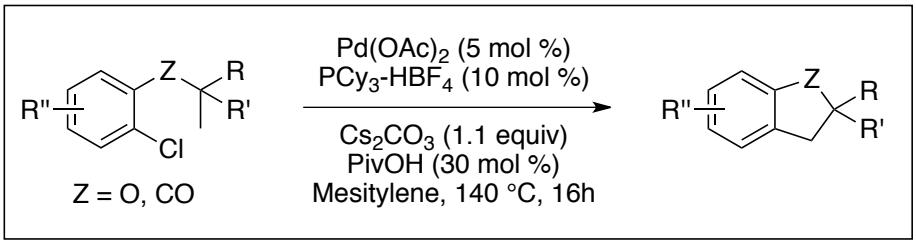


2-Benzyl-1-(2-chlorophenyl)-2-methylpropanone (2.30) To a solution of 1-(2-chlorophenyl)-2-methylpropan-1-one (600 mg, 3.29 mmol, 1.00 equiv) in dioxane (10 mL, 0.33 M) was added potassium hydride (30% dispersion in mineral oil) (659 mg, 4.93 mmol, 1.50 equiv). The reaction was stirred for 10 minutes after which benzyl bromide (843 mg, 4.93 mmol, 1.50 equiv) was added and the resulting mixture was heated to 80 °C and stirred for 48 hours. The reaction was quenched with NH_4Cl sat. and extracted with ether (3 x 50 mL). The organic extracts were dried with $MgSO_4$, filtered and concentrated. The product was purified by silica gel flash chromatography (2% Et_2O and 20% toluene in petroleum ether) to afford 636 mg of a clear oil in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.37-7.23 (m, 5H), 7.19-7.14 (m, 3H), 6.65 (ddd, J = 7.6, 1.6, 0.3 Hz, 1H), 2.99 (s, 2H), 1.22 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 211.5, 140.8, 137.6, 131.1, 129.9, 129.8, 129.3, 128.2, 126.6, 126.4, 125.9, 49.5, 45.5, 24.9. **HRMS** Calculated for $C_{17}H_{17}ClO$ (M^+) 272.0968, Found 272.0978.

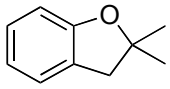
IR (ν_{max}/cm^{-1}) 3029, 2972, 2933, 1696, 703. **R_f** 0.24 (2% Et_2O and 20% Toluene in petroleum ether).

8.2.3 General Procedure and Characterization for Alkane Arylation Reactions



General Procedure for Alkane Arylation

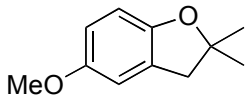
A 4 mL screw cap vial equipped with a magnetic stir bar was charged with the starting material (if a solid, 1.00 equiv), $Pd(OAc)_2$ (5.00 mol %), $PCy_3 \cdot HBF_4$ (10.0 mol %), Cs_2CO_3 (1.10 equiv) and PivOH (30.0 mol %). The vial was purged with argon for at least 5 minutes after which time the starting material (if a liquid, 1.00 equiv) was added as a stock solution in mesitylene (0.17 M). The resulting mixture was placed in a preheated bath at 140 °C and stirred overnight (16 h). Upon cooling to room temperature, the reaction was quenched with EtOAc and purified by silica gel flash chromatography.



2,3-Dihydro-2,2-dimethylbenzofuran (2.2) *General procedure for alkane arylation* was followed using 1-*tert*-butoxy-2-chlorobenzene (130 mg, 0.704 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 80 mg of clear oil in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.14-7.08 (m, 2H), 6.81 (td, J = 7.4, 0.9 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 3.01 (s, 2H), 1.47 (s, 6H).

Exhibited spectral data identical to a previous report.[169]

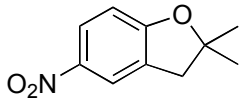


2,3-Dihydro-5-methoxy-2,2-dimethylbenzofuran (2.4) *General procedure for alkane arylation* was followed using 1-*tert*-butoxy-2-chloro-4-methoxybenzene (150 mg, 0.700 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O in petroleum ether) to afford 120 mg of yellow oil in 96% yield.

[169] Kataoka, N. ; Shelby, Q. ; Stambuli, J. P. ; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553-5566.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 6.74 (dd, J = 2.2, 1.0 Hz, 1H), 6.67-6.62 (m, 2H), 3.75 (s, 3H), 2.99 (s, 2H), 1.46 (s, 6H).

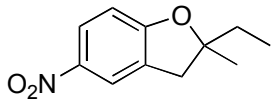
Exhibited spectral data identical to a previous report.[39]



2,3-Dihydro-2,2-dimethyl-5-nitrobenzofuran (2.6) *General procedure for alkane arylation* was followed using 1-*tert*-butoxy-2-chloro-4-nitrobenzene (62.0 mg, 0.270 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 46 mg of yellow oil in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.05 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.08 (s, 2H), 1.52 (s, 6H).

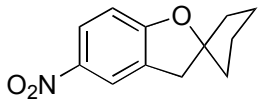
Exhibited spectral data identical to a previous report.[39]



2-Ethyl-2,3-dihydro-2-methyl-5-nitrobenzofuran (2.8) *General procedure for alkane arylation* was followed using 1-(*tert*-pentyloxy)-2-chloro-4-nitrobenzene (150 mg, 0.616 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (5% Et_2O in petroleum ether) to afford 107 mg of orange oil in 84% yield.

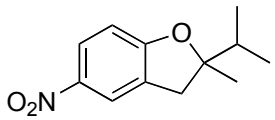
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.05 (m, 1H), 6.76 (d, J = 8.8 Hz, 1H), 3.14 (d, J = 16.0 Hz, 1H), 2.99 (d, J = 16.0 Hz, 1H), 1.81 (q, J = 7.5 Hz, 2H), 1.48 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H).

Exhibited spectral data identical to a previous report.[39]



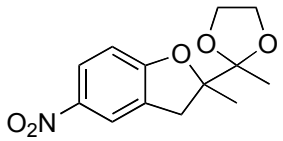
2,3-Dihydro-2,2-*spiro*cyclopentyl-5-nitrobenzofuran (2.10) *General procedure for alkane arylation* was followed using 1-(1-methylcyclopentyloxy)-2-chloro-4-nitrobenzene (150 mg, 0.665 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (4% Et_2O in petroleum ether) to afford 93 mg of a yellow solid in 64% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.09 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.04 (m, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.24 (s, 2H), 2.19-2.09 (m, 2H), 1.94-1.71 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 164.6, 141.6, 128.8, 125.9, 121.3, 109.2, 100.4, 39.6, 39.1, 23.9. **HRMS** Calculated for $C_{12}H_{13}NO_3$ (M^+) 219.0895, Found 219.0900. **IR (ν_{max}/cm^{-1})** 2963, 1597, 1340, 1276. **R_f** 0.26 (4% Et_2O in petroleum ether). **Melting Point** 74-75 °C.



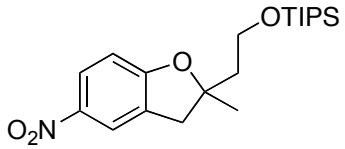
2,3-Dihydro-2-isopropyl-2-methyl-5-nitrobenzofuran (2.12) *General procedure for alkane arylation* was followed using 1-(2,3-dimethylbutan-2-yloxy)-2-chloro-4-nitrobenzene (150 mg, 0.582 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (4% Et_2O in petroleum ether) to afford 99 mg of a yellow solid in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.08 (ddd, J = 8.8, 2.4, 0.5 Hz, 1H), 8.04-8.03 (m, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.19 (d, J = 16.1 Hz, 1H), 2.87 (d, J = 16.1 Hz, 1H), 2.03 (sept, J = 6.8 Hz, 1H), 1.39 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 164.8, 141.5, 128.6, 127.0, 125.9, 121.6, 109.1, 95.4, 38.2, 37.2, 23.5, 17.4, 17.3. **HRMS** Calculated for $C_{12}H_{15}NO_3$ (M^+) 221.1052, Found 221.1045. **IR (ν_{max}/cm^{-1})** 2969, 2879, 1597, 1343, 1277. **R_f** 0.24 (4% Et_2O in petroleum ether). **Melting Point** 66-68 °C.



2,3-Dihydro-2-methyl-2-(2-methyl-1,3-dioxolan-2-yl)-5-nitrobenzofuran (2.14) *General procedure for alkane arylation* was followed using 2-(2-methyl-1,3-dioxolan-2-yl)propan-2-ol (130 mg, 0.431 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (30% Et_2O in petroleum ether) to afford 109 mg of a yellow solid in 95% yield.

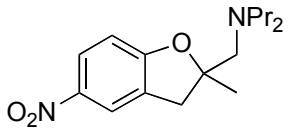
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.09 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.04 (m, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.24 (s, 2H), 2.19-2.09 (m, 2H), 1.94-1.71 (m, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 164.7, 141.9, 128.6, 125.8, 121.3, 111.2, 109.0, 95.0, 66.1, 66.1, 37.7, 23.1, 20.2. **HRMS** Calculated for $C_{13}H_{15}NO_5$ (M^+) 265.0950, Found 265.0926. **IR (ν_{max}/cm^{-1})** 2991, 2899, 1514, 1335, 1275. **R_f** 0.26 (4% Et_2O in petroleum ether). **Melting Point** 81-83 °C.



(2-(2,3-Dihydro-2-methyl-5-nitrobenzofuran-2-yl)ethoxy)triisopropylsilane (2.16) *General procedure for alkane arylation* was followed using (3-(2-chloro-4-nitrophenoxy)-3-methylbutoxy)triisopropylsilane (200 mg, 0.481 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O in petroleum ether) to afford 159 mg of a yellow oil in 87% yield.

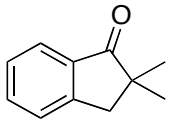
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.09 (dd, J = 8.8, 2.5 Hz, 1H), 8.04-8.03 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.88 (t, J = 6.3 Hz, 2H), 3.41 (d, J = 16.0 Hz, 1H), 3.00 (d, J = 16.0 Hz, 1H), 2.05 (td, J = 6.3, 4.3 Hz, 2H), 1.52 (s, 3H), 1.10-1.01 (m, 21H). **^{13}C NMR**

(100 MHz, $CDCl_3$, 293K, TMS) δ 164.5, 141.7, 128.9, 125.9, 121.7, 109.2, 91.6, 59.4, 43.4, 41.0, 26.9, 18.1, 12.0. **HRMS** Calculated for $C_{17}H_{26}NO_4Si$ (M^+ - C_3H_7) 336.1631, Found 336.1632. **IR (ν_{max}/cm^{-1})** 2943, 2866, 1597, 1518, 1481, 1337, 1101. **R_f** 0.27 (2% Et_2O in petroleum ether).



***N*-((2,3-Dihydro-2-methyl-5-nitrobenzofuran-2-yl)methyl)-*N*-propylpropan-1-amine (2.18)** *General procedure for alkane arylation* was followed using *N*-(2-(2-chloro-4-nitrophenoxy)-2-methylpropyl)-*N*-propylpropan-1-amine (150 mg, 0.457 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_3N and 6% Et_2O in petroleum ether) to afford 74 mg of a yellow oil in 55% yield.

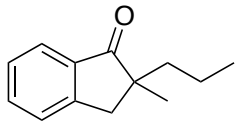
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.07 (dd, J = 8.8, 2.2 Hz, 1H), 8.03 (s, 1H), 6.71 (d, J = 8.8 Hz, 1H), 3.42 (d, J = 15.7 Hz, 1H), 2.87 (d, J = 15.7 Hz, 1H), 2.71 (d, J = 14.7 Hz, 1H), 2.57 (d, J = 14.7 Hz, 1H), 2.52-2.37 (m, 4H), 1.43 (s, 3H), 1.41-1.26 (m, 4H), 0.77 (t, J = 7.3 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 164.8, 141.6, 129.4, 125.7, 121.4, 108.9, 93.8, 62.8, 57.8, 38.3, 25.5, 20.6, 11.9. **HRMS** Calculated for $C_{16}H_{24}N_2O_3$ (M^+) 292.1787, Found 292.1754. **IR (ν_{max}/cm^{-1})** 2959, 2930, 1598, 1336, 1272, 1060. **R_f** 0.45 (2% Et_3N and 6% Et_2O in petroleum ether).



2,3-Dihydro-2,2-dimethylindenone (2.21) *General procedure for alkane arylation* was followed using 1-(2-bromophenyl)-2,2-dimethylpropanone (or 1-(2-chlorophenyl)-2,2-dimethylpropanone) (140 mg, 0.581 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (4% Et_2O in petroleum ether) to afford 92 mg of a clear oil in 98% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.77 (d, J = 7.7 Hz, 1H), 7.59 (ddd, J = 7.4, 7.4, 1.0 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.38 (dd, J = 7.4, 7.4 Hz, 1H), 3.01 (s, 2H), 1.24 (s, 6H).

Exhibited spectral data identical to a previous report.[170]

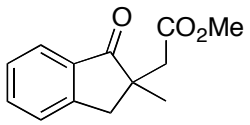


2-Methyl-2-propyl-2,3-dihydro-1H-indenone (2.23) *General procedure for alkane arylation* was followed using 1-(2-chlorophenyl)-2,2-dimethylpentan-1-one (140 mg,

[170] Murphy, J. A.; Zhou, S.-z.; Thomson, D. W.; Schoenebeck, F.; Mahesh, M.; Park, S. R.; Tuttle, T.; Berlouis, L. E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 5178-5183.

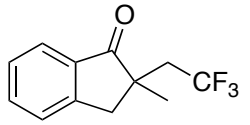
0.623 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O in petroleum ether) to afford 59 mg of a yellow oil in 50% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.74 (d, J = 7.7 Hz, 1H), 7.58 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.43 (ddd, J = 7.7, 0.8, 0.8 Hz, 1H), 7.38-7.34 (m, 1H), 3.11 (d, J = 17.2 Hz, 1H), 2.87 (d, J = 17.2 Hz, 1H), 1.64-1.50 (m, 2H), 1.32-1.24 (m, 1H), 1.20 (s, 3H), 1.16-1.08 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 211.7, 152.9, 136.3, 134.9, 127.5, 126.6, 124.3, 49.3, 40.9, 40.4, 24.1, 18.1, 14.7. **HRMS** Calculated for $C_{13}H_{16}O$ (M^+) 188.1201, Found 188.1204. **IR (ν_{max}/cm^{-1})** 3074, 3040, 2959, 2930, 1714, 1609, 1466. **R_f** 0.19 (2% Et_2O in petroleum ether).



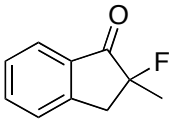
Methyl 2-(2,3-dihydro-2-methyl-1-oxo-1*H*-inden-2-yl)acetate (2.25) *General procedure for alkane arylation* was followed using methyl 4-(2-chlorophenyl)-3,3-dimethyl-4-oxobutanoate (150 mg, 0.589 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (15% Et_2O in petroleum ether) to afford 99 mg of a white solid in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.79 (d, J = 7.7 Hz, 1H), 7.60 (ddd, J = 7.4, 7.4, 0.8 Hz, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.38 (dd, J = 7.4, 7.4 Hz, 1H), 3.58 (s, 3H), 3.31 (d, J = 17.1 Hz, 1H), 2.97 (d, J = 17.1 Hz, 1H), 2.83 (d, J = 16.4 Hz, 1H), 2.69 (d, J = 16.4 Hz, 1H), 1.23 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 209.3, 171.9, 152.3, 135.3, 134.9, 127.6, 126.7, 124.5, 51.7, 46.8, 41.5, 40.3, 24.8. **HRMS** Calculated for $C_{13}H_{14}O_3$ (M^+) 218.0943, Found 218.0958. **IR (ν_{max}/cm^{-1})** 3073, 2958, 2927, 1746, 1710, 1210. **R_f** 0.17 (15% Et_2O in petroleum ether). **Melting Point** 49-52 °C.



2-Methyl-2-(2,2,2-trifluoroethyl)-2,3-dihydro-1*H*-inden-1-one (2.27) *General procedure for alkane arylation* was followed using 1-(2-chlorophenyl)-4,4,4-trifluoro-2,2-dimethylbutanone (65 mg, 0.246 mmol, 1 equiv). The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 50 mg of a yellow oil in 89% yield.

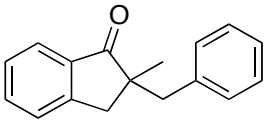
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.81 (dd, J = 7.7, 0.4 Hz, 1H), 7.65 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.48 (ddd, J = 7.7, 0.9, 0.9 Hz, 1H), 7.44-7.40 (m, 1H), 3.41 (d, J = 17.5 Hz, 1H), 3.05 (d, J = 17.4 Hz, 1H), 2.62 (dq, J = 15.3, 11.1 Hz, 1H), 2.41 (dq, J = 15.3, 11.5 Hz, 1H), 1.30 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 207.9, 152.1, 135.6, 134.2, 128.0, 126.9 (q, J = 276 Hz), 126.8, 125.0, 46.0 (q, J = 1.7 Hz), 40.0 (q, J = 27.6 Hz), 39.9 (q, J = 1.6 Hz), 24.4 (q, J = 1.4 Hz). **HRMS** Calculated for $C_{12}H_{11}OF_3$ (M^+) 228.0762, Found 228.0765. **IR (ν_{max}/cm^{-1})** 3085, 2939, 1717, 1609, 1260. **R_f** 0.29 (3% Et_2O in petroleum ether).



2-Fluoro-2,3-dihydro-2-methylindenone (2.29) *General procedure for alkane arylation* was followed using 1-(2-chlorophenyl)-2-fluoro-2-methylpropanone (139 mg, 0.691 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient of 2% to 4% Et_2O in petroleum ether) to afford 53 mg of a yellow oil in 47% yield.

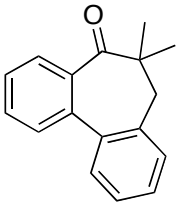
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.82 (d, J = 7.7 Hz, 1H), 7.66 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.46-7.41 (m, 2H), 3.46 (dd, J = 22.4, 17.5 Hz, 1H), 3.30 (dd, J = 17.4, 11.2 Hz, 1H), 1.63 (d, J = 22.7 Hz, 3H).

Exhibited spectral data identical to a previous report.[171]



2-Benzyl-2,3-dihydro-2-methylindenone (2.31a) *General procedure for alkane arylation* was followed using 2-benzyl-1-(2-chlorophenyl)-2-methylpropanone (109 mg, 0.400 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O and 20% toluene in petroleum ether) to afford 61 mg of a clear oil in 65% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.74 (d, J = 7.6 Hz, 1H), 7.52 (dd, J = 7.4, 7.4 Hz, 1H), 7.34-7.30 (m, J = 7.8 Hz, 2H), 7.22-7.13 (m, 5H), 3.24 (d, J = 17.2 Hz, 1H), 3.03 (d, J = 13.4 Hz, 1H), 2.82 (d, J = 13.4 Hz, 1H), 2.74 (d, J = 17.2 Hz, 1H), 1.24 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 210.9, 152.6, 137.9, 135.8, 134.9, 130.3, 128.2, 127.4, 126.6, 126.5, 124.4, 50.5, 43.4, 39.0, 24.7. **HRMS** Calculated for $C_{17}H_{16}O$ (M^+) 236.1201, Found 236.1207. **IR (ν_{max}/cm^{-1})** 3063, 3029, 2924, 1712, 1609, 980. **R_f** 0.14 (2% Et_2O and 20% toluene in petroleum ether).



Ketone 2.31b *General procedure for alkane arylation* was followed using 2-benzyl-1-(2-chlorophenyl)-2-methylpropanone (109 mg, 0.400 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% Et_2O and 20% toluene in petroleum ether) to afford 30 mg of a clear oil in 32% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.55 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.47-7.32 (m, 5H), 7.29 (ddd, J = 7.3, 7.3, 1.6 Hz, 1H), 7.22 (dd, J = 7.4, 1.1 Hz, 1H), 2.83 (s, 2H), 1.21 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 212.3, 139.9, 138.8, 138.3, 137.0, 131.4, 130.0, 129.3, 128.6, 128.1, 128.0, 127.8, 127.7, 54.0, 44.3, 25.3.

[171] Takeuchi, Y.; Suzuki, T.; Satoh, A.; Shiragami, T.; Shibata, N. *J. Org. Chem.* **1999**, *64*, 5708-5711.

HRMS Calculated for $C_{17}H_{16}O$ (M^+) 236.1201, Found 236.1193. **IR (ν_{max}/cm^{-1})** 2962, 2927, 1684, 1207, 914. **R_f** 0.19 (2% Et_2O and 20% toluene in petroleum ether)

8.2.4 Computational Details – Atom Coordinates

Agos-2.34a (Scheme 2.1)
C, 0, 2.1905692565, -1.1050942706, 2.4798493573
C, 0, 3.3299347113, -1.5390874055, 3.1572923878
C, 0, 4.5614228784, -1.5067571696, 2.5125256983
C, 0, 4.6389263588, -1.052842365, 1.1993531946
C, 0, 3.5009793514, -0.6223617848, 0.5004198585
C, 0, 2.2565127476, -0.6497924224, 1.1579597844
H, 0, 1.2329652508, -1.1085617845, 2.9922420962
H, 0, 3.2505071812, -1.8919923209, 4.1826007915
H, 0, 5.4637482929, -1.8296123621, 3.0243756976
H, 0, 5.6062405921, -1.0262170882, 0.7053177355
C, 0, 3.6251996255, -0.1480292765, -0.9580393897
H, 0, 0.9905808693, -1.5205077291, -0.7917877553
Pd, 0, 0.4571625359, -0.2127741477, 0.3472621709
C, 0, 0.4704167295, 2.0135881125, 2.0727831686
O, 0, 0.0087959818, 0.7896666519, 2.0719238946
O, 0, 0.3192078991, 2.6195727823, 3.2802930714
O, 0, 0.9689229593, 2.6255140505, 1.1421735068
H, 0, -0.0345240512, 1.9515418669, 3.8818159414
C, 0, 2.8300638989, -1.1104747321, -1.9151738812
H, 0, 3.0530036177, -0.7749855323, -2.9358262544
C, 0, 3.2057969921, 1.3637960178, -1.0868233923
H, 0, 2.2018803935, 1.4417416313, -0.6504074949
C, 0, 1.3199676883, -1.0001435904, -1.7585004512
H, 0, 0.9551162492, 0.0235995424, -1.8955985094
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Transition state **2.35c (Scheme 2.2)**
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C, 0, -3.6396706869, -0.4447789349, 0.2297978941
C, 0, -2.5272716404, -1.0033499533, -0.4078419378
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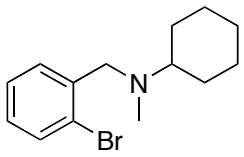
8.3 Alkane Arylation Adjacent to Amides and Sulfonamides

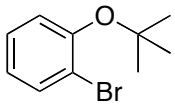
8.3.1 Synthesis and Characterization of Substrates for Reaction Development



***N*-(2-Bromobenzyl)-*N*-methylcyclohexylamine (3.6)** To a solution of K_2CO_3 (1.21 g, 8.77 mmol, 2.00 equiv) in DMF (8.8 mL, 0.5 M) was added 2-bromobenzylbromide (1.10 g, 4.39 mmol, 1.0 equiv) and *N*-methylcyclohexylamine (0.63 mL, 4.82 mmol, 1.10 equiv). The mixture was left to stir overnight after which it was diluted with H_2O and the organic components were extracted with Et_2O (x3). The combined organic phases were washed with a solution of 10% HCl (x3). The combined aqueous layers were neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (x3). Finally, the combined organic phases were dried with $MgSO_4$ and concentrated. The product was purified by silica gel flash chromatography (10% Et_2O in petroleum ether) to afford 1.23 g of a yellow oil in 99% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.52-7.49 (m, 2H), 7.27 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.08 (ddd, J = 7.6, 7.6, 2.0 Hz, 1H), 3.66 (s, 2H), 2.48 (dddd, J = 10.8, 10.8, 3.2, 3.2 Hz, 1H), 2.23 (s, 3H), 1.90-1.06 (m, 10H).

Exhibited spectral data identical to a previous report.[172]

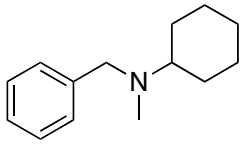


1-*tert*-Butoxy-2-bromobenzene (3.9) A large excess of isobutene was added *via* cold finger to a solution of 2-bromophenol (0.92 mL, 8.67 mmol, 1.00 equiv) in CH_2Cl_2 (8.7 mL, 1.0 M) under argon at -78 ºC. TfOH (53 μL, 0.69 mmol, 0.080 equiv) was then added dropwise and the solution was stirred at -78 ºC for 4 hours. Et_3N (0.20 mL) was added and the mixture was brought to room temperature. The crude reaction mixture was concentrated and purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 1.40 g of a clear oil in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.55 (dd, J = 8.0, 1.6 Hz, 1H), 7.20 (ddd, J = 8.2, 7.3, 1.6 Hz, 1H), 7.12 (dd, J = 8.2, 1.6 Hz, 1H), 6.92 (ddd, J = 7.9, 7.3, 1.6 Hz, 1H), 1.44 (s, 9H).

Exhibited spectral data identical to a previous report.[39]

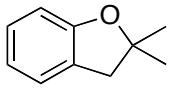
[172] Hiroi, K.; Suzuki, Y.; Abe, I.; Hasegawa, Y.; Suzuki, K. *Tetrahedron: Asymmetry* **1998**, *9*, 3797-3817.



***N*-Benzyl-*N*-methylcyclohexylamine (3.10)** To a solution of K_2CO_3 (0.480 g, 3.51 mmol, 2.00 equiv) in DMF (3.5 mL, 0.50 M) was added benzylbromide (0.21 mL, 1.75 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (0.25 mL, 1.93 mmol, 1.10 equiv). The mixture was left to stir overnight after which time it was diluted with H_2O and extracted with Et_2O (x3). The combined organic phases were washed with a solution of 10% HCl (x3). The combined aqueous layers were neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (x3). Finally, the combined organic phases were dried with $MgSO_4$ and concentrated. The product was purified by silica gel flash chromatography (5% EtOAc in petroleum ether) to afford 0.18 g of a clear oil in 50% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.34-7.19 (m, 5H), 3.56 (s, 2H), 2.48-2.39 (m, 1H), 2.19 (s, 3H), 1.90-1.04 (m, 10H).

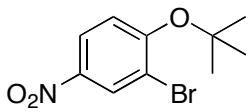
Exhibited spectral data identical to a previous report.[173]



2,3-Dihydro-2,2-dimethylbenzofuran (3.11) A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless otherwise noted. $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 5.0 mol%), $PCy_3 \cdot HBF_4$ (21.4 mg, 0.0581 mmol, 10.0 mol%) and Cs_2CO_3 (284 mg, 0.872 mmol, 1.50 equiv) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). **3.10** (59.1 mg, 0.291 mmol, 0.50 equiv), **3.9** (66.6 mg, 0.291 mmol, 0.50 equiv) and PivOH (17.8 mg, 0.174 mmol, 30.0 mol%) were added as degassed stock solutions in mesitylene (0.32 M, 0.32 M and 0.16 M respectively) after which point the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL) and the outcome was analyzed by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Formation of **3.11** was confirmed by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.14-7.08 (m, 2H), 6.81 (ddd, J = 7.4, 7.4, 0.9 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 3.01 (s, 2H), 1.47 (s, 6H).

Exhibited spectral data identical to a previous report.[39]



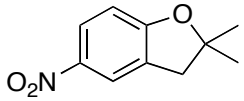
1-*tert*-Butoxy-2-bromo-4-nitrobenzene (3.12) *Tert*-butanol (0.35 mL, 3.75 mmol, 1.10 equiv) was added dropwise to a solution of KH (30 wt %) (501 mg, 3.75 mmol, 1.10 equiv)

[173] Glover, S. A.; Warkentin, J. *J. Org. Chem.* **1993**, *58*, 2115-2121.

in THF (21 mL, 0.15 M) under argon at 0 ºC. The resulting mixture was stirred for 10 minutes after which 2-bromo-1-fluoro-4-nitrobenzene (750 mg, 3.41 mmol, 1.00 equiv) was added and the flask was warmed to room temperature. The reaction was stirred for 2 hours (or until judged complete by TLC) and the crude product was extracted with CH_2Cl_2 (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (2% Et_2O in petroleum ether) and obtained in 60% yield (560 mg).

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.47 (d, J = 2.8 Hz, 1H), 8.12 (dd, J = 9.1, 2.8 Hz, 1H), 7.18 (d, J = 9.1 Hz, 1H), 1.54 (s, 9H).

Exhibited spectral data identical to a previous report.[39]

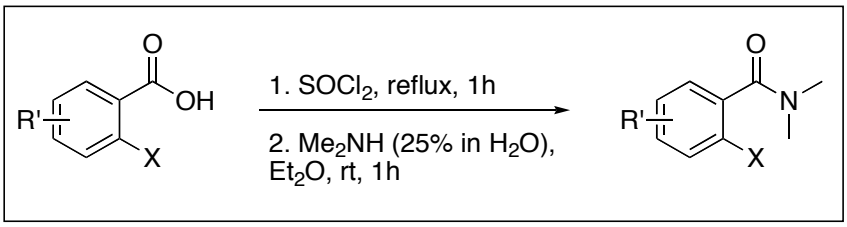


2,3-Dihydro-2,2-dimethyl-5-nitrobenzofuran (3.13) A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless otherwise noted. $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 5.0 mol%), $PCy_3 \cdot HBF_4$ (21.4 mg, 0.0581 mmol, 10.0 mol%) and Cs_2CO_3 (284 mg, 0.872 mmol, 1.50 equiv) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). **3.10** (or **3.6**) (59.1 mg, 0.291 mmol, 0.50 equiv), **3.12** (80.0 mg, 0.291 mmol, 0.50 equiv) and PivOH (17.8 mg, 0.174 mmol, 30.0 mol%) were added as degassed stock solutions in mesitylene (0.32 M, 0.32 M and 0.16 M respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL) and the outcome was analyzed by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Formation of **3.13** was confirmed by ^{1}H NMR.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.05 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H), 3.08 (s, 2H), 1.52 (s, 6H).

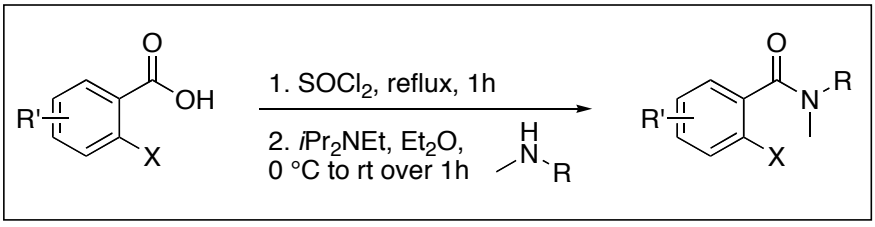
Exhibited spectral data identical to a previous report.[39]

8.3.2 Synthesis and Characterization of Amide Starting Materials



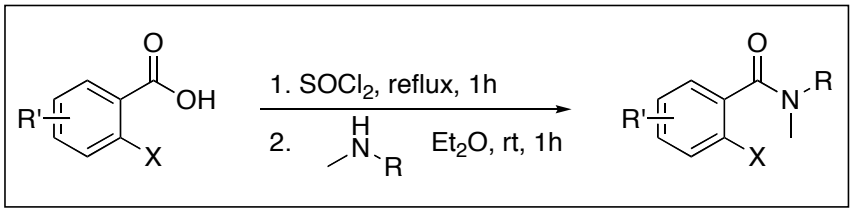
General Procedure A for the Preparation of *N*-methylamides

The desired 2-halobenzoic acid (1.00 equiv) was refluxed in neat $SOCl_2$ (1.50 equiv) for one hour after which the remaining $SOCl_2$ was removed *in vacuo*. The resulting acyl chloride was dissolved in Et_2O (1.25 M) and added dropwise to a solution of dimethylamine (25% aqueous solution, 25.0 equiv) at room temperature. The solution was stirred for one hour after which the crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



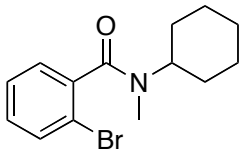
General Procedure B for the Preparation of *N*-methylamides

The desired 2-halobenzoic acid (1.00 equiv) was refluxed in neat $SOCl_2$ (1.50 equiv) for one hour after which the remaining $SOCl_2$ was removed *in vacuo*. The resulting acyl chloride was dissolved in a minimal amount of Et_2O and added dropwise to a solution of the corresponding *N*-methylamine (1.50 equiv) and iPr_2NEt (1.50 equiv) in the remaining Et_2O (0.20 M final concentration) at 0 °C. The solution was allowed to warm to room temperature and stirred for one hour after which the crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography or recrystallization.



General Procedure C for the Preparation of *N*-methylamides

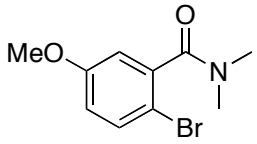
The desired 2-halobenzoic acid (1.00 equiv) was refluxed in neat $SOCl_2$ (1.50 equiv) for one hour after which the remaining $SOCl_2$ was removed *in vacuo*. The resulting acyl chloride was dissolved in a minimal amount of Et_2O and added dropwise to a solution of the corresponding *N*-methylamine (5.00 equiv) in the remaining Et_2O (0.27 M final concentration) at room temperature. The solution was stirred for one hour after which the crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



2-Bromo-*N*-cyclohexyl-*N*-methylbenzamide (3.15) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (4.00 g, 19.9 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (3.90 mL, 29.9 mmol, 1.50 equiv). The product was purified by recrystalization in hot hexanes to afford 4.50 g of a beige powder in 76% yield. Mixture of rotamers in a ratio of 1.1:1.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.58 (ddd, J = 8.0, 1.2, 0.4 Hz, 1H minor rotamer), 7.55 (ddd, J = 8.0, 1.2, 0.4 Hz, 1H major rotamer), 7.37-7.32 (m, 1H per rotamer), 7.26-7.19 (m, 2H per rotamer), 4.61 (dddd, J = 11.6, 11.6, 3.6, 3.6 Hz, 1H major rotamer), 3.15 (dddd, J = 11.6, 11.6, 4.0, 4.0 Hz, 1H minor rotamer), 3.01 (s, 3H minor rotamer), 2.69 (s, 3H major rotamer), 1.95-1.69 (m, 4H per rotamer), 1.58-1.44 (m, 4H per rotamer), 1.15-0.95 (m, 2H per rotamer).

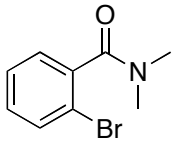
Exhibited spectral data identical to a previous report.[172]



2-Bromo-5-methoxy-*N*,*N*-dimethylbenzamide (3.17) *General procedure A* for the preparation of *N*-methylamides was followed using 2-bromo-5-methoxybenzoic acid (5.00 g, 21.6 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3% acetone in CH_2Cl_2) to afford 4.98 g of a white solid in 89% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.43 (ddd, J = 8.7, 1.2, 1.2 Hz, 1H), 7.81-6.77 (m, 2H), 3.06 (s, 3H), 3.03 (s, 3H), 2.88 (s, 3H).

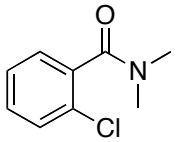
Exhibited spectral data identical to a previous report.[174]



2-Bromo-*N,N*-dimethylbenzamide (3.20) *General procedure A* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (2.00 g, 9.95 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (70% EtOAc in petroleum ether) to afford 2.21 g of a clear oil in 97% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.57 (d, J = 7.5 Hz, 1H), 7.36 (dd, J = 7.5, 7.5 Hz, 1H), 7.28-7.21 (m, 2H), 3.14 (s, 3H), 2.86 (s, 3H).

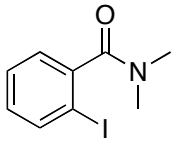
Exhibited spectral data identical to a previous report.[175]



2-Chloro-*N,N*-dimethylbenzamide (3.22) *General procedure A* for the preparation of *N*-methylamides was followed using 2-chlorobenzoic acid (1.00 g, 6.39 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (2% acetone in CH_2Cl_2) to afford 0.92 g of a yellow oil in 78% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.41-7.28 (m, 4H), 3.14 (s, 3H), 2.87 (s, 3H).

Exhibited spectral data identical to previous report.[176]



2-Iodo-*N,N*-dimethylbenzamide (3.23) *General procedure A* for the preparation of *N*-methylamides was followed using 2-iodobenzoic acid (1.00 g, 4.03 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (100% CH_2Cl_2) to afford 0.67 g of a white solid in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.82 (ddd, J = 8.0, 1.1, 0.4 Hz, 1H), 7.39 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.22 (ddd, J = 7.6, 1.7, 0.4 Hz, 1H), 7.07 (ddd, J = 8.0, 7.5, 1.7 Hz, 1H), 3.14 (3H, s), 2.85 (3H, s).

Exhibited spectral data identical to previous report.[175]

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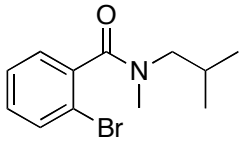
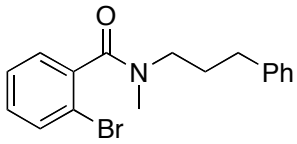
[174] Nielsen, S. F.; Larsen, M.; Boesen, T.; Schonning, K.; Kromann, H. *J. Med. Chem.* **2005**, *48*, 2667-2677.
[175] Olivera, R.; SanMartin, R.; Dominguez, E.; Solans, X.; Urtiaga, M. K.; Arriortua, M. I. *J. Org. Chem.* **2000**, *65*, 6398-6411.
[176] Keck, G. E.; McLaws, M. D.; Wager, T. T. *Tetrahedron* **2000**, *56*, 9875-9883.



