APPLICATION OF Pd-NHC COMPLEXES IN CHALLENGING AMINATION REACTIONS

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ABSTRACT

Among Pd-catalyzed carbon-heteroatom cross-coupling reactions, C-N bond formation, known as Buchwald-Hartwig amination (BHA), is by far the most studied reaction owing to the prevalence of arylated amines in pharmaceuticals, natural products, organic materials, and catalysts. Despite the tremendous progress that has been achieved with respect to improving the efficiency and expanding the scope of BHA of (hetero)aryl halides and amine nucleophilic partners, some challenges remain to be addressed. These challenges include selective monoarylation of primary alkyl amines, enantioretentive *N*-arylation of α-amino esters and arylation of amide nucleophiles. This research is mainly focused on evaluating the reactivity of Pd-NHC pre-catalysts, in particular *Pd-PEPPSI* (**P**yridine **E**nhanced **P**re-catalyst **P**reparation **S**tabilization and **I**nitiation) complexes in such challenging BHA reactions. *Pd-PEPPSI-IPent^{CI}*, was identified as one of the most reactive and selective pre-catalysts yet reported in the literature in the arylation of primary alkyl amines. The high level of selectivity that was exhibited by *Pd-PEPPSI-IPent^{CI}* is assured by the use of the mild, soluble and sterically demanding sodium salt of butylated hydroxytoluene (NaBHT) as the base in this transformation.

Pd-PEPPSI-IPent^{Cl}-o-picoline was shown to effectively couple a variety of amino acids as the *tert*-butyl ester with heteroaryl chlorides in high yields and with excellent stereoretention of the acidic proton adjacent to the ester. Control experiments revealed that racemization is base-mediated, with no evidence of Pd-mediated β-hydride elimination, and that racemization occurs only after the product is formed. Studies also revealed that increasing the steric bulk of the ester moiety on the amino acid (e.g., ethyl to *tert*-butyl) drastically slows racemization of the product.

Boron-derived Lewis acids such as (*sec*Bu)$_3$B, Et$_3$B, and BCF have been shown to effectively promote the coupling of amide nucleophiles to a wide variety of oxidative addition partners using *(DiMeIHept^{Cl})Pd(cinammyl)Cl*. Through a combination of NMR spectroscopy and control studies with and without oxygen and radical scavengers, we propose that boron-imidates form under the basic reaction conditions that aid coordination of nitrogen to Pd^{II}, which is rate limiting, and directly delivers the intermediate for reductive elimination.

During the course of optimization of aryl amidation, we found the hydrodehalogenated arene as the side product when NaBHT was employed as base. Extensive control experiments revealed that NaBHT can serve as a hydride delivering agent in Pd-catalyzed hydrodehalogenation of (hetero)aryl halides. During the course this study, the structure of the phenolate was found to be critical to the success of this protocol, that is, bulky di-*ortho*- substituents on phenolate are required to achieve optimal results.

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Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

Ad	Adamantly
Atm	atmospheric pressure
BHE	β-hydride elimination
BHT	3,5-Di-*tert*-4-butyl-4-methylphenol (butylated hydroxytoluene)
BippyPhos	5-(Di-tert-butylphosphino)-1′, 3′, 5′-triphenyl-1′H-[1,4′]bipyrazole
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BOP	(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate
BrettPhos	2-Dicyclohexylphosphino-3,6-dimethoxy-2',4',6'-triisopropylbiphenyl
*t*Bu	*tert*-butyl
˚C	degree Celsius
Cod	Cyclooctadiene
CDI	1,1′-Carbonyldiimidazole
CPent	1,3-bis(2,6-dicyclopenty1phenyl)imidazole-2-ylidine
Cy	Cyclohexyl
Dba	Dibenzylideneacetone
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPF	bis(diphenylphosphino)ferrocene
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
equiv.	molar equivalents

Et	Ethyl
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate
HOBt	Hydroxybenzotriazole
HRMS	High-resolution mass spectrometry
IAd	1,3-diadamantylimidazol-2-ylidine
IBiox	Bisoxazolinium-derived NHC
IEt	1,3-bis(2,6-diethylphenyl)imidazol-2-ylidine
IHept	1,3-bis(2,6-di(4-hepty)phenyl)imidazole-2-ylidine
$IHept^{Cl}$	1,3-bis(2,6-di(4-hepty)phenyl)-4,5-dichloroimidazol-2-ylidine
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidine
IPent	1,3-bis(2,6-di(3-pentyl)phenyl)imidazole-2-ylidine
$IPent^{Cl}$	1,3-bis(2,6-di(3-pentyl)phenyl)-4,5-dichloroimidazol-2-ylidine
IPr	1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidine
IPr*	1,3-bis(2,6-bis(di-para-tolylmethyl)phenyl)imidazole-2-ylidine
IPr^{Cl}	1,3-bis(2,6-diisopropylphenyl)-4,5-dichloroimidazol-2-ylidine
Josiphos	(R)-1-[(S_P)-2-(Diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine
LiHMDS	lithium bis(trimethylsilyl)amide
Me	Methyl
MI	Migratory insertion
MorDalPhos	Di(1-adamantyl)-2-morpholinophenylphosphine
NHC	*N*-heterocyclic carbene
NMR	Nuclear magnetic resonance

OA	Oxidative addition
$Pd[(o\text{-tol})_3P]_2$	bis(tris(o-tolyl)phosphine)palladium(0)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
$Pd(dba)_2$	bis(dibenzylideneacetone)palladium(0)
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium(0)
$Pd(PtBu_3)_2$	bis(tri-*tert*-butylphosphine)palladium(0)
PEPPSI	Pyridine-enhanced pre-catalyst preparation, stabilization, and initiation
pK_a	negative logarithmic acid dissociation constant
Rt	Room temperature
RE	Reductive elimination
RuPhos	dicyclohexy 1(2' ,6' -diisopropoxybipheny1-2-yl)phosphine
SIMes	1,3-bis(2,4,6-trimethylphenyl)imidazolidine-2-ylidine
SIPr	1,3-bis(2,6-diisopropylphenyl)imidazolidine-2-ylidine
SPhos	2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TEP	Tolman's electronic parameter
TMEDA	tetramethylethylenediamine
Tf	TrifluoromethanesulfonyI
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Publications

Some portions of this work and other related research contributions appear in the following publications:

1) Sharif, S.; Day, J.; Hunter, H. N.; Lu, Y.; Mitchell, D.; Rodriguez, M. J.; Organ, M. G. *J. Am. Chem. Soc*. **2017**, 139, 18436-18439. Cross-Coupling of Primary Amides to Aryl and Heteroaryl Partners Using (DiMeIHept^{Cl})Pd Promoted by Trialkylboranes or $B(C_6F_5)_3$.

2) Sharif, S.; Mitchell, D.; Rodriguez, M. J.; Farmer, J.L.; Organ, M. G. *Chem. Eur. J.* **2016**, 22, 14860–14863. N-Heteroarylation of Optically Pure α-Amino Esters Using the Pd-PEPPSI-IPent^{Cl}-o-picoline Pre-catalyst.

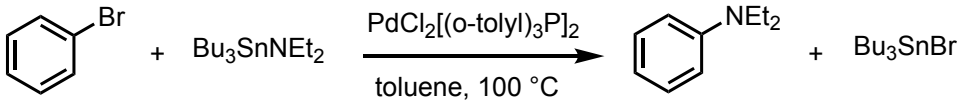
3) Sharif, S.; Rucker, R. P.; Chandrasoma, N.; Mitchell, D.; Rodriguez, M. J.; Froese, R. D. J.; Organ, M. G. *Angew. Chem., Int. Ed*. **2015**, 54, 9507-9511. Selective Monoarylation of Primary Amines Using the Pd-PEPPSI-IPent^{Cl} Precatalyst.

Chapter 1-Introduction

1.1. Buchwald-Hartwig amination

Palladium-catalyzed cross-coupling reactions have become one of the most preferred methods for constructing carbon-carbon and carbon-heteroatom bonds. The advent of these reactions has without doubt revolutionized the organic chemist's approach towards the synthesis of many important organic molecules, including biologically active compounds and materials.[1–5] The value of such reactions was well recognized in 2010 by the awarding of the Nobel Prize in Chemistry to Ei-ichi Negishi, Richard Heck, and Akira Suzuki "for Pd-catalyzed cross-coupling in organic synthesis".