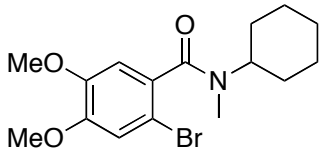
2-Bromo-*N*-isobutyl-*N*-methylbenzamide (3.24) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (4.00 g, 19.9 mmol, 1.00 equiv) and *N*-methylisobutylamine (3.60 mL, 29.9 mmol, 1.50 equiv). The product was purified by silica gel flash chromatography (30% EtOAc in petroleum ether) to afford 4.66 g of a clear oil in 87% yield. Mixture of rotamers in a ratio of 1.2:1.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.57-7.54 (m, 1H per rotamer), 7.37-7.31 (m, 1H per rotamer), 7.26-7.20 (m, 2H per rotamer), 3.51-3.46 (m, 1H major rotamer), 3.31-3.26 (m, 1H major rotamer), 3.09 (s, 3H minor rotamer), 3.00 (dd, J = 13.8, 5.8 Hz, 1H minor rotamer), 2.86 (dd, J = 13.8, 9.4 Hz, 1H minor rotamer), 2.81 (s, 3H major rotamer), 2.17-2.06 (m, 1H major rotamer), 1.96-1.86 (m, 1H minor rotamer), 1.01 (br s, 6H major rotamer), 0.80 (d, J = 6.4 Hz, 3H minor rotamer), 0.75 (d, J = 6.4 Hz, 3H minor rotamer). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 169.7, 169.4, 139.3, 138.6, 132.9, 132.8, 130.2, 130.1, 128.7, 127.9, 127.8, 127.5, 119.6, 119.0, 58.1, 54.6, 37.0, 32.7, 26.9, 26.7, 20.4, 20.3, 19.6. **HRMS** Calculated for $C_{12}H_{16}BrNO$ (M^+) 269.0415, Found 269.0402. **IR (ν_{max}/cm^{-1})** 2959, 2871, 1641, 746. **R_f** 0.28 (30% EtOAc in petroleum ether).



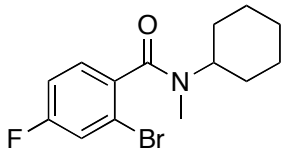
2-Bromo-*N*-methyl-*N*-(3-phenylpropyl)benzamide (3.26) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (1.21 g, 6.00 mmol, 1.00 equiv) and *N*-methyl-3-phenylpropamine (1.11 g, 7.45 mmol, 1.20 equiv). The product was purified by silica gel flash chromatography (gradient from 20% to 30% EtOAc in petroleum ether) to afford 0.621 g of a pale yellow oil in 31% yield. Mixture of rotamers in a ratio of 1.1:1.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.55-7.51 (m, 1H per rotamer), 7.35-7.13 (m, 7H per rotamer), 7.02-7.00 (m, 1H per rotamer), 3.82-3.77 (m, 1H major rotamer), 3.41-3.38 (m, 1H major rotamer), 3.14-3.10 (m, 2H minor rotamer), 3.10 (s, 3H minor rotamer), 2.80 (s, 3H major rotamer), 2.73 (br dd, J = 17.6, 8.4 Hz, 2H major rotamer), 2.43 (ddd, J = 7.5, 7.5, 5.4 Hz, 2H minor rotamer), 2.00 (dddd, J = 14.8, 7.2, 7.2, 2.4 Hz, 2H major rotamer), 1.94-1.85 (m, 1H minor rotamer), 1.83-1.73 (m, 1H minor rotamer). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 169.3, 169.1, 141.6, 141.6, 140.7, 138.8, 138.4, 132.8, 132.8, 130.1, 128.5, 128.4, 128.1, 127.8, 127.8, 127.7, 127.6, 126.1, 126.0, 119.2, 119.0, 50.3, 47.0, 36.2, 33.3, 32.8, 32.4, 29.5, 28.6. **HRMS** Calculated for $C_{17}H_{18}BrNO$ (M^+) 331.0572, Found 331.0571. **IR (ν_{max}/cm^{-1})** 3025, 2936, 1640, 1591, 1404, 1089, 665. **R_f** 0.12 (20% EtOAc in petroleum ether).



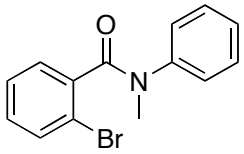
2-Bromo-*N*-cyclohexyl-4,5-dimethoxy-*N*-methylbenzamide (3.28) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromo-4,5-dimethoxybenzoic acid (0.600 g, 2.30 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (0.45 mL, 3.45 mmol, 1.50 equiv). The product was purified by silica gel flash chromatography (gradient from 70-80% EtOAc in petroleum ether) to afford 0.550 g of a pale yellow oil in 73% yield. Mixture of rotamers in a ratio of 1.4:1.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.04 (s, 1H minor rotamer), 7.01 (s, 1H major rotamer), 6.77 (s, 1H major rotamer), 6.72 (s, 1H minor rotamer), 4.65-4.55 (m, 1H major rotamer), 3.92 (s, 3H minor rotamer), 3.90 (s, 3H major rotamer), 3.88 (s, 3H major rotamer), 3.86 (s, 3H minor rotamer), 3.30-3.20 (m, 1H minor rotamer), 3.01 (s, 3H minor rotamer), 2.74 (s, 3H major rotamer), 1.99-1.00 (m, 10H per rotamer). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 169.0, 168.8, 149.7, 149.7, 148.9, 148.7, 131.4, 131.1, 115.5, 115.4, 110.3, 110.0, 109.6, 109.4, 58.5, 56.3, 56.3, 56.3, 56.2, 52.7, 31.0, 31.0, 30.7, 29.9, 29.5, 27.2, 25.7, 25.7, 25.5, 25.3. **HRMS** Calculated for $C_{16}H_{22}BrNO_3$ (M^+) 355.0783, Found 355.0789. **IR (ν_{max}/cm^{-1})** 3433, 2933, 2856, 1631, 1256, 1213. **R_f** 0.40 (80% EtOAc in petroleum ether).



2-Bromo-*N*-cyclohexyl-4-fluoro-*N*-methylbenzamide (3.30) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromo-4-fluorobenzoic acid (0.650 g, 2.99 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (0.58 mL, 4.48 mmol, 1.50 equiv). The product was purified by silica gel flash chromatography (45% EtOAc in petroleum ether) to afford 0.49 g of a white solid in 52% yield. Mixture of rotamers in a ratio of 1.1:1.

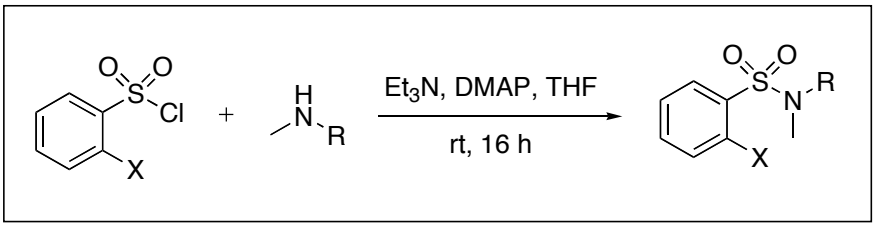
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.35 (dd, J = 8.2, 2.6 Hz, 1H minor rotamer), 7.31 (dd, J = 8.4, 2.4 Hz, 1H major rotamer), 7.28-7.18 (m, 1H per rotamer), 7.08 (ddd, J = 8.4, 8.4, 2.0 Hz, 1H per rotamer), 4.62-4.56 (m, 1H major rotamer), 3.16-3.09 (m, 1H minor rotamer), 3.00 (s, 3H minor rotamer), 2.69 (s, 3H major rotamer), 1.91-0.97 (m, 10H per rotamer). **^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS)** Due to the presence of rotamers and ^{19}F-^{13}C coupling, peaks are listed as they appear on the spectrum. 168.4, 168.2, 163.9, 163.8, 160.5, 160.5, 135.7, 135.7, 135.5, 135.4, 128.9, 128.8, 128.4, 128.3, 120.6, 120.4, 120.3, 120.1, 119.9, 119.7, 119.7, 119.5, 115.5, 115.3, 115.2, 115.0, 58.7, 52.8, 31.0, 30.8, 30.8, 29.9, 29.5, 27.2, 25.7, 25.7, 25.6, 25.2. **HRMS** Calculated for $C_{14}H_{17}BrFNO$ (M^+) 313.0478, Found 313.0480. **IR (ν_{max}/cm^{-1})** 2931, 2856, 1637, 1597, 1407, 1257, 1072, 870, 584. **R_f** 0.26 (40% EtOAc in petroleum ether). **Melting Point** 118-120 °C.



2-Bromo-*N*-methyl-*N*-phenylbenzamide (3.44) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (0.600 g, 2.99 mmol, 1.00 equiv) and *N*-methylphenylamine (0.48 mL, 4.48 mmol, 1.50 equiv). The product was purified by silica gel flash chromatography (20% EtOAc in petroleum ether) to afford 0.83 g of a clear oil in 96% yield. Mixture of rotamers in a ratio of 7.5:1.

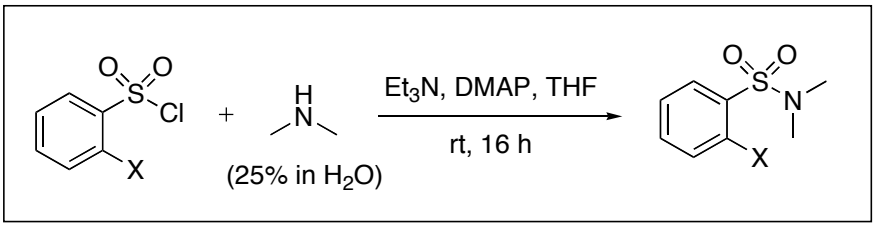
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.45-6.99 (m, 9H per rotamer), 3.51 (s, 3H major rotamer), 3.21 (s, 3H minor rotamer). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** (only signals for major rotamer were found) δ 169.0, 143.3, 138.7, 132.8, 129.9, 129.1, 129.0, 127.3, 127.0, 126.8, 119.9, 37.3. **HRMS** Calculated for $C_{14}H_{12}BrNO$ (M^+) 289.0102, Found 289.0081. **IR (ν_{max}/cm^{-1})** 3060, 2941, 1655, 1564, 1475, 698. **R_f** 0.16 (20% EtOAc in petroleum ether).

8.3.3 Synthesis and Characterization of Sulfonamide Starting Materials



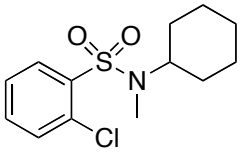
General Procedure A for the Preparation of *N*-methylsulfonamides

To a solution of the desired *N*-methylamine (1.00 equiv) in THF (0.050 M) at room temperature and under argon was added the corresponding 2-halobenzenesulfonyl chloride (1.00 equiv), triethylamine (1.10 equiv) and 4-dimethylaminopyridine (0.20 equiv). The resulting solution was stirred overnight after which the reaction was quenched with 1M HCl, extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



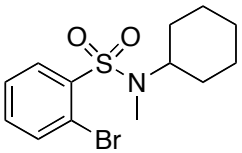
General Procedure B for the Preparation of *N*-methylsulfonamides

To a solution of dimethylamine (25% aqueous solution, 2.00 equiv) in THF (0.050 M) at room temperature and under argon was added the desired 2-halobenzenesulfonyl chloride (1.00 equiv), triethylamine (1.10 equiv) and 4-dimethylaminopyridine (0.20 equiv). The resulting solution was stirred overnight after which the reaction was quenched with 1M HCl, extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



2-Chloro-*N*-cyclohexyl-*N*-methylbenzenesulfonamide (3.31) *General procedure A* for the preparation of *N*-methylsulfonamides was followed using 2-chlorobenzenesulfonyl chloride (0.600 g, 2.84 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (0.37 mL, 2.84 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in petroleum ether) to afford 0.68 g of a white solid in 83% yield.

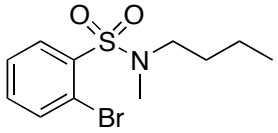
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.11 (1H, dd, *J* = 7.8, 1.5 Hz), 7.51-7.44 (2H, m), 7.40-7.36 (1H, m), 3.65 (1H, dddd, *J* = 11.8, 11.8, 3.7, 3.7 Hz), 2.85 (3H, s), 1.78-0.97 (10H, m). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 137.9, 133.2, 132.0, 132.0, 131.9, 126.8, 56.5, 30.4, 28.5, 25.7, 25.3. **HRMS** calculated for $C_{13}H_{18}ClNO_2S$ (M+) 287.0747; Found: 287.0755. **IR (ν_{max}/cm^{-1})** 3436, 2934, 2858, 1453, 1332, 1042, 1002, 961, 771, 604. **R_f** 0.26 on silica gel (20% EtOAc in petroleum ether).



2-Bromo-*N*-cyclohexyl-*N*-methylbenzenesulfonamide (3.32) *General procedure A* for the preparation of *N*-methylsulfonamides was followed using 2-bromobenzenesulfonyl chloride (0.700 g, 2.74 mmol, 1.00 equiv) and *N*-methylcyclohexylamine (0.36 mL, 2.74 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (8% EtOAc in petroleum ether) to afford 0.87 g of a white solid in 96% yield.

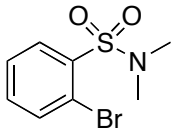
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) *δ* 8.16 (dd, *J* = 7.8, 2.1 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.44 (ddd, *J* = 7.5, 7.5, 1.5 Hz, 1H), 7.36 (ddd, *J* = 7.8, 7.5, 1.8 Hz, 1H), 3.65 (dddd, *J* = 11.7, 11.7, 3.6, 3.6 Hz, 1H), 2.84 (s, 3H), 1.79-0.96 (m, 10H). **^{13}C NMR**

(100 MHz, $CDCl_3$, 293K, TMS) δ 139.6, 135.7, 133.4, 132.5, 127.5, 120.5, 56.7, 30.6, 28.8, 25.9, 25.5. **HRMS** Calculated for $C_{13}H_{18}BrNO_2S$ (M^+) 331.0242, Found 331.0240. **IR (ν_{max}/cm^{-1})** 3070, 2934, 2857, 1575, 1330, 1156, 592. **R_f** 0.33 (10% EtOAc in petroleum ether). **Melting Point** 100-101 °C.



2-Bromo-*N*-butyl-*N*-methylbenzenesulfonamide (3.34) *General procedure A* for the preparation of *N*-methylsulfonamides was followed using 2-bromobenzenesulfonyl chloride (0.700 g, 2.74 mmol, 1.00 equiv) and *N*-methylbutylamine (0.33 mL, 2.74 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in petroleum ether) to afford 0.79 g of a clear oil in 94% yield.

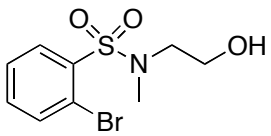
^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 7.8, 1.8 Hz, 1H), 7.73 (dd, J = 7.8, 1.2 Hz, 1H), 7.44 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.37 (ddd, J = 7.5, 7.5, 1.8 Hz, 1H), 3.24 (t, J = 7.5 Hz, 2H), 2.88 (s, 3H), 1.62-1.49 (m, 2H), 1.34-1.23 (m, 2H), 0.87 (t, J = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 138.8, 135.7, 133.4, 132.2, 127.5, 120.3, 49.9, 34.2, 29.8, 19.7, 13.7. **HRMS** Calculated for $C_{11}H_{16}BrNO_2S$ (M^+ - C_3H_7) 263.9517, Found 263.9531. **IR (ν_{max}/cm^{-1})** 3089, 3066, 2959, 2932, 2872, 1575, 1337, 1027, 758. **R_f** 0.29 (10% EtOAc in petroleum ether).



2-Bromo-*N*,*N*-dimethylbenzenesulfonamide (3.36) *General procedure B* for the preparation of *N*-methylsulfonamides was followed using 2-bromobenzenesulfonyl chloride (0.700 g, 2.74 mmol, 1.00 equiv) and dimethylamine (0.99 mL, 5.48 mmol, 2.00 equiv). The product was purified by silica gel flash chromatography (15% EtOAc in petroleum ether) to afford 0.66 g of a beige solid in 91% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 8.08 (dd, J = 7.8, 2.1 Hz, 1H), 7.74 (dd, J = 7.8, 1.5 Hz, 1H), 7.44 (ddd, J = 7.5, 7.5, 1.5 Hz, 1H), 7.37 (ddd, J = 7.8, 7.5, 2.1 Hz, 1H), 2.89 (s, 6H).

Exhibited spectral data identical to a previous report.[177]

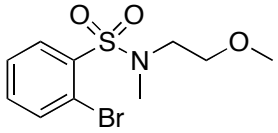


2-Bromo-*N*-(2-hydroxyethyl)-*N*-methylbenzenesulfonamide *General procedure A* for the preparation of *N*-methylsulfonamides was followed using 2-bromobenzenesulfonyl chloride (0.700 g, 2.74 mmol, 1.00 equiv) and *N*-methylethanolamine (0.22 mL, 2.74 mmol,

[177] Pines, S. H.; Purick, R. M.; Reamer, R. A.; Gal, G. *J. Org. Chem.* **1978**, *43*, 1337-1342.

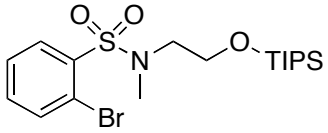
1.00 equiv). The product was purified by silica gel flash chromatography (60% EtOAc in petroleum ether) to afford 0.70 g of a cloudy oil in 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.12 (dd, J = 7.8, 1.8 Hz, 1H), 7.76 (dd, J = 7.8, 1.3 Hz, 1H), 7.47 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.40 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 3.79 (br t, J = 4.8 Hz, 2H), 3.42 (t, J = 5.3 Hz, 2H), 2.99 (s, 3H), 2.18 (br s, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 138.2, 135.7, 133.7, 132.5, 127.6, 120.2, 60.1, 52.2, 35.4. **HRMS** Calculated for $C_9H_{12}BrNO_3S$ (M^+) 294.9701, Found 294.9694. **IR (ν_{max}/cm^{-1})** 3423, 1643, 1448, 1329, 1158, 1026, 981, 912, 745. **R_f** 0.19 (50% EtOAc in petroleum ether)



2-Bromo-*N*-(2-methoxyethyl)-*N*-methylbenzenesulfonamide (3.38) Sodium hydride (60 wt%) (0.270 g, 6.80 mmol, 2.00 equiv) was suspended in *N*,*N*-dimethylformamide (3.0 mL) and stirred at 0 °C under argon for 10 minutes. A solution of 2-bromo-*N*-(2-hydroxyethyl)-*N*-methylbenzenesulfonamide (1.00 g, 3.40 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (3.8 mL) was then added to the suspension and stirred for 15 minutes. Next, iodomethane (0.42 mL, 6.80 mmol, 2.00 equiv) was added dropwise and stirred for an additional 30 minutes. A saturated solution of NH_4Cl (10 mL) was then added to the reaction mixture and the organic products were extracted with dichloromethane (10 mL x 3). The organic phases were combined and washed with brine, dried with $MgSO_4$, and evaporated under reduced pressure. The product was purified by silica gel flash chromatography (30% EtOAc in petroleum ether) to afford 0.95 g of a yellow oil in 90% yield.

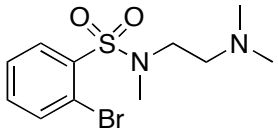
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 7.7, 1.9 Hz, 1H), 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.44 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.38 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 3.57-3.54 (m, 2H), 3.48-3.45 (m, 2H), 3.32 (s, 3H), 2.98 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 138.8, 135.6, 133.4, 132.2, 127.5, 120.3, 71.4, 58.8, 49.7, 35.9. **HRMS** Calculated for $C_{10}H_{14}BrNO_3S$ (M^+) 306.9878, Found 306.9876. **IR (ν_{max}/cm^{-1})** 2929, 2886, 1443, 1333, 1156, 1114, 1026, 762, 745, 579. **R_f** 0.65 (50% ethyl acetate in petroleum ether)



2-Bromo-*N*-methyl-*N*-(2-(triisopropylsilyloxy)ethyl)benzenesulfonamide (3.40) Imidazole (0.280 g, 4.08 mmol, 2.00 equiv) was dissolved in *N*,*N*-dimethylformamide (3.5 mL). A solution of 2-bromo-*N*-(2-hydroxyethyl)-*N*-methylbenzenesulfonamide (0.600 g, 2.04 mmol, 1.00 equiv) in *N*,*N*-dimethylformamide (4.0 mL) and chlorotriisopropylsilane (0.430 g, 2.24 mmol, 1.10 equiv) were added to the solution, which was left to stir overnight. The reaction mixture was then extracted with ether (10 mL x 3). The organic phases were combined and washed with brine, dried with $MgSO_4$, and concentrated under reduced

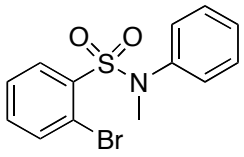
pressure. The product was purified by silica gel flash chromatography (5% EtOAc in petroleum ether) to afford 0.83 g of a white solid in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 7.8, 1.8 Hz, 1H), 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.43 (ddd, J = 7.6, 7.6, 1.3 Hz, 1H), 7.37 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 3.87 (t, J = 5.9 Hz, 2H), 3.42 (t, J = 5.9 Hz, 2H), 3.02 (s, 3H), 1.13-1.01 (m, 21H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 138.9, 135.7, 133.3, 132.2, 127.4, 120.2, 62.8, 52.4, 36.3, 17.9, 11.8. **HRMS** Calculated for $C_{18}H_{32}BrNO_3SSi$ (M^+ - C_3H_7) 406.0508, Found 406.0521. **IR (ν_{max}/cm^{-1})** 2949, 2867, 1462, 1337, 1157, 1098, 989, 879, 770, 687. **R_f** 0.27 (5% ethyl acetate in petroleum ether). **Melting Point** 60-61°C.



2-Bromo-*N*-(2-(dimethylamino)ethyl)-*N*-methylbenzenesulfonamide (3.42) *General procedure A* for the preparation of *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (60% EtOAc and 5% triethylamine in petroleum ether) to afford the product as a dark orange oil in 49% yield.

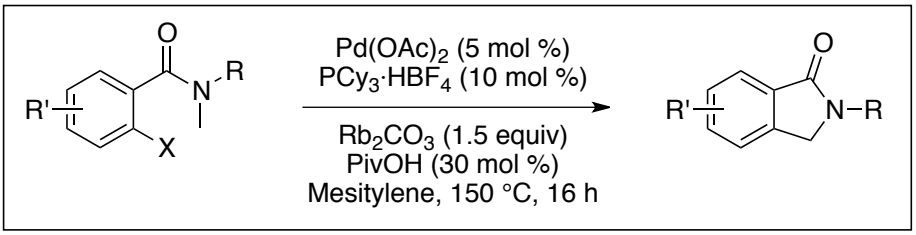
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.11 (dd, J = 7.8, 1.8 Hz, 1H), 7.74 (dd, J = 7.8, 1.3 Hz, 1H), 7.44 (ddd, J = 7.6, 7.6, 1.4 Hz, 1H), 7.38 (ddd, J = 7.6, 7.6, 1.8 Hz, 1H), 3.36 (t, J = 7.2 Hz, 2H), 2.95 (s, 3H), 2.49 (t, J = 7.2 Hz, 2H), 2.22 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 138.7, 135.6, 133.3, 132.2, 127.4, 120.3, 57.3, 48.0, 45.5, 35.0. **HRMS** Calculated for $C_{11}H_{17}BrN_2O_2S$ (M^+ - C_2H_6N) 275.9694, Found 275.9718. **IR (ν_{max}/cm^{-1})** 3422, 2944, 2771, 1576, 1446, 1333, 1157, 1026, 747, 580. **R_f** 0.34 (60% ethyl acetate and 5% triethylamine in petroleum ether).



2-Bromo-*N*-methyl-*N*-phenylbenzenesulfonamide (3.46) *General procedure A* for the preparation of *N*-methylsulfonamides was followed using 2-bromobenzenesulfonyl chloride (0.600 g, 2.35 mmol, 1.00 equiv) and *N*-methylaniline (0.25 mL, 2.35 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in petroleum ether) to afford 0.56 g of a pale yellow oil in 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.91-7.88 (m, 1H), 7.74-7.71 (m, 1H), 7.37-7.19 (m, 7H), 3.44 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 140.8, 138.0, 135.5, 133.6, 132.8, 129.1, 127.4, 127.3, 127.0, 120.5, 39.5. **HRMS** Calculated for $C_{13}H_{12}BrNO_2S$ (M^+) 324.9772, Found 324.9766. **IR (ν_{max}/cm^{-1})** 3436, 1631, 1493, 1339, 1158, 1068, 1026, 879, 763. **R_f** 0.26 (10% EtOAc in petroleum ether)

8.3.4 General Procedures and Characterization for C(sp^3)-H Arylation Adjacent to Amides and Sulfonamides



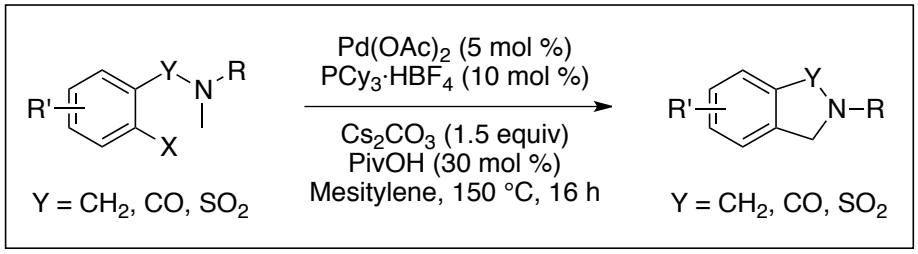
General Procedure A for the Arylation of *N*-Methylamides

A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The flame-dried test tube was brought into the glovebox and dry Rb_2CO_3 (0.872 mmol, 1.50 equiv) was added after which the tube was brought back onto the bench top. $Pd(OAc)_2$ (0.0291 mmol, 5.00 mol %) and $PCy_3{\cdot}HBF_4$ (0.0581 mmol, 10.0 mol %) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). The desired starting material (0.581 mmol, 1.00 equiv) and PivOH (0.174 mmol, 30.0 mol %) were added as degassed stock solutions in mesitylene (0.32 M and 0.16 M respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL) and transferred to a 200 mL round bottom flask containing 60 mL of CH_2Cl_2 and 60 mL of a saturated solution of NH_4Cl. After stirring at room temperature for 15-30 minutes, the mixture was separated and the aqueous layer was extracted with 60 mL CH_2Cl_2 (x2). The combined organic phases were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure and purified by silica gel flash chromatography.

General Procedure B for the Arylation of *N*-Methylamides

A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The flame-dried test tube was brought into the glovebox and dry Rb_2CO_3 (0.872 mmol, 1.50 equiv) was added after which the tube was brought back onto the bench top. The desired starting material (0.581 mmol, 1.00 equiv), $Pd(OAc)_2$ (0.0291 mmol, 5.00 mol %) and $PCy_3{\cdot}HBF_4$ (0.0581 mmol, 10.0 mol %) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). PivOH (0.174 mmol, 30.0 mol %) was added as a degassed stock solution in mesitylene (0.20 M) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL)

and transferred to a 200 mL round bottom flask containing 60 mL of CH_2Cl_2 and 60 mL of a saturated solution of NH_4Cl. After stirring at room temperature for 15-30 minutes, the mixture was separated and the aqueous layer was extracted with 60 mL CH_2Cl_2 (x2). The combined organic phases were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure and purified by silica gel flash chromatography.



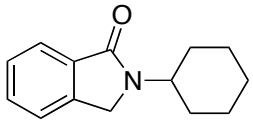
General Procedure C for the Arylation of *N*-Methylamides or *N*-Methylsulfonamides

A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The desired starting material (0.581 mmol, 1.00 equiv), $Pd(OAc)_2$ (0.0291 mmol, 5.00 mol %), $PCy_3{\cdot}HBF_4$ (0.0581 mmol, 10.0 mol %) and Cs_2CO_3 (0.872 mmol, 1.50 equiv) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). PivOH (0.174 mmol, 30.0 mol %) was added as a degassed stock solution in mesitylene (0.20 M) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL) and transferred to a 200 mL round bottom flask containing 60 mL of CH_2Cl_2 and 60 mL of a saturated solution of NH_4Cl. After stirring at room temperature for 15-30 minutes, the mixture was separated and the aqueous layer was extracted with 60 mL CH_2Cl_2 (x2). The combined organic phases were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure and purified by silica gel flash chromatography.

General Procedure D for the Arylation of *N*-Methylamides or *N*-Methylsulfonamides

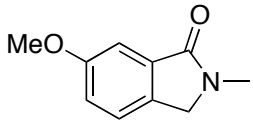
A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. $Pd(OAc)_2$ (0.0291 mmol, 5.00 mol %), $PCy_3{\cdot}HBF_4$ (0.0581 mmol, 10.0 mol %) and Cs_2CO_3 (0.872 mmol, 1.50 equiv) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). The desired starting material (0.581 mmol, 1.00 equiv) and PivOH (0.174 mmol, 30.0 mol %) were added as degassed stock solutions in mesitylene (0.32 M and 0.16 M respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Upon cooling to room temperature, the reaction was quenched with EtOAc (1 mL) and transferred to a 200 mL round bottom flask containing 60 mL of CH_2Cl_2 and 60 mL of a

saturated solution of NH_4Cl. After stirring at room temperature for 15-30 minutes, the mixture was separated and the aqueous layer was extracted with 60 mL CH_2Cl_2 (x2). The combined organic phases were washed with brine, dried with Na_2SO_4, concentrated under reduced pressure and purified by silica gel flash chromatography.



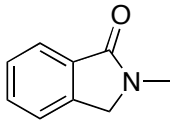
2-Cyclohexylisoindolin-1-one (3.16) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (30% EtOAc in petroleum ether) to afford the product as a beige solid in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.86-7.84 (m, 1H), 7.54-7.52 (m, 1H), 7.47-7.44 (m, 2H), 4.35 (s, 2H), 4.30-4.22 (m, 1H), 1.89-1.45 (m, 10H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 168.0, 141.4, 133.6, 131.1, 128.0, 123.7, 122.8, 50.6, 46.1, 31.6, 25.8, 25.7. **HRMS** Calculated for $C_{14}H_{17}NO$ (M^+) 215.1310, Found 215.1288. **IR (ν_{max}/cm^{-1})** 2931, 2852, 1681, 735. **R_f** 0.27 (30% EtOAc in petroleum ether). **Melting Point** 78-82 °C.



6-Methoxy-2-methylisoindolin-1-one (3.18) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (70% EtOAc in petroleum ether) to afford the product as a beige solid in 56% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.30-7.34 (m, 2H), 7.08 (dd, J = 8.4, 2.4 Hz, 1H), 4.31 (s, 2H), 3.86 (s, 3H), 3.20 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 168.8, 160.1, 134.4, 133.2, 123.5, 119.7, 106.6, 55.8, 51.8, 29.7. **HRMS** Calculated for $C_{10}H_{11}NO_2$ (M^+) 177.0790, Found 177.0797. **IR (ν_{max}/cm^{-1})** 2923, 1675, 1494, 1276. **R_f** 0.24 (70% EtOAc in petroleum ether). **Melting Point** 83-84 °C.

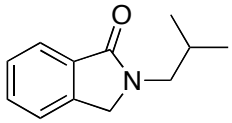


2-Methylisoindolin-1-one (3.21) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (70% EtOAc in petroleum ether) to afford the product as a yellow solid in 76% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.84 (d, J = 7.2 Hz, 1H), 7.55-7.43 (m, 3H), 4.38 (s, 2H), 3.21 (s, 3H).

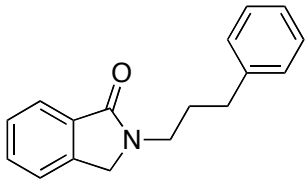
Exhibited spectral data identical to a previous report.[178]

[178] Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. L. *J. Org. Chem.* **1978**, *43*, 3719-3723.



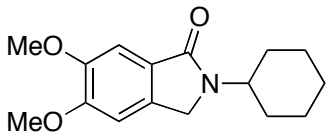
2-Cyclohexylisoindolin-1-one (3.25) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford the product as a beige solid in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.84 (d, J = 7.6 Hz, 1H), 7.52 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.47-7.42 (m, 2H), 4.38 (s, 2H), 3.43 (d, J = 7.6 Hz, 2H), 2.11-2.01 (m, 1H), 0.96 (d, J = 6.8 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 168.8, 141.1, 133.0, 131.1, 128.0, 123.8, 122.6, 50.5, 50.0, 27.8, 20.1. **HRMS** Calculated for $C_{12}H_{15}NO$ (M^+) 189.1154, Found 189.1128. **IR (ν_{max}/cm^{-1})** 2959, 2871, 1687, 1620, 1471, 1456, 1415, 1388, 1297, 1225, 1212, 1101, 735, 685. **R_f** 0.24 (40% EtOAc in petroleum ether).



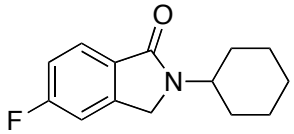
2-(3-Phenylpropyl)isoindolin-1-one (3.27) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford the product as a beige solid in 37% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.86 (d, J = 7.5 Hz, 1H), 7.53 (ddd, J = 7.3, 7.3, 0.9 Hz, 1H), 7.45 (m, 2H), 7.29-7.18 (m, 5H), 4.36 (s, 2H), 3.68 (t, J = 7.3 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.01 (tt, J = 7.6, 7.6 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 168.7, 141.5, 141.2, 133.1, 131.3, 128.6, 128.5, 128.2, 126.1, 123.8, 122.8, 50.0, 42.3, 33.3, 30.3. **HRMS** Calculated for $C_{17}H_{17}NO$ (M^+) 251.1310, Found 251.1330. **IR (ν_{max}/cm^{-1})** 2936, 2865, 1685, 1453. **R_f** 0.26 (40% EtOAc in petroleum ether). **Melting Point** 52-54 °C.



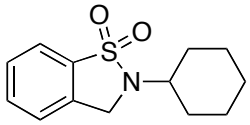
2-Cyclohexyl-5,6-dimethoxyisoindolin-1-one (3.29) *General procedure A* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (80% EtOAc in petroleum ether) to afford the product as a orange oil in 44% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.32 (s, 1H), 6.92 (s, 1H), 4.27 (s, 2H), 4.24-4.18 (m, 1H), 3.94 (s, 6H), 1.89-1.40 (m, 10H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 168.3, 152.4, 149.8, 134.9, 125.9, 105.4, 105.1, 56.4, 50.7, 45.8, 31.7, 29.8, 25.8, 25.7. **HRMS** Calculated for $C_{16}H_{21}NO_3$ (M^+) 275.1521, Found 275.1516. **IR (ν_{max}/cm^{-1})** 2930, 2849, 1669, 1501, 1301, 1221, 1096. **R_f** 0.33 (90% EtOAc in petroleum ether).



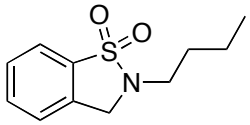
2-Cyclohexyl-5-fluoroisoindolin-1-one (3.31) *General procedure C* for the arylation at *N*-methylamides was followed. The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford the product as a beige solid in 70% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.83-7.80 (m, 1H), 7.17-7.12 (m, 2H), 4.33 (s, 2H), 4.26-4.19 (m, 1H), 1.88-1.15 (m, 10H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 167.0, 165.0 (d, J_F = 248.7 Hz), 143.7 (d, J_F = 9.9 Hz), 129.5 (d, J_F = 2.0 Hz), 125.6 (d, J_F = 9.7 Hz), 115.8 (d, J_F = 23.2 Hz), 110.2 (d, J_F = 23.9 Hz), 50.8, 45.9 (d, J_F = 2.7 Hz), 31.5, 25.7, 25.6. **HRMS** Calculated for $C_{14}H_{16}FNO$ (M^+) 233.1216, Found 233.1223 **IR (ν_{max}/cm^{-1})** 3420, 2934, 1635, 1252. **R_f** 0.32 (40% EtOAc in petroleum ether). **Melting Point** 52-53 °C.



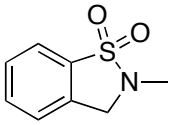
2-Cyclohexyl-2,3-dihydro-1,1-dioxo-1,2-benzisothiazole (3.33) *General procedure C* for the arylation at *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (20% EtOAc in petroleum ether) to afford the product as a beige solid in 62% yield.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.79 (dd, J = 7.7, 0.4 Hz, 1H), 7.58 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.53-7.48 (m, 1H), 7.40-7.37 (m, 1H), 4.40 (s, 2H), 3.69 (dddd, J = 11.1, 11.1, 3.6, 3.6 Hz, 1H), 2.12-1.10 (m, 10H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 135.5, 133.7, 132.4, 129.0, 124.4, 121.2, 52.9, 45.6, 31.4, 25.5, 25.5. **HRMS** Calculated for $C_{13}H_{17}NO_2S$ (M^+) 251.0980, Found 251.1007. **IR (ν_{max}/cm^{-1})** 3422, 1635, 1340. **R_f** 0.26 (20% EtOAc in petroleum ether). **Melting Point** 131-133 °C.



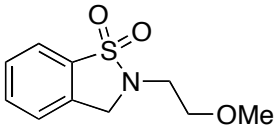
2-Butyl-2,3-dihydro-1,1-dioxo-1,2-benzisothiazole (3.35) *General procedure D* for the arylation at *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (20% to 25% EtOAc in petroleum ether) to afford the product as an orange oil in 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.81 (d, J = 7.6 Hz, 1H), 7.59 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.52 (dd, J = 7.6, 7.6 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 4.36 (s, 2H), 3.29 (dd, J = 7.2, 7.2 Hz, 2H), 1.77-1.70 (m, 2H), 1.51-1.42 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 135.2, 133.7, 132.6, 129.1, 124.4, 121.4, 50.5, 43.8, 29.9, 20.0, 13.6. **HRMS** Calculated for $C_{11}H_{15}NO_2S$ (M^+) 225.0823, Found 225.0799. **IR (ν_{max}/cm^{-1})** 2960, 2874, 1732, 1336, 1297. **R_f** 0.26 (20% EtOAc in petroleum ether).



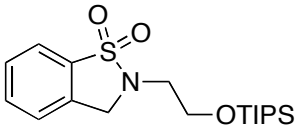
2,3-Dihydro-1,1-dioxo-2-methyl-1,2-benzisothiazole (3.37) *General procedure C* for the arylation at *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (30% EtOAc in petroleum ether) to afford the product as a while solid in 56% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.81 (d, J = 7.6 Hz, 1H), 7.60 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H), 7.55-7.51 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 4.34 (s, 2H), 2.96 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 134.9, 133.8, 132.7, 129.1, 124.4, 121.5, 52.6, 30.1. **HRMS** Calculated for $C_8H_9NO_2S$ (M^+) 183.0354, Found 183.0335. **IR (ν_{max}/cm^{-1})** 3068, 2931, 2821, 1476, 1286, 1165. **R_f** 0.20 (30% EtOAc in petroleum ether). **Melting Point** 124-126 °C.



2,3-Dihydro-1,1-dioxo-2-(2-methoxyethyl)-1,2-benzisothiazole (3.39) *General procedure D* for the arylation of *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (35% EtOAc to 50% EtOAc in petroleum ether) to afford the product as a dark orange oil in 59% yield.