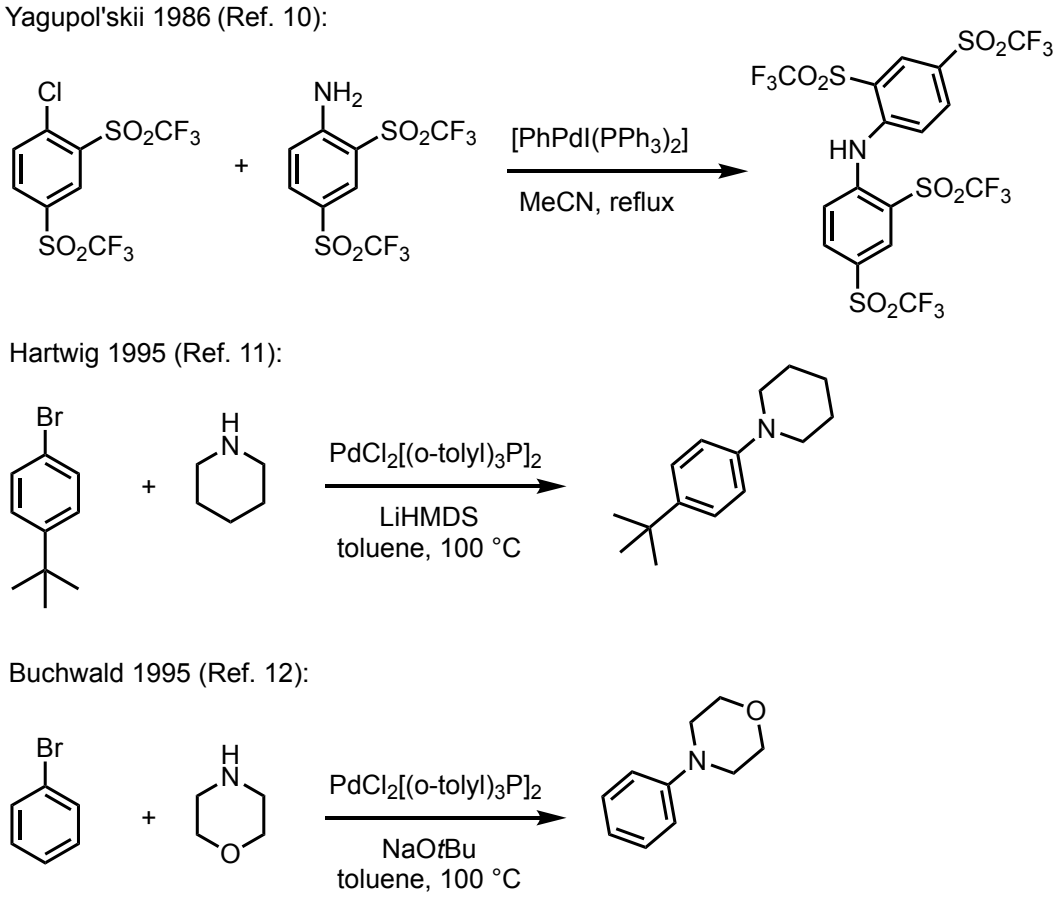
Among Pd-catalyzed carbon-heteroatom cross-coupling reactions, C-N bond formation, known as Buchwald-Hartwig amination (BHA), is by far the most studied reaction owing to the prevalence of arylated amines in pharmaceuticals, natural products, organic materials, and catalysts.[5–8] The first report of C-N coupling reaction was in 1983 by Migita and co-workers in which tin amides were coupled to aryl bromides in the presence of a palladium catalyst containing a sterically hindered, monodentate phosphine ligand (Scheme 1).[9]



Scheme 1. The first C–N Pd-catalyzed coupling.[9]

The possibility of using free amines in the Pd-catalyzed amination was first demonstrated by Yagupol'skii and co-workers in 1985.[10] Since that work was published in a Russian journal it remained unknown to most working in the field for years. Following this ground-breaking work, in 1995, Buchwald[11] and Hartwig[12] independently reported the Pd-catalyzed coupling of free

amines with aryl halides in the presence of a strong base such as LiHMDS (HMDS=1,1,1,3,3,3-hexamethyldisilazane) or NaO*t*Bu (Scheme 2).



Scheme 2. The Buchwald–Hartwig C-N cross-coupling reactions.

Since then, BHA has been investigated widely and recognized as one of the most important tools to establish C–N bonds in both academia and industry.[5,13] So far, (hetero)aryl halides, triflates, tosylates, and mesylates have been coupled readily with a wide variety of free amines including primary and secondary aliphatic and aromatic amines, amides, sulfonamides, imines, nitrogen-containing heterocycles, and ammonia under a variety of reaction conditions.[5]

1.2. **Mechanism of Buchwald-Hartwig amination (BHA)**

The mechanism for the Pd-catalyzed BHA is depicted in Figure 1. The catalytic cycle initiates by oxidative addition (OA) of the carbon halide bond of the aryl halide to Pd^0, followed by amine coordination/deprotonation (DEP) and, finally, reductive elimination (RE) to furnish the desired product concomitant with the regeneration of Pd^0.[14]

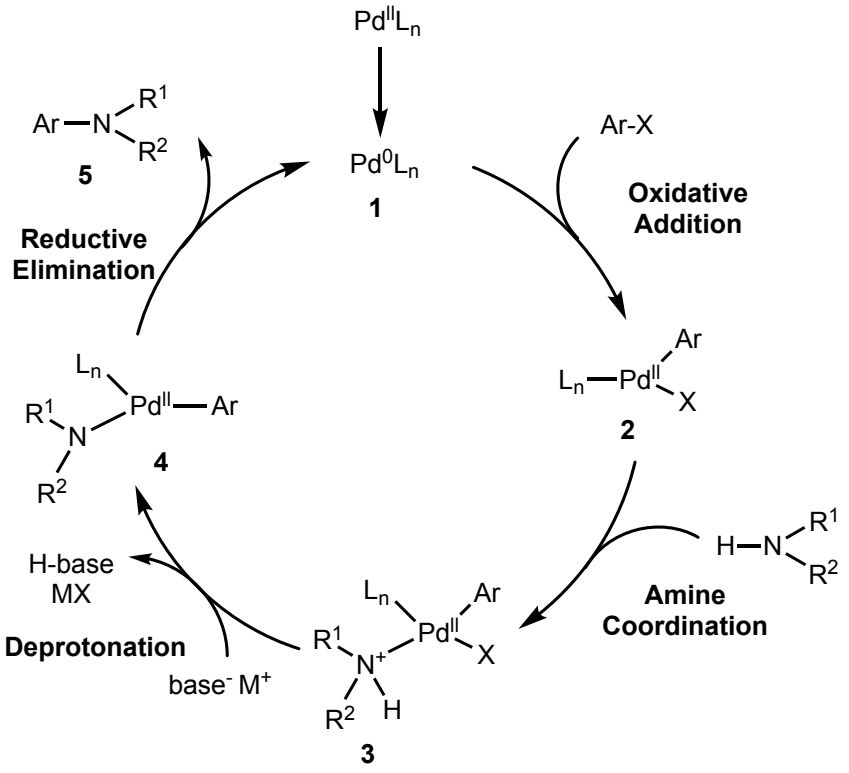
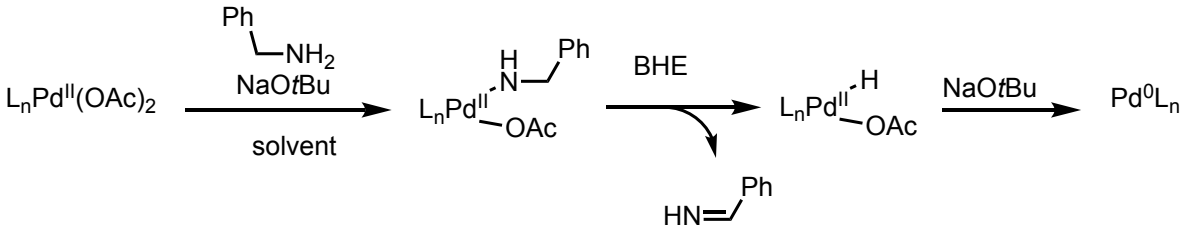


Figure 1. Mechanism of Pd-catalyzed Buchwald-Hartwig amination (BHA).

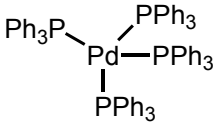
1.2.1. Pre-catalyst activation

For the catalytic cycle to initiate, a Pd^0 species is required and there are several means to obtain this active catalyst for amination reactions. If a Pd^{II} precursor, such as $Pd(OAc)_2$ is used, the reduction of Pd^{II} to Pd^0 must happen prior to amination reaction and it can easily take place through β-hydride elimination (BHE) when alkyl amines are employed (Scheme 3).[15]

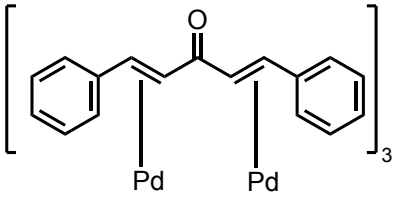


Scheme 3. Reduction of Pd^{II} to Pd^0 using alkyl amines.

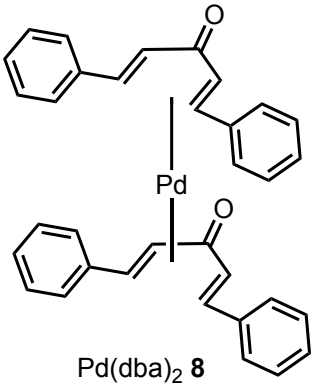
With amines lacking a β-hydrogen such as amides, anilines or ammonia, another reductant (e.g., tertiary amines, boronic acids) is required.[16] Phosphine ligands are also shown to facilitate the reduction of Pd^{II} to Pd^0.[17] A stable Pd^0 species such as $Pd(PPh_3)_4$ (**6**), $Pd_2(dba)_3$ (**7**) or $Pd(dba)_2$ (**8**) can be used to avoid the need for a reduction step to Pd^0. Such species in conjunction with many phosphines are demonstrated to be suitable in many amination reactions.[11,18,19]



$Pd(PPh_3)_4$ **6**



$Pd_2(dba)_3$ **7**

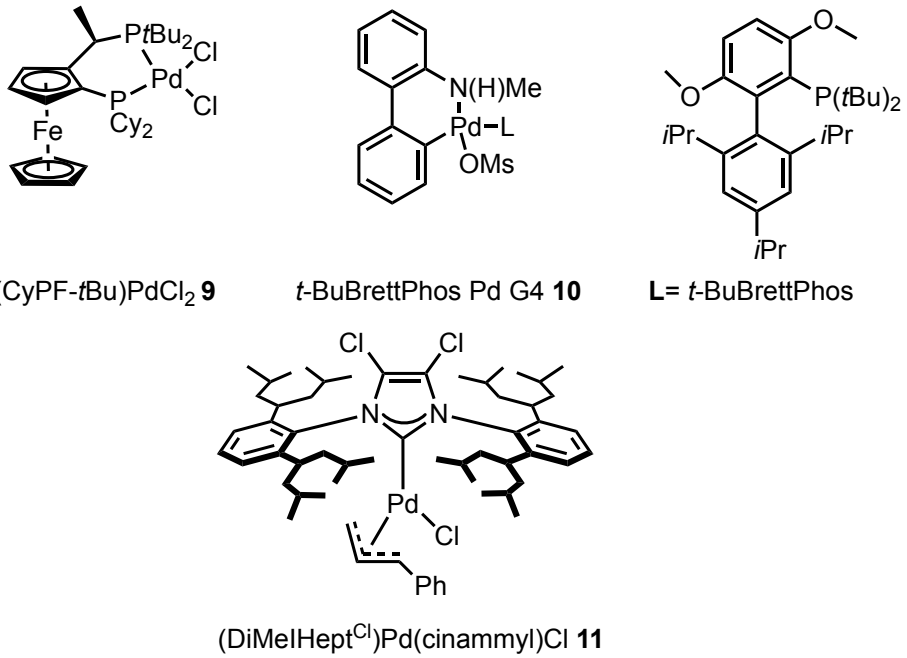


$Pd(dba)_2$ **8**

Figure 2. Commonly used Pd^0 precursors for amination.