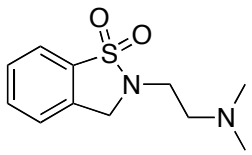
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.80 (d, J = 7.7 Hz, 1H), 7.59 (ddd, J = 7.3, 7.3, 1.2 Hz, 1H), 7.51 (ddd, J = 7.6, 7.6, 0.8 Hz, 1H), 7.39 (ddd, J = 7.4, 0.8, 0.8 Hz, 1H), 4.52 (s, 2 H), 3.72 (t, J = 5.1 Hz, 2H), 3.50 (t, J = 5.1 Hz, 2H), 3.40 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 134.6, 134.1, 132.6, 128.9, 124.3, 121.2, 71.7, 58.8, 51.8, 43.4. **HRMS** Calculated for $C_{10}H_{13}NO_3S$ (M^+ - CH_3O) 196.0432, Found 196.0419. **IR (ν_{max}/cm^{-1})** 3462, 2927, 1638, 1456, 1291, 1175, 1120, 759, 737, 696, 570. **R_f** 0.15 (35% ethyl acetate in petroleum ether)



2,3-Dihydro-1,1-dioxo-2-(2-triisopropylsilyloxyethyl)-1,2-benzisothiazole (3.41) *General procedure C* for the arylation of *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (5% EtOAc and 20% toluene in petroleum ether) to afford the product as a yellow oil in 47% yield.

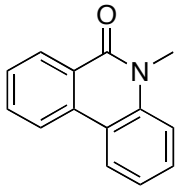
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.80 (dd, J = 7.7, 0.4 Hz, 1H), 7.59 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.52 (ddd, J = 7.6, 7.6, 0.9 Hz, 1H), 7.38 (ddd, J = 7.7, 0.8, 0.8 Hz, 1H), 4.58 (s, 2H), 4.04 (t, J = 5.3 Hz, 2H), 3.46 (t, J = 5.3 Hz, 2H), 1.17-1.04 (m, 21H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 134.7, 134.3, 132.5, 128.9, 124.3, 121.3, 63.2, 52.1, 46.1, 17.9, 11.8. **HRMS** Calculated for $C_{18}H_{31}NO_3SSi$ (M^+ - C_3H_7) 326.1246, Found

326.1248. **IR (ν_{max}/cm^{-1})** 3422, 2943, 2866, 1645, 1463, 1345, 1167, 1111, 991, 883, 634, 691. **R_f** 0.27 (5% ethyl acetate in petroleum ether).



2,3-Dihydro-1,1-dioxo-2-(2-dimethylaminoethyl)-1,2-benzisothiazole (3.43) *General procedure D* for the arylation of *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (80% EtOAc and 5% triethylamine in petroleum ether) to afford the product as a dark yellow oil in 71% yield.

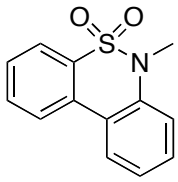
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.80 (d, J = 7.7 Hz, 1H), 7.59 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 7.52 (dd, J = 7.4, 7.4 Hz, 1H), 7.38 (dd, J = 7.7 Hz, 1H), 4.48 (s, 2H), 3.41 (t, J = 6.6 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.31 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 134.9, 134.0, 132.7, 129.0, 124.4, 121.4, 57.6, 51.0, 45.5, 41.7. **HRMS** Calculated for $C_{11}H_{16}N_2O_2S$ (M^+ - C_2H_6N) 196.0432, Found 196.0415. **IR (ν_{max}/cm^{-1})** 3442, 2108, 1642, 1462, 1287, 1169, 1157, 1130, 914, 750, 570. **R_f** 0.21 (80% ethyl acetate and 5% triethylamine in petroleum ether).



5-Methylphenanthridin-6(5*H*)-one (3.45) *General procedure A* for the arylation of *N*-methylamides was followed. The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford the product as a white solid in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.56 (ddd, J = 8.0, 1.5, 0.5 Hz, 1H), 8.29 (dd, J = 8.0, 1.2 Hz, 1H), 8.28 (ddd, J = 8.0, 0.4, 0.4 Hz, 1H), 7.76 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 7.59 (ddd, J = 8.0, 7.2, 1.2 Hz, 1H), 7.56 (ddd, J = 7.9, 6.5, 1.3 Hz, 1H), 7.42 (dd, J = 8.4, 1.0 Hz, 1H), 7.33 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 3.82 (s, 3H).

Exhibited spectral data identical to a previous report.[179]



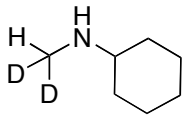
***N*-Methyl-5,5-dioxo-6*H*-dibenzo[*c*,*e*][1,2]thiazine (3.47)** *General procedure D* for the arylation of *N*-methylsulfonamides was followed. The product was purified by silica gel flash chromatography (20% EtOAc in petroleum ether) to afford the product as a pale yellow solid in 83% yield.

[179] Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron* **1991**, *47*, 10119-10128.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.03-8.01 (m, 2H), 7.98 (ddd, J = 8.0, 0.5, 0.5 Hz, 1H), 7.72 (ddd, J = 8.0, 7.5, 1.4 Hz, 1H), 7.58 (ddd, J = 7.6, 7.6, 1.0 Hz, 1H), 7.52 (ddd, J = 8.1, 7.4, 1.5 Hz, 1H), 7.37-7.31 (m, 2H), 3.46 (s, 3H).
Exhibited spectral data identical to a previous report.[180]

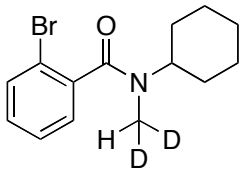
8.3.5 Kinetic Isotope Effect Experiments

Preparation of Amide Starting Materials



***N*-(Dideuteromethyl)cyclohexylamine** Synthesized according to a reported procedure,[181] using *N*-phenylformamide (0.800 g, 6.29 mmol, 1.00 equiv), $LiAlD_4$ (0.530 g, 12.6 mmol, 2.00 equiv) and THF (16 mL, 0.40 M). The bulk of remaining THF was distilled off after work-up and a portion of the crude mixture (0.200 g, 1.74 mmol) was used in the subsequent reaction for the preparation of *N*-methylamide **3.x**. The remaining crude mixture was further purified by distillation for characterization purposes.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 2.87 (tt, J = 11.5, 3.8 Hz, 1H), 2.59 (dt, J = 3.3, 1.7 Hz, 1H), 2.18 (br d, J = 11.9 Hz, 2H), 1.89-1.84 (m, 2H), 1.66-1.53 (m, 3H), 1.31-1.19 (m, 3H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS)** δ 58.5, 29.3 (quintuplet, J_D = 21.5 Hz), 29.1, 24.9, 24.5. **HRMS** Calculated for $C_7H_{13}HD_2N$ (M^+) 115.1330, Found 115.1323. **IR (ν_{max}/cm^{-1})** 3416, 2934, 2859.



2-Bromo-*N*-(dideuteromethyl)-*N*-cyclohexylbenzamide (3.48) *General procedure B* for the preparation of *N*-methylamides was followed using 2-bromobenzoic acid (0.230 g, 1.16 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford 0.31 g of a white solid in 90% yield. Mixture of rotamers in a ratio of 1.1:1.

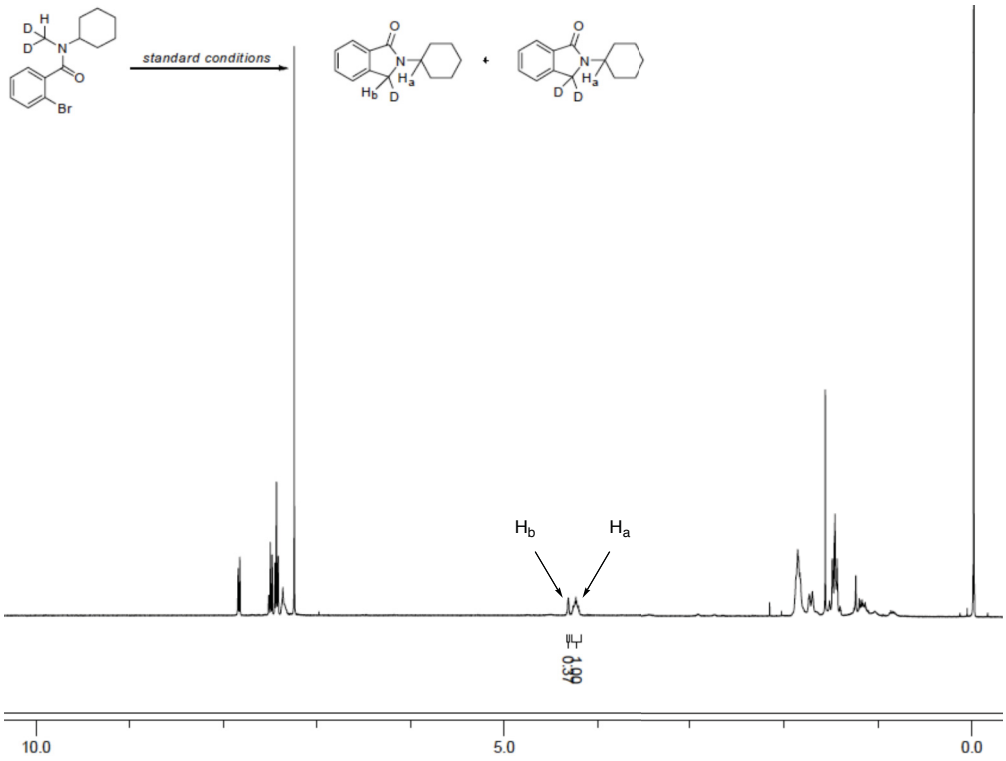
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.58 (dd, J = 8.0, 0.8 Hz, 1H minor rotamer), 7.55 (dd, J = 8.0, 0.8 Hz, 1H major rotamer), 7.34 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H major rotamer), 7.33 (ddd, J = 7.6, 7.6, 1.2 Hz, 1H minor rotamer), 7.25-7.18 (m, 2H per rotamer), 4.60 (dddd, J = 12.0, 12.0, 3.6, 3.6 Hz, 1H major rotamer), 3.14 (dddd, J = 11.5, 11.5, 4.0, 4.0 Hz, 1H minor rotamer), 2.97 (dt, J = 3.8, 1.9 Hz, 1H minor rotamer), 2.65 (dt, J = 3.9, 1.9 Hz, 1H major rotamer), 1.94-1.43 (m, 8H per rotamer), 1.14-0.94 (m, 2H per rotamer).
^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS) δ 169.1, 168.9, 139.5, 139.2, 133.0, 132.8, 130.0,

[180] Ryokawa, A.; Togo, H. *Tetrahedron* **2001**, *57*, 5915-5921.
[181] Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684-11688.

127.9, 127.7, 127.6, 127.2, 119.2, 119.1, 58.6, 52.5, 31.0, 30.8, 30.3 (quintuplet, J_D = 21.3 Hz), 30.0, 29.5, 26.7 (quintuplet, J_D = 20.9 Hz), 25.7, 25.7, 25.6, 25.2. **HRMS** Calculated for $C_{14}H_{16}D_2NOBr$ (M^+) 297.0697, Found 297.0698. **IR (ν_{max}/cm^{-1})** 3061, 2931, 2856, 2240, 1635, 1436, 1026. **R_f** 0.34 (40% EtOAc in petroleum ether). **Melting Point** 111-112 °C.

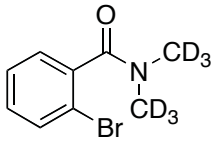
Intramolecular Arylation of 2-bromo-*N*-(dideuteromethyl)-*N*-cyclohexylbenzamide

General procedure A for the arylation at *N*-methylamides was followed using 2-bromo-*N*-(dideuteromethyl)-*N*-cyclohexylbenzamide **3.48** (0.100 g, 0.335 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (30% EtOAc in petroleum ether) to afford the product as a yellow oil in 65% yield. The ratio of products was determined by ^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) as outlined in Figure S1.



$k_H/k_D = 0.63/(0.37/2) = 3.4$

Figure S3.1 Intramolecular KIE determination



***d*$_6$-2-Bromo-*N,N*-dimethylbenzamide (*d*$_6$-3.20)** To a solution of NaH (60 wt %) (0.440 g, 11.0 mmol, 2.20 equiv) in dry DMF at 0 ˚C was added 2-bromobenzamide (1.00 g, 5.00 mmol, 1.00 equiv). The mixture was stirred for 10 minutes after which *d*$_3$-iodomethane (0.93 mL, 15.0 mmol, 3.00 equiv) was added dropwise and the reaction brought to room temperature. When judged complete by TLC, the reaction was quenched with D_2O and the organic products were extracted with EtOAc (x3). The combined organic layers were dried with $MgSO_4$, concentrated and purified by silica gel flash chromatography (10% EtOAc in CH_2Cl_2) to afford the product as a yellow oil in 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.58-7.55 (m, 1H), 7.38-7.34 (m, 1H), 7.28-7.21 (m, 2H). **^{2}H NMR (500 MHz, $CDCl_3$, 293K)** δ 3.10 (s, 3D), 2.82 (s, 3D). **^{13}C NMR (500 MHz, $CDCl_3$, 293K, TMS)** δ 169.1, 138.4, 132.6, 130.0, 127.6, 127.6, 119.0, 37.3 (septuplet, J_D = 21.0 Hz), 33.7 (septuplet, J_D = 21.1 Hz). **HRMS** Calculated for $C_9H_5D_6NOBr$ (M^+) 233.0322, Found 233.0322. **IR (ν_{max}/cm^{-1})** 3057, 2073, 1634, 1420, 1250. **R_f** 0.31 (10% EtOAc in CH_2Cl_2).

Intermolecular KIE Experiment

Side-by-side reactions were set-up following *general procedure D* for the arylation at *N*-methylamides with 2-bromo-*N,N*-dimethylbenzamide **3.20** (0.133 g, 0.581 mmol, 1.00 equiv) and *d*$_6$-2-bromo-*N,N*-dimethylbenzamide ***d*$_6$-3.20** (0.133 g, 0.581 mmol, 1.00 equiv). Aliquots were taken at 30 minute intervals for the first 2 hours and then at 1 hour intervals until 30% product formation. Product yield was determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard. Data points represent the average of two runs.

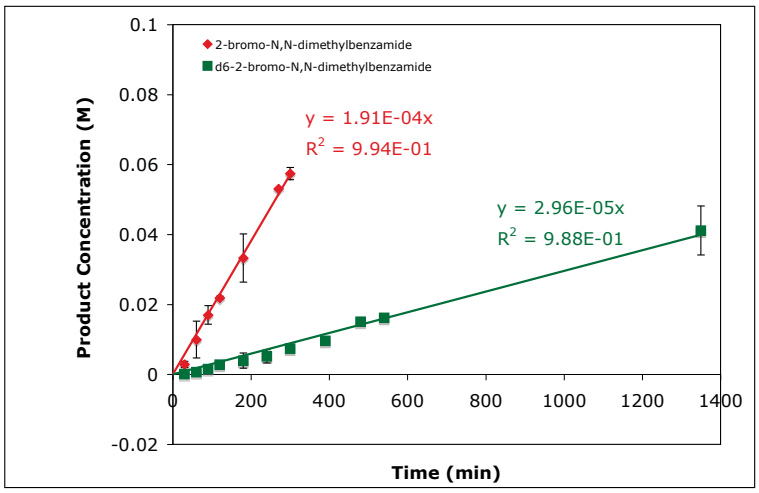


Figure S3.2 Rate comparison for the arylation of 2-bromo-*N,N*-dimethylbenzamide **3.20** (red) and *d*$_6$-2-bromo-*N,N*-dimethylbenzamide ***d*$_6$-3.20** (green). Data points represent the average of two runs.

$k_H/k_D = (1.91 \times 10^{-4}$ M/min) / (2.96×10^{-5} M/min) = 6.5

8.3.6 Kinetic Experiments

Initial rate dependence on the concentration of starting material

Reactions were performed using a modified version of *general procedure D* with 4 different concentrations of starting material (0.10 M, 0.20 M, 0.25 M and 0.40 M). A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The flame-dried test tube was brought into the glovebox. $Pd(PCy_3)_2$ (18.3 mg, 0.0291 mmol, 5.00 mol %), Cs_2CO_3 (0.284 g, 0.872 mmol, 1.50 equiv) and 1,3,5-trimethoxybenzene (97.7 mg, 0.581 mmol, 1.00 equiv) were added and the test tube was brought back onto the bench top. The test tube was placed under vacuum for 5 minutes and refilled with argon (x3). 2-Bromo-*N,N*-dimethylbenzamide (0.500 equiv, 1.00 equiv, 1.25 equiv and 2.00 equiv) and PivOH (17.8 mg, 0.174 mmol, 30.0 mol %) were added as degassed stock solutions in mesitylene (1.8 mL and 1.1 mL respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C. Aliquots were taken at 30 minute intervals for the first 2 hours and then at 1 hour intervals for a total of 5 hours. Product yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

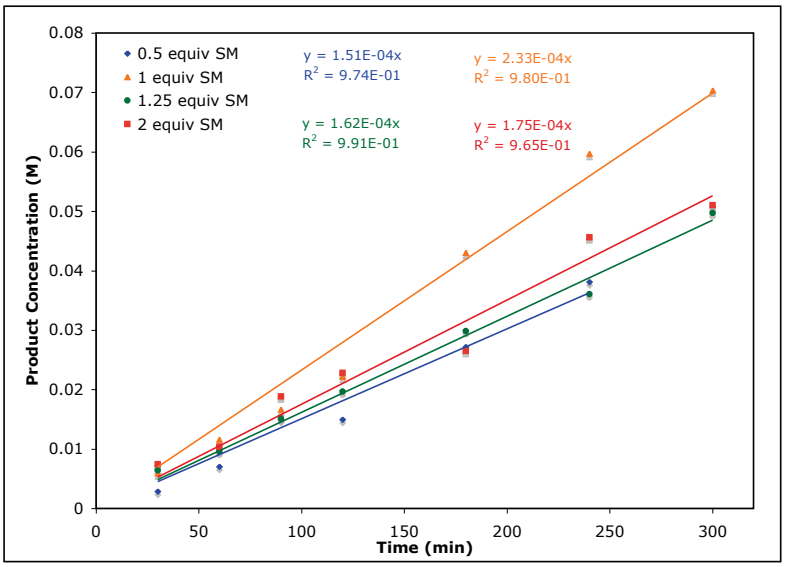


Figure S3.3 Increase in product concentration over the course of the reaction with various concentrations of 2-bromo-*N,N*-dimethylbenzamide : 0.10 M (blue), 0.20 M (orange), 0.25 M (green) and 0.40 M (red).

Logarithm of the initial rate dependence on the logarithm of the concentration of palladium

Reactions were performed using a modified version of *general procedure D* with 4 different concentrations of $Pd(PCy_3)_2$ (0.0050 M, 0.010 M, 0.015 M and 0.020 M). A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was

removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The flame-dried test tube was brought into the glovebox. $Pd(PCy_3)_2$ (2.50 mol %, 5.00 mol %, 7.50 mol % and 10.0 mol %), Cs_2CO_3 (0.284 g, 0.872 mmol, 1.50 equiv) and 1,3,5-trimethoxybenzene (97.7 mg, 0.581 mmol, 1.00 equiv) were added and the test tube was brought back onto the bench top. The test tube was put under vacuum for 5 minutes and refilled with argon (x3). 2-Bromo-*N,N*-dimethylbenzamide (132.5 mg, 0.5811 mmol, 1.000 equiv) and PivOH (17.8 mg, 0.174 mmol, 30.0 mol%) were added as degassed stock solutions in mesitylene (0.32 M and 0.16 M respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C. Aliquots were taken at 30 minute intervals for the first 2 hours and then at 1 hour intervals for a total of 5 hours. Product yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

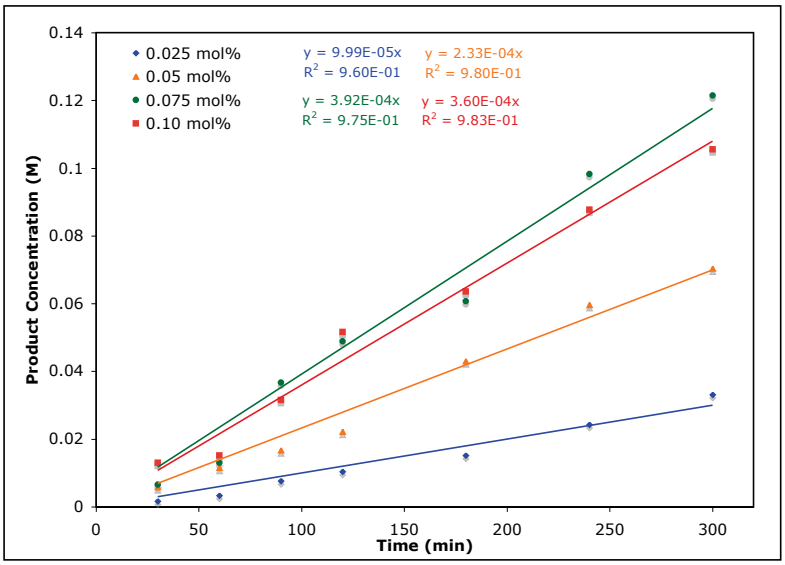


Figure S3.4 Increase in product concentration over the course of the reaction with various concentrations of $Pd(PCy_3)_2$: 0.005 M (blue), 0.010 M (orange), 0.015 M (green) and 0.020 M (red).

Initial rate dependence on the concentration of phosphine

Reactions were carried out using a modified version of *general procedure D* with 5 different concentrations of $PCy_3 \cdot HBF_4$ (0.020 M, 0.030 M, 0.040 M, 0.050 M and 0.120 M). A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 5.0 mol %), $PCy_3 \cdot HBF_4$ (10 mol %, 15 mol %, 20 mol %, 25 mol % and 60 mol %), Cs_2CO_3 (1.40 equiv + x mol % where x corresponds to the mol % of added $PCy_3 \cdot HBF_4$) and 1,3,5-trimethoxybenzene (97.7 mg, 0.581 mmol, 1.00 equiv) were quickly added and the test tube was put under vacuum for 10 minutes and refilled with argon (x3). The desired starting material (132.5 mg, 0.5811 mmol, 1.000 equiv) and PivOH (17.8 mmol,

0.174 mmol, 30.0 mol %) were added as degassed stock solutions in mesitylene (0.32 M and 0.16 M respectively) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C for 16 hours. Aliquots were taken at 30 minute intervals for the first 2 hours and then at 1 hour intervals for a total of 5 hours. Product yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

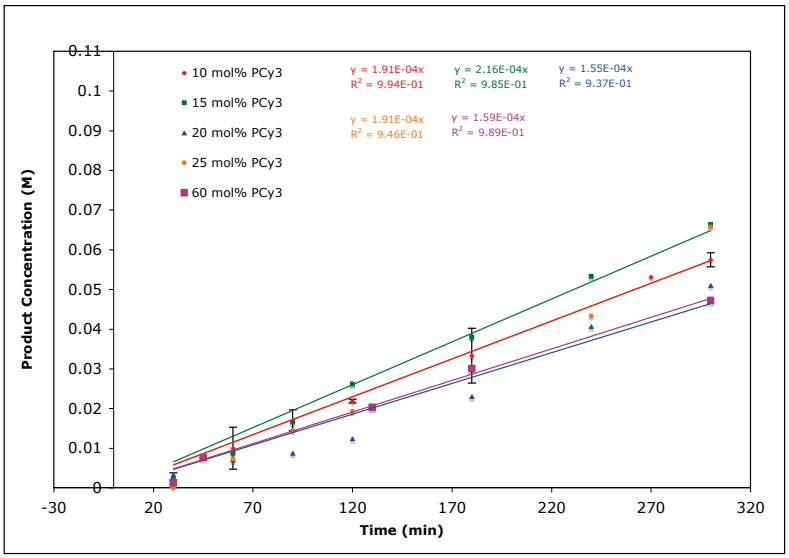


Figure S3.5 Increase in product concentration over the course of the reaction with various concentrations of $PCy_3 \cdot HBF_4$: 0.020 M (red), 0.030 M (green), 0.040 M (blue), 0.050 M (orange) and 0.120 M (purple).

Initial rate dependence on the concentration of pivalate

Reactions were carried out using a modified version of *general procedure D* with 6 different concentrations of CsOPiv (0.010 M, 0.020 M, 0.030 M, 0.060 M, 0.120 M and 0.200 M). A Radley test tube equipped with a magnetic stir bar and a rubber septum was flame-dried under vacuum and a constant flow of argon. Once the test tube was cooled to room temperature, the vacuum was removed. Subsequent manipulations were performed under constant argon flow unless noted otherwise to give reproducible results. The flame-dried test tube was brought into the glovebox. $Pd(PCy_3)_2$ (18.3 mg, 0.0291 mmol, 5.00 mol %), Cs_2CO_3 (284 mg, 0.872 mmol, 1.50 equiv), 1,3,5-trimethoxybenzene (97.7 mg, 0.581 mmol, 1.00 equiv) and CsOPiv (5.0 mol %, 10 mol %, 15 mol %, 30 mol %, 60 mol %, 100 mol %) were added and the test tube was brought back onto the bench top. The test tube was put under vacuum for 5 minutes and refilled with argon (x3). 2-Bromo-*N,N*-dimethylbenzamide (132.5 mg, 0.5811 mmol, 1.000 equiv) was added as degassed stock solutions in mesitylene (0.20 M) after which the tube was sealed with parafilm and electrical tape around the rubber septum and placed in a pre-heated oil bath at 150 °C. Aliquots were taken at 30 minute intervals for the first 2 hours and then at 1 hour intervals for a total of 5 hours. Product yields were determined by GC-MS using 1,3,5-trimethoxybenzene as an internal standard.

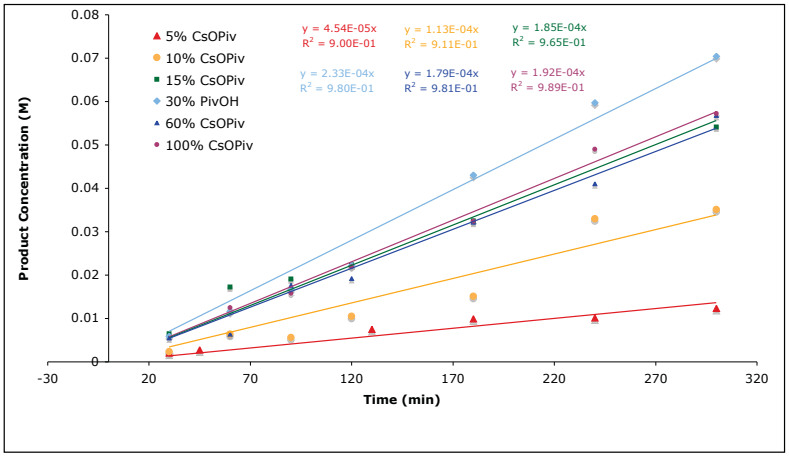
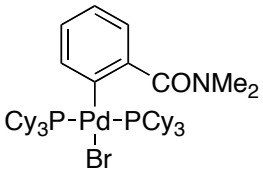


Figure S3.6 Increase in product concentration over the course of the reaction with various concentrations of CsOPiv: 0.020 M (red), 0.030 M (green), 0.040 M (blue), 0.050 M (orange) and 0.120 M (purple).

8.3.7 Mechanistic Studies Performed with [$(PCy_3)_2Pd(Ar)(Br)$]

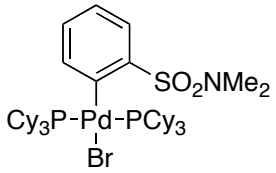
Synthesis and Characterization of Pd(II) Intermediates



[$(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)$] (3.50) Synthesized according to a reported procedure.[182] In a glovebox, a stock solution of 2-bromo-*N,N*-dimethylbenzamide (0.46 mL, 0.26 M, 1.5 equiv) in benzene (degassed under sonication for 2h prior to its use) was added to a small screw cap vial containing $Pd(PCy_3)_2$ (50.0 mg, 0.0794 mmol, 1.00 equiv). The resulting solution was stirred at room temperature for 24 hours after which the resulting white solid was allowed to precipitate from the solution. The mother liqueur was pipetted off and the remaining solid was washed with pentane several times to remove any leftover aryl bromide. The vial was removed from the glovebox and the solid was dried under vacuum to afford the product as an air-stable white powder in 70% yield.

^{1}H NMR {^{31}P} (300 MHz, $CDCl_3$, 293K, TMS) δ 8.00 (dd, J = 7.5, 1.2 Hz, 1H), 7.06 (dd, J = 7.5, 1.5 Hz, 1H), 6.97 (ddd, J = 7.2, 7.2, 1.5 Hz, 1H), 6.80 (ddd, J = 7.5, 7.5, 0.9 Hz, 1H), 2.77 (s, 6H), 2.41-1.03 (m, 66H). **^{31}P {^{1}H} NMR (120 MHz, C_6D_6, 293K)** δ 14.5.

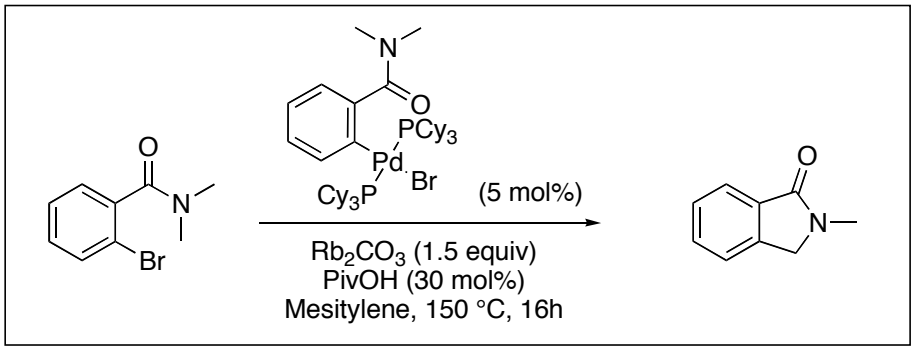
[182] Stambuli, J. P.; Incarvito, C. D.; Bühl, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 1184-1194.



[$(PCy_3)_2Pd(C_6H_4SO_2NMe_2)(Br)$] (3.51) Synthesized according to a reported procedure.[182] In a glovebox, a stock solution of 2-bromo-*N,N*-dimethylbenzenesulfonamide (1.4 mL, 0.26 M, 1.5 equiv) in benzene (degassed under sonication for 2h prior to its use) was added to a small screw cap vial containing $Pd(PCy_3)_2$ (150 mg, 0.238 mmol, 1.00 equiv). The resulting solution was stirred at room temperature for 24 hours after which the resulting white solid was allowed to precipitate from the solution. The mother liqueur was pipetted off and the remaining solid was washed with pentane several times to remove any leftover aryl bromide. The vial was removed from the glovebox and the solid was dried under vacuum to afford the product as an air-stable white powder in 76% yield.

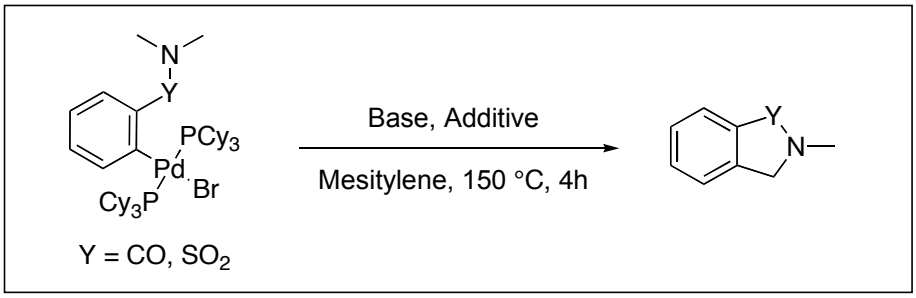
^1H {^{31}P} NMR (300 MHz, C_6D_6, 293K, TMS) δ 8.03 (d, J = 7.3 Hz, 1H), 7.42 (dd, J = 7.8, 1.4 Hz, 1H), 6.84 (ddd, J = 7.3, 7.3, 1.3 Hz, 1H), 6.72 (dd, J = 7.6, 7.6 Hz, 1H), 2.53 (s, 6H), 2.25-1.00 (m, 66H). **^{31}P {^1H} NMR (120 MHz, C_6D_6, 293K)** δ 17.9.

General Procedures for the Mechanistic Studies Performed with [$(PCy_3)_2Pd(Ar)(Br)$]



[$(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)$] 3.50 Catalyzed Intramolecular Arylation of 2-Bromo-*N*,*N*-dimethylbenzamide

General procedure A for the arylation at *N*-methylamides was followed using 2-bromo-*N*,*N*-dimethylbenzamide **3.20** (25.5 mg, 0.112 mmol, 1.00 equiv), [$(PCy_3)_2Pd(C_6H_4CONMe_2)(Br)$] **3.50** (5.0 mg, 0.0056 mmol, 0.050 equiv), Rb_2CO_3 (38.7 mg, 0.168 mmol, 1.50 equiv), PivOH (3.4 mg, 0.034 mmol, 0.30 equiv) and mesitylene (0.60 mL, 0.20 M). After 16 hours at 150 °C, the reaction was cooled to room temperature and filtered over celite. The product yield was determined to be 67% by ^1H NMR of the crude reaction mixture (using 1,3,5-trimethoxybenzene as an internal standard and susbstracting an additional 5% due to the nature of the catalyst).



Stoichiometric Base Studies with [$(PCy_3)_2Pd(Ar)(Br)$]

A small screw cap vial was charged with [$(PCy_3)_2Pd(Ar)(Br)$] (0.0223 mmol, 1.00 equiv), the base (0.223 mmol, 10.0 equiv), the additive (if added) (0.0669 mmol, 3.00 equiv) and a small magnetic stir bar. The vial was purged with argon for 10 minutes. Mesitylene (0.010 M) was added to the mixture and the vial was heated at 150 °C for 4 hours. The reaction was cooled to room temperature and filtered over celite. The product yield was determined by ^{1}H NMR of the crude reaction mixture (using 1,3,5-trimethoxybenzene as an internal standard).

Stoichiometric Phosphine Studies with [$(PCy_3)_2Pd(C_6H_4SO_2NMe_2)(Br)$] (3.51)

In the glovebox, a small screw cap vial was charged with [$(PCy_3)_2Pd(C_6H_4SO_2NMe_2)(Br)$] (20.0 mg, 0.0215 mmol, 1.00 equiv) CsOPiv (if added) (30.2 mg, 0.129 mmol, 6.00 equiv) and a small magnetic stir bar. Mesitylene (0.25 mL, 0.086 M) was added to the mixture and the vial was heated at 120 °C for 20 minutes after which ^{31}P {^{1}H} NMR (120 MHz, 328 K) was taken.

Crystal Structure

Crystals of $[C_{45}H_{76}BrNOP_2Pd]\cdot 1.5C_6H_6$ were grown from benzene. A single colorless needle suitable for X-ray diffraction measurements was mounted on a glass fiber. Unit cell measurements and intensity data collections were performed on a Bruker-AXS SMART 1 k CCD diffractometer using graphite monochromatized Mo K_α radiation (λ = 0.71073 Å). The data reduction included a correction for Lorentz and polarization effects, with an applied multi-scan absorption correction (SADABS). The crystal data and refinement parameters for $[C_{45}H_{76}BrNOP_2Pd]\cdot 1.5C_6H_6$ are listed in Table 1. Interatomic distances and angles are listed in Table 3. The reflection data were consistent with a monoclinic system; P2(1)/c.

The crystal structure was solved and refined using the SHELXTL program suite. Direct methods yielded all non-hydrogen atoms which were refined with anisotropic thermal parameters. All hydrogen atom positions were calculated geometrically and were riding on their respective atoms. One of the benzene solvent molecules is disordered and was modeled over two positions as a 50:50 mixture. The largest residual electron density peak (0.977 e/Å^3) was associated with the Br1 atom. Full-matrix least-squares refinement on F^2 gave R_1 = 0.0528 and wR_2 = 0.1199 at convergence.

Table 1. Crystal data and structure refinement for sad.

Identification code	sad	
Empirical formula	C54 H85 Br N O P2 Pd	
Formula weight	1012.48	
Temperature	202(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 10.122(3) Å	α= 90°.
	b = 21.299(6) Å	β= 98.052(4)°.
	c = 24.651(6) Å	γ = 90°.
Volume	5262(2) $Å^3$	
Z	4	
Density (calculated)	1.278 Mg/m^3	
Absorption coefficient	1.209 mm^{-1}	
F(000)	2140	
Crystal size	0.50 x 0.10 x 0.10 mm^3	
Theta range for data collection	2.09 to 25.02°.	
Index ranges	-12<=h<=12, -25<=k<=25, -29<=l<=29	
Reflections collected	49135	
Independent reflections	9241 [R(int) = 0.0971]	
Completeness to theta = 25.02°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8886 and 0.5831	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9241 / 98 / 556	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0528, wR2 = 0.1199	
R indices (all data)	R1 = 0.1093, wR2 = 0.1445	
Largest diff. peak and hole	0.977 and -0.501 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sad. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Pd(1)	1448(1)	2713(1)	5456(1)	20(1)
Br(1)	-924(1)	2319(1)	5384(1)	30(1)
P(1)	1024(2)	3021(1)	4526(1)	22(1)
P(2)	1703(2)	2590(1)	6431(1)	24(1)
N(1)	4801(6)	1718(3)	4790(3)	54(2)
O(1)	3341(5)	1589(2)	5384(2)	45(1)
C(1)	579(6)	2408(3)	3994(2)	27(1)
C(2)	-799(7)	2105(3)	3983(3)	37(2)

C(3)	-1072(7)	1643(3)	3504(3)	43(2)
C(4)	-5(8)	1146(3)	3532(3)	48(2)
C(5)	1385(8)	1431(3)	3549(3)	47(2)
C(6)	1665(7)	1910(3)	4022(3)	36(2)
C(7)	-478(6)	3529(3)	4450(2)	26(1)
C(8)	-473(6)	4023(3)	4904(3)	30(2)
C(9)	-1850(7)	4337(3)	4877(3)	39(2)
C(10)	-2272(7)	4631(3)	4316(3)	43(2)
C(11)	-2277(7)	4134(3)	3864(3)	42(2)
C(12)	-914(6)	3816(3)	3885(3)	31(2)
C(13)	2421(6)	3448(3)	4259(2)	25(1)
C(14)	2472(6)	3447(3)	3635(3)	32(2)
C(15)	3768(7)	3758(3)	3505(3)	39(2)
C(16)	3954(7)	4414(3)	3743(3)	36(2)
C(17)	3884(6)	4419(3)	4353(3)	35(2)
C(18)	2572(6)	4124(3)	4474(3)	28(2)
C(19)	854(6)	3240(3)	6753(3)	28(2)
C(20)	1414(7)	3883(3)	6628(3)	32(2)
C(21)	779(8)	4413(4)	6921(3)	50(2)
C(22)	-747(8)	4409(4)	6770(3)	54(2)
C(23)	-1298(7)	3777(4)	6895(3)	46(2)
C(24)	-675(7)	3245(3)	6609(3)	39(2)
C(25)	825(6)	1884(3)	6633(3)	28(2)
C(26)	788(7)	1779(3)	7249(3)	40(2)
C(27)	-189(8)	1251(4)	7325(3)	49(2)
C(28)	146(8)	650(4)	7047(3)	54(2)
C(29)	217(8)	762(3)	6435(3)	47(2)
C(30)	1194(7)	1277(3)	6353(3)	34(2)
C(31)	3444(6)	2608(3)	6808(3)	28(2)
C(32)	4208(6)	1999(3)	6735(3)	36(2)
C(33)	5701(7)	2085(4)	6932(3)	48(2)
C(34)	5944(7)	2294(4)	7525(3)	49(2)
C(35)	5154(7)	2877(4)	7617(3)	48(2)
C(36)	3674(7)	2801(4)	7413(3)	41(2)
C(37)	3354(6)	2987(3)	5517(2)	26(2)
C(38)	3736(7)	3588(3)	5716(3)	34(2)
C(39)	5056(8)	3785(4)	5821(3)	45(2)
C(40)	6048(7)	3381(4)	5725(3)	49(2)
C(41)	5725(7)	2784(4)	5516(3)	40(2)
C(42)	4394(6)	2600(3)	5400(2)	29(2)
C(43)	4128(7)	1941(4)	5187(3)	41(2)
C(44)	5499(8)	2124(5)	4431(3)	68(3)
C(45)	4689(9)	1066(5)	4641(4)	82(3)
C(46)	4631(15)	4751(5)	7697(4)	188(8)
C(47)	3793(8)	5094(6)	7987(6)	184(8)

C(48)	4282(12)	5345(4)	8496(6)	150(6)
C(49)	5609(14)	5253(4)	8716(4)	121(5)
C(50)	6447(8)	4909(5)	8426(6)	114(5)
C(51)	5958(13)	4658(4)	7917(5)	155(6)
C(52)	-980(40)	460(20)	4993(18)	82(10)
C(53)	350(60)	660(15)	5031(15)	66(8)
C(54)	1270(30)	170(30)	5031(12)	66(8)
C(52A)	-450(60)	591(15)	5045(17)	76(9)
C(53A)	910(50)	486(18)	5039(14)	64(8)
C(54A)	1410(30)	-120(30)	5024(16)	76(9)

Table 3. Bond lengths [Å] and angles [°] for sad.