Lastly, an active catalyst can be obtained through the use of a stable but highly activated Pd^{II} precursor (pre-catalyst) that is already bound to the ligand with desirable electronic and steric properties for catalysis (Figure 3). These complexes contain other stabilizing ligands that are either displaced or reductively eliminated under the reaction conditions and are typically air stable and do not require inert atmosphere for their storage or handling. In this case, reduction of Pd^{II} to Pd^0

can be brought about by β-hydrogen-containing amines or bases used in the reaction.[20] The activation could also be facilitated by the use of additives containing β-hydrogens such as LiO*i*Pr or organometallic reagents such as MO*t*Bu (M=Na, K) in case of π-allyl containing pre-catalysts.[21]



Josiphos (CyPF-*t*Bu)$PdCl_2$ **9** *t*-BuBrettPhos Pd G4 **10** **L**= *t*-BuBrettPhos

(DiMeIHept^{Cl})Pd(cinammyl)Cl **11**

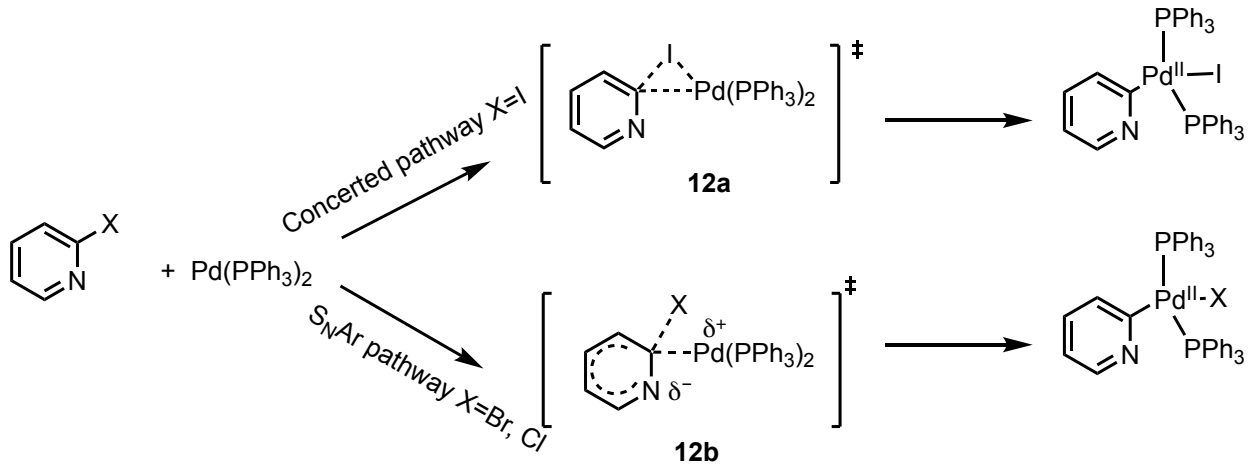
Figure 3. A selection of pre-catalysts for BHA

1.2.2. Oxidative Addition (OA)

Once Pd^0 is generated, the catalytic cycle initiates by OA of the C-X bond (X= Cl, Br, I, OSO_2R) of the electrophile to Pd^0, which can be considered to be basic or nucleophilic during this step. The reactivity of Ar-X in the oxidative addition step decreases in the following order ArI >> ArBr > ArCl, which is often attributed to the bond dissociation energy of C-X bonds with the C–Cl bond (95 kcal mol^{-1}) being the most difficult one to break and C-I bond (64 kcal mol^{-1}) being the easiest one to break.[22,23] Pseudohalides such as sulfonates[23–25] and triflates[26] have been shown to undergo OA in amination reactions. In general, electron-rich metal centers tend to undergo OA faster than

electron-poor metal centers. During OA step the oxidation state of the metal changes from 0 to II, meaning that electron-rich ligands assist this step. With respect to the electrophile, electron-poor and unhindered substrates react most readily.[27]

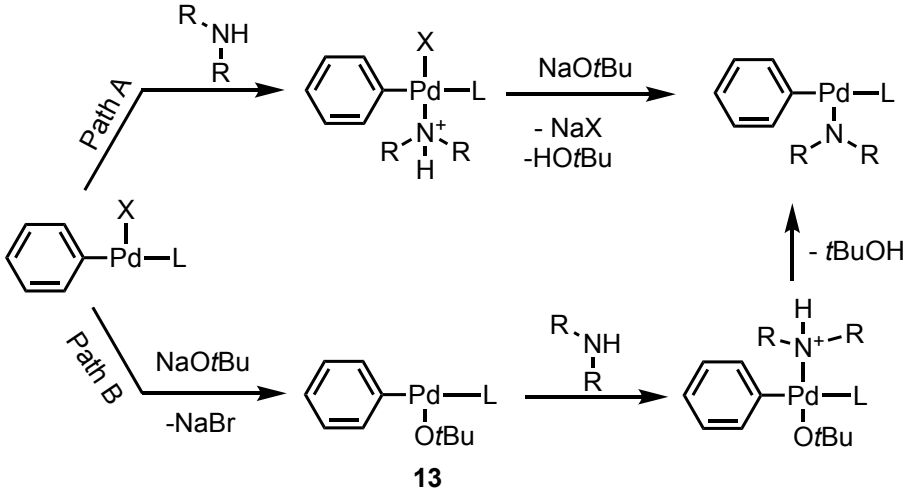
The mechanism of OA step has been the subject of extensive investigations and two pathways have emerged as the most likely, a concerted pathway and an S_NAr-type route. The concerted mechanism involves a three-centered transition state (**12a**) between palladium and the two atoms of the C-X bonds with no significant ionic character.[28,29] While aryl halides typically oxidatively add to Pd^0 complexes via the concerted mechanism, there are few exceptions in the literature where the S_NAr type mechanism is operative. For example, Maes and co-workers showed that the OA mechanism of 2-halopyridines to $[Pd^0(PPh_3)_2]$ could be changed by the nature of halide. While with 2-iodopyridines the concerted pathway is operative (Scheme 4, concerted pathway), with 2-chloro and 2-bromopyridine proceed by S_NAr and a charged transition state is involved (**12b**, Scheme 4, S_NAr pathway).[30]



Scheme 4. Oxidative Addition (OA) Mechanism.[30]

1.2.3. Amine Coordination/Deprotonation (DEP) steps

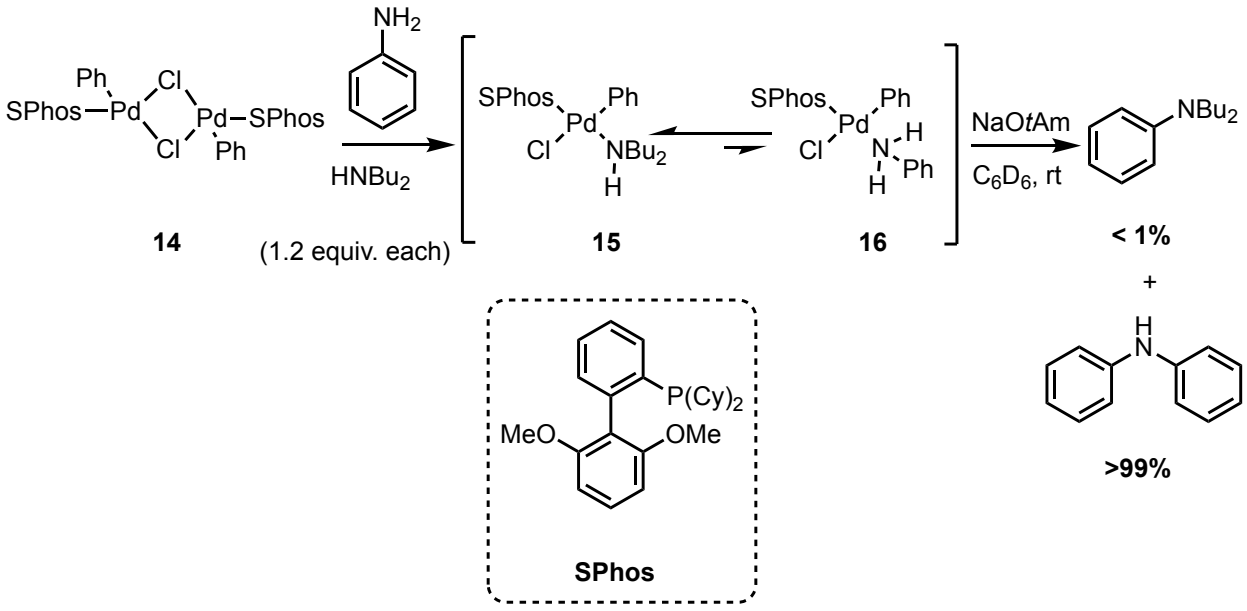
While the order of amine coordination and deprotonation depends on the reaction conditions, it is well accepted that the amine nucleophilic partner (e.g., alkyl amines, ammonia, anilines) can be deprotonated by commonly used bases in BHA (e.g., NaO*t*Bu, LiHMDS, Cs_2CO_3) only if it is first coordinated to the metal center. There are two possible pathways with respect to the order of amine coordination/deprotonation. The most likely pathway is the coordination of the amine to the metal center followed by deprotonation by the base (Scheme 5, Path A).[31,32] Depending on the nature of aryl halide and reaction conditions (e.g., ligand and base) , the order of events could be inverted, i.e., coordination of the base to the metal followed by the amine and intramolecular proton transfer (Scheme 5, Path B). For instance, Hartwig and co-workers showed that the reaction of DPPF-ligated aryl palladium complexes with NaO*t*Bu and dialkyl amines led to the formation of alkoxide complex **13,** which supports Path B. This alkoxide complex was then reacted with the amine and reductively eliminated the dialkylaniline.[33]



Scheme 5. Amine coordination/deprotonation step pathways. In path A, the amine coordinates first followed by deprotonation by the base. In path B, the base coordinates first followed by the amine, after which intramolecular proton transfer and dissociation of the conjugate acid (i.e., *tert*-butanol) takes place.

Following OA, the metal center becomes electrophilic (Pd^{II}), thus the more electron-rich (basic) the amine the more favorably it binds to the metal. The pK_a of alkyl amines and ammonia are approximately 40, whereas anilines have lower pK_a, ranging from 21 to 32 depending on the nature of substituent on the ring (all values in DMSO).[34] The most commonly used bases in amination reactions are alkoxide bases such as *tert*-butoxide (pK_a of *tert*-butyl alcohol ca. 29), carbonate (pK_a of $HCO3^-$ ca. 18) and phenoxides (pK_a of phenol ca. 18) (all values in DMSO). By comparing these numbers, it is apparent that for deprotonation to take place the amine must first coordinate to the metal center to lower its pK_a by approximately 20 pK_a units.

In 2007, Buchwald and co-workers investigated the relative binding affinity of different amines to OA complex **14** (formed from PhCl and [SPhosPd^0]) and in all instances the more nucleophilic alkyl amines exhibited much greater affinity than the aniline substrates.[35] In a competition experiment between Bu_2NH and aniline with complex **14**, complex **15** was formed predominantly owing to the greater binding affinity of the alkyl amine. However, after addition of the base to the reaction mixture diphenylamine, the product of reductive elimination of the aniline, was the only species observed (Scheme 6).[35] This can be rationalized by slow deprotonation of **15**, which gives alkyl amine dissociation time to occur and that once any **16** forms, despite how little it is in the equilibrium (i.e., less than 1 percent is likely based on relative basicity/nucleophilicity of the two competing amines), it will rapidly deprotonate.



Scheme 6. Comparison of binding affinity of different amines to OA complex **14**.

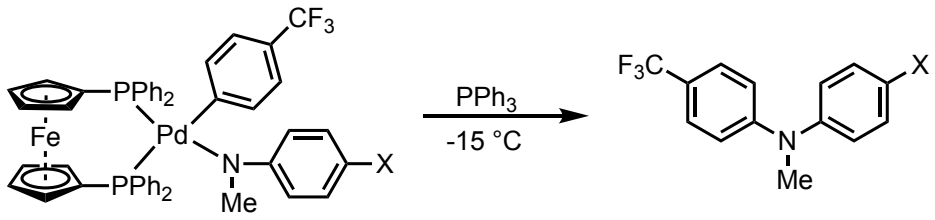
Depending on the strength of the base, this step can become rate-limiting step for the whole BHA process. For example, in 2011 Organ and co-workers reported that the rate of the coupling of alkyl amines with aryl halides in the presence of Pd-NHC pre-catalysts increases dramatically when strong base is used. They reported couplings that completed in less than a minute when KO*t*Bu was used at room temperature, whereas the same reaction using Cs_2CO_3 at 80 °C required 12 h to complete.[36,37]

1.2.4. Reductive Elimination (RE)

The final and C-N bond forming step of the catalytic cycle is RE with concomitant regeneration of Pd^0 species. The success of this step is greatly influenced by the electronic and steric properties of the ancillary ligand, with the steric factors appearing to exert the greatest influence. In contrast to OA step, electron-withdrawing ligands facilitate the rate of RE.[38–40] With respect to steric properties, it is now well appreciated that the rate of RE is remarkably enhanced with sterically

demanding ligands. This, presumably, is the result of pushing the aryl and amine substituents into the most favourable orbital overlap to establish the bond between them, while relieving steric congestion around the metal cente.[41]

The electronic and steric nature of coupling partners also impacts the rate of RE. In general, complexes with more electron-rich amido substituents undergo faster reductive elimination. For example, Hartwig studied the relative rate of RE from (DPPF)-ligated arylpalladium amido complexes with varied electronic properties and the results are summarized in Scheme 7. The more electron-rich amido complex (X= OMe) underwent reductive elimination much faster than the electron poor counterparts.[39]



X	k_{obs} (x10^4 s^{-1})
OMe	37.7
Me	12.8
H	2.94

Scheme 7. The relative rate of RE with different amido ligands.[39]

Similar investigations using DPPF-ligated complexes have also revealed that, as one might expect, RE is accelerated by electron-withdrawing groups on the OA partner.[38,42] Bulky substituent(s) on the amine nucleophile and/or OA (electrophile) partner also promote the RE step.[41]

1.3. **Ancillary ligands**

Ancillary ligands in Pd-catalyzed amination reactions are of paramount importance as they impart key steric and electronic properties to the metal center to enable a successful catalysis. Several

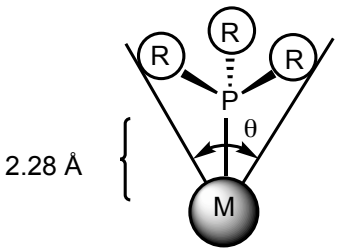
mechanistic investigations have shown that the rate of OA is enhanced by an electron-rich, less sterically congested Pd center, whereas RE is facilitated by electron-deficient and more sterically congested one. Consequently, for a catalytic system to be successful, a balance between steric and electronic properties of the ligand is necessary.

Considerable effort has been devoted to the rational design of new ligands with the aim of improving the efficiency of the catalytic system and overcoming the inherent challenges of BHA. To date, phosphine and N-heterocyclic carbene (NHC) ligands are the two most intensively studied ancillary ligands in Pd-catalysed BHA reactions.

1.3.1. Phosphine ligands

Phosphine ligands are the first and most common class of ligands used in Pd-catalyzed BHA reactions. The steric and electronic properties of these ligands can be altered in a predictable manner by varying the substituents on the phosphorus atom. Parameters to measure the electron-donating ability and steric topology of phosphine ligands were established by Tolman.[43–45] The steric parameter, now called the "Tolman cone angle (θ)", measures the space a ligand occupies around the metal center, and can be obtained by measuring the angle of a cone containing the metal at its apex with a metal-phosphorus distance of 2.28 Å with edges of the cone touching the van der Waals radii of the outermost ligand atoms (Figure 4a). As the size of the substituent on phosphorus increases (R=*t*Bu vs R=Et), the Tolman cone angle increases in a predictable fashion (Figure 4b).[45] This, in turn, leads to a boost in the steric influence of the ligand on the metal center, which has been repeatedly shown to positively impact the catalyst performance in many cross-coupling applications. For instance, it had been reported by Negishi and co-workers that $Pd(PR_3)_2X_2$ complexes containing bulky substituents (R= ph) undergo faster RE than those containing less bulky substituents (R=Et).[46]

(a)



(b)

R	Cone angle (θ)
Me	118
Et	132
Ph	145
*t*Bu	182

Figure 4. (a) Tolman cone angle analysis in phosphine ligands. (b) Cone angle in selected phosphine ligands.

The electronic parameter, coined the "Tolman's electronic parameter or TEP", measures σ - electron donating properties of phosphine ligands, and is determined by measuring the A_1-symmetrical CO stretching frequency of $LNi(CO)_3$ where L is the phosphine ligand being studied (Figure 5).[47] Phosphine ligands (PR_3) are σ-donors and depending on the nature of the R group can act as π-acceptors. Their donor ability is highest when R is an electron-donating moiety, such as alkyl, and decreases when R is electron-withdrawing, such as aryl group. Upon ligation of a strong σ-donor phosphine to the metal center, the electron density at the metal increases, and consequently, metal to carbonyl π-back donation into the π^* orbital of the CO ligand increases. In turn, this results in a weaker CO bond with a lower ν(CO) stretching frequency. With π-acceptor phosphines, the metal pushes electron density into the σ^* orbital of the phosphine via π-back donation leading to higher ν(CO) stretching frequencies.[44,45]

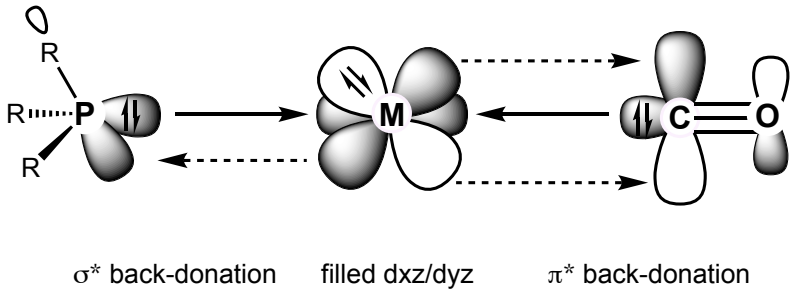
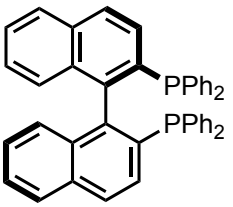
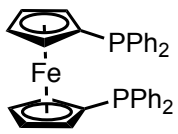


Figure 5. Schematic representation of the bonding situation in phosphine-metal-CO complexes.