Pd(1)-C(37)	2.001(6)
Pd(1)-P(1)	2.3646(17)
Pd(1)-P(2)	2.3961(17)
Pd(1)-Br(1)	2.5264(9)
P(1)-C(7)	1.855(6)
P(1)-C(1)	1.861(6)
P(1)-C(13)	1.876(6)
P(2)-C(25)	1.849(6)
P(2)-C(19)	1.863(6)
P(2)-C(31)	1.874(6)
N(1)-C(43)	1.355(9)
N(1)-C(45)	1.436(11)
N(1)-C(44)	1.484(10)
O(1)-C(43)	1.242(8)
C(1)-C(6)	1.522(9)
C(1)-C(2)	1.533(9)
C(2)-C(3)	1.532(9)
C(3)-C(4)	1.508(10)
C(4)-C(5)	1.528(10)
C(5)-C(6)	1.543(9)
C(7)-C(12)	1.527(8)
C(7)-C(8)	1.536(8)
C(8)-C(9)	1.539(9)
C(9)-C(10)	1.523(10)
C(10)-C(11)	1.537(10)
C(11)-C(12)	1.531(9)
C(13)-C(18)	1.534(8)
C(13)-C(14)	1.547(8)
C(14)-C(15)	1.542(9)
C(15)-C(16)	1.517(9)

C(16)-C(17)	1.515(9)
C(17)-C(18)	1.536(8)
C(19)-C(20)	1.530(9)
C(19)-C(24)	1.538(9)
C(20)-C(21)	1.529(9)
C(21)-C(22)	1.537(11)
C(22)-C(23)	1.505(11)
C(23)-C(24)	1.519(9)
C(25)-C(30)	1.537(9)
C(25)-C(26)	1.541(9)
C(26)-C(27)	1.526(9)
C(27)-C(28)	1.513(11)
C(28)-C(29)	1.541(10)
C(29)-C(30)	1.508(9)
C(31)-C(36)	1.533(9)
C(31)-C(32)	1.533(9)
C(32)-C(33)	1.532(9)
C(33)-C(34)	1.515(10)
C(34)-C(35)	1.511(10)
C(35)-C(36)	1.520(9)
C(37)-C(42)	1.398(9)
C(37)-C(38)	1.406(9)
C(38)-C(39)	1.390(9)
C(39)-C(40)	1.368(11)
C(40)-C(41)	1.392(11)
C(41)-C(42)	1.394(9)
C(42)-C(43)	1.510(10)
C(46)-C(47)	1.3900
C(46)-C(51)	1.3900
C(47)-C(48)	1.3900
C(48)-C(49)	1.3900
C(49)-C(50)	1.3900
C(50)-C(51)	1.3900
C(52)-C(54)#1	1.392(7)
C(52)-C(53)	1.393(10)
C(53)-C(54)	1.390(10)
C(54)-C(52)#1	1.392(7)
C(52A)-C(54A)#1	1.391(7)
C(52A)-C(53A)	1.391(10)
C(53A)-C(54A)	1.387(10)
C(54A)-C(52A)#1	1.391(7)

C(37)-Pd(1)-P(1)	91.93(16)
C(37)-Pd(1)-P(2)	89.41(16)
P(1)-Pd(1)-P(2)	169.22(6)

C(37)-Pd(1)-Br(1)	177.46(19)
P(1)-Pd(1)-Br(1)	88.99(4)
P(2)-Pd(1)-Br(1)	90.12(4)
C(7)-P(1)-C(1)	102.9(3)
C(7)-P(1)-C(13)	109.2(3)
C(1)-P(1)-C(13)	102.3(3)
C(7)-P(1)-Pd(1)	107.2(2)
C(1)-P(1)-Pd(1)	118.8(2)
C(13)-P(1)-Pd(1)	115.6(2)
C(25)-P(2)-C(19)	102.8(3)
C(25)-P(2)-C(31)	109.7(3)
C(19)-P(2)-C(31)	103.4(3)
C(25)-P(2)-Pd(1)	111.7(2)
C(19)-P(2)-Pd(1)	110.7(2)
C(31)-P(2)-Pd(1)	117.2(2)
C(43)-N(1)-C(45)	119.6(8)
C(43)-N(1)-C(44)	123.7(7)
C(45)-N(1)-C(44)	116.0(7)
C(6)-C(1)-C(2)	110.9(5)
C(6)-C(1)-P(1)	110.9(4)
C(2)-C(1)-P(1)	116.0(4)
C(3)-C(2)-C(1)	110.4(5)
C(4)-C(3)-C(2)	111.3(6)
C(3)-C(4)-C(5)	111.9(6)
C(4)-C(5)-C(6)	110.7(6)
C(1)-C(6)-C(5)	111.8(5)
C(12)-C(7)-C(8)	111.3(5)
C(12)-C(7)-P(1)	117.0(4)
C(8)-C(7)-P(1)	114.0(4)
C(7)-C(8)-C(9)	110.8(5)
C(10)-C(9)-C(8)	110.9(5)
C(9)-C(10)-C(11)	110.3(6)
C(12)-C(11)-C(10)	111.7(6)
C(7)-C(12)-C(11)	110.7(5)
C(18)-C(13)-C(14)	109.2(5)
C(18)-C(13)-P(1)	112.2(4)
C(14)-C(13)-P(1)	118.7(4)
C(15)-C(14)-C(13)	110.7(5)
C(16)-C(15)-C(14)	112.3(5)
C(17)-C(16)-C(15)	111.7(5)
C(16)-C(17)-C(18)	110.6(5)
C(13)-C(18)-C(17)	111.4(5)
C(20)-C(19)-C(24)	109.7(5)
C(20)-C(19)-P(2)	111.9(4)
C(24)-C(19)-P(2)	114.6(4)

C(21)-C(20)-C(19)	112.0(6)
C(20)-C(21)-C(22)	110.9(6)
C(23)-C(22)-C(21)	110.1(6)
C(22)-C(23)-C(24)	112.5(6)
C(23)-C(24)-C(19)	111.5(6)
C(30)-C(25)-C(26)	111.1(5)
C(30)-C(25)-P(2)	114.0(4)
C(26)-C(25)-P(2)	117.5(5)
C(27)-C(26)-C(25)	109.5(6)
C(28)-C(27)-C(26)	112.3(6)
C(27)-C(28)-C(29)	110.8(6)
C(30)-C(29)-C(28)	111.4(6)
C(29)-C(30)-C(25)	110.3(6)
C(36)-C(31)-C(32)	109.3(5)
C(36)-C(31)-P(2)	119.4(5)
C(32)-C(31)-P(2)	112.3(4)
C(33)-C(32)-C(31)	110.7(6)
C(34)-C(33)-C(32)	111.2(6)
C(35)-C(34)-C(33)	111.6(6)
C(34)-C(35)-C(36)	112.4(6)
C(35)-C(36)-C(31)	111.0(6)
C(42)-C(37)-C(38)	115.5(6)
C(42)-C(37)-Pd(1)	124.0(5)
C(38)-C(37)-Pd(1)	120.4(5)
C(39)-C(38)-C(37)	123.3(7)
C(40)-C(39)-C(38)	119.2(7)
C(39)-C(40)-C(41)	119.9(7)
C(40)-C(41)-C(42)	120.1(7)
C(41)-C(42)-C(37)	121.8(7)
C(41)-C(42)-C(43)	116.9(6)
C(37)-C(42)-C(43)	121.1(6)
O(1)-C(43)-N(1)	119.0(8)
O(1)-C(43)-C(42)	121.3(6)
N(1)-C(43)-C(42)	119.6(7)
C(47)-C(46)-C(51)	120.0
C(48)-C(47)-C(46)	120.0
C(47)-C(48)-C(49)	120.0
C(50)-C(49)-C(48)	120.0
C(49)-C(50)-C(51)	120.0
C(50)-C(51)-C(46)	120.0
C(54)#1-C(52)-C(53)	119(3)
C(54)-C(53)-C(52)	115(3)
C(53)-C(54)-C(52)#1	126(3)
C(54A)#1-C(52A)-C(53A)	124(3)
C(54A)-C(53A)-C(52A)	121(3)

C(53A)-C(54A)-C(52A)#1 115(3)

Symmetry transformations used to generate equivalent atoms:
#1 -x,-y,-z+1

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sad. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Pd(1)	19(1)	23(1)	19(1)	1(1)	3(1)	-1(1)
Br(1)	22(1)	41(1)	27(1)	1(1)	4(1)	-4(1)
P(1)	23(1)	24(1)	20(1)	-1(1)	2(1)	0(1)
P(2)	25(1)	25(1)	20(1)	3(1)	3(1)	0(1)
N(1)	44(4)	81(5)	40(4)	-11(4)	15(3)	19(4)
O(1)	53(3)	39(3)	43(3)	-6(2)	6(3)	2(3)
C(1)	35(4)	24(3)	20(3)	-2(3)	-3(3)	-3(3)
C(2)	38(4)	41(4)	33(4)	-6(3)	8(3)	-9(3)
C(3)	49(5)	47(5)	34(4)	-12(4)	6(3)	-11(4)
C(4)	84(6)	32(4)	26(4)	-11(3)	4(4)	-13(4)
C(5)	72(6)	35(4)	32(4)	-13(3)	3(4)	14(4)
C(6)	39(4)	34(4)	32(4)	-1(3)	1(3)	3(3)
C(7)	28(4)	26(3)	25(4)	2(3)	4(3)	1(3)
C(8)	39(4)	30(4)	23(4)	1(3)	6(3)	3(3)
C(9)	40(4)	31(4)	50(5)	-5(3)	19(4)	0(3)
C(10)	29(4)	34(4)	66(6)	3(4)	6(4)	6(3)
C(11)	31(4)	49(5)	43(5)	8(4)	-5(3)	1(3)
C(12)	35(4)	34(4)	24(4)	5(3)	6(3)	3(3)
C(13)	22(3)	28(3)	25(4)	3(3)	2(3)	-3(3)
C(14)	32(4)	39(4)	26(4)	-5(3)	8(3)	-4(3)
C(15)	40(4)	52(5)	25(4)	-3(3)	11(3)	-4(4)
C(16)	32(4)	41(4)	38(4)	11(3)	9(3)	-10(3)
C(17)	31(4)	37(4)	37(4)	3(3)	5(3)	-10(3)
C(18)	27(3)	33(4)	23(4)	3(3)	2(3)	0(3)
C(19)	27(4)	33(4)	24(4)	-2(3)	3(3)	-2(3)
C(20)	38(4)	33(4)	27(4)	-5(3)	6(3)	3(3)
C(21)	69(6)	39(4)	43(5)	-9(4)	11(4)	0(4)
C(22)	67(6)	56(5)	38(5)	-8(4)	2(4)	33(5)
C(23)	39(4)	63(5)	35(4)	-15(4)	-4(3)	14(4)
C(24)	36(4)	48(4)	33(4)	-13(3)	4(3)	14(3)
C(25)	24(3)	31(4)	30(4)	8(3)	2(3)	0(3)
C(26)	42(4)	47(4)	30(4)	12(3)	4(3)	-9(3)
C(27)	57(5)	60(5)	31(4)	9(4)	13(4)	-14(4)

C(28)	58(5)	57(5)	45(5)	20(4)	1(4)	-16(4)
C(29)	65(5)	28(4)	48(5)	3(3)	5(4)	-10(4)
C(30)	37(4)	28(4)	36(4)	4(3)	2(3)	0(3)
C(31)	27(3)	25(4)	32(4)	5(3)	2(3)	-3(3)
C(32)	28(4)	40(4)	38(4)	6(3)	3(3)	4(3)
C(33)	32(4)	57(5)	52(5)	5(4)	-2(4)	8(4)
C(34)	28(4)	67(5)	48(5)	12(4)	-7(3)	-1(4)
C(35)	45(5)	61(5)	33(4)	-3(4)	-8(3)	-13(4)
C(36)	43(4)	47(5)	31(4)	2(3)	0(3)	-3(4)
C(37)	23(3)	47(4)	9(3)	11(3)	0(2)	-7(3)
C(38)	40(4)	36(4)	26(4)	5(3)	4(3)	-8(3)
C(39)	49(5)	54(5)	30(4)	10(4)	-3(3)	-31(4)
C(40)	21(4)	86(7)	38(5)	19(4)	-3(3)	-13(4)
C(41)	33(4)	58(5)	27(4)	13(4)	0(3)	-1(4)
C(42)	20(3)	47(4)	17(3)	9(3)	-1(3)	5(3)
C(43)	26(4)	63(5)	33(4)	9(4)	2(3)	14(4)
C(44)	50(5)	114(8)	44(5)	-6(5)	22(4)	8(5)
C(45)	70(7)	92(8)	85(8)	-39(6)	10(6)	35(6)
C(46)	171(16)	107(12)	256(19)	-61(12)	-76(15)	-6(11)
C(47)	108(12)	132(14)	290(20)	-22(14)	-48(14)	3(10)
C(48)	126(13)	107(11)	222(18)	37(12)	37(12)	22(10)
C(49)	140(12)	84(9)	133(12)	42(8)	-1(10)	-28(9)
C(50)	91(9)	73(9)	173(14)	10(8)	4(9)	-15(7)
C(51)	135(13)	82(9)	241(18)	-23(11)	2(12)	5(9)
C(52)	130(30)	50(20)	58(15)	11(16)	-15(19)	-21(16)
C(53)	120(20)	38(14)	36(10)	-9(11)	8(18)	-10(16)
C(54)	111(17)	40(20)	49(11)	10(20)	7(12)	-10(18)
C(52A)	150(30)	31(11)	48(14)	-3(11)	10(20)	-30(18)
C(53A)	130(20)	16(17)	46(11)	-1(15)	11(17)	-19(15)
C(54A)	118(17)	32(19)	74(14)	0(20)	2(13)	-3(19)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^{-3}) for sad.

	x	y	z	U(eq)
H(1A)	565	2622	3633	32
H(2A)	-837	1880	4332	45
H(2B)	-1493	2435	3946	45
H(3A)	-1950	1441	3511	52
H(3B)	-1109	1876	3154	52
H(4A)	-190	867	3209	58
H(4B)	-30	886	3864	58
H(5A)	1453	1643	3197	56
H(5B)	2063	1093	3600	56
H(6A)	1725	1686	4376	43
H(6B)	2534	2116	4004	43
H(7A)	-1222	3239	4506	31
H(8A)	209	4346	4864	37
H(8B)	-236	3820	5266	37
H(9A)	-2518	4020	4950	47
H(9B)	-1815	4665	5163	47
H(10A)	-1648	4973	4256	52
H(10B)	-3176	4813	4302	52
H(11A)	-2961	3813	3906	50
H(11B)	-2517	4336	3502	50
H(12A)	-967	3482	3603	37
H(12B)	-245	4128	3804	37
H(13A)	3253	3227	4425	30
H(14A)	2426	3009	3498	38
H(14B)	1692	3678	3445	38
H(15A)	4539	3495	3655	46
H(15B)	3747	3780	3103	46
H(16A)	4831	4579	3676	44
H(16B)	3253	4693	3555	44
H(17A)	3944	4857	4489	42
H(17B)	4648	4182	4547	42
H(18A)	2552	4125	4874	33
H(18B)	1811	4379	4299	33
H(19A)	1053	3179	7158	34
H(20A)	2391	3885	6745	39
H(20B)	1253	3957	6228	39
H(21A)	1136	4822	6816	60
H(21B)	1013	4363	7322	60
H(22A)	-1143	4738	6981	65
H(22B)	-987	4503	6375	65

H(23A)	-2275	3776	6779	56
H(23B)	-1136	3706	7295	56
H(24A)	-916	3290	6207	47
H(24B)	-1038	2839	6718	47
H(25A)	-130	1958	6478	34
H(26A)	1690	1667	7433	47
H(26B)	505	2170	7417	47
H(27A)	-175	1172	7721	59
H(27B)	-1102	1385	7172	59
H(28A)	-544	330	7087	65
H(28B)	1014	487	7228	65
H(29A)	491	369	6267	57
H(29B)	-679	878	6247	57
H(30A)	1184	1353	5956	41
H(30B)	2106	1145	6509	41
H(31A)	3913	2936	6616	34
H(32A)	3854	1657	6946	43
H(32B)	4075	1877	6344	43
H(33A)	6171	1683	6894	57
H(33B)	6068	2402	6701	57
H(34A)	5689	1951	7762	59
H(34B)	6906	2380	7632	59
H(35A)	5506	3235	7425	57
H(35B)	5273	2975	8013	57
H(36A)	3209	3202	7459	49
H(36B)	3294	2477	7634	49
H(38A)	3057	3874	5783	41
H(39A)	5267	4195	5958	54
H(40A)	6955	3507	5801	59
H(41A)	6414	2502	5453	47
H(44A)	5513	2557	4565	102
H(44B)	5029	2108	4056	102
H(44C)	6416	1974	4436	102
H(45A)	4204	842	4900	124
H(45B)	5582	885	4653	124
H(45C)	4203	1026	4270	124
H(46)	4297	4579	7349	226
H(47)	2886	5157	7836	221
H(48)	3709	5579	8694	181
H(49)	5943	5424	9064	145
H(50)	7354	4846	8576	136
H(51)	6531	4424	7719	186
H(52)	-1673	764	4983	99
H(53)	601	1089	5054	79
H(54)	2178	290	5049	79

H(52A)	-731	1008	5098	91
H(53A)	1499	833	5046	76
H(54A)	2335	-206	5057	91

8.3.8 Computational Details – Atom Coordinates

[Pd^{II}(OAc)(PMe_3)(C_6H_4-CO-NMe_2)] Reaction Intermediate before the CMD Transition State – Structure I (Figures 3.3 and 3.5)

Pd	-0.875040	0.069202	-0.422460
P	-0.763021	2.086366	0.678981
C	-1.195724	1.854205	2.453054
C	-2.078709	3.212981	0.038878
C	0.754710	3.121678	0.713023
H	-1.302023	2.819859	2.952224
H	-2.132100	1.301000	2.524279
H	-0.399384	1.278935	2.924105
H	-2.151529	4.113106	0.653154
H	-1.850341	3.496385	-0.988588
H	-3.033229	2.686925	0.048141
H	0.562691	4.049739	1.255384
H	1.540716	2.554410	1.210053
H	1.070016	3.350420	-0.304154
O	-2.960473	-0.636057	-0.090742
C	-2.702754	-1.710470	-0.718229
O	-1.545798	-1.924165	-1.192035
C	-3.793090	-2.730889	-0.928152
H	-4.273052	-2.538581	-1.891012
H	-3.373538	-3.735673	-0.956963
H	-4.547466	-2.650878	-0.147039
C	3.707171	0.335961	-1.902325
C	2.676828	0.808501	-2.708751
C	1.361868	0.788087	-2.247047
C	1.058677	0.286966	-0.980634
C	2.096702	-0.190339	-0.175924
C	3.415153	-0.164873	-0.639308
C	1.811931	-0.648542	1.233309
H	4.731593	0.357374	-2.253479
H	2.893194	1.195513	-3.697875
H	0.570972	1.155441	-2.890827

H	4.212741	-0.536033	-0.005063
N	1.692620	-1.984570	1.453571
C	1.397930	-2.464031	2.796382
H	0.361312	-2.809588	2.864710
H	2.058218	-3.299192	3.042184
H	1.551377	-1.655137	3.504220
C	1.632944	-2.991359	0.400423
H	0.618129	-3.387319	0.304619
H	1.919882	-2.563174	-0.553937
H	2.313678	-3.812777	0.639273
O	1.711914	0.184622	2.136760

Trans-[Pd^{II}(Br)(PMe_3)$_2$(C_6H_4-CO-NMe_2)] Reaction Intermediate – Structure II (Figure 3.3)

Pd	-0.678458	0.016085	-0.254273
Br	-3.085114	0.267360	0.705390
P	-0.598599	2.411925	-0.412475
C	-0.852977	3.267827	1.203874
H	-0.915544	4.350013	1.071298
H	-1.772782	2.891006	1.649333
H	-0.023763	3.033110	1.871860
C	0.888154	3.271288	-1.101260
H	1.109912	2.882947	-2.094752
H	0.716685	4.347857	-1.161837
H	1.752578	3.082950	-0.466386
C	-1.956134	3.081419	-1.470643
H	-2.904968	2.697619	-1.099029
H	-1.958886	4.173416	-1.455673
H	-1.818823	2.736805	-2.496084
C	3.751270	-0.526131	-2.268287
C	3.623709	-0.554950	-0.886232
C	2.373037	-0.396483	-0.274779
C	1.218696	-0.204394	-1.050520
C	1.374254	-0.162302	-2.441366
C	2.617423	-0.324910	-3.048398
H	4.721790	-0.662997	-2.729326
H	4.501567	-0.718257	-0.269967
H	0.505886	-0.010597	-3.073183
H	2.697168	-0.299494	-4.129496
P	-0.925361	-2.363280	-0.159755
C	0.434909	-3.469584	-0.731556

H	0.119107	-4.513597	-0.677429
H	0.705403	-3.225507	-1.758489
H	1.299313	-3.309699	-0.090273
C	-1.305185	-2.982094	1.531501
H	-2.175377	-2.448095	1.910504
H	-1.503420	-4.056055	1.512153
H	-0.447331	-2.773589	2.168394
C	-2.364642	-2.921198	-1.175475
H	-2.174542	-2.702700	-2.226873
H	-2.529790	-3.994328	-1.057335
H	-3.249614	-2.370745	-0.859852
C	2.285989	-0.588264	1.219550
O	1.688052	-1.558075	1.681037
N	2.937819	0.300248	2.030184
C	2.945926	0.077196	3.469442
H	2.314596	0.810994	3.980975
H	2.565868	-0.918537	3.675096
H	3.965567	0.170744	3.852666
C	3.533111	1.551756	1.594553
H	3.424014	1.673612	0.522278
H	3.049278	2.395088	2.099164
H	4.599168	1.578662	1.841598

Trans-[Pd^{II}(Br)(PMe_3)(C_6H_4-C<u>O</u>-NMe_2)] – Structure III (Figure 3.3)

Pd	0.462859	-0.129700	-0.184804
Br	2.105124	-2.091910	-0.386676
C	-3.424554	2.770885	-0.575032
C	-3.500430	1.402189	-0.359377
C	-2.339081	0.652693	-0.138286
C	-1.059926	1.263500	-0.178001
C	-1.019736	2.641224	-0.385748
C	-2.180229	3.389561	-0.576684
H	-4.325339	3.343575	-0.756907
H	-4.466537	0.918205	-0.406402
H	-0.073076	3.157490	-0.436226
H	-2.106689	4.456842	-0.753399
P	2.293642	1.153468	0.421379
C	2.144744	2.946083	0.860728
H	3.091320	3.285391	1.285901
H	1.931402	3.545630	-0.023054
H	1.350450	3.096507	1.590435

C	3.091892	0.475839	1.940188
H	3.320974	-0.574388	1.772027
H	4.002110	1.033554	2.170846
H	2.397039	0.555409	2.776639
C	3.635353	1.181010	-0.842083
H	3.267255	1.668227	-1.745356
H	4.504947	1.723821	-0.465125
H	3.902685	0.154017	-1.083153
C	-2.319844	-0.828587	-0.040617
O	-1.275917	-1.416740	-0.414455
N	-3.368316	-1.565184	0.391636
C	-3.290956	-3.021666	0.281918
H	-4.281806	-3.409391	0.038994
H	-2.585420	-3.292153	-0.496795
H	-2.956441	-3.466776	1.223771
C	-4.460148	-1.067456	1.221184
H	-4.246908	-0.068261	1.586633
H	-5.408962	-1.058608	0.676771
H	-4.569460	-1.729461	2.083389

Trans-[Pd^{II}(Br)(PMe_3)(C_6H_4-CO-NMe_2)] – Structure IV (Figure 3.3)

Pd	0.262031	-0.103801	-0.072394
Br	2.428648	-1.514073	-0.245834
C	-4.250393	1.736266	-0.205845
C	-3.953972	0.450767	0.216759
C	-2.627271	0.008496	0.204225
C	-1.563173	0.846000	-0.170938
C	-1.890581	2.133797	-0.597495
C	-3.215113	2.567471	-0.629716
H	-5.274527	2.087550	-0.217120
H	-4.732561	-0.225896	0.548012
H	-1.123547	2.816571	-0.931796
H	-3.439160	3.567086	-0.985234
P	1.660794	1.751326	0.246526
C	1.008512	3.461159	0.524328
H	1.822971	4.099275	0.872445
H	0.613213	3.880987	-0.399058
H	0.216129	3.449433	1.271302
C	2.674074	1.496047	1.767209
H	3.193599	0.543551	1.686180
H	3.390804	2.311345	1.885691

H	2.015731	1.465308	2.635788
C	2.893040	2.014888	-1.098579
H	2.370362	2.276752	-2.019001
H	3.584564	2.817711	-0.834513
H	3.436088	1.085123	-1.257087
C	-2.319112	-1.380644	0.590674
O	-2.951286	-2.059964	1.360533
N	-1.101039	-1.894375	-0.054478
C	-0.583759	-3.094295	0.643790
H	0.363925	-3.367106	0.188813
H	-0.417302	-2.859550	1.691952
H	-1.300440	-3.915401	0.574026
C	-1.359600	-2.220570	-1.488175
H	-1.777070	-1.357464	-1.999750
H	-0.413789	-2.490864	-1.952820
H	-2.055392	-3.062842	-1.561732

Pd^{II}(OAc) Intramolecular CMD Transition State – TS-I (Figure 3.5)

Pd	-0.494719	0.082810	-0.356739
C	4.318544	0.492899	-0.809373
C	3.478115	1.392225	-1.456598
C	2.096046	1.281207	-1.311012
C	1.532212	0.262338	-0.541385
C	2.379527	-0.671543	0.066651
C	3.767051	-0.530219	-0.051059
C	1.896599	-1.858903	0.859155
H	5.393956	0.581749	-0.902862
H	3.892574	2.187548	-2.066007
H	1.461456	1.999815	-1.817538
H	4.398237	-1.246724	0.460007
N	0.813577	-2.521891	0.364266
C	0.243254	-3.621633	1.126767
H	-0.799700	-3.412345	1.381935
H	0.274222	-4.546028	0.542172
H	0.824322	-3.752441	2.034990
C	0.109330	-2.132490	-0.857315
H	0.807969	-1.808979	-1.622788
H	-0.327406	-3.048127	-1.273764
P	-0.656703	2.233974	0.627401
C	0.796784	2.921768	1.529091
C	-1.995473	2.269470	1.896608

C	-1.141112	3.589061	-0.531967
H	0.548065	3.881970	1.985190
H	1.098548	2.217464	2.304323
H	1.633629	3.044866	0.843927
H	-2.139934	3.280212	2.283317
H	-2.915418	1.903065	1.444429
H	-1.727821	1.604888	2.718337
H	-1.281655	4.531207	0.001922
H	-0.368019	3.720223	-1.288896
H	-2.070138	3.312938	-1.030530
H	-1.329000	-1.879146	-0.753782
O	-2.723315	0.025169	-0.248738
C	-3.235701	-1.092011	-0.491884
O	-2.546636	-2.135024	-0.750876
C	-4.735157	-1.252420	-0.484179
H	-5.062987	-1.644493	-1.447955
H	-5.015492	-1.984474	0.275060
H	-5.225401	-0.303444	-0.281972
O	2.492758	-2.215628	1.874441

Reaction Product After The CMD Transition State – Structure VI (Figure 3.5)

Pd	-0.408076	-0.183831	-0.048443
C	3.988462	1.496417	-1.273828
C	2.833978	2.080426	-1.786777
C	1.584050	1.563290	-1.453026
C	1.457241	0.455396	-0.608826
C	2.625513	-0.152090	-0.132605
C	3.878649	0.386176	-0.450487
C	2.638954	-1.388651	0.723359
H	4.963764	1.897421	-1.521604
H	2.902374	2.943745	-2.439816
H	0.700393	2.041303	-1.860900
H	4.757391	-0.096945	-0.041620
N	1.577425	-2.237997	0.576719
C	1.485979	-3.411703	1.431362
H	0.522120	-3.427181	1.949017
H	1.580145	-4.330225	0.843919
H	2.291408	-3.373871	2.159894
C	0.531523	-2.027795	-0.404156
H	0.908290	-2.132598	-1.422500
H	-0.249247	-2.768635	-0.229313

P	-1.318756	2.004719	0.754485
C	-0.078730	3.116106	1.560123
C	-2.603264	1.830376	2.080464
C	-2.157542	3.153819	-0.437829
H	-0.541406	4.033359	1.930309
H	0.387178	2.585198	2.390660
H	0.703937	3.363720	0.843563
H	-2.956406	2.802367	2.431222
H	-3.444893	1.254067	1.696364
H	-2.177887	1.279772	2.920064
H	-2.511890	4.060002	0.058320
H	-1.459120	3.432718	-1.227107
H	-3.005246	2.645415	-0.898645
H	-1.658537	-0.960365	-1.856026
O	-2.551161	-1.172315	0.240863
C	-3.087970	-1.559834	-0.785253
O	-2.535970	-1.399379	-1.987852
C	-4.412805	-2.259445	-0.828575
H	-5.090808	-1.733464	-1.502152
H	-4.277824	-3.267446	-1.225142
H	-4.836600	-2.309656	0.170310
O	3.574572	-1.626081	1.484682

[Pd^{II}(OAc)(PMe_3)(C_6H_4-CH_2-NMe_2)] – Structure VII (Figure 3.6)

Pd	0.893083	0.226787	-0.259111
C	-3.165745	-1.901309	-1.763629
C	-1.966113	-2.096084	-2.441099
C	-0.794167	-1.531769	-1.944082
C	-0.809111	-0.761166	-0.778805
C	-2.012672	-0.561450	-0.093302
C	-3.181839	-1.140347	-0.602787
C	-2.102039	0.249511	1.186622
H	-4.083622	-2.336741	-2.140150
H	-1.939428	-2.679335	-3.354495
H	0.131299	-1.676346	-2.489989
H	-4.114409	-0.959150	-0.080890
N	-3.145796	1.272064	1.154756
C	-3.401385	1.813182	2.479912
H	-2.528667	2.337527	2.910927
H	-4.227657	2.525023	2.431985
H	-3.686737	1.010457	3.163398

C	-2.852878	2.332269	0.195276
H	-2.704996	1.909754	-0.797533
H	-3.696429	3.023743	0.151877
P	1.578159	-1.670180	0.832751
C	2.129870	-3.058875	-0.248605
C	0.437804	-2.484963	2.029456
C	3.073601	-1.276078	1.838546
H	2.525286	-3.881562	0.350669
H	1.286153	-3.413052	-0.839474
H	2.904645	-2.701431	-0.926696
H	0.930788	-3.326461	2.520047
H	0.127108	-1.760704	2.782060
H	-0.447580	-2.836841	1.501678
H	3.486216	-2.175551	2.299896
H	3.820941	-0.809979	1.197144
H	2.806752	-0.557382	2.613128
H	-1.945383	2.902160	0.455414
O	2.543460	1.709818	-0.037387
C	1.878640	2.551544	-0.719750
O	0.726483	2.261118	-1.160867
C	2.457520	3.917170	-0.990393
H	2.117979	4.288142	-1.956770
H	2.103273	4.608615	-0.220789
H	3.545305	3.886319	-0.948294
H	-2.341182	-0.424856	2.016339
H	-1.111781	0.686403	1.406949

CMD Transition State TS-VII (Figure 3.6)

Pd	-0.375242	0.058737	-0.278714
C	4.465850	-0.174592	-0.418970
C	3.808801	0.812817	-1.141563
C	2.417988	0.917560	-1.072810
C	1.670551	0.036779	-0.292596
C	2.332508	-0.978128	0.412525
C	3.723628	-1.068959	0.346854
C	1.526490	-1.984548	1.187927
H	5.545078	-0.258983	-0.461106
H	4.371406	1.504491	-1.758679
H	1.927518	1.690232	-1.654699
H	4.228903	-1.856265	0.896359
N	0.772657	-2.901533	0.324810

C	-0.088593	-3.751757	1.131493
H	-0.848710	-3.184603	1.697055
H	-0.606389	-4.469084	0.493633
H	0.517971	-4.310957	1.847800
C	0.073567	-2.253886	-0.774208
H	0.782223	-1.886762	-1.509738
H	-0.487793	-3.027102	-1.310285
P	-0.434514	2.337337	0.437115
C	0.978622	3.042306	1.394049
C	-1.875768	2.660902	1.545946
C	-0.683507	3.571645	-0.919458
H	0.780953	4.080262	1.669489
H	1.127530	2.450950	2.297732
H	1.890521	2.985573	0.802014
H	-1.945547	3.720423	1.800729
H	-2.784197	2.334234	1.042777
H	-1.763773	2.077829	2.460411
H	-0.791832	4.582579	-0.520311
H	0.166868	3.546863	-1.601055
H	-1.580305	3.305618	-1.478938
H	-1.350632	-1.868862	-0.498101
O	-2.608174	0.168696	-0.343662
C	-3.189210	-0.938612	-0.390300
O	-2.567791	-2.054353	-0.423419
C	-4.696128	-1.001150	-0.419637
H	-5.017421	-1.429219	-1.371021
H	-5.051628	-1.663681	0.370313
H	-5.126752	-0.009844	-0.301157
H	2.180731	-2.582527	1.827458
H	0.824426	-1.439381	1.850890

[Pd^{II}(OAc)(PMe_3)(C_6H_4-CH_2-NMe_2)] – Structure VIII (Figure 3.6)

Pd	-0.185171	-0.041150	0.064209
C	4.637460	0.330397	-0.288604
C	3.886269	1.384223	-0.792062
C	2.493708	1.365235	-0.693806
C	1.823735	0.302863	-0.088616
C	2.596867	-0.772342	0.390306
C	3.986262	-0.754268	0.291681
C	1.859286	-1.939428	0.981721
H	5.718013	0.340702	-0.363643

H	4.379066	2.224122	-1.268731
H	1.941892	2.193753	-1.115067
H	4.564269	-1.596272	0.658325
N	0.565623	-2.125995	0.269829
C	0.774830	-2.722415	-1.070847
H	1.170580	-3.742125	-0.971373
H	-0.180518	-2.739349	-1.590452
H	1.485241	-2.119833	-1.632037
C	-0.333917	-2.993002	1.053835
H	-0.566066	-2.519725	2.006720
H	-1.252458	-3.144061	0.494146
P	-0.967532	2.162903	0.157052
C	-2.168729	2.540323	-1.190414
C	0.102012	3.671351	0.183912
C	-1.958492	2.346639	1.701113
H	-2.643585	3.510798	-1.031920
H	-1.651630	2.543162	-2.150034
H	-2.923378	1.756472	-1.204234
H	-0.505186	4.545518	0.427052
H	0.889717	3.559107	0.927783
H	0.565167	3.830008	-0.788939
H	-2.511479	3.288224	1.700121
H	-2.644424	1.503020	1.757147
H	-1.291666	2.321477	2.563383
H	0.139992	-3.965997	1.240057
O	-2.320171	-0.425274	0.307933
C	-2.918136	-1.267197	-0.470271
O	-2.375365	-1.938811	-1.350798
C	-4.412724	-1.418430	-0.198748
H	-4.890840	-1.971811	-1.004652
H	-4.552468	-1.963298	0.738407
H	-4.887007	-0.443276	-0.078058
H	2.450847	-2.864091	0.944326
H	1.621089	-1.746224	2.031178

CMD Transition State TS-VIII (Figure 3.6)

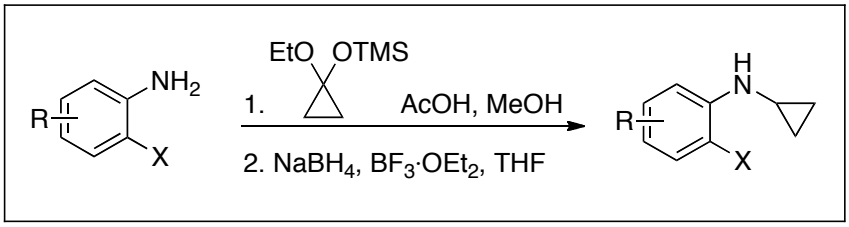
Pd	-0.443917	-0.060976	-0.311847
C	4.274690	0.974334	0.039632
C	3.476237	1.741802	-0.798614
C	2.110792	1.468442	-0.898821
C	1.534548	0.428182	-0.171950

C	2.344350	-0.372745	0.643954
C	3.707179	-0.082349	0.745851
C	1.754353	-1.611158	1.290218
H	5.333461	1.185020	0.131997
H	3.907939	2.551715	-1.375842
H	1.507954	2.074350	-1.565901
H	4.332490	-0.700094	1.382737
N	1.382557	-2.644730	0.319233
C	2.531628	-3.315391	-0.275102
H	3.190670	-3.694646	0.510368
H	2.182791	-4.168968	-0.859919
H	3.125480	-2.669413	-0.943268
C	0.417948	-2.198615	-0.683690
H	0.904435	-1.696054	-1.538183
H	-0.039037	-3.083576	-1.143730
P	-1.110265	2.147529	0.227443
C	-0.034851	3.177914	1.318173
C	-2.729926	2.176863	1.113104
C	-1.426610	3.248799	-1.225388
H	-0.488746	4.155151	1.494546
H	0.101089	2.665376	2.270661
H	0.944664	3.303339	0.860213
H	-3.056253	3.202850	1.294166
H	-3.468813	1.647198	0.514632
H	-2.627765	1.657950	2.066407
H	-1.804558	4.222198	-0.905347
H	-0.505856	3.392990	-1.790307
H	-2.159416	2.773241	-1.877290
H	-0.904086	-2.193242	-0.045740
O	-2.616820	-0.597786	-0.458882
C	-2.886257	-1.739742	-0.019415
O	-1.995181	-2.579971	0.346120
C	-4.323016	-2.188617	0.082731
H	-4.504997	-2.964247	-0.664114
H	-4.503718	-2.632214	1.062041
H	-5.001900	-1.356758	-0.089094
H	2.466125	-2.045715	1.996786
H	0.853929	-1.345633	1.850862

8.4 Arylation at Cyclopropane C(sp^3)-H Bonds

8.4.1 Synthesis and Characterization of Starting Materials

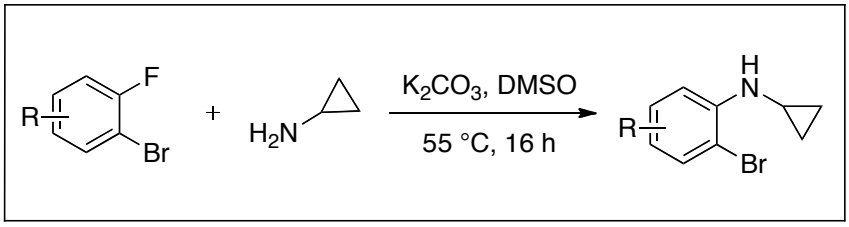
General Procedure A for the Preparation of *N*-Cyclopropylbenzenamines



Step 1. To a solution of the desired 2-haloaniline (1.00 equiv) in AcOH (3.00 equiv) and MeOH (1.5 M) at room temperature under argon was added (1-ethoxycyclopropoxy)trimethylsilane (1.20 equiv) dropwise. The mixture was stirred at reflux for 24 h then concentrated under reduced pressure.

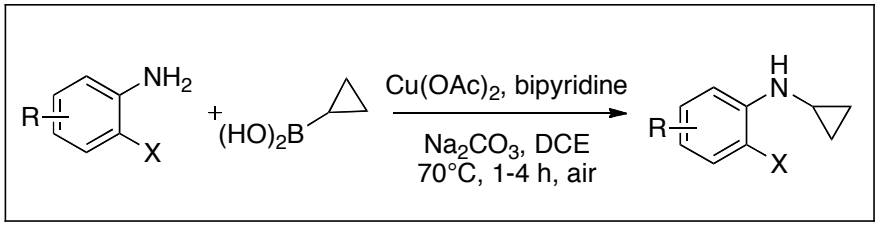
Step 2. To a solution of $NaBH_4$ (2.00 equiv) in THF (0.50 M) at 0 °C was added $BF_3{\cdot}OEt_2$ (2.00 equiv) dropwise. The resulting mixture was stirred for 1 h after which time the crude concentrated mixture from Step 1 was added dropwise as a solution in a minimal amount of THF. The solution was brought to room temperature and then stirred at reflux for 24 h. The reaction was quenched by the slow addition of H_2O and the crude product was extracted with Et_2O (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

General Procedure B for the Preparation of *N*-Cyclopropylbenzenamines



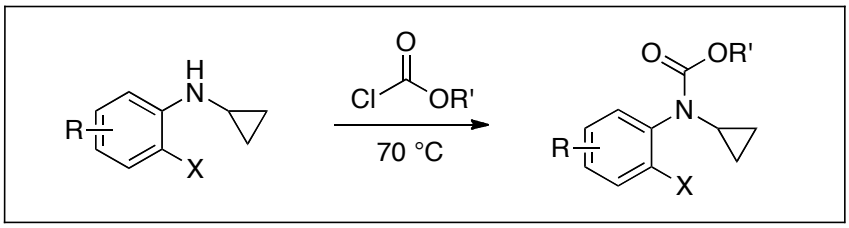
To a solution of the desired 1-bromo-2-fluoroarene (1.00 equiv) and K_2CO_3 (1.10 equiv) in DMSO (0.45 M) was added cyclopropylamine (3.00 equiv). The resulting mixture was heated at 55 °C for 16 h. The crude product was extracted with Et_2O (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

General Procedure C for the Preparation of *N*-Cyclopropylbenzenamines

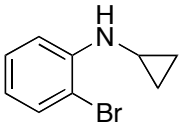


Prepared according to a literature procedure.[183] A solution of $Cu(OAc)_2$ (1.00 equiv) and bipyridine (1.00 equiv) in DCE (0.12 M) at 70 °C was added to a room temperature suspension of the desired 2-haloaniline (1.00 equiv), cyclopropylboronic acid (2.00 equiv) and Na_2CO_3 (2.00 equiv) in DCE (0.6 M). The mixture was heated at 70 °C until the reaction was judged to be complete by TLC (1-4 hours). After cooling to room temperature, an aqueous solution of NH_4OH (25%) was added. The organic layer was separated and the aqueous layer was extracted with DCM (x3). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

General Procedure for the Protection of *N*-Cyclopropylbenzenamines



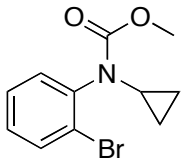
A solution of *N*-cyclopropylbenzenamine (1.00 equiv) in the desired chloroformate (0.4 M) was heated at 70 °C for 2.5 to 24 h (until judged complete by TLC). The reaction was slowly poured over H_2O and the crude product was extracted with $CHCl_3$ (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



2-Bromo-*N*-cyclopropylbenzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromoaniline (3.44 g, 20.0 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 2.49 g (59% yield) of an orange oil.

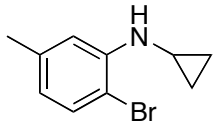
[183] Bénard, S.; Neuville, L.; Zhu, J. *Chem. Commun.* **2010**, *46*, 3393-3395.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.41 (dd, J = 7.9, 1.5 Hz, 1H), 7.21 (ddd, J = 8.1, 7.3, 1.4 Hz, 1H), 7.07 (dd, J = 8.1, 1.5 Hz, 1H), 6.61 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 4.73 (br s, 1H), 2.45 (tt, J = 6.7, 3.4 Hz, 1H), 0.85-0.73 (m, 2H), 0.64-0.53 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 145.7, 132.3, 128.4, 118.3, 112.8, 109.3, 25.3, 7.6. **HRMS** Calculated for $C_9H_{10}NBr$ (M^+) 210.9997, Found 210.9969. **IR (ν_{max}/cm^{-1})** 3400, 3287, 3072, 2971, 1499, 668. **R_f** 0.34 (100% petroleum ether).



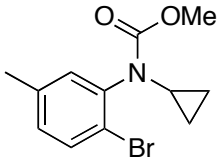
Methyl 2-bromophenylcyclopropylcarbamate (4.26) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropylbenzenamine (1.27 g, 5.97 mmol, 1.00 equiv) and methyl chloroformate (15 mL, 0.40 M). The product was purified by silica gel flash chromatography (20% Et_2O in petroleum ether) to afford 1.42 g (88% yield) of a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.61 (dd, J = 8.0, 1.4 Hz, 1H), 7.31 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H), 7.16 (ddd, J = 7.9, 7.5, 1.7 Hz, 1H), 7.11 (br d, J = 7.7 Hz, 1H), 3.65 (br s, 3H), 3.15-3.09 (m, 1H), 0.74 (d, J = 5.8 Hz, 2H), 0.63-0.58 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 156.7, 141.1, 133.3, 130.4, 128.8, 128.2, 124.2, 53.0, 31.2, 7.6. **HRMS** Calculated for $C_{11}H_{12}NO_2Br$ (M^+) 271.0031, Found 271.0029. **IR (ν_{max}/cm^{-1})** 3091, 3013, 2953, 1720, 1340, 1212. **R_f** 0.23 (20% Et_2O in petroleum ether).



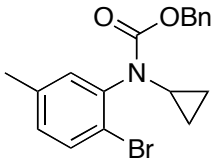
2-Bromo-*N*-cyclopropyl-5-methylbenzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-5-methylaniline (0.67 mL, 5.4 mmol, 1.0 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 963 mg (66% yield) of an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.27 (d, J = 8.0 Hz, 1H), 6.88 (dd, J = 2.1, 0.5 Hz, 1H), 6.44 (ddd, J = 8.0, 2.1, 0.6 Hz, 1H), 4.66 (br s, 1H), 2.43 (tt, J = 6.7, 3.4 Hz, 1H), 2.31 (s, 3H), 0.85-0.72 (m, 2H), 0.64-0.52 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 145.4, 138.5, 132.0, 119.3, 113.6, 106.2, 25.3, 21.7, 7.6. **HRMS** Calculated for $C_{10}H_{12}NBr$ (M^+) 225.0153, Found 225.0132. **IR (ν_{max}/cm^{-1})** 3410, 3008, 2972, 2921, 1598, 1502, 1305, 1017. **R_f** 0.60 (100% petroleum ether).



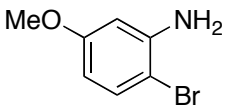
Methyl 2-bromo-5-methylphenylcyclopropylcarbamate (4.30a) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-5-methylbenzenamine (300 mg, 1.33 mmol, 1.00 equiv) and methyl chloroformate (3.3 mL, 0.40 M). The product was purified by silica gel flash chromatography (25% Et_2O in petroleum ether) to afford 291 mg (77% yield) of a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$, 328K, TMS) δ 7.46 (d, J = 8.1 Hz, 1H), 6.96 (d, J = 8.2 Hz, 1H), 6.93 (s, 1H), 3.70 (s, 3H), 3.15-3.08 (m, 1H), 2.31 (s, 3H), 0.75-0.71 (m, 2H), 0.65-0.58 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 156.7, 140.7, 138.4, 132.9, 131.0, 129.7, 120.7, 53.0, 31.3, 20.9, 7.6. **HRMS** Calculated for $C_{11}H_{11}NOBr$ (M^+ - OCH_3) 252.0024, Found 252.0027. **IR (ν_{max}/cm^{-1})** 3014, 2953, 1718, 1442, 1340, 1091, 1021. **R_f** 0.35 (30% Et_2O in petroleum ether).



Benzyl 2-bromo-5-methylphenylcyclopropylcarbamate (4.30b) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-5-methylbenzenamine (300 mg, 1.33 mmol, 1.00 equiv) and benzyl chloroformate (3.3 mL, 0.40 M). The product was purified by silica gel flash chromatography (60% CH_2Cl_2 in petroleum ether) to afford 323 mg (68% yield) of a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$, 328K, TMS) δ 7.47 (d, J = 8.0 Hz, 1H), 7.32-7.23 (m, 5H), 6.98-6.93 (m, 2H), 5.18 (s, 2H), 3.20-3.12 (m, 1H), 2.30 (s, 3H), 0.77-0.61 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 156.2, 140.7, 138.4, 137.0, 132.9, 131.1, 129.8, 128.5, 127.9, 127.7, 120.7, 67.5, 31.2, 20.9, 7.7. **HRMS** Calculated for $C_{11}H_{11}NO_2Br$ (M^+ - $CH_2C_6H_5$) 267.9973, Found 267.9941. **IR (ν_{max}/cm^{-1})** 3033, 2959, 1717, 1477, 1329, 1088. **R_f** 0.32 (70% CH_2Cl_2 in petroleum ether).

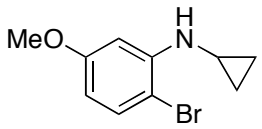


2-Bromo-5-methoxybenzenamine Prepared according to a modified literature procedure.[184] To a mixture of concentrated HCl (0.15 M, 17 mL) and glacial acetic acid (0.15 M, 17 mL) at 0 °C was added 1-bromo-4-methoxy-2-nitrobenzene (600 mg, 2.59 mmol, 1.00 equiv). Zinc powder (4.31 g) was then added portionwise over 1h after which point the reaction mixture was stirred for an additional 15 minutes at 0 °C and then quenched by addition of concentrated ammonium hydroxide until slightly basic. The crude product was extracted with CH_2Cl_2 (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced

[184] Jung, M. E.; Yuk-Sun Lam, P.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087-1105.

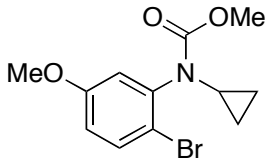
pressure. The product was purified by silica gel flash chromatography (15% Et_2O in petroleum ether) to afford 522 mg (80% yield) of a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.27 (d, J = 8.8 Hz, 1H), 6.33 (d, J = 2.8 Hz, 1H), 6.23 (dd, J = 8.8, 2.8 Hz, 1H), 3.89 (br s, 1H), 3.74 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 160.0, 144.8, 132.9, 105.6, 101.3, 100.5, 55.4. **HRMS** Calculated for C_7H_8NOBr (M^+) 200.9789, Found 200.9773. **IR (ν_{max}/cm^{-1})** 3481, 3374, 3006, 2943, 1492, 1301, 1210. **R_f** 0.25 (15% Et_2O in petroleum ether).



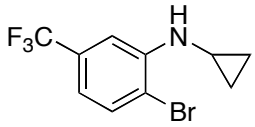
2-Bromo-*N*-cyclopropyl-5-methoxybenzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-5-methoxyaniline (400 mg, 1.98 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 318 mg (66% yield) of a pale pink oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.28 (d, J = 8.7 Hz, 1H), 6.64 (d, J = 2.9 Hz, 1H), 6.20 (dd, J = 8.7, 2.9 Hz, 1H), 4.69 (br , 1H), 3.80 (s, 3H), 2.43 (tt, J = 6.7, 3.4 Hz, 1H), 0.81-0.72 (m, 2H), 0.64-0.55 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 160.2, 146.6, 132.5, 103.3, 100.6, 99.5, 55.5, 25.2, 7.6. **HRMS** Calculated for C_9H_9NOBr (M^+ - CH_3) 227.9847, Found 227.9837. **IR (ν_{max}/cm^{-1})** 3397, 3091, 2961, 1600, 1215, 1016. **R_f** 0.47 (4% Et_2O in petroleum ether).



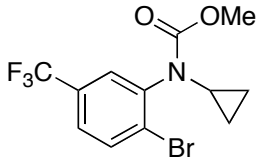
Methyl 2-bromo-5-methoxyphenylcyclopropylcarbamate (4.32) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-5-methoxybenzenamine (200 mg, 0.826 mmol, 1.00 equiv) and methyl chloroformate (2.1 mL, 0.40 M). The product was purified by silica gel flash chromatography (40% Et_2O in petroleum ether) to afford 190 mg (77% yield) of a white solid.

^{1}H NMR (300 MHz, $CDCl_3$, 328K, TMS) δ 7.47 (d, J = 8.8 Hz, 1H), 6.73 (dd, J = 8.8, 3.0 Hz, 1H), 6.67 (d, J = 3.0 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.11 (tt, J = 7.1, 3.7 Hz, 1H), 0.76-0.72 (m, 2H), 0.67-0.61 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 159.7, 156.7, 141.8, 133.4, 116.4, 114.8, 114.7, 55.8, 53.1, 31.3, 7.7. **HRMS** Calculated for $C_{12}H_{14}NO_3Br$ (M^+) 301.0114, Found 301.0137. **IR (ν_{max}/cm^{-1})** 3012, 2954, 2838, 1718, 1593, 1340, 1230. **R_f** 0.18 (30% Et_2O in petroleum ether). **Melting point** 64-66 ºC



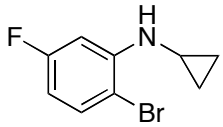
2-Bromo-*N*-cyclopropyl-5-(trifluoromethyl)benzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-5-(trifluoromethyl)aniline (0.60 mL, 4.2 mmol, 1.0 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 710 mg (61% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.49 (dd, J = 8.2, 0.7 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 6.85-6.82 (m, 1H), 4.90 (br s, 1H), 2.51-2.45 (m, 1H), 0.88-0.79 (m, 2H), 0.62-0.58 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 146.0, 132.6, 130.9 (q, J_F = 32.1 Hz), 124.3 (q, J_F = 271 Hz), 114.6 (q, J_F = 3.8 Hz), 112.5, 108.9 (q, J_F = 3.7 Hz), 25.1, 7.7. **HRMS** Calculated for $C_{10}H_9NBrF_3$ (M^+) 278.9870, Found 278.9861. **IR (ν_{max}/cm^{-1})** 3419, 3096, 3010, 2978, 1600, 1437, 1334, 1276, 1128, 1081. **R_f** 0.48 (100% petroleum ether).



Methyl 2-bromo-5-(trifluoromethyl)phenylcyclopropylcarbamate (4.34) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-5-(trifluoromethyl)benzenamine (550 mg, 1.96 mmol, 1.00 equiv) and methyl chloroformate (5.0 mL, 0.40 M). The product was purified by silica gel flash chromatography (15% Et_2O in petroleum ether) to afford 575 mg (87% yield) of a yellow oil.

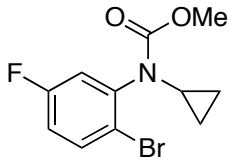
^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 7.75 (d, J = 8.2 Hz, 1H), 7.41 (br d, J = 8.3 Hz, 1H), 7.39 (br s, 1H), 3.73 (br s, 3H), 3.14 (tt, J = 7.2, 3.8 Hz, 1H), 0.81-0.76 (m, 2H), 0.62 (br s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 156.1, 141.8, 133.9, 130.9 (q, J_F = 33.2 Hz), 128.2, 127.1 (q, J_F = 3.6 Hz), 125.3 (q, J_F = 3.7 Hz), 123.4 (q, J_F = 271 Hz), 53.0, 31.0, 7.7. **HRMS** Calculated for $C_{11}H_8NOBrF_3$ (M^+ - OCH_3) 305.9741, Found 305.9757. **IR (ν_{max}/cm^{-1})** 3017, 2956, 1727, 1607, 1443, 1335, 1131, 1078, 1016, 822. **R_f** 0.21 (10% Et_2O in petroleum ether).



2-Bromo-*N*-cyclopropyl-5-fluorobenzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-5-fluoroaniline (1.00 g, 5.26 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 696 mg (57% yield) of a clear oil.

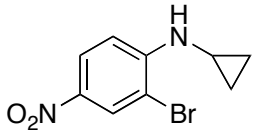
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.32 (dd, J = 8.7, 6.0 Hz, 1H), 6.77 (dd, J = 11.3, 2.9 Hz, 1H), 6.33 (ddd, J = 8.7, 8.1, 2.9 Hz, 1H), 4.80 (br s, 1H), 2.45-2.40 (m, 1H), 0.87-0.75 (m, 2H), 0.65-0.53 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 163.3

(d, J_F = 241 Hz), 147.1 (d, J_F = 11.2 Hz), 132.8 (d, J_F = 9.7 Hz), 104.9 (d, J_F = 23.2 Hz), 103.2 (d, J_F = 2.8 Hz), 100.1 (d, J_F = 27.6 Hz), 25.2, 7.6. **HRMS** Calculated for C_9H_9NBrF (M^+) 228.9902, Found 228.9891. **IR (ν_{max}/cm^{-1})** 3407, 3090, 3007, 2974, 1613, 1503, 1176, 1029. **R_f** 0.46 (100% petroleum ether).



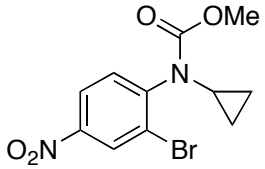
Methyl 2-bromo-5-fluorophenylcyclopropylcarbamate (4.36) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-5-fluorobenzenamine (550 mg, 2.39 mmol, 1.00 equiv) and methyl chloroformate (6.0 mL, 0.40 M). The product was purified by silica gel flash chromatography (15% Et_2O in petroleum ether) to afford 586 mg (85% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 7.55 (dd, J = 8.7, 5.8 Hz, 1H), 6.93-6.87 (m, 2H), 3.71 (br s, 3H), 3.11 (tt, J = 7.1, 3.8 Hz, 1H), 0.78-0.75 (m, 2H), 0.62 (br s, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 161.9 (d, J_F = 247 Hz), 156.2, 147.1 (d, J_F = 9.8 Hz), 133.8 (d, J_F = 8.7 Hz), 118.5 (d, J_F = 3.8 Hz), 117.6 (d, J_F = 22.6 Hz), 115.9 (d, J_F = 22.1 Hz), 53.0, 31.0, 7.6. **HRMS** Calculated for $C_{10}H_8NO_2BrF$ (M^+ - CH_3) 271.9722, Found 271.9727. **IR (ν_{max}/cm^{-1})** 3010, 2955, 1724, 1474, 1442, 1339, 1219, 1084. **R_f** 0.18 (10% Et_2O in petroleum ether).



2-Bromo-*N*-cyclopropyl-4-nitrobenzenamine *General procedure B for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-1-fluoro-4-nitrobenzene (1.00 g, 4.55 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% Et_2O in petroleum ether) to afford 1.05 g (90% yield) of a yellow solid.

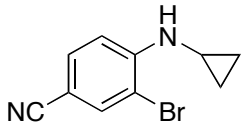
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.34 (d, J = 2.5 Hz, 1H), 8.12 (dd, J = 9.1, 2.5 Hz, 1H), 7.02 (d, J = 9.1 Hz, 1H), 5.39 (br s, 1H), 2.56 (ttd, J = 6.8, 3.4, 1.3 Hz, 1H), 0.95-0.90 (m, 2H), 0.67-0.63 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 150.8, 138.4, 128.7, 125.2, 110.7, 107.5, 25.2, 7.9. **HRMS** Calculated for $C_9H_9N_2O_2Br$ (M^+) 257.9827, Found 257.9889. **IR (ν_{max}/cm^{-1})** 3391, 3086, 1593, 1323. **R_f** 0.24 (10% Et_2O in petroleum ether). **Melting point** 91 ºC.



Methyl 2-bromo-4-nitrophenylcyclopropylcarbamate (4.38) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-4-

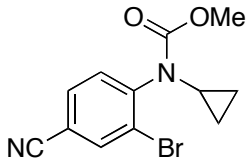
nitrobenzenamine (800 mg, 3.11 mmol, 1.00 equiv) and methyl chloroformate (8.0 mL, 0.40 M). The product was purified by silica gel flash chromatography (gradient from 20% to 30% EtOAc in petroleum ether) to afford 358 mg (37% yield) of a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.49 (d, J = 2.5 Hz, 1H), 8.19 (dd, J = 8.7, 2.6 Hz, 1H), 7.32 (d, J = 8.7 Hz, 1H), 3.72 (br s, 3H), 3.13 (tt, J = 7.0, 3.6 Hz, 1H), 0.82-0.80 (m, 2H), 0.59 (br s, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K, TMS)** δ 155.8, 147.2, 147.1, 130.6, 128.8, 124.7, 123.3, 53.4, 31.2, 8.1. **HRMS** Calculated for $C_{10}H_8N_2O_3Br$ (M^+ - OCH_3) 284.9698, Found 284.9680. **IR (ν_{max}/cm^{-1})** 3099, 3014, 295, 1729, 1527, 1345 cm^{-1}. **R_f** 0.24 (20% EtOAc in petroleum ether). **Melting point** 87-89 ºC.



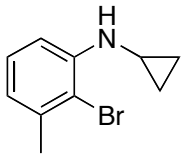
3-Bromo-4-(cyclopropylamino)benzonitrile *General procedure B for the preparation of N-cyclopropylbenzenamines* was followed using 3-bromo-4-fluorobenzonitrile (1.00 g, 4.55 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% Et_2O in petroleum ether) to afford 0.954 g (89% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.64 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 5.18 (br s, 1H), 2.52-2.47 (m, 1H), 0.93-0.81 (m, 2H), 0.67-0.55 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 149.1, 135.7, 132.8, 119.1, 112.1, 108.3, 100.3, 24.9, 7.8. **HRMS** Calculated for $C_{10}H_9N_2Br$ (M^+) 235.9949, Found 235.9924. **IR (ν_{max}/cm^{-1})** 3404, 3091, 3007, 2221, 1596, 1334, 1192, 815. **R_f** 0.28 (10% Et_2O in petroleum ether). **Melting point** 100-101 ºC.



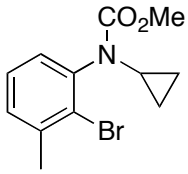
Methyl 2-bromo-4-cyanophenylcyclopropylcarbamate (4.40) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 3-bromo-4-(cyclopropylamino)benzonitrile (700 mg, 2.95 mmol, 1.00 equiv) and methyl chloroformate (7.0 mL, 0.40 M). The product was purified by silica gel flash chromatography (25% EtOAc in petroleum ether) to afford 674 mg (77% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.92 (d, J = 1.8 Hz, 1H), 7.63 (dd, J = 8.1, 1.9 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 3.71 (br s, 3H), 3.11 (tt, J = 7.1, 3.6 Hz, 1H), 0.81-0.79 (m, 2H), 0.57 (br s, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 155.9, 145.7, 136.9, 131.9, 131.0, 124.9, 116.9, 112.9, 53.3, 31.2, 30.9, 8.0. **HRMS** Calculated for $C_{11}H_8N_2OBr$ (M^+ - OCH_3) 264.9800, Found 264.9767. **IR (ν_{max}/cm^{-1})** 3529, 3096, 3014, 2955, 2233, 1725, 1442, 1340, 1214, 534. **R_f** 0.28 (25% EtOAc in petroleum ether).



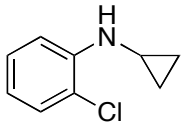
2-Bromo-*N*-cyclopropyl-3-methylaniline *General procedure C for the preparation of N-cyclopropylbenzenamines* was followed using 2-bromo-3-methylaniline (0.37 mL, 3.0 mmol, 1.0 equiv). The product was purified by silica gel flash chromatography (100% hexanes) to afford 350 mg (52% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.09 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.62 (d, *J* = 7.4 Hz, 1H), 4.89 (br s, 1H), 2.45-2.40 (m, 1H), 2.35 (s, 3H), 0.78-0.70 (m, 2H), 0.62-0.56 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** *δ* 145.8, 138.2, 127.5, 119.4, 111.9, 110.1, 25.4, 23.6, 7.5. **IR (ν_{max}/cm^{-1})** 3404, 2922, 1595, 1469, 1323, 1016, 766. **R_f** 0.36 (100% hexanes).



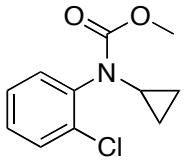
Methyl (2-bromo-3-methylphenyl)(cyclopropyl)carbamate (4.42) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclopropyl-3-methylaniline (590 mg, 2.61 mmol, 1.00 equiv) and methyl chloroformate (5.2 mL, 0.50 M). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 632 mg (85% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 328K) *δ* 7.22-7.16 (m, 2H), 6.94 (dd, *J* = 6.8, 2.6 Hz, 1H), 3.70 (br s, 3H), 3.15 (tt, *J* = 7.2, 3.8 Hz, 1H), 2.46 (s, 3H), 0.78-0.68 (m, 2H), 0.65-0.60 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** *δ* 156.7, 141.1, 139.6, 129.6, 127.6, 127.2, 126.7, 52.8, 31.0, 23.7, 7.4. **IR (ν_{max}/cm^{-1})** 3013, 2953, 1722, 1469, 1442, 1340, 1217, 1087, 550. **R_f** 0.18 (10% EtOAc in hexanes). **Melting point** 66-68 ºC.



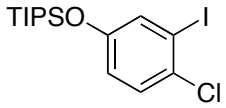
2-Chloro-*N*-cyclopropylbenzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-chloroaniline (2.1 mL, 20 mmol, 1.0 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 2.0 g (60% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) *δ* 7.23 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.3, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.66 (ddd, *J* = 7.6, 7.6, 1.6 Hz, 1H), 4.72 (s, 1H), 2.44 (tt, *J* = 6.7, 3.4 Hz, 1H), 0.84-0.71 (m, 2H), 0.63-0.51 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** *δ* 144.7, 129.1, 127.8, 118.9, 117.8, 112.7, 25.1, 7.6. **HRMS** Calculated for $C_9H_{10}NCl$ (M^+) 167.0502, Found 167.0500. **IR (ν_{max}/cm^{-1})** 3408, 3288, 2957, 2898, 1595, 1036, 747. **R_f** 0.35 (100% petroleum ether).



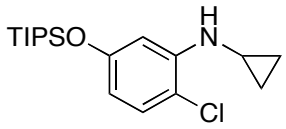
Methyl 2-chlorophenylcyclopropylcarbamate (4.44) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-chloro-*N*-cyclopropylbenzenamine (175 mg, 1.04 mmol, 1.00 equiv) and methyl chloroformate (4.7 mL, 0.22 M). The product was purified by silica gel flash chromatography (20% Et_2O in petroleum ether) to afford 219 mg (93% yield) of a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 328K, TMS) δ 7.48-7.44 (m, 1H), 7.32-7.22 (m, 2H), 7.17-7.13 (m, 1H), 3.73 (s, 3H), 3.15 (tt, J = 7.1, 3.6 Hz, 1H), 0.81-0.74 (m, 2H), 0.65-0.59 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 156.8, 139.2, 133.3, 130.1, 130.0, 128.5, 127.4, 53.0, 31.0, 7.5. **HRMS** Calculated for $C_{10}H_9NOCl$ (M^+ - OCH_3) 194.0373, Found 194.0354. **IR (ν_{max}/cm^{-1})** 3100, 3018, 2956, 1719, 1442, 1341, 753. **R_f** 0.30 (20% Et_2O in petroleum ether).



(4-Chloro-3-iodophenoxy)triisopropylsilane To a solution of 4-chloro-2-iodophenol (1.00 g, 3.93 mmol, 1.00 equiv) and imidazole (401 mg, 5.90 mmol, 1.50 equiv) in DMF (20 mL, 0.20 M) at room temperature was added triisopropylsilyl chloride (1.7 mL, 7.9 mmol, 2.0 equiv) via syringe. The resulting solution was stirred at room temperature for four hours. The crude reaction mixture was then diluted with H_2O and extracted with Et_2O (x3). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (gradient 0 to 5% EtOAc in hexanes) to afford 1.49 g (93% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.36 (d, J = 2.8 Hz, 1H), 7.23 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 8.7, 2.8 Hz, 1H), 1.26-1.17 (m, 3H), 1.07 (d, J = 6.8 Hz, 18H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 154.9, 131.3, 130.3, 129.1, 120.9, 97.7, 17.8, 12.6. **IR (ν_{max}/cm^{-1})** 3063, 2946, 2867, 1579, 1461, 1283, 1230, 932, 883, 686. **R_f** 0.60 (100% hexanes).

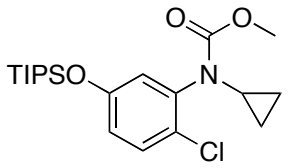


2-Chloro-N-cyclopropyl-5-((triisopropylsilyl)oxy)aniline An oven-dried test tube equipped with a magnetic stir bar and a teflon septum was charged with BrettPhos Palladacycle Precatalyst[185] (24.3 mg, 0.0304 mmol, 1.00 mol%), BrettPhos[185] (16.3 mg, 0.0304 mmol, 1.00 mol%) and NaOtBu (351 mg, 3.65 mmol, 1.2 equiv). The test tube was evacuated and backfilled with argon (x3). (4-Chloro-3-iodophenoxy)triisopropylsilane

[185] Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552-13554.

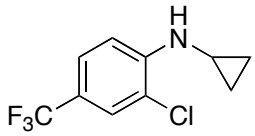
(1.25g, 3.04 mmol, 1.00 equiv) was then added as a solution in toluene (3.0 mL, 1.0 M) followed by cyclopropylamine (0.25 mL, 3.7 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature for 12 hours after which point it was diluted with EtOAc. After addition of H_2O, the organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (gradient 0 to 2% EtOAc in hexanes) to afford 508 mg (49% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.04 (d, J = 8.6 Hz, 1H), 6.66 (d, J = 2.8 Hz, 1H), 6.22 (dd, J = 8.5, 2.8 Hz, 1H), 4.64 (br s, 1H), 2.44-2.38 (m, 1H), 1.31-1.22 (m, 3H), 1.12 (d, J = 7.0 Hz, 18H), 0.83-0.70 (m, 2H), 0.63-0.55 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 155.8, 145.2, 129.0, 110.9, 109.4, 104.6, 24.9, 17.9, 12.7, 7.3. **IR (ν_{max}/cm^{-1})** 3417, 3089, 2945, 2867, 1599, 1505, 1464, 1426, 1308, 1196, 1009, 883, 686. **R_f** 0.27 (100% hexanes).



Methyl (2-chloro-5-((triisopropylsilyl)oxy)phenyl)(cyclopropyl)carbamate (4.45) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-chloro-*N*-cyclopropyl-5-((triisopropylsilyl)oxy)aniline (450 mg, 1.32 mmol, 1.00 equiv) and methyl chloroformate (3.0 mL, 0.44 M). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 398 mg (76% yield) of a clear oil.

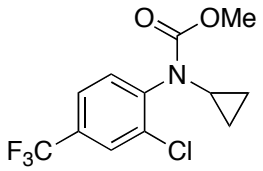
^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 7.24 (d, J = 8.8 Hz, 1H), 6.77 (dd, J = 8.7, 2.8 Hz, 1H), 6.65 (d, J = 2.8 Hz, 1H), 3.69 (br s, 3H), 3.10 (tt, J = 7.2, 3.8 Hz, 1H), 1.29-1.20 (m, 3H), 1.11 (d, J = 7.1 Hz, 18H), 0.77-0.72 (m, 2H), 0.61-0.57 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 156.6, 155.3, 139.7, 130.0, 125.2, 121.9, 120.1, 52.8, 31.0, 17.8, 12.7, 7.3. **IR (ν_{max}/cm^{-1})** 2947, 2868, 1728, 1595, 1480, 1337, 1259. **R_f** 0.32 (10% EtOAc in hexanes).



2-Chloro-*N*-cyclopropyl-4-(trifluoromethyl)benzenamine *General procedure A for the preparation of N-cyclopropylbenzenamines* was followed using 2-chloro-4-(trifluoromethyl)aniline (0.57 mL, 4.1 mmol, 1.0 equiv). The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 0.56 mg (29% yield) of a clear oil.

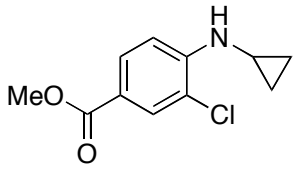
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.31 (dd, J = 8.2, 0.7 Hz, 1H), 7.26 (d, J = 2.6 Hz, 1H), 6.91 (ddt, J = 8.2, 1.4, 0.7 Hz, 1H), 4.88 (br s, 1H), 2.47 (tt, J = 6.7, 3.4 Hz, 1H), 0.87-0.82 (m, 2H), 0.61-0.57 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 145.0, 130.2 (q, J_F = 32 Hz), 129.3, 124.2 (q, J_F = 270 Hz), 122.0, 114.2 (q, J_F = 4.2 Hz), 108.9 (q, J_F = 4.1 Hz), 24.9, 7.7. **HRMS** Calculated for $C_{10}H_9NF_3Cl$ (M^+)

235.0376, Found 235.0353. **IR (ν_{max}/cm^{-1})** 3422, 3097, 2981, 1511, 1278. **R_f** 0.39 (100% petroleum ether).



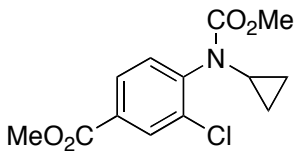
Methyl 2-chloro-4-(trifluoromethyl)phenylcyclopropylcarbamate (4.47) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-chloro-*N*-cyclopropyl-4-(trifluoromethyl)benzenamine (450 mg, 1.91 mmol, 1.00 equiv) and methyl chloroformate (3.8 mL, 0.50 M). The product was purified by silica gel flash chromatography (10% Et_2O in petroleum ether) to afford 350 mg (62% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 7.56 (d, J = 8.4 Hz, 1H), 7.51-7.48 (m, 1H), 7.40 (br s, 1H), 3.70 (br s, 3H), 3.10 (tt, J = 7.1, 3.6 Hz, 1H), 0.80-0.77 (m, 2H), 0.61-0.55 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 328K, TMS)** δ 156.5, 140.4, 137.6, 130.8, 130.4 (q, J_F = 33 Hz), 127.4 (q, J_F = 3.6 Hz), 125.3 (q, J_F = 4.0 Hz), 123.5 (q, J_F = 271 Hz), 53.3, 31.2, 8.0. **HRMS** Calculated for $C_{11}H_8NOF_3Cl$ (M^+ - OCH_3) 264.0217, Found 264.0204. **IR (ν_{max}/cm^{-1})** 3024, 2958, 1727, 1646, 1336, 1131. **R_f** 0.25 (10% Et_2O in petroleum ether).



Methyl 3-chloro-4-(cyclopropylamino)benzoate *General procedure C for the preparation of N-cyclopropylbenzenamines* was followed using methyl 4-amino-3-chlorobenzoate (742 mg, 4.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 427 mg (47% yield) of a white solid.