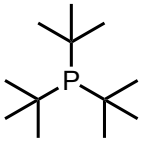
Since the first report of palladium-mediated C–N cross-coupling using phosphine ligands, intensive effort has gone into the development of new phosphine ligands and several mono-and bidentate ligands have been invented with the aim of improving the process (Figure 6). All of these ligand design features led to a remarkable progress in accommodating challenging coupling partners, along with increasing the functional group compatibility by allowing the application of increasingly milder reaction conditions. In light of these ligand developments, challenges arising in BHA such as β-hydride elimination (BHE) with alkyl amines and difficult OA with aryl chlorides have been mitigated. For instance, bidentate phosphine ligands such as BINAP (**17**) and DPPF (**18**) were shown to be very effective in suppressing the BHE in the coupling of alkyl amines.[48] Strong electron-donating trialkyl phosphines such as **19**[49], **20**[50] and **21**[51] were found to facilitate the OA of palladium species into Ar-Cl substrates in amination reactions. To address challenges in BHA, considerable effort has been invested in designing more architecturally complex phosphine ligands. Some representative examples of these developments by Buchwald (**22-23**),[7,52] Hartwig (**24**),[53,54] Stradiotto (**25**)[55,56] and Singer (**26**)[57] are shown in Figure 6.



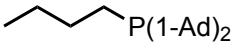
BINAP **17** (Ref. 48)



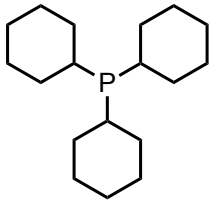
DPPF **18** (Ref. 48)



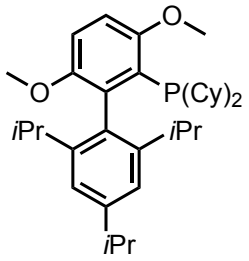
P(*t*Bu)$_3$ **19** (Ref. 49)



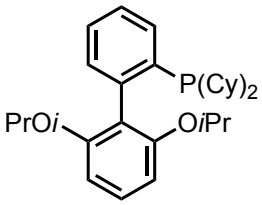
cataCXlum A **20** (Ref. 50)



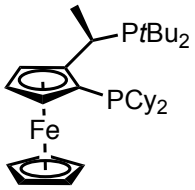
P(Cy)$_3$ **21** (Ref. 51)



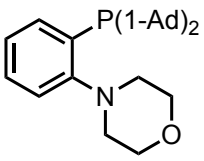
BrettPhos **22** (Ref. 7)



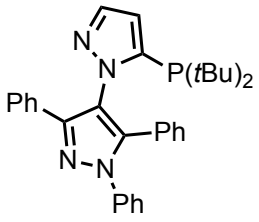
RuPhos **23** (Ref. 52)



JosiPhos **24** (Ref. 53, 54)



MorDalPhos **25** (Ref. 55, 56)



BippyPhos **26** (Ref. 57)

Figure 6. Examples of state-of-the-art phosphine ligands used in BHA chemistry.

While phosphines have proven to be highly useful ligands for BHA, there exist some disadvantages associated with their use. First, the steric bulk of phosphines projects away from the metal center, which in turn diminishes the influence of this bulk on catalyst performance. Next, trialkyl phosphines are pyrophoric and prone to oxidation in air, and need to be handled in an inert-atmosphere. Finally, phosphines are prone to degradation at high temperatures, so the use of excess

ligand is required. These shortcomings have led to the exploration of alternative ligands, and N-heterocyclic carbenes (NHCs) have emerged as an attractive alternative to phosphines due to their high thermal stability and ease of steric and electronic tunability.[58]

1.3.2. NHCs ligands

N-Heterocyclic carbenes, first prepared independently by Wanzlick[59] and Öfele[60] in 1968 and first isolated by Arduengo[61] (**27**) in 1991, have attracted considerable attention and emerged as an alternative to phosphines in many Pd-catalyzed cross-couplings. In 1995, Herrmann and co-workers, for the first time, reported that NHCs could be used as ligands in Pd-catalyzed reactions in place of phosphines.[62] Since then, much effort has been devoted to synthesizing a wide variety of NHCs, and the number of processes utilizing them as ligands has grown immensely.[63] Examples of the most common NHCs in Pd-catalysis are shown in Figure 7, and all are derived from imidazole or imidazolidine. Notable examples include IMes (**28**) and IPr (**30**) synthesised by Arduengo along with their saturated congener SIMes (**29**) and SIPr (**32**), which are arguably the most widely employed NHCs.[64] Further developments of more sterically hindered NHC ligands by Glorius (**38**, **39**),[65] Organ (**34-37**),[66] Dorta (**40-43**),[67,68] Markó (**33**),[69] and Lavigne (**31**)[70] have led to highly active palladium-NHC complexes that have proven to be very efficient in many C–C and C–heteroatom cross-coupling reactions.

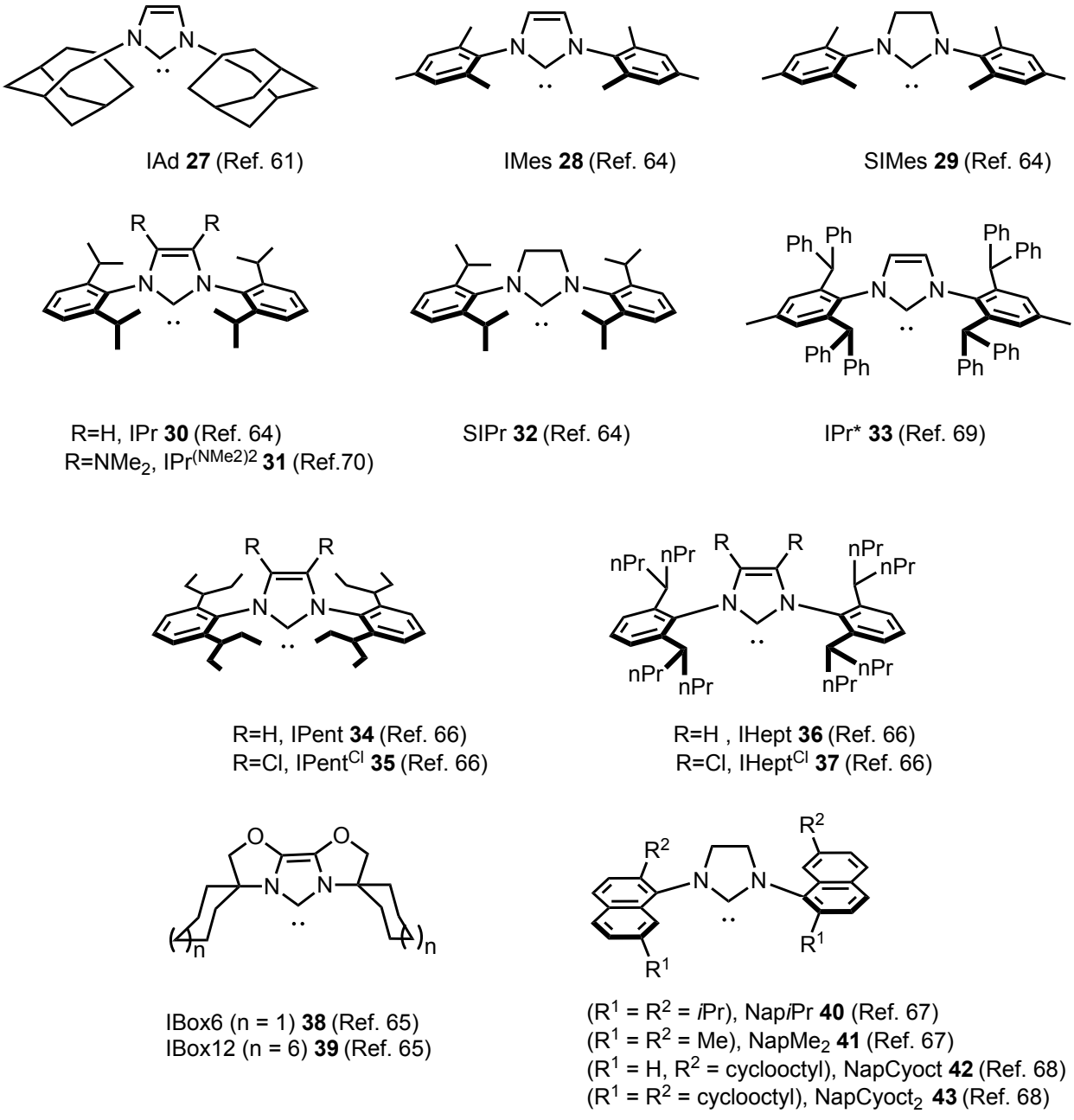


Figure 7. Selected imidazole and imidazoline-based NHCs used in cross-coupling.

NHCs are strong σ-donor ligands and their electron-donating ability can be quantified by comparing the carbonyl streching frequencies (ν) of a series of $[(L)Ir(CO)_2Cl]$ (L = NHC, PR_3, $P(OR)_3$) complexes, a strategy developed independently by Crabtree[71,72] and Nolan[73]. These studies revealed that NHCs are considerably more electron donating than even the most electron-

rich trialkyl phosphines such as PCy_3. This, in turn, results in a stronger M-L bond in NHCs compared to their phosphine counterparts. Furthermore, these studies showed that the donating ability of NHCs is independent of the nature of the *ortho*-substituents on the N-aryl ring (Figure 8). This implies that, unlike phosphine, the electronic and steric properties of NHCs can be tuned quite independently.

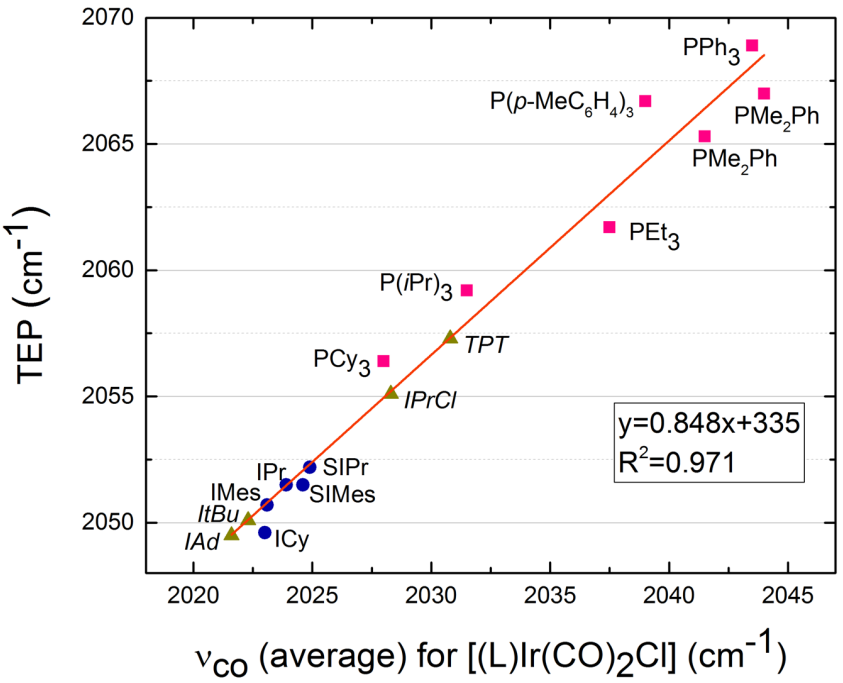


Figure 8. Nolan's correlation of average ν_{co} values for $[(L)Ir(CO)_2Cl]$ complexes with the Tolman electronic parameter (TEP).[73] (■) Experimental values for phosphines; (●) Experimental values for NHCs; (▲) Values obtained by linear regression.

In contrast to phosphines, where the three substituents on the phosphorous atom are pointing away from the metal (M) center (cone shape), the R substituents on the nitrogen atoms of NHCs are pointing towards the metal center to form a more intimate pocket around the metal (Figure 9).

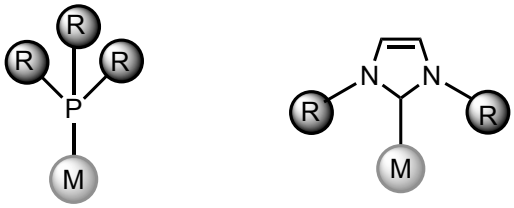
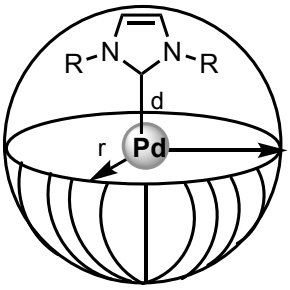


Figure 9. A comparison of the steric topographies of the two ligand classes.

Because of these topological differences between phosphines and NHCs, Tolman's cone angle could not be used to quantify the steric properties of NHCs. Nolan and Cavallo introduced a new steric parameter called percent buried volume $\%V_{bur}$,[71] which is the portion of the volume of a sphere centered around the metal that is occupied by a given ligand (Figure 10a). $\%V_{bur}$ can be calculated using crystallographic data of $[(NHC)Ir(CO)_2Cl]$ complexes. As the size of substituents on the *N*-aryl ring increases, the $\%V_{bur}$ increases proportionally. The $\%V_{bur}$ can also be used to quantify the steric properties of phosphines, thus allowing a direct comparison between the two ligand classes. The $\%V_{bur}$ of some common NHCs and phosphines are shown in Figure 10b.

(a)



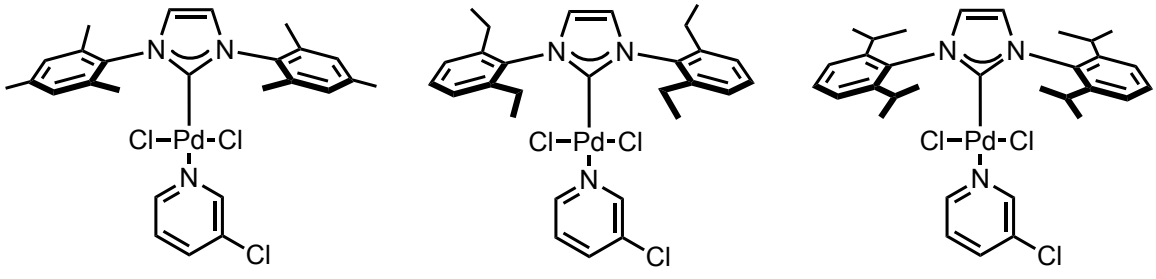
(b)

NHC	% V_{Bur}
IAd	36.1
IMes	31.6
IPr	33.6
SIMes	32.7
SIPr	35.7
IPent	37.9
$IPent^{Cl}$	38.4
PPh_3	30.5
PCy_3	35.3

Figure 10. (a) Schematic representation of the sphere used for the $\%V_{Bur}$ calculation. (b). Comparison of $\%V_{Bur}$ some of common NHC ligands with two popular phosphines.[74]

1.3.3. Pd-PEPPSI pre-catalysts

As mentioned previously, owing to the strong σ-electron donating nature of NHCs, these ligands form a very stable bond with the metal. As a result, pre-formed NHC-Pd complexes have been increasingly employed as ancillary ligands in catalysis.[63] The NHC-Pd pre-catalysts developed by Organ and co-workers are perhaps the most popular pre-catalysts employed in cross-coupling reactions to date. These complexes feature a *trans*-ligated 3-chloropyridine as a throwaway ligand that plays a key role in their stabilization, giving rise to the generic name of *PEPPSI* (Pyridine Enhanced Pre-catalyst, Preparation, Stabilization, and Initiation) for this family of pre-catalysts. These pre-catalysts have attracted great interest as they are air and moisture stable and readily reduce to Pd^0 species under typical cross-coupling conditions. The reactivity of the first generation of *Pd-PEPPSI* pre-catalysts (**44**, **45** and **46**) (Figure 11) was assessed in a variety of cross-coupling reactions, including Negishi,[75] Suzuki-Miyaura,[76] Kumada-Tamao-Corriu (KTC),[77] and Buchwald-Hartwig amination reactions[78] and **46** was shown to be the most reactive and efficient pre-catalyst.

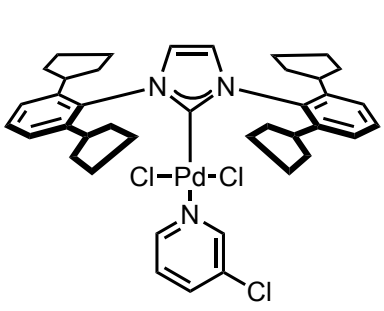


Pd-PEPPSI-IMes **44** (Ref. 75) *Pd-PEPPSI-IEt* **45** (Ref. 75) *Pd-PEPPSI-IPr* **46** (Ref. 75)

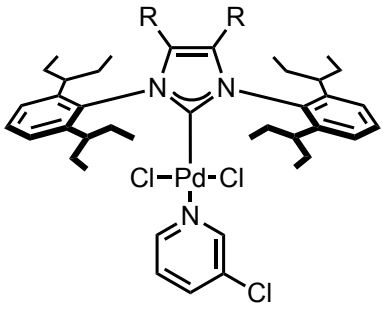
Figure 11. First generation *Pd-PEPPSI* pre-catalysts

Knowing that *IPr* and *IMes* have very similar σ−donor abilities, Organ and co-workers concluded that the increased steric bulk of *IPr* is responsible for its improved catalytic performance. With

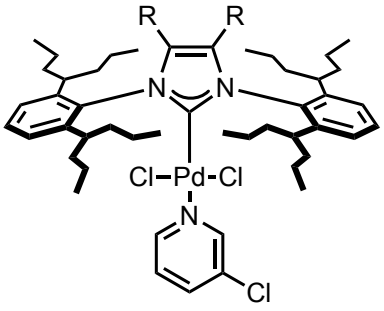
this knowledge, their team developed second generation *Pd-PEPPSI* complexes containing more sterically hindered *ortho*-substituents on the N-aryl rings of the NHC: *Pd-PEPPSI-cPent* (**47**), *Pd-PEPPSI-IPent* (**48**) and *Pd-PEPPSI-IHept* (**49**) (Figure 12).[79] Screening these complexes in the Suzuki-Miyaura coupling of tetra-*ortho* substituted biaryls revealed that **48** is the most active pre-catalyst in this generation.[79] These results support the "flexible-steric-bulk" concept, coined by Frank Glorius, where ligand bulk was not fixed, but capable of being moved about as best suits the catalytic cycle of cross-coupling applications.[80] Since then, *Pd-PEPPSI-IPent* has shown superior activity to any first-generation *Pd-PEPPSI* complex in Negishi (Scheme 8a),[81,82] Suzuki-Miyaura (Scheme 8b),[83] Stille-Migita (Scheme 8c),[84] BHA (Scheme 8d and 8e),[36,37] and C-S cross-coupling reactions (Scheme 8f).[85]



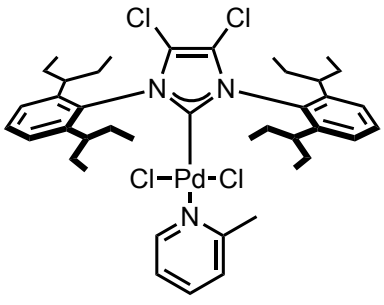
Pd-PEPPSI-cPent **47**
(Ref. 79)



R=H, *Pd-PEPPSI-IPent* **48**
(Ref. 79)
R= Cl, *Pd-PEPPSI-IPent*^{Cl} **50**
(Ref. 86)