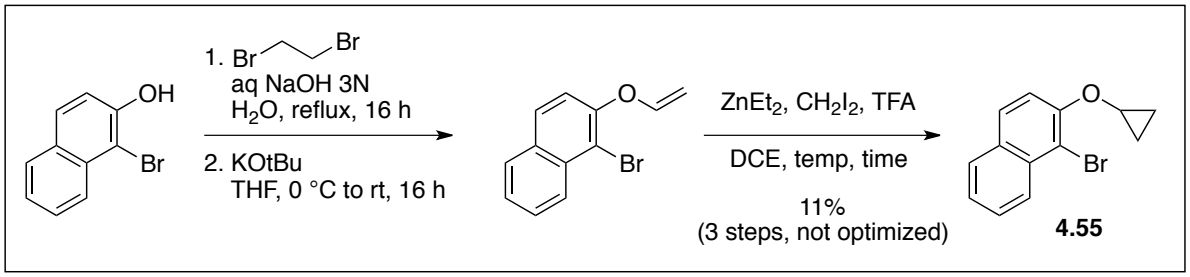
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.91 (d, J = 2.0 Hz, 1H), 7.83 (dd, J = 8.6, 2.0 Hz, 1H), 7.02 (d, J = 8.6 Hz, 1H), 5.08 (br s, 1H), 3.84 (s, 3H), 2.52-2.47 (m, 1H), 0.86-0.81 (m, 2H), 0.61-0.57 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 166.4, 148.2, 130.5, 129.8, 119.2, 118.0, 111.3, 51.8, 24.7, 7.6. **IR (ν_{max}/cm^{-1})** 3411, 3374, 3090, 2992, 2950, 1712, 1603, 1281, 1114, 764. **R_f** 0.26 (10% EtOAc in hexanes). **Melting point** 51-52 ºC.

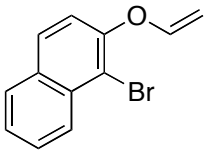


Methyl 3-chloro-4-(cyclopropyl(methoxycarbonyl)amino)benzoate (4.49) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using methyl 3-chloro-4-(cyclopropylamino)benzoate (563 mg, 2.50 mmol, 1.00 equiv) and methyl chloroformate (5.0 mL, 0.50 M). The product was purified by silica gel flash chromatography (20% EtOAc in hexanes) to afford 472 mg (67% yield) of a yellow solid.

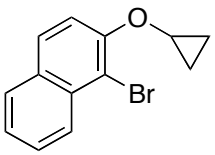
^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 8.09 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 8.2, 1.9 Hz, 1H), 7.20 (d, J = 8.2 Hz, 1H), 3.92 (s, 3H), 3.70 (br s, 3H), 3.14-3.08 (m, 1H), 0.78-0.69 (m, 2H), 0.63-0.55 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 165.3, 156.2, 143.4, 133.6, 131.3, 130.5, 130.0, 128.5, 52.9, 52.3, 30.9, 7.6. **IR (ν_{max}/cm^{-1})** 3093, 3014, 2955, 2852, 1726, 1339, 1288, 760. **R_f** 0.19 (20% EtOAc in hexanes). **Melting point** 78-79 ºC.

Synthesis and Characterization of Starting Materials 4.22, 4.27, 4.55 and 4.57





1-Bromo-2-(vinyloxy)naphthalene. Prepared according to a modified literature procedure.[186] A solution of 1-bromonaphthalen-2-ol (5.59 g, 24.0 mmol, 1.00 equiv) and 1,2-dibromoethane (3.1 mL, 36 mmol, 1.5 equiv) in water (20 mL) was stirred under reflux for 30 min. A 3N aqueous solution of sodium hydroxide (10.4 mL, 31.2 mmol, 1.30 equiv) was then added dropwise via an addition funnel. The reaction mixture was then stirred at reflux for 16 h, cooled to room temperature, extracted with CH_2Cl_2, washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The resulting crude product was then dissolved in dry THF (20 mL) and slowly added via syringe to a solution of potassium *tert*-butoxide (2.69 g, 24.0 mmol, 1.00 equiv) in THF (60 mL) at 0 ºC under argon. The reaction mixture was stirred at room temperature for 16 h, quenched with water, extracted with EtOAc, washed with water and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The residue was passed over a plug of silica gel to provide 1.1 g of crude 1-bromo-2-(vinyloxy)naphthalene (Rf = 0.39, 100% petroleum ether).

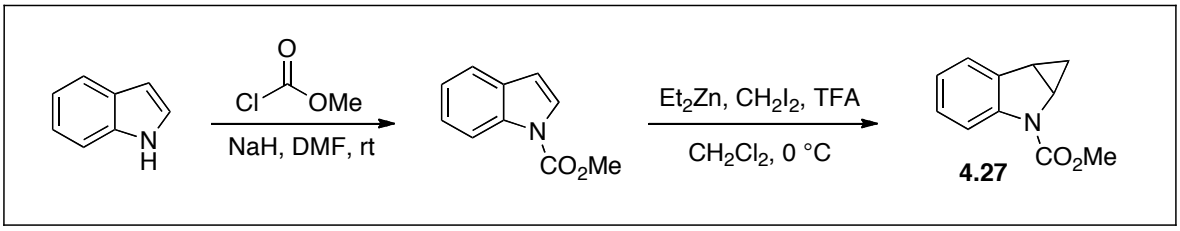


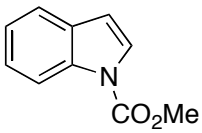
1-Bromo-2-cyclopropoxynaphthalene (4.55) To a solution of diethylzinc (1M in hexanes, 8.0 mL, 8.0 mmol, 2.0 equiv) in dichloroethane (20 mL) at -5 °C under argon was added dropwise, and very slowly, a solution of trifluoroacetic acid (592 μL, 8.00 mmol, 2.00 equiv)

[186] Solinas, M.; Gladiali, S.; Marchetti, M. *J. Mol. Catal. A: Chem.* **2005**, *226*, 141-147.

in dichloroethane (10 mL). The reaction mixture was stirred for 20 min then a solution of diiodomethane (643 μL, 8.00 mmol, 2.00 equiv) in dichloroethane (10 mL) was added dropwise. The reaction mixture was again stirred for 20 min then a solution of 1-bromo-2-(vinyloxy)naphthalene (1.00 g, 4.00 mmol, 1.00 equiv) in dichloroethane (10 mL) was added dropwise. The mixture was allowed to warm to room temperature and then stirred until the reaction was judged to be complete by TLC. The reaction was then quenched at 0 °C by addition of a saturated solution of NH_4Cl (stir for 1 h). The crude product was then extracted with CH_2Cl_2, washed with water and brine, dried with $MgSO_4$, concentrated under reduced pressure and purified by silica gel flash chromatography to give 613 mg of **4.55**.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.21 (dd, J = 8.6, 0.8 Hz, 1H), 7.79 (dd, J = 9.1, 9.1 Hz, 2H), 7.60 (d, J = 9.0 Hz, 1H), 7.55 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.39 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 3.99-3.94 (m, 1H), 0.95-0.90 (m, 2H), 0.89-0.83 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 153.4, 133.1, 129.9, 128.6, 128.0, 127.6, 126.1, 124.3, 115.3, 108.4, 52.5, 6.7. **HRMS** Calculated for $C_{13}H_{11}OBr$ (M^+) 261.9993, Found 261.9988. **R_f** 0.44 (5% Et_2O in petroleum ether).





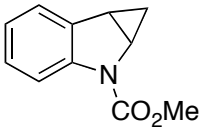
Methyl 1H-indole-1-carboxylate Prepared according to a literature procedure.[187] To a solution of indole (1.17 g, 10.0 mmol, 1.00 equiv) in DMF (33 mL, 0.30 M) at room temperature under an atmosphere of argon was added NaH (0.505 g, 20.0 mmol, 2.00 equiv). The resulting mixture was stirred at room temperature for 30 min after which point methyl chloroformate (1.16 mL, 15.0 mmol, 1.50 equiv) was added via syringe. The mixture was allowed to stir until the reaction was judged to be complete by TLC. The reaction was quenched by the slow addition of H_2O. The crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford 1.52 g (87% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.21 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 3.6 Hz, 1H), 7.59 (dd, J = 7.8, 0.6 Hz, 1H), 7.36 (dd, J = 7.8, 7.8 Hz, 1H), 7.27 (ddd, J = 7.5, 7.5, 0.4 Hz, 1H), 6.62 (d, J = 3.7 Hz, 1H), 4.06 (s, 3H).

Exhibited spectral data identical to a previous report.[188]

[187] Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039-10047.

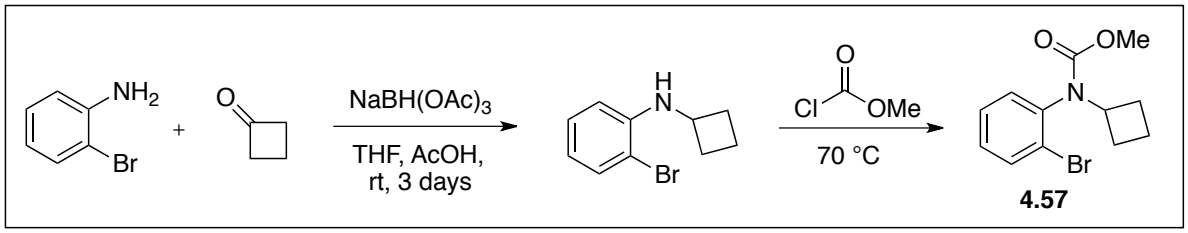
[188] Shieh, W.-C.; Dell, S.; Bach, A.; Repič, O.; Blacklock, T. J. *J. Org. Chem.* **2003**, *68*, 1954-1957.

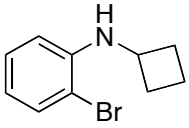


Methyl 1,6b-dihydrocyclopropa[b]indole-2(1aH)-carboxylate (4.27) To a solution of diethylzinc (1M in hexanes, 5.0 mL, 5.0 mmol, 2.0 equiv) in dichloromethane (5.0 mL) at 0 °C under argon was added dropwise, and very slowly, a solution of trifluoroacetic acid (0.37 mL, 5.0 mmol, 2.0 equiv) in dichloromethane (2.5 mL). The reaction mixture was stirred for 20 min then a solution of diiodomethane (0.40 mL, 5.0 mmol, 2.0 equiv) in dichloromethane (2.5 mL) was added dropwise. The reaction mixture was again stirred for 20 min then a solution of methyl 1H-indole-1-carboxylate (0.438 g, 2.50 mmol, 1.00 equiv) in dichloromethane (2.5 mL) was added dropwise. The mixture was allowed to warm to room temperature and then stirred until the reaction was judged to be complete by TLC. The reaction was then quenched at 0 °C by addition of a saturated solution of NH_4Cl (stir for 30 min). The crude product was then extracted with CH_2Cl_2 (x3), washed with water and brine, dried with $MgSO_4$, concentrated under reduced pressure and purified by silica gel flash chromatography (50% CH_2Cl_2 in hexanes) to give 180 mg (38% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.86 (br s, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.18 (dd, J = 7.7, 7.7 Hz, 1H), 6.98 (ddd, J = 7.5, 7.5, 1.1 Hz, 1H), 4.18 (br s, 1H), 3.90 (br s, 3H), 2.65 (ddd, J = 8.6, 6.6, 4.0 Hz, 1H), 1.09-1.07 (m, 1H), 0.29-0.28 (m, 1H).

Exhibited spectral data identical to a previous report.[189]

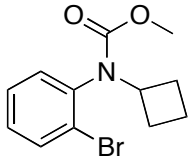




2-Bromo-*N*-cyclobutylaniline Prepared according to a literature procedure.[190] To a solution of 2-bromoaniline (2.70 g, 15.7 mmol, 1.10 equiv) in THF at room temperature under an atmosphere of argon was added cyclobutanone (1.00 g, 14.3 mmol, 1.00 equiv) via syringe followed by $NaBH(OAc)_3$ (4.54 g, 21.4 mmol, 1.50 equiv), portionwise. AcOH (0.82 mL, 14.3 mmol, 1.00 equiv) was then added via syringe. The resulting mixture was stirred at room temperature for 3 days. The crude product was extracted with Et_2O (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (100% hexanes) to afford 1.63 g (50% yield) of a clear oil.

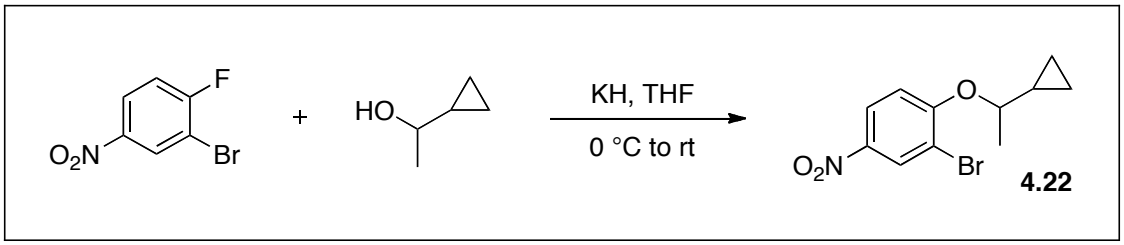
[189] Klärner, F.-G.; Kleine, A. E.; Oebels, D.; Scheidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 479-490.
[190] Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, *31*, 5595-5598.

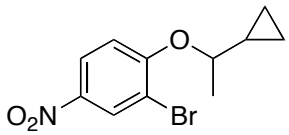
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.45 (dd, J = 7.7, 1.5 Hz, 1H), 7.19 (ddd, J = 7.5, 7.5, 1.4 Hz, 1H), 6.61-6.57 (m, 2H), 4.47 (br s, 1H), 3.97 (sextuplet, J = 6.7 H, 1Hz), 2.53-2.46 (m, 2H), 2.00-1.78 (m, 4H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 144.0, 132.3, 128.4, 117.6, 111.6, 109.3, 48.7, 31.0, 15.3. **IR (ν_{max}/cm^{-1})** 3406, 3066, 2980, 2935, 1595, 1507, 1319, 1170, 1017, 741. **R_f** 0.47 (100% hexanes).



Methyl (2-bromophenyl)(cyclobutyl)carbamate (4.57) *General procedure for the protection of N-cyclopropylbenzenamines* was followed using 2-bromo-*N*-cyclobutylaniline (1.50 g, 6.63 mmol, 1.00 equiv) and methyl chloroformate (13.0 mL, 0.51 M). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 1.60 g (85% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 7.65 (dd, J = 7.8, 1.0 Hz, 1H), 7.35 (ddd, J = 7.6, 7.6, 0.7 Hz, 1H), 7.22-7.16 (m, 2H), 4.72 (br s, 1H), 3.66 (br s, 3H), 2.22-2.15 (m, 2H), 1.95 (quintet, J = 10.0 Hz, 1H), 1.83 (quintet, J = 10.1 Hz, 1H), 1.66-1.51 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 155.4, 138.7, 133.4, 131.6, 129.1, 128.0, 125.8, 52.9, 52.8, 29.7, 28.7, 15.1. **IR (ν_{max}/cm^{-1})** 2988, 2951, 1714, 1442, 1322, 1293, 1039. **R_f** 0.24 (10% EtOAc in hexanes). **Melting point** 46-47 ºC.



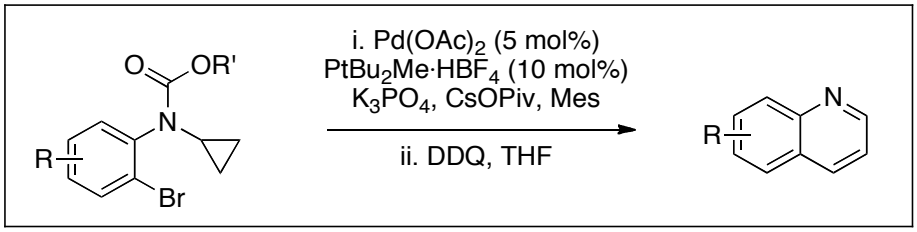


2-Bromo-1-(1-cyclopropylethoxy)-4-nitrobenzene (4.22) 1-Cyclopropylethanol (0.37 mL, 3.8 mmol, 1.1 equiv) was added dropwise via syringe to a solution of KH (0.500 g, 3.75 mmol, 1.10 equiv) in THF (23 mL, 0.15 M) at 0 °C under an atmosphere of argon. The resulting mixture was stirred for 10 minutes after which time 2-bromo-1-fluoro-4-nitrobenzene (0.750 g, 3.41 mmol, 1.00 equiv) was added and the solution was brought to room temperature. Once judged complete by TLC, the reaction was quenched by slow addition of water. The crude product was extracted with CH_2Cl_2 (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (3% Et_2O in petroleum ether) to afford 0.819 g (84% yield) of a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 8.46 (d, J = 2.8 Hz, 1H), 8.15 (dd, J = 9.1, 2.8 Hz, 1H), 6.92 (dd, J = 9.2, 0.5 Hz, 1H), 4.13 (quintet, J = 6.4 Hz, 1H), 1.46 (d, J = 6.2 Hz, 3H), 1.21 (tdt, J = 8.3, 6.9, 5.1 Hz, 1H), 0.65-0.56 (m, 2H), 0.48-0.32 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 160.0, 141.1, 129.3, 124.4, 113.3, 113.2, 80.0, 19.5, 16.5, 3.5, 2.1. **R_f** 0.27 (3% Et_2O in petroleum ether).

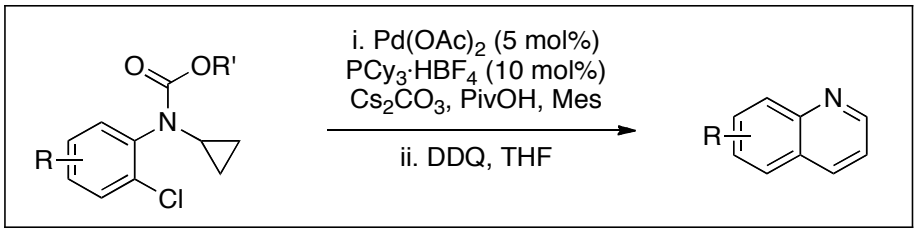
8.4.2 General Procedures and Characterization for Arylation Products

General Procedure A for Arylation at sp^3 C–H Bonds of Cyclopropanes – Quinoline Synthesis



A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with the starting material (if a solid, 1.00 equiv), $Pd(OAc)_2$ (5.00 mol %), P(t-Bu)$_2$Me·HBF_4 (10.0 mol %), K_3PO_4 (1.50 equiv) and CsOPiv (30.0 mol%). The vial was purged with argon. The starting material (if a liquid, 1.00 equiv) was added as a solution in mesitylene (0.20 M). The resulting mixture was placed in a preheated bath and stirred for the indicated time. The reaction was then cooled to 0 °C and diluted with THF (0.20 M) after which point DDQ (1.20 equiv) was added. The mixture was then brought to room temperature and stirred until the reaction was judged complete by TLC. The crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

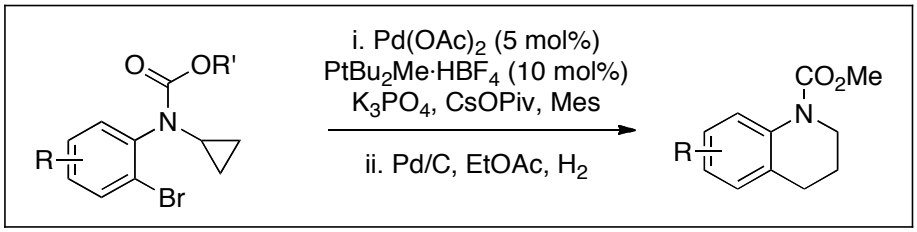
General Procedure B for Arylation at sp^3 C–H Bonds of Cyclopropanes – Quinoline Synthesis



A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with the starting material (if a solid, 1.00 equiv), $Pd(OAc)_2$ (5.00 mol %), PCy_3·HBF_4 (10.0 mol %), Cs_2CO_3 (1.50 equiv) and PivOH (30.0 mol %). The vial was purged with

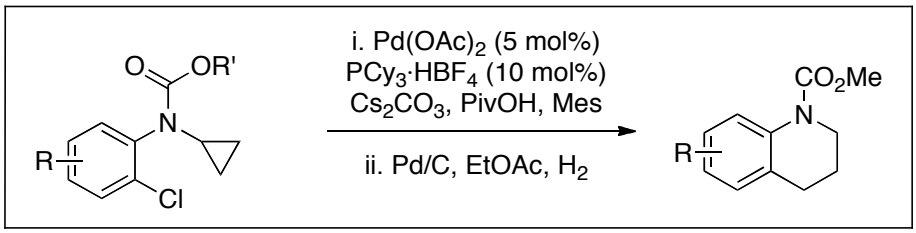
argon. The starting material (if a liquid, 1.00 equiv) was added as a solution in mesitylene (0.20 M). The resulting mixture was placed in a preheated bath and stirred for the indicated time. The reaction was then cooled to 0 °C and diluted with THF (0.20 M) after which point DDQ (1.20 equiv) was added. The mixture was then brought to room temperature and stirred until the reaction was judged complete by TLC. The crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

General Procedure C for Arylation at sp^3 C–H Bonds of Cyclopropanes – Tetrahydroquinoline Synthesis



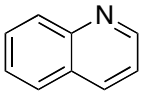
A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with the starting material (if a solid, 1.00 equiv), $Pd(OAc)_2$ (5.00 mol %), P(*t*-Bu)$_2$Me·HBF_4 (10.0 mol %), K_3PO_4 (1.50 equiv) and CsOPiv (30.0 mol %). The vial was purged with argon. The starting material (if a liquid, 1.00 equiv) was added as a solution in mesitylene (0.20 M). The resulting mixture was placed in a preheated bath and stirred for the indicated time. The reaction was then cooled to room temperature and diluted with EtOAc (0.20 M) after which point Pd/C (10 mol%) was added. The mixture was then vigorously stirred under H_2 bubbling for 10 minutes after which point the reaction was stirred under an atmosphere of H_2 (no bubbling) until judged complete by TLC. The crude product was filtered over celite and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.

General Procedure D for Arylation at sp^3 C–H Bonds of Cyclopropanes – Tetrahydroquinoline Synthesis



A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with the starting material (if a solid, 1.00 equiv), $Pd(OAc)_2$ (5.00 mol %), PCy_3·HBF_4 (10.0 mol %), Cs_2CO_3 (1.50 equiv) and PivOH (30.0 mol %). The vial was purged with

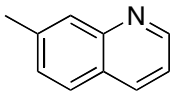
argon. The starting material (if a liquid, 1.00 equiv) was added as a solution in mesitylene (0.20 M). The resulting mixture was placed in a preheated bath and stirred for the indicated time. The reaction was then cooled to room temperature and diluted with EtOAc (0.20 M) after which point Pd/C (10 mol%) was added. The mixture was then vigorously stirred under H_2 bubbling for 10 minutes after which point the reaction was stirred under an atmosphere of H_2 (no bubbling) until judged complete by TLC. The crude product was filtered over celite and concentrated under reduced pressure. The product was purified by silica gel flash chromatography.



Quinoline (4.29) Synthesized according to *General Procedure A* using methyl 2-bromophenylcyclopropylcarbamate (110 mg, 0.409 mmol, 1.00 equiv) at 90 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (40% Et_2O in petroleum ether) to afford 46 mg (87% yield) of an orange oil. Synthesized according to *General Procedure B* using methyl 2-chlorophenylcyclopropylcarbamate (92.3 mg, 0.409 mmol, 1.00 equiv) at 140 °C for 4 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (40% Et_2O in petroleum ether) to afford 40 mg (76% yield) of an orange oil.

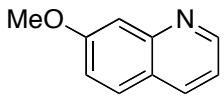
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.93 (dd, J = 4.1, 1.4 Hz, 1H), 8.16 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.72 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.58-7.52 (m, 1H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H).

Commercially available - CAS#: 91-22-5.



7-Methylquinoline (4.31) Synthesized according to *General Procedure A* using methyl 2-bromo-5-methylphenylcyclopropylcarbamate (128 mg, 0.450 mmol, 1.00 equiv) at 90 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (40% Et_2O in petroleum ether) to afford 43 mg (67% yield) of an orange oil. Synthesized according to *General Procedure A* using benzyl 2-bromo-5-methylphenylcyclopropylcarbamate (162 mg, 0.450 mmol, 1.00 equiv) at 90 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (40% Et_2O in petroleum ether) to afford 38 mg (59% yield) of an orange oil.

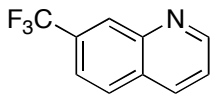
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.87 (dd, J = 4.2, 1.5 Hz, 1H), 8.10 (dd, J = 8.2, 1.1 Hz, 1H), 7.88 (d, J = 0.7 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.3, 1.6 Hz, 1H), 7.32 (dd, J = 8.2, 4.2 Hz, 1H), 2.57 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 150.5, 148.7, 139.9, 135.8, 128.9, 128.6, 127.5, 126.5, 120.4, 22.0. **HRMS** Calculated for $C_{10}H_9N$ (M^+) 143.0735, Found 143.0727. **IR (ν_{max}/cm^{-1})** 3048, 2924, 1627, 1503. **R_f** 0.20 (30% Et_2O in petroleum ether).



7-Methoxyquinoline (4.33) Synthesized according to *General Procedure A* using methyl 2-bromo-5-methoxyphenylcyclopropylcarbamate (150 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (70% Et_2O in petroleum ether) to afford 73 mg (91% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.83 (d, J = 3.1 Hz, 1H), 8.06 (dd, J = 8.2, 1.3 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 7.8, 4.7 Hz, 1H), 7.20 (dd, J = 9.0, 2.5 Hz, 1H), 3.95 (s, 3H).

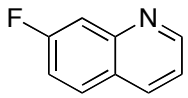
Exhibited spectral data identical to a previous report.[191]



7-(Trifluoromethyl)quinoline (4.35) Synthesized according to *General Procedure A* using methyl 2-bromo-5-(trifluoromethyl)phenylcyclopropylcarbamate (169 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 20 h). The product was purified by silica gel flash chromatography (15% EtOAc and 15% toluene in hexanes) to afford 77 mg (78% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 9.01 (d, J = 3.1 Hz, 1H), 8.41 (br s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 8.5, 1.6 Hz, 1H), 7.51 (dd, J = 8.3, 4.2 Hz, 1H).

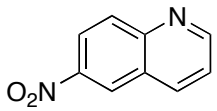
Exhibited spectral data identical to a previous report.[192]



7-Fluoroquinoline (4.37) Synthesized according to *General Procedure A* using methyl 2-bromo-5-fluorophenylcyclopropylcarbamate (144 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 2 h). The product was purified by silica gel flash chromatography (15% EtOAc and 15% toluene in hexanes) to afford 54 mg (73% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.89 (dd, J = 4.2, 1.6 Hz, 1H), 8.13 (dd, J = 8.3, 1.0 Hz, 1H), 7.79 (dd, J = 9.0, 6.0 Hz, 1H), 7.71 (dd, J = 10.1, 2.5 Hz, 1H), 7.37-7.29 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 162.9 (d, J_F = 249 Hz), 151.3, 149.1 (d, J_F = 12 Hz), 136.0, 129.8 (d, J_F = 10 Hz), 125.3 (d, J_F = 1 Hz), 120.4 (d, J_F = 3 Hz), 117.2 (d, J_F = 26 Hz), 113.0 (d, J_F = 20 Hz). **IR (ν_{max}/cm^{-1})** 3055, 3005, 2927, 1630, 1507, 1322, 1258, 1108. **R_f** 0.19 (15% EtOAc and 15% toluene in hexanes).

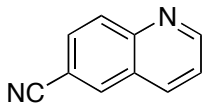
[191] Mash, E. A.; Aavula, B. R. *Synth. Commun.* **2000**, *30*, 367-375.
[192] Huff, J. R.; King, S. W.; Saari, W. S.; Springer, J. P.; Martin, G. E.; Williams, M. *J. Med. Chem.* **1985**, *28*, 945-948.



6-Nitroquinoline (4.39) Synthesized according to *General Procedure A* using methyl 2-bromo-4-nitrophenylcyclopropylcarbamate (129 mg, 0.409 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 8 h). The product was purified by silica gel flash chromatography (40% EtOAc in petroleum ether) to afford 44 mg (61% yield) of a yellow solid.

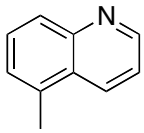
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 9.11 (dd, J = 4.2, 1.7 Hz, 1H), 8.81 (d, J = 2.5 Hz, 1H), 8.49 (dd, J = 9.3, 2.5 Hz, 1H), 8.38-8.36 (m, 1H), 8.25 (d, J = 9.3 Hz, 1H), 7.59 (dd, J = 8.4, 4.2 Hz, 1H).

Exhibited spectral data identical to a previous report.[193]



Quinoline-6-carbonitrile (4.41) Synthesized according to *General Procedure A* using methyl 2-bromo-4-cyanophenylcyclopropylcarbamate (133 mg, 0.450 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (45% EtOAc in petroleum ether) to afford 45 mg (65% yield) of a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 9.05 (dd, J = 4.2, 1.5 Hz, 1H), 8.24-8.21 (m, 2H), 8.19 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 8.7, 1.8 Hz, 1H), 7.54 (dd, J = 8.3, 4.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 153.4, 149.3, 136.5, 134.2, 131.2, 130.3, 127.7, 122.9, 118.6, 110.5. **HRMS** Calculated for $C_{10}H_6N_2$ (M^+) 154.0531, Found 154.0529. **IR (ν_{max}/cm^{-1})** 3050, 2230, 1496, 1321, 1216, 838, 755. **R_f** 0.24 (45% EtOAc in petroleum ether). **Melting point** 131-132 ºC.



5-Methylquinoline (4.43) Synthesized according to *General Procedure A* using methyl (2-bromo-3-methylphenyl)(cyclopropyl)carbamate (142 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 16 h (DDQ oxidation at room temperature for 3.5 h). The product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to afford 62 mg (87% yield) of an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.90 (d, J = 3.1 Hz, 1H), 8.31 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.58 (dd, J = 7.1, 7.1 Hz, 1H), 7.40 (dd, J = 8.5, 4.2 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 2.67 (s, 3H).

Exhibited spectral data identical to a previous report.[194]

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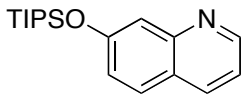
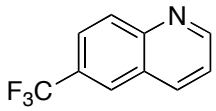
[193] Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 12898-12899.
[194] Cho, C. S.; Oh, B. H.; Shim, S. C. *J. Heterocyclic Chem.* **1999**, *36*, 1175-1178.



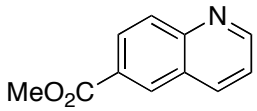
7-((Triisopropylsilyl)oxy)quinoline (4.46) Synthesized according to *General Procedure B* using methyl (2-chloro-5-((triisopropylsilyl)oxy)phenyl)(cyclopropyl)carbamate (128 mg, 0.322 mmol, 1.00 equiv) at 140 °C for 3.5 h (DDQ oxidation at room temperature for 2 h). The product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford 83 mg (85% yield) of a red oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.83 (dd, J = 4.3, 1.7 Hz, 1H), 8.07 (dd, J = 8.3, 1.2 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.4 Hz, 1H), 7.25 (dd, J = 8.2, 4.3 Hz, 1H), 7.20 (dd, J = 8.8, 2.4 Hz, 1H), 1.40-1.29 (m, 3H), 1.14 (d, J = 7.4 Hz, 18H). **^{13}C NMR (100 MHz, $CDCl_3$, 328K)** δ 157.2, 150.5, 149.7, 135.7, 128.7, 123.7, 123.0, 119.0, 115.7, 17.9, 12.7. **IR (ν_{max}/cm^{-1})** 3062, 2945, 2868, 1619, 1499, 1322, 1271, 1211, 1072, 969, 836. **R_f** 0.13 (5% EtOAc in hexanes).



6-(Trifluoromethyl)quinoline (4.48) Synthesized according to *General Procedure B* using methyl 2-chloro-4-(trifluoromethyl)phenylcyclopropylcarbamate (120 mg, 0.409 mmol, 1.00 equiv) at 140 °C for 8 h (DDQ oxidation at room temperature for 2.5 h). The product was purified by silica gel flash chromatography (30% Et_2O in petroleum ether) to afford 42 mg (52% yield) of a yellow solid.

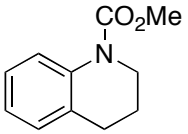
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 9.03 (dd, J = 4.2, 1.7 Hz, 1H), 8.43 (d, J = 0.8 Hz, 1H), 8.23 (dd, J = 8.4, 0.9 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 8.5, 1.8 Hz, 1H), 7.53 (dd, J = 8.3, 4.2 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 151.9, 147.4, 136.1, 131.4 (q, J_F = 32.4 Hz), 129.8, 129.2, 127.5 (q, J_F = 4.4 Hz), 124.1 (q, J_F = 271 Hz), 123.1, 122.4 (q, J_F = 3.1 Hz). **HRMS** Calculated for $C_{10}H_6NF_3$ (M^+) 197.0452, Found 197.0456. **IR (ν_{max}/cm^{-1})** 3060, 1510, 1321, 1153, 1145, 1117, 933, 842. **R_f** 0.26 (30% Et_2O in petroleum ether). **Melting point** 60-62 ºC.



Methyl quinoline-6-carboxylate (4.50) Synthesized according to *General Procedure B* using methyl 3-chloro-4-(cyclopropyl(methoxycarbonyl)amino)benzoate (143 mg, 0.500 mmol, 1.00 equiv) at 140 °C for 3 h (DDQ oxidation at room temperature for 3 h). The product was purified by silica gel flash chromatography (50% EtOAc in hexanes) to afford 77 mg (82% yield) of an orange solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.98 (dd, J = 4.2, 1.7 Hz, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.27 (dd, J = 8.8, 1.9 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 8.3, 4.2 Hz, 1H), 3.97 (s, 3H).

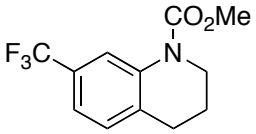
Exhibited spectral data identical to a previous report.[195]



Methyl 3,4-dihydroquinoline-1(2H)-carboxylate (4.51) Synthesized according to *General Procedure C* using methyl 2-bromophenylcyclopropylcarbamate (135 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 13 h. The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 78 mg (82% yield) of a yellow oil.

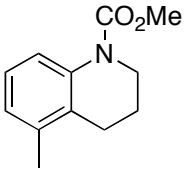
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.65 (br d, J = 7.9 Hz, 1H), 7.16-7.12 (m, 1H), 7.08-7.06 (m, 1H), 6.99 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 3.78 (s, 3H), 3.76-3.73 (m, 2H), 2.76 (t, J = 6.6 Hz, 2H), 1.93 (tt, J = 6.4, 6.4 Hz, 2H).

Exhibited spectral data identical to a previous report.[196]



Methyl 7-(trifluoromethyl)-3,4-dihydroquinoline-1(2H)-carboxylate (4.52) Synthesized according to *General Procedure C* using methyl 2-bromo-5-(trifluoromethyl)phenylcyclopropylcarbamate (84.5 mg, 0.250 mmol, 1.00 equiv) at 110 °C for 15 h. The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 29 mg (45% yield) of a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.07 (br s, 1H), 7.25 (dd, J = 7.9, 1.1 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 3.83 (s, 3H), 3.81-3.78 (m, 2H), 2.82 (t, J = 6.5 Hz, 2H), 1.98 (dd, J = 12.6, 6.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 155.1, 138.5, 133.4, 129.0, 128.5 (q, J_F = 32.1 Hz), 124.1 (q, J_F = 271 Hz), 120.7 (q, J_F = 3.7 Hz), 119.9 (q, J_F = 3.7 Hz), 53.1, 44.8, 27.5, 23.0. **IR (ν_{max}/cm^{-1})** 2957, 1714, 1511, 1435, 1328, 1122, 1079. **R_f** 0.19 (10% EtOAc in hexanes).

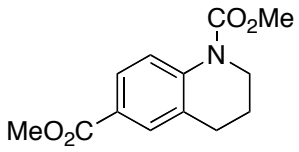


Methyl 5-methyl-3,4-dihydroquinoline-1(2H)-carboxylate (4.53) Synthesized according to *General Procedure C* using methyl (2-bromo-3-methylphenyl)(cyclopropyl)carbamate (142 mg, 0.500 mmol, 1.00 equiv) at 110 °C for 13 h. The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 102 mg (99% yield) of a clear oil.

[195] Cho, C. S.; Lee, N. Y.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *J. Heterocyclic Chem.* **2003**, *40*, 929-932.
[196] Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2007**, *9*, 4821-4824.

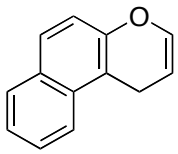
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.43 (d, J = 7.9 Hz, 1H), 7.06 (dd, J = 7.8, 7.8 Hz, 1H), 6.91 (d, J = 7.4 Hz, 1H), 3.76 (s, 3H), 3.75-3.72 (m, 2H), 2.65 (t, J = 6.9 Hz, 2H), 2.21 (s, 3H), 2.00-1.93 (m, 2H).

Exhibited spectral data identical to a previous report.[196]



Dimethyl 3,4-dihydroquinoline-1,6(2H)-dicarboxylate (4.54) Synthesized according to *General Procedure D* using methyl 3-chloro-4-(cyclopropyl(methoxycarbonyl)amino)benzoate (143 mg, 0.500 mmol, 1.00 equiv) at 140 °C for 3 h. The product was purified by silica gel flash chromatography (15% EtOAc in hexanes) to afford 119 mg (95% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.83 (br s, 2H), 7.79 (br s, 1H), 3.90 (s, 3H), 3.84-3.78 (m, 2H), 3.83 (s, 3H), 2.82 (t, J = 6.5 Hz, 2H), 1.96 (dt, J = 12.5, 6.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 166.8, 155.1, 142.4, 130.2, 129.4, 127.5, 124.7, 123.1, 53.1, 51.9, 45.2, 27.5, 23.0. **IR (ν_{max}/cm^{-1})** 2953, 2847, 1717, 1611, 1440, 1283, 1192, 1109. **R_f** 0.27 (20% EtOAc in hexanes).

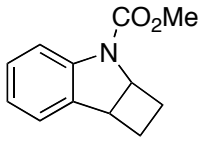


1*H*-benzo[*f*]chromene (4.56) A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with 1-bromo-2-cyclopropoxynaphthalene (148 mg, 0.563 mmol, 1.00 equiv), $Pd(OAc)_2$ (6.3 mg, 2.82 x 10^{-2} mmol, 5.00 mol %), $PCy_3{\cdot}HBF_4$ (20.7 mg, 5.63 x 10^{-2} mmol, 10.0 mol %), Cs_2CO_3 (275 mg, 0.845 mmol, 1.50 equiv) and PivOH (17.3 mg, 0.169 mmol, 30.0 mol %). The vial was purged with argon. Mesitylene (2.8 mL, 0.2 M) was then added and the resulting mixture was placed in a preheated oil bath at 110 °C and stirred for 16 h. The reaction was then cooled to room temperature and the crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (100% petroleum ether) to afford 91 mg (91% yield) of a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$, 293K, TMS) δ 7.81 (dd, J = 8.1, 1.3 Hz, 1H), 7.72-7.66 (m, 2H), 7.54 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.43 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.61 (dt, J = 6.3, 2.0 Hz, 1H), 5.15 (dt, J = 6.3, 3.5 Hz, 1H), 3.69 (dd, J = 3.4, 2.0 Hz, 2H).

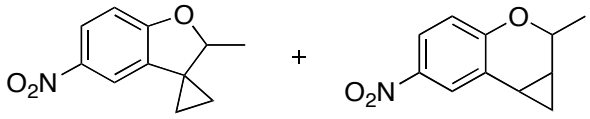
Exhibited spectral data identical to a previous report.[197]

[197] van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; de Koning, C. B. *Tetrahedron* **2005**, *61*, 9996-10006.



Methyl 2,2a-dihydro-1H-cyclobuta[b]indole-3(7bH)-carboxylate (4.58) A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with methyl (2-bromophenyl)(cyclobutyl)carbamate (142 mg, 0.500 mmol, 1.00 equiv), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5.0 mol %), $PCy_3{\cdot}HBF_4$ (18.4 mg, 0.050 mmol, 10.0 mol %), Cs_2CO_3 (244 mg, 0.750 mmol, 1.50 equiv) and PivOH (15.3 mg, 0.150 mmol, 30.0 mol %). The vial was evacuated and backfilled with argon. This procedure was repeated 3 times. Mesitylene (2.5 mL, 0.2 M) was then added and the resulting mixture was placed in a preheated oil bath at 140 °C and stirred for 16 h. The reaction was then cooled to room temperature and the crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford 66 mg (65% yield) of an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 328K) δ 7.86 (br s, 1H), 7.22 (dd, J = 7.7, 7.7 Hz, 1H), 7.14 (d, J = 7.4 Hz, 1H), 7.00 (ddd, J = 7.4, 7.4, 0.9 Hz, 1H), 4.86 (br s, 1H), 3.98-3.93 (m, 1H), 3.83 (s, 3H), 2.66-2.49 (m, 2H), 2.29-2.21 (m, 1H), 2.06-1.98 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.1, 143.6, 135.6, 127.8, 124.5, 122.9, 115.2, 58.4, 52.4, 40.9, 29.3, 26.6. **IR (ν_{max}/cm^{-1})** 2989, 2949, 1715, 1602, 1383, 1067, 762. **R_f** 0.24 (5% EtOAc in hexanes).

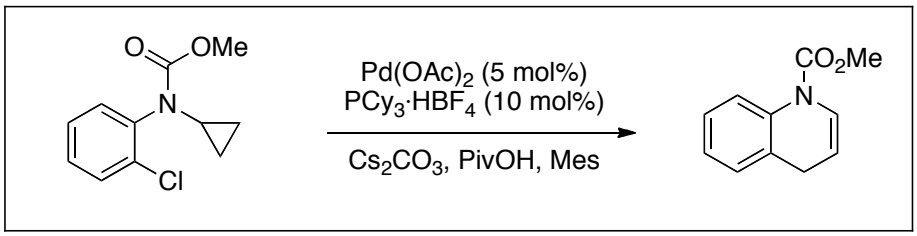


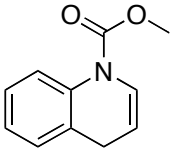
2-Methyl-5-nitro-2H-spiro[benzofuran-3,1'-cyclopropane] (4.24) and **2-methyl-6-nitro-1,1a,2,7b-tetrahydrocyclopropa[c]chromene (4.25)** A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged with 2-bromo-1-(1-cyclopropylethoxy)-4-nitrobenzene (150 mg, 0.524 mmol, 1.00 equiv), $Pd(OAc)_2$ (5.9 mg, 0.0262 mmol, 5.00 mol %), $PCy_3{\cdot}HBF_4$ (19.3 mg, 0.0524 mmol, 10.0 mol %), Cs_2CO_3 (188 mg, 0.577 mmol, 1.10 equiv) and PivOH (16.1 mg, 0.157 mmol, 30.0 mol %). The vial was evacuated and backfilled with argon. This procedure was repeated 3 times. Mesitylene (3.1 mL, 0.17 M) was then added and the resulting mixture was placed in a preheated oil bath at 140 °C and stirred for 16 h. The reaction was then cooled to room temperature and the crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (gradient from 3% to 4% Et_2O in petroleum ether) to afford 72 mg (67% yield) of a yellow solid as an inseparable mixture of **11** and **12** in a 3:1 ratio.

^{1}H NMR (400 MHz, $CDCl_3$, 328K, TMS) δ 8.14 (d, J = 2.4 Hz, 1H, **12**), 8.07 (dd, J = 8.8, 2.4 Hz, 1H, **11**), 7.96 (dd, J = 8.8, 2.4 Hz, 1H, **12**), 7.55 (d, J = 2.4 Hz, 1H, **11**), 6.83 (d, J = 8.8 Hz, 1H, **12**), 6.79 (d, J = 8.8 Hz, 1H, **11**), 4.98 (q, J = 6.4 Hz, 1H, **11**), 4.65 (qd, J = 6.5, 0.8 Hz, 1H, **12**), 2.07 (td, J = 8.5, 4.4 Hz, 1H, **12**), 1.67 (tdd, J = 8.3, 5.6, 1.2 Hz, 1H, **12**), 1.35 (d, J = 6.4 Hz, 3H, **11**), 1.31-0.93 (m, remaining 9H, **11** and **12**). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** Product **11**: δ 165.0, 142.0, 134.7, 125.0, 115.3, 108.6,

85.7, 28.4, 18.1, 15.4, 13.8. Product **12**: δ 156.0, 141.7, 128.1, 123.9, 122.4, 118.3, 69.6, 22.6, 20.5, 12.0, 11.8.

Characterization of the 1,2-Dihydroquinoline Intermediate



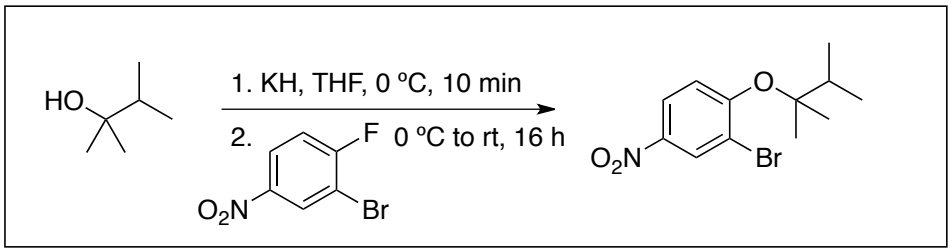


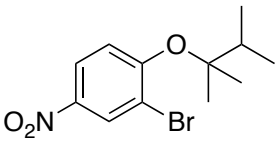
Methyl quinoline-1(4*H*)-carboxylate (4.28) A 4 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged $Pd(OAc)_2$ (3.9 mg, 1.7 x 10^{-2} mmol, 5.0 mol %), $PCy_3{\cdot}HBF_4$ (12.7 mg, 3.47 x 10^{-2} mmol, 10.0 mol %), Cs_2CO_3 (124 mg, 0.380 mmol, 1.10 equiv) and PivOH (10.6 mg, 0.104 mmol, 30.0 mol %). The vial was purged with argon. Methyl 2-chlorophenylcyclopropylcarbamate (78.0 mg, 0.346 mmol, 1.00 equiv) was then added as a 0.2 M solution in mesitylene and the resulting mixture was placed in a preheated oil bath at 140 °C and stirred for 16 h. The reaction was then cooled to room temperature and the crude product was extracted with CH_2Cl_2 (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (4% Et_2O in petroleum ether) to afford 53 mg (82% yield) of a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.10 (dd, J = 8.3 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.12-7.06 (m, 2H), 6.94 (d, J = 7.6 Hz, 1H), 5.33 (dt, J = 7.8, 4.0 Hz, 1H), 3.87 (d, J = 0.6 Hz, 3H), 3.34 (d, J = 3.7 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 153.4, 136.8, 128.3, 128.0, 127.0, 126.4, 125.0, 121.7, 109.6, 53.3, 27.6. **IR (ν_{max}/cm^{-1})** 3028, 2959, 1730 1667, 1460, 1334. **R_f** 0.29 (5% Et_2O in petroleum ether).

8.5 Enantioselective Alkane Arylation

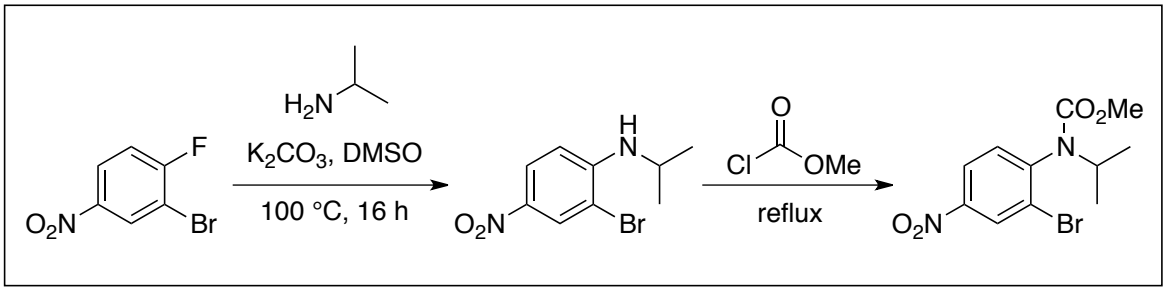
8.5.1 Preparation of Starting Materials

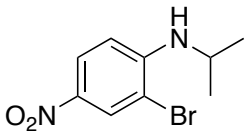




2-Bromo-1-((2,3-dimethylbutan-2-yl)oxy)-4-nitrobenzene (5.34) 2,3-Dimethylbutan-2-ol (0.75 mL, 6.00 mmol, 1.10 equiv) was added dropwise to a solution of KH (0.800 g, 6.00 mmol, 1.10 equiv) in THF (20 mL) under argon at 0 ºC. The resulting mixture was stirred for 10 minutes after which 2-bromo-1-fluoro-4-nitrobenzene (1.20 g, 5.46 mmol, 1.00 equiv) was added and the flask was warmed to room temperature. The reaction was stirred overnight and quenched by addition of a saturated solution of NH_4Cl. The crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (1% Et_2O in petroleum ether) to afford 962 mg (58% yield) of the desired compound.

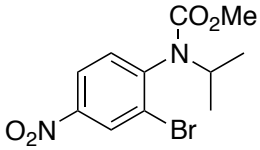
^{1}H NMR (400 MHz, $CDCl_3$, 293K, TMS) δ 8.47 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 9.1, 2.8 Hz, 1H), 7.16 (d, J = 9.2 Hz, 1H), 2.18 (sept, J = 6.8 Hz, 1H), 1.46 (s, 6H), 1.07 (d, J = 6.8 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K, TMS)** δ 159.2, 141.6, 129.2, 123.7, 118.6, 116.8, 88.2, 38.4, 23.6, 17.6. **R_f** 0.26 (1% Et_2O in petroleum ether).





2-Bromo-*N*-isopropyl-4-nitroaniline To a solution of 2-bromo-1-fluoro-4-nitrobenzene (2.00 g, 9.09 mmol, 1.00 equiv) and K_2CO_3 (1.38 g, 10.0 mmol, 1.10 equiv) in DMSO (20 mL, 0.45 M) was added isopropylamine (3.90 mL, 45.5 mmol, 5.00 equiv). The resulting mixture was heated at 100 °C for 16 h and then allowed to cool to room temperature. The crude product was extracted with EtOAc (x3), washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (4% Et_2O in petroleum ether) to afford 1.84 g (78% yield) of the desired compound as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 8.38 (d, J = 2.6 Hz, 1H), 8.11 (ddd, J = 9.2, 2.6, 0.6 Hz, 1H), 6.60 (d, J = 9.2 Hz, 1H), 4.96 (br s, 1H), 3.86-3.70 (m, 1H), 1.33 (d, J = 6.4 Hz, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 149.0, 137.3, 129.0, 125.4, 109.0, 107.7, 44.7, 22.5. **R_f** 0.29 (10% Et_2O in petroleum ether).

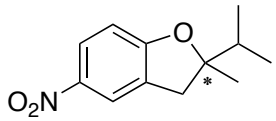


Methyl (2-bromo-4-nitrophenyl)(isopropyl)carbamate (5.43) A solution of 2-bromo-*N*-isopropyl-4-nitroaniline (1.00 g, 3.85 mmol, 1.00 equiv) in methyl chloroformate (17.6 mL, 0.22 M) was heated at 70 °C for 48 h. The reaction was allowed to cool to room temperature, then slowly poured over H_2O. The crude product was extracted with $CHCl_3$ (x3), dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by silica gel flash chromatography (gradient from 10-15% Et_2O in petroleum ether) to afford 0.580 g (48% yield) of the desired compound as a light yellow solid.

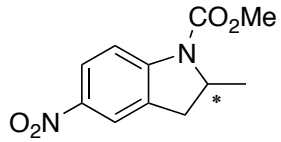
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.53 (d, J = 2.6 Hz, 1H), 8.21 (dd, J = 8.7, 2.6 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 4.54 (br s, 1H), 3.66 (br s, 1H), 1.37 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.9 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 154.3, 146.9, 144.9, 130.9, 128.6, 126.7, 122.9, 53.0, 50.9, 22.6, 19.7. **R_f** 0.25 (15% Et_2O in petroleum ether).

8.5.2 General Procedure for Enantioselective Alkane Arylation

A 1.8 mL screw-cap vial equipped with a magnetic stir bar and a teflon septum was charged $Pd(OAc)_2$ (5.00-10.0 mol %), chiral ligand (10.0-20.0 mol %), Cs_2CO_3 (1.10 equiv) and PivOH (30.0 mol %). The vial was purged with argon. The starting material (1.00 equiv) was then added as a 0.2 M solution in mesitylene and the resulting mixture was placed in a preheated oil bath at 140 °C and stirred for 16 h. The reaction was then cooled to room temperature. The crude mixture was filtered over a pad of celite and analyzed by GC-MS and HPLC.



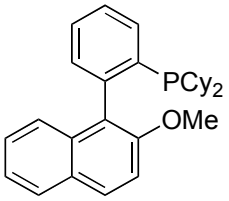
2-Isopropyl-2-methyl-5-nitro-2,3-dihydrobenzofuran (5.35) Enantiomeric excess (up to 57% ee) was determined by HPLC [Chiralcel AS-H, hexanes/*i*PrOH 98:2, 1 mL/min: (major) t_r = 7.94 min, (minor) t_r = 9.37 min]. **^{1}H NMR (400 MHz, $CDCl_3$, 293K)** δ 8.10 (dd, J = 8.8, 2.5 Hz, 1H), 8.06-8.05 (m, 1H), 6.76 (d, J = 8.9 Hz, 1H), 3.20 (d, J = 15.7 Hz, 1H), 2.89 (d, J = 16.1 Hz, 1H), 2.05 (sept, J = 6.8 Hz, 1H), 1.41 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 164.6, 141.4, 128.4, 125.8, 121.5, 109.0, 95.3, 38.1, 37.0, 23.4, 17.2, 17.2. **R_f** 0.28 (4% Et_2O in petroleum ether).



Methyl 2-methyl-5-nitroindoline-1-carboxylate (5.44) Enantiomeric excess (up to 30% ee) was determined by HPLC [Chiralcel AS-H, hexanes/*i*PrOH 99:1, 1 mL/min: (major) t_r = 31.08 min, (minor) t_r = 34.63 min]. **^{1}H NMR (400 MHz, $CDCl_3$, 293K)** δ 8.14 (dd, J = 8.9, 2.3 Hz, 1H), 8.05-8.04 (m, 1H), 7.84 (br s, 1H), 4.67 (dqd, J = 9.4, 6.4, 2.8 Hz, 1H), 3.90 (s, 3H), 3.43 (dd, J = 16.4, 9.8 Hz, 1H), 2.75 (dd, J = 16.4, 2.1 Hz, 1H), 1.35 (d, J = 6.4 Hz, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.3, 143.2, 131.3, 124.8, 120.9, 114.6, 56.7, 53.1, 35.3, 21.2. **R_f** 0.30 (10% EtOAc in petroleum ether).

8.6 Pd(0)-Catalyzed Arylative Dearomatization of Phenols

8.6.1 Synthesis and Characterization of Ligand 7.37

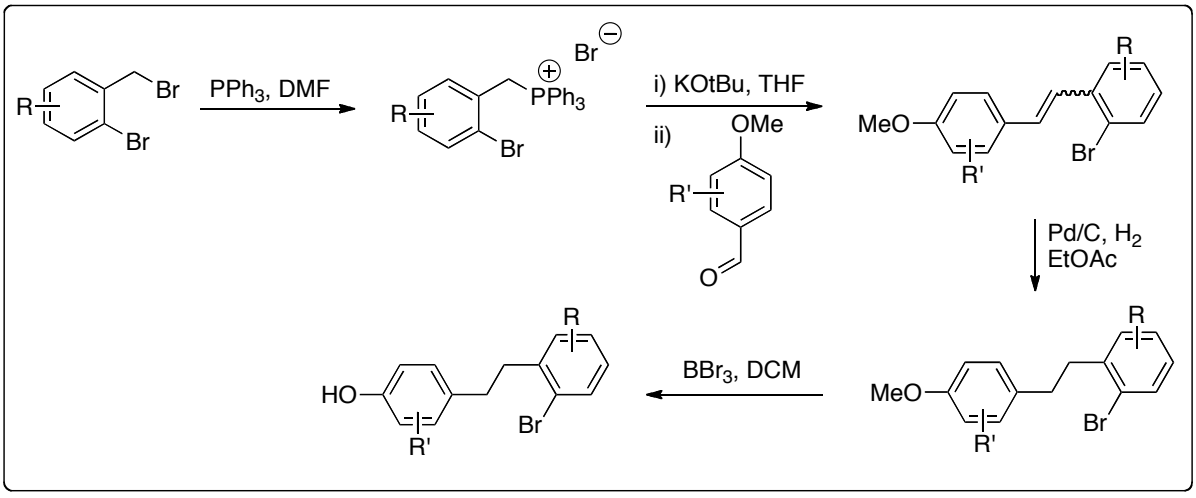


Dicyclohexyl(2-(2-methoxynaphthalen-1-yl)phenyl)phosphine (7.37). A flame-dried 500 mL, 3-neck, round bottom flask equipped with a Teflon-coated magnetic stir bar, reflux condenser, glass stopper, gas inlet adapter and rubber septum was purged with argon and charged with Mg turnings (1.43 g, 58.6 mmol, 2.50 equiv), THF (100 mL) and 1-bromo-2-methoxynaphthalene (5.56 g, 23.5 mmol, 1.00 equiv). While stirring vigorously under an argon atmosphere, 1,2-dibromoethane (45 µL) was added dropwise via syringe and the reaction mixture was stirred at reflux. After 45 min, Grignard formation was complete as judged by GC analysis of the consumption of the starting material into the corresponding dehalogenated product (after quenching with a small amount of MeOH). 1-Bromo-2-

chlorobenzene (2.75 mL, 23.5 mmol, 1.00 equiv) was then added at reflux over 2.5 hours via syringe pump. After an additional 1 h of stirring at reflux, the reaction mixture was cooled to room temperature. Anhydrous CuCl (2.35 g, 23.5 mmol, 1.00 equiv) was added in one portion. To this, $ClPCy_2$ (5.4 mL, 24.6 mmol, 1.05 eq) was added via syringe and the resulting mixture was allowed to stir at 60 ºC for 20 h. The reaction mixture was quenched by addition of H_2O (75 mL), and it was transferred to an Erlenmeyer flask using ethyl acetate (75 mL) and hexanes (75 mL). Concentrated NH_4OH (20 mL) was added after which point the mixture was stirred at ambient temperature for 15 min, then filtered through a pad of Celite. An additional portion of ethyl acetate (50 mL) was used to wash the Celite pad. The organic phase was separated and the aqueous layer was washed with EtOAc (2 x 25 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. The crude product was purified by recrystallization from EtOH to afford 3.56 g of the title compound as a yellowish crystalline compound. **^{1}H NMR (300 MHz, $CDCl_3$, 293K)** δ 7.92 (d, J = 9.0 Hz, 1H), 7.83-7.80 (m, 1H), 7.72-7.68 (m, 1H), 7.50-7.42 (m, 2H), 7.34 (d, J = 9.0 Hz, 1H), 7.31-7.19 (m, 4H), 3.84 (s, 3H), 1.80-0.84 (m, 22H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 153.4, 153.4, 144.8, 144.4, 137.0, 136.8, 133.8, 133.8, 132.8, 132.8, 131.5, 131.4, 129.2, 128.5, 128.4, 128.4, 127.8, 126.6, 125.9, 125.6, 125.0, 123.0, 112.2, 55.6, 34.5, 34.3, 34.0, 33.8, 30.3, 30.1, 30.1, 29.8, 29.6, 29.5, 29.4, 29.2, 27.6, 27.5, 27.4, 27.3, 27.2, 27.1, 26.5, 26.4 (observed complexity is due to P-C splitting). **^{31}P NMR (121 MHz, $CDCl_3$, 293K)** δ -9.45 ppm. **IR (neat, cm^{-1})** 3050, 2923, 2848, 2361, 1622, 1593, 1510, 1446, 1262, 1075. **Anal.** Calculated for $C_{29}H_{35}OP$: C, 80.90; H, 8.19. Found C, 80.80; H, 8.09. **Melting point** 156-158 ºC.

8.6.2 Preparation and Characterization of Starting Materials

General route for the preparation of phenol starting materials



General Procedure A - Synthesis of the Phosphonium Salt

To a round bottom flask charged with the desired 2-bromobenzyl bromide derivative (1.00 equiv) and a teflon-coated magnetic stir bar was added DMF (2 M) under an argon

atmosphere. Triphenylphosphine (1.00 equiv) was then added to the solution and the reaction mixture was stirred at room temperature for 10 h. At this point, the mixture was diluted with toluene (1 M) and the resulting suspension was filtered. The collected solid was dissolved in a minimal amount of CH_2Cl_2 and the product was once again precipitated by the addition of diethylether. The phosphonium salt was finally collected via filtration, dried under vacuum and used without further purification in the Wittig reaction.

General Procedure B - Wittig Olefination

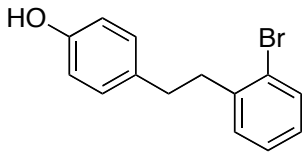
To a 0.2 M solution of the phosphonium salt (1.20 equiv) in THF, at 0 ºC and under an argon atmosphere, was added KO*t*-Bu (1.40 equiv). The mixture was stirred at 0 ºC for 30 min after which point the desired aldehyde (1.00 equiv) was added via syringe. The resulting mixture was allowed to warm to room temperature and stirred for 12 h. After slow addition of water, the organic products were extracted with EtOAc. This process was repeated three times. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography.

General Procedure C - Alkene Hydrogenation

H_2 was bubbled through a 0.2 M solution of Pd/C (10 mol %) in EtOAc under vigorous stirring for 10 min. The alkene (1.00 equiv) was then added as a 1.0 M solution in EtOAc and the resulting mixture was vigorously stirred under an atmosphere of H_2 (without bubbling). The reaction progress was closely monitored by GC analysis of the disappearance of the starting material (note: longer reaction times lead to protodehalogenated products). When the reaction was judged complete, the mixture was filtered through a pad of Celite, which was subsequently washed with two additional portions of EtOAc and one portion of MeOH. The solvent was removed *in vacuo* and the crude product was purified by silica gel flash chromatography.

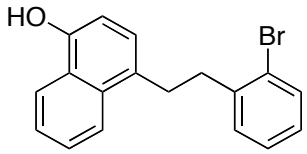
General Procedure D - Conversion of the Anisole Derivative into the Free Phenol

To a 0.2 M solution of the anisole derivative (1.00 equiv) in CH_2Cl_2, at -78 ºC and under an argon atmosphere, was added BBr_3 (1.0 M in hexanes, 1.25 equiv) via syringe. The resulting mixture was allowed to warm to room temperature and stirred until the reaction was judged complete by TLC. At this point, the reaction mixture was quenched by addition of a saturated aqueous solution of $NaHCO_3$ until neutral pH was reached. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography.



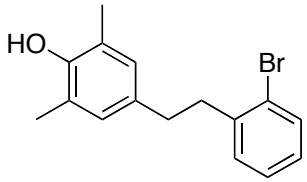
4-(2-Bromophenethyl)phenol (7.35) The title compound was obtained as a white solid from 2-bromobenzyl bromide and *p*-anisaldehyde using *General Procedures A-D*.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.54 (dd, J = 8.0, 1.2 Hz, 1H), 7.20 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.13 (dd, J = 7.6, 1.8 Hz, 1H), 7.09-7.02 (m, 3H), 6.77-6.73 (m, 2H), 4.73 (br s, 1H), 2.98 (dd, J = 10.5, 6.4 Hz, 2H), 2.83 (dd, J = 9.2, 5.2 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.6, 140.9, 133.8, 132.8, 130.5, 129.6, 127.7, 127.3, 124.4, 115.2, 38.6, 35.2. **IR (neat, cm^{-1})** 3386, 3021, 2927, 1512, 1223, 657. **Anal.** Calculated for $C_{14}H_{13}BrO$: C, 60.67; H, 4.73. Found C, 60.54; H, 4.87. **Melting point** 48-52 ºC.



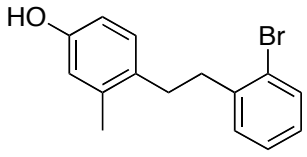
4-(2-Bromophenethyl)naphthalen-1-ol (7.57) The title compound was obtained as an orange solid from 2-bromobenzyl bromide and 4-methoxy-1-naphtaldehyde using *General Procedures A-D*.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.23 (dd, J = 8.4, 1.3 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.58-7.53 (m, 2H), 7.50 (ddd, J = 8.3, 6.8, 1.4 Hz, 1H), 7.20 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 7.16 (dd, J = 7.6, 2.1 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.07 (ddd, J = 7.9, 7.2, 2.1 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 5.11 (br s, 1H), 3.29-3.25 (m, 2H), 3.13-3.09 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 150.1, 141.2, 132.8, 132.8, 130.6, 130.1, 127.7, 127.4, 126.4, 125.9, 124.9, 124.7, 124.4, 123.8, 122.2, 108.1, 37.8, 33.0. **IR (neat, cm^{-1})** 3384, 3065, 2934, 2866, 1587, 1471, 1380, 1274, 764. **Melting point** 95-97 ºC.



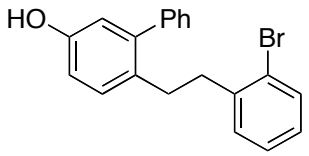
4-(2-Bromophenethyl)-2,6-dimethylphenol (7.53) The title compound was obtained as a white solid from 2-bromobenzyl bromide and 4-(benzyloxy)-3,5-dimethylbenzaldehyde using *General Procedures A-C* (note: the benzyl protecting group was removed during the General Procedure C).

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.57 (dd, J = 8.0, 1.8 Hz, 1H), 7.27-7.20 (m, 2H), 7.09 (ddd, J = 8.0, 8.0, 2.2 Hz, 1H), 6.88 (s, 2H), 4.51 (s, 1H), 3.01-2.97 (m, 2H), 2.81-2.77 (m, 2H), 2.26 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 150.6, 141.4, 133.4, 133.0, 130.7, 128.7, 127.8, 127.6, 124.6, 123.1, 39.1, 35.6, 16.1. **IR (neat, cm^{-1})** 3413, 2919, 1486, 1470, 1211, 1027, 744. **Melting point** 61-62 ºC.



4-(2-Bromophenethyl)-3-methylphenol The title compound was obtained as a white solid from 2-bromobenzyl bromide and 4-methoxy-2-methylbenzaldehyde using *General Procedures A-D*.

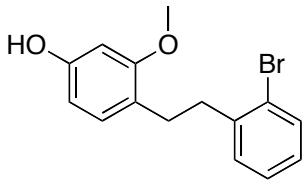
^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.54 (dd, J = 8.0, 1.1 Hz, 1H), 7.20 (ddd, J = 7.4, 7.4, 1.1 Hz, 1H), 7.14 (dd, J = 7.6, 1.8 Hz, 1H), 7.06 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.61 (dd, J = 8.1, 2.6 Hz, 1H), 4.64 (br s, 1H), 2.93 (dd, J = 10.7, 6.0 Hz, 2H), 2.81 (dd, J = 9.5, 5.0 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.6, 141.1, 137.6, 132.8, 131.9, 130.5, 130.2, 127.7, 127.4, 124.4, 116.9, 112.7, 37.5, 32.8, 19.4. **IR (neat, cm^{-1})** 3335, 3057, 3021, 2934, 2865, 1609, 1500, 1471, 1246, 1157, 1025, 750. **Anal.** Calculated for $C_{15}H_{15}BrO$: C, 61.87; H, 5.19. Found C, 62.09; H, 4.99. **Melting point** 72-75 ºC.



6-(2-Bromophenethyl)-[1,1'-biphenyl]-3-ol The title compound was obtained as a colorless oil from 2-bromobenzyl bromide and 5-methoxy-[1,1'-biphenyl]-2-carbaldehyde using *General Procedures A-D*.

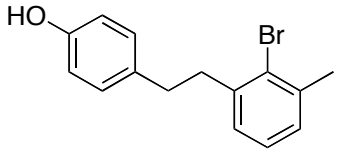
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.55 (dd, J = 8.0, 1.2 Hz, 1H), 7.50-7.43 (m, 4H), 7.41-7.37 (m, 1H), 7.21 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.16 (dd, J = 7.6, 1.9 Hz, 1H), 7.12 (dd, J = 8.2, 2.3 Hz, 1H), 7.09-7.04 (m, 2H), 6.92 (d, J = 8.2 Hz, 1H), 5.13 (s, 1H), 3.06-3.02 (m, 2H), 2.91-2.87 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 150.6, 140.9, 137.2, 133.7, 132.8, 130.5, 130.2, 129.2, 129.1, 129.0, 127.9, 127.8, 127.7, 127.4, 124.4, 115.7, 38.7, 35.3. **IR (neat, cm^{-1})** 3542, 3054, 2928, 2861, 1332, 1025, 751. **Anal.** Calculated for $C_{20}H_{17}BrO$: C, 68.00; H, 4.85. Found C, 67.93; H, 4.81.

Synthesis of 5-methoxy-[1,1'-biphenyl]-2-carbaldehyde: An oven-dried Schlenk flask equipped with a magnetic stir bar was charged with 2-bromo-5-methoxybenzaldehyde (5.00 g, 23.3 mmol, 1.00 equiv), phenylboronic acid (4.25 g, 34.9 mmol, 1.50 equiv), $Pd(OAc)_2$ (106 mg, 0.47 mmol, 2.0 mol %), SPhos (290 mg, 0.70 mmol, 3.0 mol %) and K_3PO_4 (9.87g, 46.5 mmol, 2.00 equiv). The flask was evacuated and backfilled with argon. This sequence was repeated a total of three times. Toluene (100 mL, 0.23 M) was then added via syringe. The resulting mixture was placed in a preheated oil bath at 60 °C and stirred for 16 hours. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with additional EtOAc (100 mL) and the solvent was removed *in vacuo*. The crude product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford 4.59 g (93% yield) of the title compound as a pale yellow solid. This compound was directly used as the aldehyde starting material in *General Procedure B*.



4-(2-Bromophenethyl)-3-methoxyphenol The title compound was obtained as an orange solid from 2-bromobenzyl bromide and 4-(benzyloxy)-2-methoxybenzaldehyde using *General Procedures A-C* (note: the benzyl protecting group was removed during the General Procedure C).

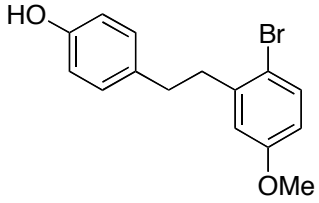
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.52 (dd, J = 8.1, 1.1 Hz, 1H), 7.19-7.12 (m, 2H), 7.02 (ddd, J = 7.9, 7.9, 2.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.30 (dd, J = 8.0, 2.4 Hz, 1H), 4.68 (br s, 1H), 3.76 (s, 3H), 2.96-2.92 (m, 2H), 2.83-2.79 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 158.6, 155.0, 141.6, 132.6, 130.5, 130.3, 127.4, 127.2, 124.5, 122.1, 106.4, 98.8, 55.3, 36.6, 30.0. **IR (neat, cm^{-1})** 3354, 3004, 2935, 1615, 1600, 1508, 1469, 1283, 1195, 953, 830. **Melting point** 44-46 ºC.



4-(2-Bromo-3-methylphenethyl)phenol The title compound was obtained as a white solid from 2-bromo-1-(bromomethyl)-3-methylbenzene and *p*-anisaldehyde using *General Procedures A-D*.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.17-7.12 (m, 4H), 7.06-7.02 (m, 1H), 6.84-6.79 (m, 2H), 5.02 (s, 1H), 3.09-3.03 (m, 2H), 2.91-2.86 (m, 2H), 2.49 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 153.5, 141.3, 138.6, 134.0, 129.6, 128.6, 127.8, 127.0, 126.7, 115.1, 39.4, 35.2, 24.0. **IR (neat, cm^{-1})** 3407, 3020, 2929, 1600, 1511, 1225, 1022, 818, 770, 516. **Anal.** Calculated for $C_{15}H_{15}BrO$: C, 61.87; H, 5.19. Found C, 61.97; H, 5.26. **Melting point** 82-84 ºC.

Synthesis of 2-bromo-1-(bromomethyl)-3-methylbenzene: To a 0.5 M solution of *N*-bromosuccinimide (recrystallized from 95 ºC water) (8.9 g, 50 mmol, 1.0 equiv) and AIBN (0.82 g, 5.0 mmol, 0.10 equiv) in CCl_4 was added 2-bromo-1,3-dimethylbenzene via syringe (7.0 mL, 52.5 mmol, 1.05 equiv) at room temperature. The resulting mixture was stirred at reflux for 16 hours at which point it was cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with additional Et_2O (100 mL) and the solvent was removed *in vacuo*. The crude product was purified by silica gel flash chromatography (100% hexanes) to afford 5.95 g (43% yield) of the title compound. This compound was directly used as the aryl bromide starting material in *General Procedure A*.

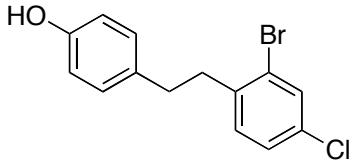


4-(2-Bromo-5-methoxyphenethyl)phenol The title compound was obtained as a colorless oil from 2-bromo-5-methoxybenzyl bromide and 4-(methoxymethoxy)benzaldehyde using *General Procedures A-C* (note: the MOM protecting group was removed according to the procedure described below).

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.44 (d, J = 8.7 Hz, 1H), 7.12-7.09 (m, 2H), 6.80-6.77 (m, 2H), 6.71 (d, J = 3.0 Hz, 1H), 6.66 (dd, J = 8.7, 3.0 Hz, 1H), 4.84 (s, 1H), 3.76 (s, 3H), 2.99-2.92 (m, 2H), 2.87-2.81 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 158.7, 153.7, 141.9, 133.6, 133.2, 129.6, 116.1, 115.1, 114.8, 113.3, 55.4, 38.8, 35.2. **IR (neat, cm^{-1})** 3395, 2934, 2836, 1596, 1514, 1472, 1241, 827. **Anal.** Calculated for $C_{15}H_{15}BrO_2$: C, 58.65; H, 4.92. Found C, 58.59; H, 4.99.

Removal of the MOM protecting group: To a solution of the aryl bromide (5.47 g, 15.6 mmol, 1.00 equiv) in CH_2Cl_2 (125 mL, 0.12 M), at 0 ºC and under an argon atmosphere, was added freshly activated 4Å molecular sieves (6.0 g) and TMSBr (4.1 mL, 31 mmol, 2.0 equiv) dropwise. The resulting mixture was allowed to warm to room temperature overnight after which point it was poured into H_2O. After separation of the organic and aqueous layers, the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to afford the free phenol in quantitative yield.

Synthesis of 4-(methoxymethoxy)benzaldehyde: To a solution of 4-hydroxybenzaldehyde (4.88 g, 40.0 mmol, 1.00 equiv) and K_2CO_3 (11.1 g, 80.0 mmol, 2.00 equiv) in acetone (60 mL, 0.67 M) was added MOMCl (3.35 mL, 44.0 mmol, 1.10 equiv) via syringe. The resulting mixture was stirred at room temperature for 15 min and then at reflux for 2 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The Celite pad was washed with additional acetone (50 mL) and the solvent was removed *in vacuo*. The crude product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to afford 6.16 g (93% yield) of the title compound. This compound was directly used as the aldehyde starting material in *General Procedure B*.

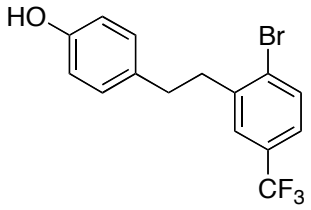


4-(2-Bromo-4-chlorophenethyl)phenol The title compound was obtained as a white solid from 2-bromo-1-(bromomethyl)-4-chlorobenzene and *p*-anisaldehyde using *General Procedures A-D*.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.58 (d, J = 1.8 Hz, 1H), 7.19 (dd, J = 8.4, 2.1 Hz, 1H), 7.08-7.03 (m, 3H), 6.80-6.77 (m, 2H), 5.03 (s, 1H), 3.00-2.95 (m, 2H), 2.86-2.80 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 153.6, 139.3, 133.3, 132.3, 132.2, 131.1, 129.6,

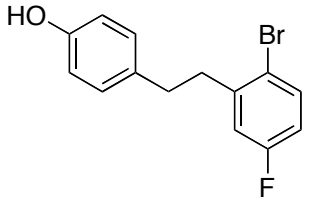
127.5, 124.5, 115.2, 37.9, 35.0. **IR (neat, cm^{-1})** 3340, 2930, 2861, 1514, 1469, 1232, 826, 540. **Anal.** Calculated for $C_{14}H_{12}BrClO$: C, 53.96; H, 3.88. Found C, 54.16; H, 3.87. **Melting point** 44-46 ºC.