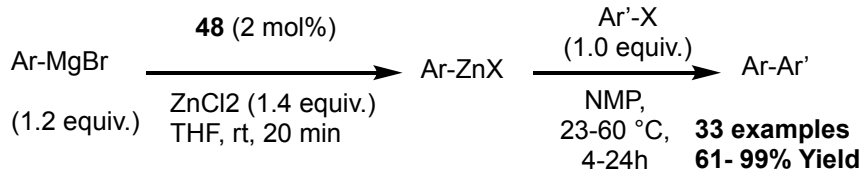
R= H, *Pd-PEPPSI-IHept* **49**
(Ref. 79)
R=Cl, *Pd-PEPPS-IHept*^{Cl} **51**
(Ref. 89)



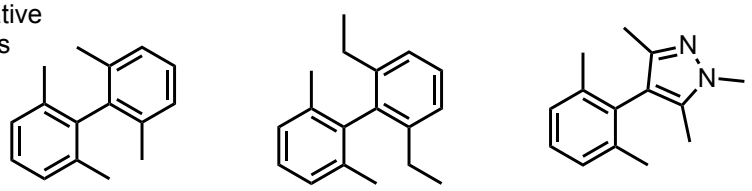
Pd-PEPPSI-IPent^{Cl}*-o-picoline* **52** (Ref. 91)

Figure 12. Second generation *Pd-PEPPSI* pre-catalysts

a) Negishi coupling (Ref. 82):

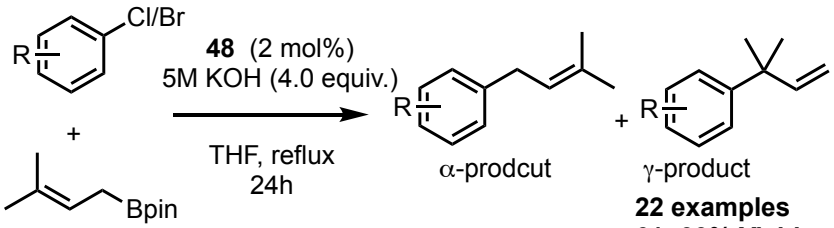


Representative examples

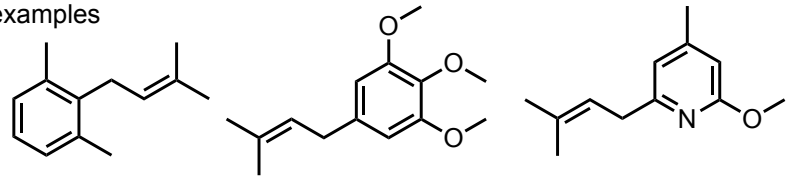


99 % 73% 99%

b) Suzuki-Miyaura coupling (Ref. 83):

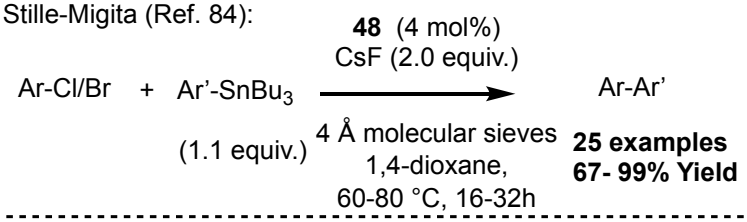


Representative examples

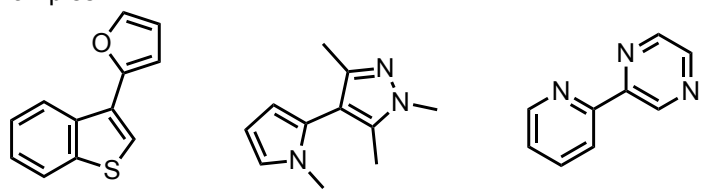


74% 78% 83%

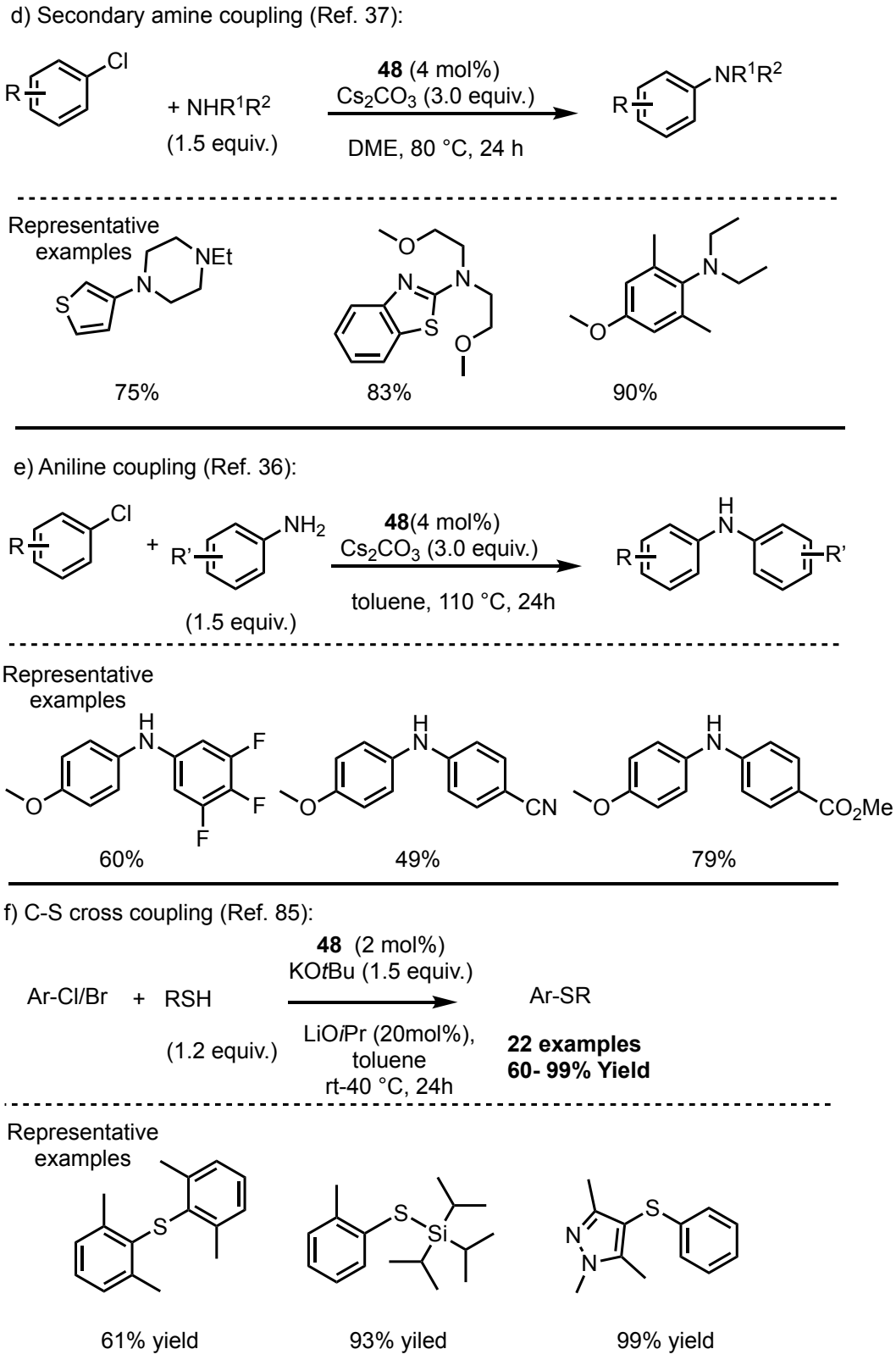
c) Stille-Migita (Ref. 84):