Synthesis of 2-bromo-1-(bromomethyl)-4-chlorobenzene: A 0.5 M solution of *N*-bromosuccinimide (recrystallized from 95 ºC water) (4.67 g, 26.3 mmol, 1.05 equiv), 2-bromo-4-chlorotoluene (5.14 g, 25.0 mmol, 1.00 equiv) and AIBN (410 mg, 2.50 mmol, 0.10 equiv) in CCl_4 was stirred at reflux for 16 hours. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with additional Et_2O (50 mL) and the solvent was removed *in vacuo*. The crude product was purified by silica gel flash chromatography (100% hexanes) to afford 5.08 g (71% yield) of the title compound. This compound was directly used as the aryl bromide starting material in *General Procedure A*.



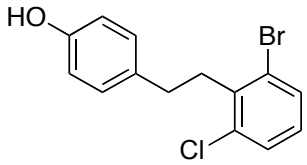
4-(2-Bromo-5-(trifluoromethyl)phenethyl)phenol The title compound was obtained as a white solid from 2-bromo-5-(trifluoromethyl)benzyl bromide and *p*-anisaldehyde using *General Procedures A-D*.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.69 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.34 (dd, J = 8.1, 2.1 Hz, 1H), 7.11-7.07 (m, 2H), 6.82-6.79 (m, 2H), 5.10 (br s, 1H), 3.09-3.03 (m, 2H), 2.90-2.85 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.9, 141.9, 133.3, 133.0, 129.8 (q, J_F = 33 Hz), 129.6, 128.2 (q, J_F = 1.5 Hz), 127.1 (q, J_F = 3.7 Hz), 124.3 (q, J_F = 3.6 Hz), 123.8 (q, J_F = 271 Hz), 115.3, 38.6, 35.0. **IR (neat, cm^{-1})** 3312, 3025, 2925, 1514, 1326, 1119, 1080. **Melting point** 83-86 ºC.



4-(2-Bromo-5-fluorophenethyl)phenol The title compound was obtained as a white solid from 1-bromo-2-(bromomethyl)-4-fluorobenzene and *p*-anisaldehyde using *General Procedures A-D*.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.47 (dd, J = 8.7, 5.4 Hz, 1H), 7.07-7.03 (m, 2H), 6.85 (dd, J = 9.3, 3.0 Hz, 1H), 6.81-6.73 (m, 3H), 4.62 (br s, 1H), 2.96-2.92 (m, 2H), 2.83-2.79 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 161.9 (d, J_F = 244 Hz), 153.8, 143.0 (d, J_F = 7.5 Hz), 133.8 (d, J_F = 8.0 Hz), 133.2, 129.6, 118.4 (d, J_F = 3.5 Hz), 117.3 (d, J_F = 22 Hz), 115.3, 114.8 (d, J_F = 22 Hz), 38.6 (d, J_F = 1.4 Hz), 34.9. **IR (neat, cm^{-1})** 3347, 3023, 2931, 1611, 1579, 1514, 1469, 1234, 1031. **Anal.** Calculated for $C_{14}H_{12}BrFO$: C, 56.97; H, 4.10. Found C, 57.14; H, 4.18. **Melting point** 53-55 ºC.

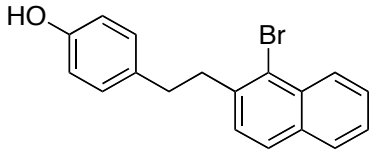


4-(2-Bromo-6-chlorophenethyl)phenol The title compound was obtained as a white solid from 1-bromo-2-(bromomethyl)-3-chlorobenzene and *p*-anisaldehyde using *General Procedures A,B and D* (note: the intermediate alkene was hydrogenated according to the procedure described below).

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.46 (dd, J = 8.0, 1.2 Hz, 1H), 7.32 (dd, J = 8.0, 1.2 Hz, 1H), 7.18-7.14 (m, 2H), 6.99 (dd, J = 8.0, 8.0 Hz, 1H), 6.80-6.76 (m, 2H), 4.70 (s, 1H), 3.20-3.15 (m, 2H), 2.79-2.75 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.8, 139.0, 135.0, 133.7, 131.5, 129.6, 128.9, 128.1, 125.5, 115.2, 36.7, 33.3. **IR (neat, cm^{-1})** 3411, 3025, 2966, 2943, 1556, 1512, 1429, 1237, 1126, 773, 730. **Melting point** 100-103 ºC.

Reduction of the alkene intermediate: To a flame-dried round bottom flask charged with a magnetic stir bar was added the alkene intermediate (10.8 g, 33.3 mmol, 1.00 equiv) under an argon atmosphere. Trifluoroacetic acid (5.2 mL, 67 mmol, 2.0 equiv) and Et_3SiH (5.3 mL, 33 mmol, 1.0 equiv) were then added via syringe and the resulting mixture was stirred at 60 ºC for 2 hours. The reaction mixture was cooled to room temperature and quenched by slow addition of H_2O. The organic products were extracted with EtOAc (repeated three times in total) and the combined organic layers were washed with brine, dried and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography (30% EtOAc in hexanes) to afford the desired compound in quantitative yield.

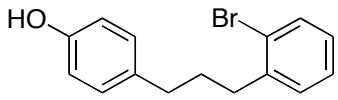
Synthesis of 1-bromo-2-(bromomethyl)-3-chlorobenzene: A 1.8 M solution of *N*-bromosuccinimide (recrystallized from 95 ºC water) (14.7 g, 82.3 mmol, 1.2 equiv), 1-bromo-3-chloro-2-methylbenzene (14.1 g, 68.6 mmol, 1.00 equiv) and AIBN (1.13 g, 6.86 mmol, 0.10 equiv) in CCl_4 was stirred at reflux for 16 hours. The reaction mixture was then cooled to room temperature and filtered through a pad of Celite. The Celite pad was washed with additional Et_2O (50 mL) and the solvent was removed *in vacuo*. The crude product was used without further purification as the aryl bromide starting material in *General Procedure A*.



4-(2-(1-Bromonaphthalen-2-yl)ethyl)phenol The title compound was obtained as a white solid, from 1-bromo-2-(bromomethyl)naphthalene and *p*-anisaldehyde using *General Procedures A-D*.

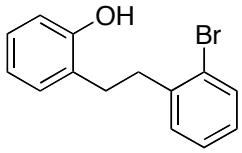
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.32 (dd, J = 8.5, 0.7 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.57 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.47 (ddd, J = 8.1, 6.8, 1.2 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.11-7.08 (m, 2H), 6.76-6.73 (m, 2H), 4.54 (s, 1H),

3.24-3.19 (m, 2H), 2.93-2.89 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.7, 139.2, 133.8, 133.2, 132.6, 129.6, 128.2, 128.0, 127.5, 127.3, 127.2, 125.9, 123.7, 115.2, 39.9, 35.4. **IR (neat, cm^{-1})** 3372, 3027, 2969, 1512, 1240, 816, 740. **Anal.** Calculated for $C_{18}H_{15}BrO$: C, 66.07; H, 4.62. Found C, 65.78; H, 4.60. **Melting point** decomposed at 125 ºC.



4-(3-(2-Bromophenyl)propyl)phenol The title compound was obtained as a brownish solid from 2-bromobenzyl bromide and 2-(4-methoxyphenyl)acetaldehyde using *General Procedures A-D*.

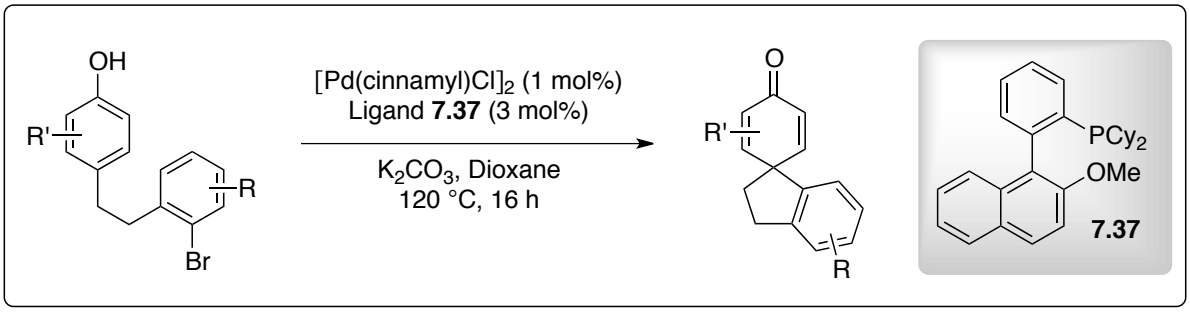
^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.54 (dd, J = 8.7, 1.2 Hz, 1H), 7.25-7.22 (m, 2H), 7.11-7.07 (m, 3H), 6.80-6.77 (m, 2H), 4.74 (s, 1H), 2.77 (dd, J = 7.8, 7.8 Hz, 2H), 2.65 (dd, J = 7.8, 7.8 Hz, 2H), 1.98-1.88 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 153.4, 141.6, 134.3, 132.7, 130.3, 129.5, 127.4, 127.3, 124.4, 115.1, 35.7, 34.6, 31.6. **IR (neat, cm^{-1})** 3342, 3020, 2929, 2858, 1613, 1513, 1230, 1026, 751, 658. **Melting point** 45-47 ºC.



2-(2-Bromophenethyl)phenol (7.54) The title compound was obtained as a white solid from 2-bromobenzyl bromide and 2-methoxybenzaldehyde using *General Procedures A-D*.

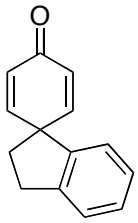
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.55 (dd, J = 8.7, 1.0 Hz, 1H), 7.22-7.18 (m, 2H), 7.13-7.05 (m, 3H), 6.87 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 6.78 (d, J = 7.9 Hz, 1H), 4.79 (s, 1H), 3.05-3.00 (m, 2H), 2.92-2.88 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 153.6, 140.9, 132.7, 130.5, 130.4, 127.8, 127.5, 127.5, 127.1, 124.3, 120.9, 115.4, 36.6, 30.6. **IR (neat, cm^{-1})** 3263, 3064, 2938, 1590, 1457, 1232, 752. **Melting point** 72-74 ºC.

8.6.3 General Procedure and Characterization for the Pd(0)-Catalyzed Dearomatization of Phenols



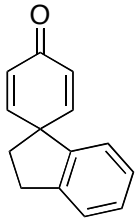
General Procedure for the Pd(0)-Catalyzed Dearomatization

An oven-dried test tube equipped with a magnetic stir bar and a teflon septum was charged with the starting material (if a solid) (1.00 equiv), $[Pd(cinnamyl)Cl]_2$ (1.0 mol %), Ligand **7.37** (3.0 mol%) and K_2CO_3 (1.50 equiv). The test tube was evacuated and backfilled with argon. This sequence was repeated a total of three times. The starting material (if an oil) (1.00 equiv) was added via syringe as a 0.2 M solution in dioxane. The resulting mixture was placed in a preheated oil bath at 120 °C and stirred for 16 h. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The crude product was filtered over a pad of celite and concentrated. The product was purified by silica gel flash chromatography.



2',3'-Dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.36) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)phenol (277 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient from 20% to 30% EtOAc in hexanes) to afford 153 mg (78% yield) of a white solid.

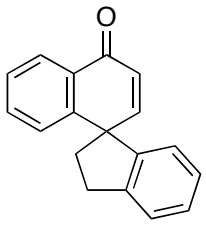
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.31 (d, J = 7.4 Hz, 1H), 7.24 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.16 (dddd, J = 7.4, 7.4, 0.6, 0.6 Hz, 1H), 6.93-6.87 (m, 3H), 6.29-6.25 (m, 2H), 3.16 (t, J = 7.3 Hz, 2H), 2.33 (t, J = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 186.2, 152.6, 143.8, 142.2, 128.2, 127.5, 127.2, 125.4, 124.1, 53.9, 37.4, 31.0. **IR (neat, cm^{-1})** 2950, 1659, 1617, 1404, 1250, 1094. **Anal.** Calculated for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found C, 85.83; H, 6.09. **Melting point** 121-122 °C



2',3'-Dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.36) (10 mmol scale) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)phenol (2.77 g, 10.0 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient from 20% to 30% EtOAc in hexanes) to afford 1.78 g (91% yield) of a white solid.

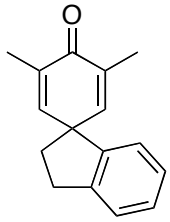
^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.33 (d, J = 7.5 Hz, 1H), 7.25 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 7.16 (dddd, J = 7.2, 7.2, 0.6, 0.6 Hz, 1H), 6.94 (d, J = 0.3 Hz, 1H), 6.93-6.87 (m, 2H), 6.30-6.25 (m, 2H), 3.18 (t, J = 7.2 Hz, 2H), 3.35 (t, J = 7.2 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 186.2, 152.6, 143.8, 142.1, 128.2, 127.3, 127.1, 125.3, 124.0,

53.8, 37.3, 31.0. **IR (neat, cm^{-1})** 2974, 2950, 1658, 1617, 1403, 1250, 868. **Anal.** Calculated for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found C, 85.39; H, 6.20. **Melting point** 121-123 °C.



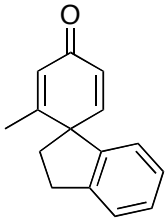
2,3-Dihydro-4'H-spiro[indene-1,1'-naphthalen]-4'-one (7.38) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)naphthalen-1-ol (327 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 228 mg (93% yield) of colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 8.23 (dd, J = 7.8, 1.8 Hz, 1H), 7.45 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.40-7.34 (m, 2H), 7.25 (ddd, J = 7.5, 7.5, 0.6 Hz, 1H), 7.14-7.07 (m, 2H), 6.99 (d, J = 9.9 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.40 (d, J = 10.2 Hz, 1H), 3.33-3.27 (m, 2H), 2.67-2.49 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 184.9, 153.0, 148.7, 146.1, 143.5, 132.6, 131.1, 128.0, 127.7, 127.2, 126.8, 126.1, 125.3, 124.9, 124.5, 54.1, 41.5, 31.2. **IR (neat, cm^{-1})** 3066, 2943, 1663, 1601, 1455, 1302, 1155. **Anal.** Calculated for $C_{18}H_{14}O$: C, 87.78; H, 5.73. Found C, 87.64; H, 5.73. **Melting point** 131-133 °C.



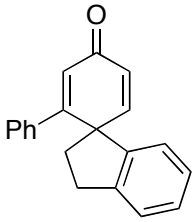
3,5-Dimethyl-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.39) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)-2,6-dimethylphenol (305 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (5% EtOAc in hexanes) to afford 201 mg (90% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.29 (ddd, J = 6.5, 1.0, 1.0 Hz, 1H), 7.21 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.13 (dd, J = 7.4, 7.4 Hz, 1H), 6.88 (dd, J = 7.5, 0.7 Hz, 1H) 6.67 (s, 2H), 3.13 (t, J = 7.3 Hz, 2H), 2.28 (t, J = 7.3 Hz, 2H), 1.91 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 187.7, 148.2, 144.0, 143.8, 133.5, 128.0, 127.1, 125.5, 124.1, 53.6, 37.9, 31.2, 16.4. **IR (neat, cm^{-1})** 3067, 3006, 2951, 2923, 1666, 1636, 1455, 1373, 1049. **Anal.** Calculated for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found C, 85.41; H, 7.28. **Melting point** 93-96 °C.



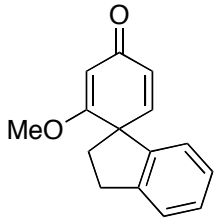
2-Methyl-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.40) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)-3-methylphenol (292 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (20% EtOAc in hexanes) to afford 169 mg (80% yield) of colorless crystals.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.32 (d, J = 7.5 Hz, 1H), 7.23 (dd, J = 7.5, 1.2 Hz, 1H), 7.16 (dd, J = 7.5Hz, 1H), 6.86 (d, J = 10.2 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.21-6.17 (m, 2H), 3.24-3.18 (m, 2H), 2.48-2.38 (m, 1H), 2.31-2.22 (m, 1H), 1.77 (d, J = 1.2 Hz, 3H) ppm. **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 186.8, 162.3, 153.6, 144.0, 142.9, 128.1, 127.4, 127.2, 125.4, 125.2, 123.9, 56.8, 35.6, 31.6, 19.9 ppm. **IR (neat, cm^{-1})** 3036, 2948, 2855, 1784, 1662, 1624, 1455, 1396, 1308, 1149. **Anal.** Calculated for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found C, 85.56; H, 6.72. **Melting point** 77-79 °C.



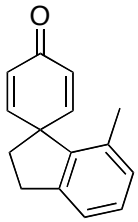
1-Phenyl-2',3'-dihydrospiro[cyclohexa[3,6]diene-2,1'-inden]-5-one (7.41) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 6-(2-bromophenethyl)-[1,1'-biphenyl]-3-ol (305 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 160 mg (75% yield) of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.44-7.41 (m, 2H), 7.38-7.29 (m, 4H), 7.27 (ddd, J = 7.4, 7.4, 1.2 Hz, 1H), 7.19 (dddd, J = 7.6, 7.6, 0.6, 0.6 Hz, 1H), 7.01 (dd, J = 7.5, 0.4 Hz, 1H) 6.98-6.92 (m, 2H), 6.42 (d, J = 9.7 Hz, 1H), 3.20 (t, J = 7.3 Hz, 2H), 2.43 (t, J = 7.3 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 184.9, 151.6, 150.2, 143.8, 142.6, 137.6, 135.8, 128.8, 128.2, 128.1, 128.1, 127.9, 127.2, 125.5, 124.2, 54.2, 37.8, 31.1. **IR (neat, cm^{-1})** 3022, 2941, 2854, 1661, 1631, 1475, 1205. **Melting point** 93-96 °C.



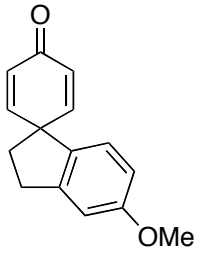
2-Methoxy-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.42) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromophenethyl)-3-methoxyphenol (246 mg, 0.80 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (40% EtOAc in hexanes) to afford 115 mg (69% yield) of a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.29 (d, J = 7.5 Hz, 1H), 7.23 (ddd, J = 7.3, 7.3, 1.1 Hz, 1H), 7.14 (dd, J = 7.2, 7.2 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 6.60 (d, J = 9.8 Hz, 1H), 6.15 (dd, J = 9.8, 1.5 Hz, 1H), 5.62 (d, J = 1.5 Hz, 1H), 3.62 (s, 3H), 3.27-3.19 (m, 1H), 3.15-3.07 (m, 1H), 2.63-2.56 (m, 1H), 2.27-2.20 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 188.6, 178.2, 148.9, 144.6, 142.7, 128.2, 126.9, 125.4, 125.1, 123.6, 101.8, 55.7, 55.7, 36.4, 31.7. **IR (neat, cm^{-1})** 3069, 3020, 2941, 2849, 1659, 1591, 1456, 1365, 1222, 1086. **Anal.** Calculated for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found C, 79.22; H, 6.21. **Melting point** 103-105 °C.



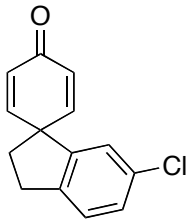
7'-Methyl-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.43) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-3-methylphenethyl)phenol (305 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 172 mg (82% yield) of a white solid.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.19-7.17 (m, 2H), 6.99-6.93 (m, 3H), 6.38-6.33 (m, 2H), 3.14 (t, J = 7.5 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.07 (s, 3H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 185.9, 152.8, 144.3, 139.6, 135.8, 129.1, 128.4, 127.8, 122.9, 54.2, 38.3, 31.1, 17.9. **IR (neat, cm^{-1})** 2925, 1662, 1619, 1402, 1072. **Anal.** Calculated for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found C, 85.40; H, 6.65. **Melting point** 155-157 °C.



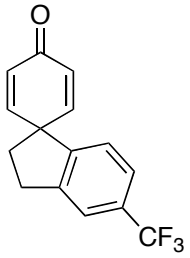
5'-Methoxy-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.44) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-5-methoxyphenethyl)phenol (307 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (40% EtOAc in hexanes) to afford 212 mg (94% yield) of a white solid.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 6.88-8.82 (m, 3H), 6.78 (d, J = 8.4 Hz, 1H), 6.67 (dd, J = 8.4, 2.4 Hz, 1H), 6.23-6.18 (m, 2H), 3.74 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 2.31 (t, J = 7.2 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 186.0, 159.8, 152.9, 145.2, 133.5, 126.8, 124.4, 112.8, 110.4, 55.1, 52.9, 37.4, 30.9. **IR (neat, cm^{-1})** 2941, 1663, 1488, 1401, 1312, 1258, 1165, 1029. **Anal.** Calculated for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found C, 79.25; H, 6.21. **Melting point** 61-63 °C.



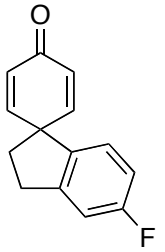
6'-Chloro-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.45) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-4-chlorophenethyl)phenol (312 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (25% EtOAc in hexanes) to afford 176 mg (76% yield) of a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.25 (dd, J = 8.1, 0.6 Hz, 1H), 7.21 (dd, J = 8.1, 1.8 Hz, 1H), 6.90-6.85 (m, 3H), 6.33-6.27 (m, 2H), 3.14 (t, J = 7.2 Hz, 2H), 2.37 (t, J = 7.2 Hz, 2H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 185.8, 151.6, 144.2, 142.1, 132.8, 128.4, 127.8, 126.4, 124.3, 53.6, 37.6, 30.5. **IR (neat, cm^{-1})** 2924, 1665, 1620, 1401, 1247, 1105, 859. **Melting point** 61-63 °C.



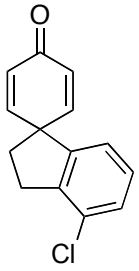
5'-(Trifluoromethyl)-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.46) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-5-(trifluoromethyl)phenethyl)phenol (276 mg, 0.800 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (20% EtOAc in hexanes) to afford 86 mg (41% yield) of an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.57 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.86 (d, J = 15.8 Hz, 2H), 6.31 (d, J = 15.8 Hz, 2H), 3.21 (t, J = 7.3 Hz, 2H), 2.40 (t, J = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 185.7, 151.3, 146.5, 144.5, 130.7 (q, J_F = 32 Hz), 127.9, 124.4, 124.4 (q, J_F = 4 Hz), 123.9 (q, J_F = 271 Hz), 122.3 (q, J_F = 4 Hz), 53.5, 37.4, 30.8. **IR (neat, cm^{-1})** 3042, 2947, 2860, 1663, 1625, 1330, 1136, 858. **Anal.** Calculated for $C_{15}H_{11}F_3O$: C, 68.18; H, 4.20. Found C, 67.98; H, 4.21.

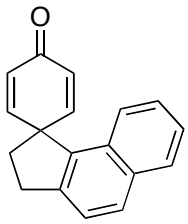


5'-Fluoro-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.47) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-5-fluorophenethyl)phenol (207 mg, 0.700 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient from 15 to 20% EtOAc in hexanes) to afford 114 mg (76% yield) of a yellow solid.

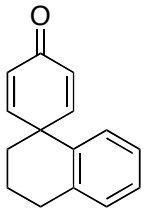
^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 6.98 (br d, J = 8.7 Hz, 1H), 6.87-6.83 (m, 4H), 6.27-6.24 (m, 2H), 3.13 (t, J = 7.2 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 186.0, 163.0 (d, J_F = 245 Hz), 152.3, 146.0 (d, J_F = 9 Hz), 137.7 (d, J_F = 2 Hz), 127.5, 125.2 (d, J_F = 9 Hz), 114.3 (d, J_F = 23 Hz), 112.4 (d, J_F = 23 Hz), 53.0, 37.8, 31.0 (d, J_F = 2 Hz). **IR (neat, cm^{-1})** 3039, 2945, 2855, 1669, 1626, 1256, 859, 568. **Melting point** 62-65 °C.



4'-Chloro-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.48) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-bromo-6-chlorophenethyl)phenol (187 mg, 0.600 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (15% EtOAc in hexanes) to afford 104 mg (75% yield) of a white semi-solid. **^{1}H NMR (400 MHz, $CDCl_3$, 293K)** δ 7.23 (dd, J = 8.0, 1.0 Hz, 1H), 7.11 (dddd, J = 7.6, 7.6, 0.7, 0.7 Hz, 1H), 6.89-6.85 (m, 2H), 6.81 (dd, J = 7.6, 0.4 Hz, 1H), 6.29-6.25 (m, 2H), 3.19 (t, J = 7.3 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 185.9, 151.8, 144.2, 142.1, 131.5, 128.8, 128.4, 127.6, 122.4, 54.5, 36.5, 30.4. **IR (neat, cm^{-1})** 3066, 3038, 2933, 2852, 1664, 1451, 1246, 856, 789.



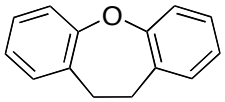
2',3'-Dihydrospiro[cyclohexa[2,5]diene-1,1'-cyclopenta[*a*]naphthalen]-4-one (7.49) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(2-(1-bromonaphthalen-2-yl)ethyl)phenol (164 mg, 0.500 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (15% EtOAc in hexanes) to afford 69 mg (56% yield) of a white solid. **^{1}H NMR (400 MHz, $CDCl_3$, 293K)** δ 7.83 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.67 (dd, J = 8.2, 0.7 Hz, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.40 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.35 (ddd, J = 8.4, 6.9, 1.6 Hz, 1H), 7.13-7.09 (m, 2H), 6.45-6.41 (m, 2H), 3.29 (t, J = 7.4 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 186.1, 154.5, 142.6, 136.3, 133.3, 130.6, 129.7, 128.7, 128.0, 126.7, 125.4, 123.5, 122.6, 54.8, 38.8, 32.0. **IR (neat, cm^{-1})** 3060, 2966, 2928, 1662, 1620, 1514, 861. **Melting point** 139-140 °C.



3',4'-Dihydro-2'H-spiro[cyclohexa[2,5]diene-1,1'-naphthalen]-4-one (7.50) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 4-(3-(2-bromophenyl)propyl)phenol (292 mg, 1.00 mmol, 1.00 equiv). The product was purified by

silica gel flash chromatography (20% EtOAc in hexanes) to afford 185 mg (88% yield) of a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$, 293K) δ 7.17 (dd, J = 4.8, 1.2 Hz, 2H), 7.09 (dd, J = 7.8, 4.2 Hz, 1H), 7.04-7.00 (m, 2H), 6.95 (d, J = 7.8 Hz, 1H), 6.30-6.25 (m, 2H), 2.94-2.01 (m, 2H), 2.01-1.97 (m, 4H). **^{13}C NMR (75 MHz, $CDCl_3$, 293K)** δ 186.1, 155.3, 136.4, 133.2, 130.2, 128.7, 127.4, 126.7, 126.2, 44.6, 34.0, 29.4, 19.1. **IR (neat, cm^{-1})** 3017, 2928, 2874, 1706, 1665, 1622, 1445, 1262, 1237, 1085. **Anal.** Calculated for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found C, 85.61; H, 6.73. **Melting point** 144-146 °C.



10,11-dihydrodibenzo[b,f]oxepine (7.55) Synthesized according to the *General Procedure for the Pd(0)-catalyzed Dearomatization* using 2-(2-bromophenethyl)phenol (277 mg, 1.00 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (gradient from 1% to 2% Et_2O in hexanes) to afford 176 mg (89% yield) of a clear oil.

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.16-7.11 (m, 6H), 7.03-6.99 (m, 2H), 3.13 (s, 4H). Exhibited spectral data identical to a previous report.[198]

8.6.4 Procedures and Characterization for the Asymmetric Dearomatization of Phenols

General Procedure A (one-pot) for the Pd(0)-Catalyzed Asymmetric Dearomatization

An oven-dried test tube equipped with a magnetic stir bar and a teflon septum was charged with the starting material (0.100 mmol, 1.00 equiv), $[Pd(cinnamyl)Cl]_2$ (1.0 mg, 2.0 mol %), **7.15** (3.0 mg, 6.0 mol %) and K_2CO_3 (20.7 mg, 1.50 equiv). The test tube was evacuated and backfilled with argon. This sequence was repeated a total of three times. Dioxane (0.5 mL, 0.20 M) was then added via syringe. The resulting mixture was placed in a preheated oil bath at the indicated temperature (100-120 ˚C) and stirred for 16 h. The reaction mixture was then cooled to room temperature, diluted with MeOH and dodecane (23 μL, 0.100 mmol, 1.00 equiv) was added as an internal standard. The crude mixture was filtered through a plug of silica gel and analyzed by GC and HPLC.

General Procedure B (water activation) for the Pd(0)-Catalyzed Asymmetric Dearomatization

A water-mediated catalyst activation protocol was employed.[160] An oven-dried test tube equipped with a magnetic stir bar and a teflon septum was charged with $Pd(OAc)_2$ (0.9 mg, 4 mol %) and **7.15** (8-16 mol %). The test tube was evacuated and backfilled with argon. This sequence was repeated a total of three times. Dioxane (0.5 mL, 0.20 M) was then added via syringe followed by H_2O (16 mol %, minimum of 1 μL). The resulting mixture was placed in a preheated oil bath at 80 ˚C and stirred for 1.5 min at which point the solution was cannulated into a second oven-dried test tube containing the starting material (0.100 mmol,

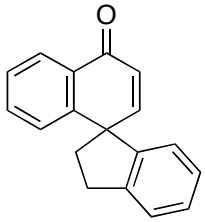
[198] Hess, B. A., Jr.; Bailey, A. S.; Bartusek, B.; Boekelheide, V. *J. Am. Chem. Soc.* **1969**, *91*, 1665-1672.

1.00 equiv) and K_2CO_3 (20.7 mg, 0.150 mmol, 1.00 equiv) under argon. This second test tube was finally placed in the oil bath at the indicated temperature (80-100) ˚C and stirred for 16 h. The reaction mixture was then cooled to room temperature, diluted with MeOH and dodecane (23 μL, 0.100 mmol, 1.00 equiv) was added as an internal standard. The crude mixture was filtered through a plug of silica gel and analyzed by GC and HPLC.

General Procedure C (water activation) for the Pd(0)-Catalyzed Asymmetric Dearomatization

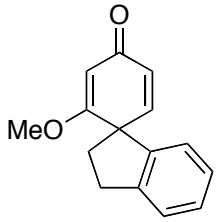
A water-induced catalyst activation protocol was employed.[160] An oven-dried test tube equipped with a magnetic stir bar and a teflon septum was charged with $Pd(OAc)_2$ (0.9 mg, 4 mol %) and **7.58** (6.3 mg, 12 mol %). The test tube was evacuated and backfilled with argon. This sequence was repeated a total of three times. Dioxane (0.5 mL, 0.20 M) was then added via syringe followed by H_2O (16 mol %, minimum of 1 μL). The resulting mixture was placed in a preheated oil bath at 110 ˚C and stirred for 1.5 min at which point the solution was cannulated into a second oven-dried test tube containing the starting material (0.100 mmol, 1.00 equiv) and K_2CO_3 (20.7 mg, 0.150 mmol, 1.00 equiv) under argon. This second test tube was finally placed in the oil bath at the indicated temperature (80-100 ˚C) and stirred for 16 h. The reaction mixture was then cooled to room temperature, diluted with MeOH and dodecane (23 μL, 0.100 mmol, 1.00 equiv) was added as an internal standard. The crude mixture was filtered through a plug of silica gel and analyzed by GC and HPLC.

Characterization of Enantioenriched Spirocyclohexadienones



2,3-Dihydro-4'H-spiro[indene-1,1'-naphthalen]-4'-one (7.38) Prepared according to the *General Procedure C for the Pd(0)-Catalyzed Asymmetric Dearomatization* using 4-(2-bromophenethyl)naphthalen-1-ol (32.7 mg, 0.100 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (10% EtOAc in hexanes) to afford 23.3 mg (94% yield) of a pale yellow solid. Enantiomeric excess (91%) was determine by HPLC [Chiralpak AD-H, hexanes/*i*PrOH 95:5, 1 mL/min: (minor) t_r = 9.61 min, (major) t_r = 12.31 min]. $[\alpha]_D^{24}$ = +164.3 (*c* = 0.019, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 8.20 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.45 (ddd, *J* = 7.3, 7.3, 1.0 Hz, 1H), 7.39-7.35 (m, 2H), 7.24 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.12-7.08 (m, 2H), 6.99 (d, *J* = 10.1 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.39 (d, *J* = 10.1 Hz, 1H), 3.34-3.21 (m, 2H), 2.64-2.50 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 185.1, 153.1, 148.8, 146.3, 143.7, 132.7, 131.3, 128.1, 127.8, 127.4, 126.9, 126.3, 125.5, 125.1, 124.7, 54.3, 41.7, 31.4.



2-Methoxy-2',3'-dihydrospiro[cyclohexa[2,5]diene-1,1'-inden]-4-one (7.42) Synthesized according to the *General Procedure C for the Pd(0)-Catalyzed Asymmetric Dearomatization* using 4-(2-bromophenethyl)-3-methoxyphenol (30.7 mg, 0.100 mmol, 1.00 equiv). The product was purified by silica gel flash chromatography (40% EtOAc in hexanes) to afford 12.4 mg (55% yield) of a pale yellow solid. Enantiomeric excess (81%) was determine by HPLC [Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min: (minor) t_r = 9.89 min, (major) t_r = 11.81 min]. $[\alpha]_D^{24}$ = +53.7 (*c* = 0.011, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 7.29 (d, *J* = 7.4 Hz, 1H), 7.23 (ddd, *J* = 7.2, 7.2, 1.0 Hz, 1H), 7.14 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 6.60 (d, *J* = 9.8 Hz, 1H), 6.15 (dd, *J* = 9.8, 1.5 Hz, 1H), 5.62 (d, *J* = 1.4 Hz, 1H), 3.62 (s, 3H), 3.27-3.19 (m, 1H), 3.15-3.07 (m, 1H), 2.63-2.56 (m, 1H), 2.27-2.20 (m, 1H). **^{13}C NMR (100 MHz, $CDCl_3$, 293K)** δ 188.5, 178.2, 148.9, 144.6, 142.7, 128.2, 126.9, 125.4, 125.1, 123.6, 101.8, 55.7, 55.7, 36.4, 31.7.

9 Appendix

9.1 Claims to Original Research

1. Development of reaction conditions for the synthesis of dihydrobenzofurans and indanones via palladium(0)-catalyzed intramolecular alkane arylation from aryl chlorides.
2. Development of reaction conditions for palladium(0)-catalyzed alkane arylation adjacent to amides and sulfonamides.
3. Mechanistic investigations for palladium(0)-catalyzed alkane arylation adjacent to amides and sulfonamides.
4. Isolation and characterization of a catalytic intermediate in alkane arylation.
5. Development of reaction conditions for arylation of cyclopropane C(sp^3)-H bonds.
6. Investigation of the use of chiral carboxylic acids and chiral phosphine ligands for enantioselective alkane arylation.
7. Development of reaction conditions for the palladium(0)-catalyzed arylative dearomatization of phenols.
8. Development of reaction conditions for the preparation of chiral spirocyclohexadienones via asymmetric palladium(0)-catalyzed arylative dearomatization of phenols.

9.2 Publications from this Work

1. *Investigation of the Mechanism of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation Adjacent to Amides and Sulfonamides*. Rousseaux, S.; Gorelsky, S. I.; Chung, B. K. W.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 10692-10705.
2. *Intramolecular Palladium-Catalyzed Alkane C-H Arylation from Aryl Chlorides*. Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.
3. *Palladium(0)-Catalyzed Arylative Dearomatization of Phenols*. Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *113*, 9282-9285.

4. *Palladium(0)-Catalyzed Cyclopropane C-H bond Functionalization: Synthesis of Quinoline and Tetrahydroquinoline Derivatives.* Rousseaux, S.; Liégault, B.; Fagnou, K. *Chem. Sci.* **2012**, *3*, 244-248.
5. *C-H Functionalization: A New Strategy for the Synthesis of Biologically Active Natural Products*. Rousseaux, S.; Liégault, B.; Fagnou, K. in *Modern Tools for the Synthesis of Complex Bioactive Molecules.* Cossy, J.; Arseniyadis, S., Eds.; Wiley-VCH, *In Press.*

9.3 Presentations from this Work

1. "Palladium-Catalyzed Alkane Arylation" (Poster). Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, Montreal, Quebec, **2007**. *Winner of an Outstanding Poster Award.*
2. "Palladium-Catalyzed Alkane Arylation" (Poster). Ottawa Carleton Chemistry Institute Day, Ottawa, Ontario, **2008**.
3. "Palladium-Catalyzed Intramolecular Alkane Arylation" (Poster). Spring Organic Synthesis Symposium, Ottawa, Ontario, **2008**.
4. "Palladium-Catalyzed Intramolecular Arylation of sp^3 C-H Bonds" (Poster). Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, Toronto, Ontario, **2008**.
5. "Arylation intramoléculaire aux liaisons C(sp^3)-H catalysée par le palladium" (Oral). Congrès de l'ACFAS (Association francophone pour le savoir), Ottawa, Ontario, **2009**.
6. "Intramolecular Arylation at sp^3 C-H Bonds Adjacent to Amides and Sulfonamides (Poster). Ottawa Carleton Chemistry Institute Day, Ottawa, Ontario, **2009**.
7. "Palladium-Catalyzed Intramolecular Arylation at sp^3 C-H Bonds Adjacent to Amides and Sulfonamides" (Poster). Canadian Chemistry Conference and Exhibition, Hamilton, Ontario, **2009**.
8. "Palladium-Catalyzed Intramolecular Arylation at sp^3 C-H Bonds Adjacent to Amides and Sulfonamides" (Poster). Spring Organic Synthesis Symposium, Ottawa, Ontario, **2009**. *Winner of an Outstanding Poster Award.*
9. "Pd-Catalyzed Alkane Arylation Adjacent to a Heteroatom: Reaction Development and Mechanistic Studies" (Oral). Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry, Quebec, Quebec, **2009**.
10. "Investigation of the Mechanism of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation" (Poster). Keith Fagnou Organic chemistry Symposium, Ottawa, Ontario, **2010**.
11. "Mechanistic Study of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation" (Oral). Canadian Chemistry Conference and Exhibition, Toronto, Ontario, **2010**.
12. "Investigation of the Mechanism of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation" (Poster). Northeast Regional Meeting of the American Chemical Society, Potsdam, USA, **2010**.

13. "Investigation of the Mechanism of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation" (Poster). Heterocyclic Compounds Gordon Research Conference, Newport, USA, **2010**.
14. "Mechanistic Study of C(sp^3)-H Bond Cleavage in Pd(0)-Catalyzed Intramolecular Alkane Arylation" (Oral). Journée Grand Sud-Ouest et de Catalogne, Montpellier, France, **2010**.