Representative examples

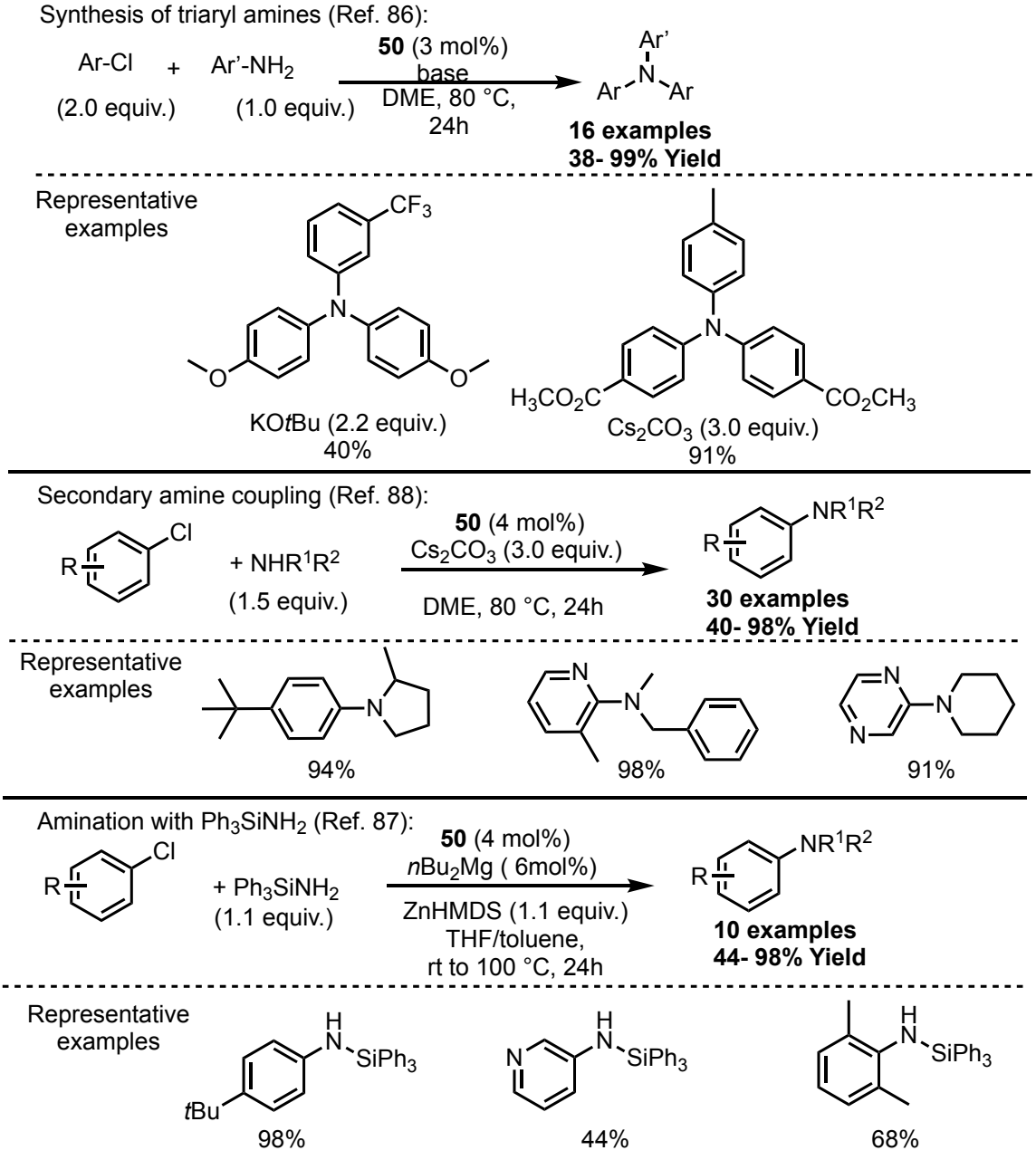


81% 98% 75%

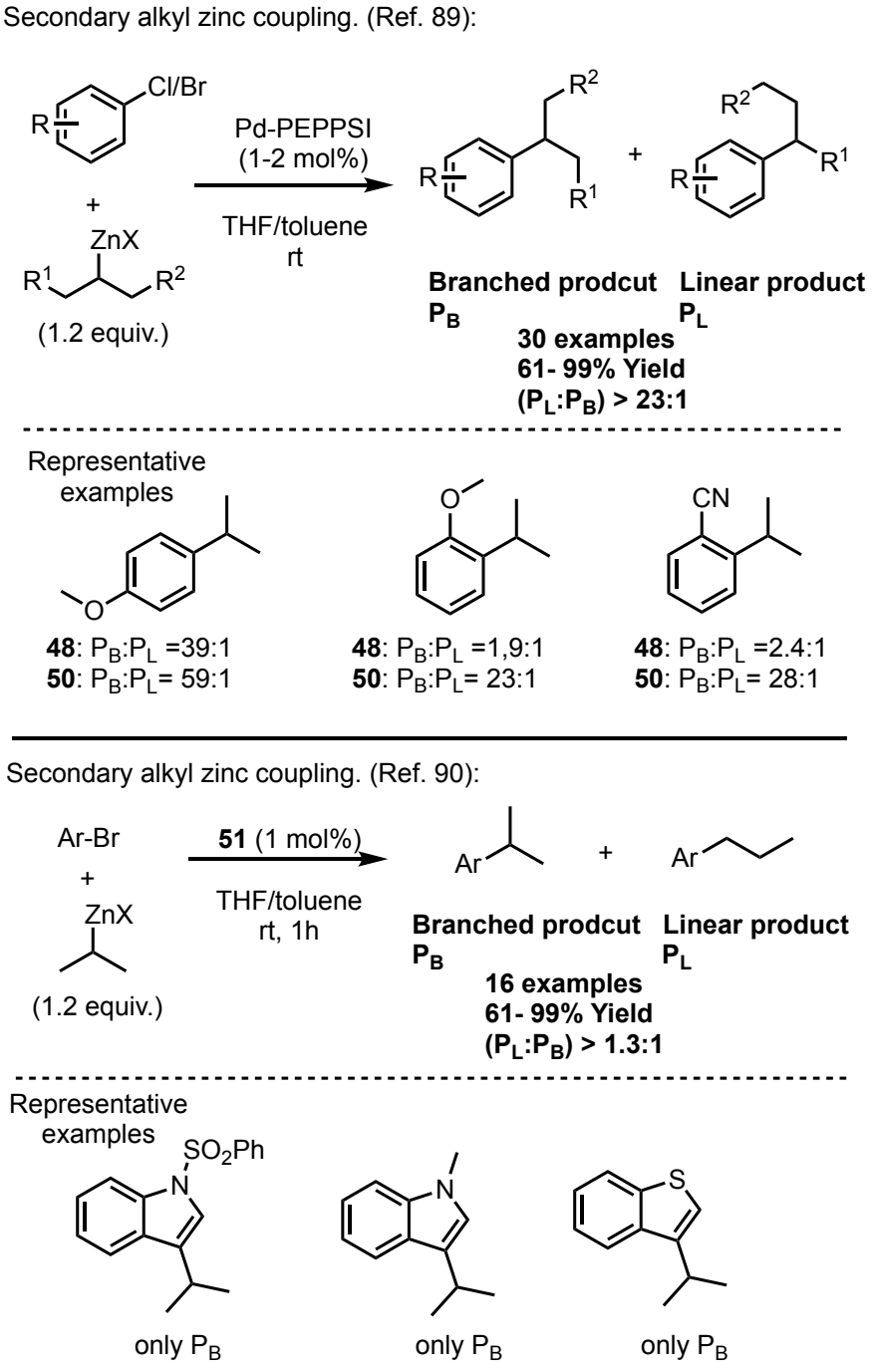


Scheme 8. Selected examples of Pd-catalyzed cross-coupling reactions with *Pd-PEPPSI-IPent* (**48**).

In an attempt to improve the reactivity of *Pd-PEPPSI*-complexes, Organ and co-workers prepared the backbone-modified *Pd-PEPPSI-IPent*^{Cl} (**50**) and *Pd-PEPPSI-IHept*^{Cl} (**51**) (Figure 12), which have demonstrated among the highest levels of reactivity reported in BHA reaction (Scheme 9)[86–88] and deft selectivity for the coupling of secondary alkylzinc reagents (Scheme 10).[89,90]



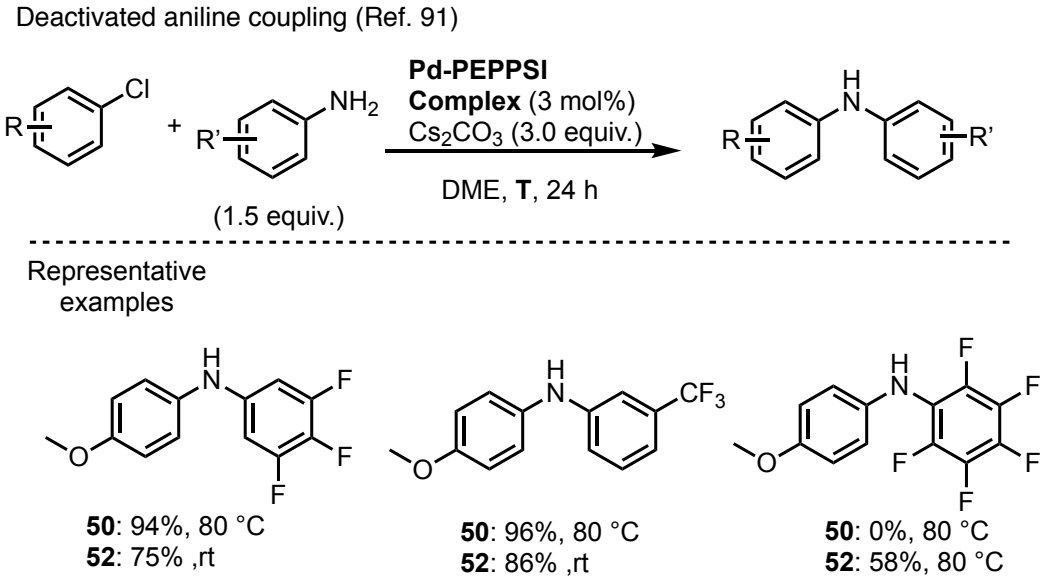
Scheme 9. Selected examples of Pd-catalyzed challenging aminations with *Pd-PEPPSI-IPent*^{Cl} (**50**).



Scheme 10. Selected examples of Pd-catalyzed secondary alkyl zinc coupling with *Pd-PEPPSI-IPent*^{Cl} (**50**) and *Pd-PEPPSI-IHept*^{Cl} (**51**).

Moreover, further optimization of the structure of the pyridine ligand in the pre-catalyst led Organ group to synthesize *Pd-PEPPSI-IPent*^{Cl}*-o-picoline* (**52**) (Figure 12), which subsequently was

shown to be the most reactive pre-catalyst for room temperature amination of electron rich aryl halides with electronically deactivated anilines using only carbonate as mild base (Scheme 11).[91]



Scheme 11. *Pd-PEPPSI-IPent^{Cl}-o-picoline* (**52**) in BHA with secondary amine and aniline nucleophilic partners.

1.4. **Challenges in Buchwald-Hartwig amination**

Despite the tremendous progress that has been achieved with respect to improving the efficiency and expanding the scope of BHA of (hetero)aryl halides and amine nucleophilic partners, some challenges remain to be addressed. These challenges include selective monoarylation of primary alkyl amines, enantioretentive *N*-arylation of amino esters and arylation of amide nucleophiles.

1.4.1. Selective monoarylation of primary alkyl amines

The main challenge associated with utilization of primary alkyl amines in BHA is that either secondary (**54)** or tertiary aniline (**56**) products can be formed as a result of mono and diarylation of the primary amine, respectively (Figure 13).[14,15,92] Once the secondary aniline is formed it can re-enter the catalytic cycle and undergo another *N*-arylation to form the undesired tertiary aniline

product. Formation of the undesired diarylated product is a consequence of the catalyst's inability to discriminate between the starting alkyl amine and the monoarylated product.

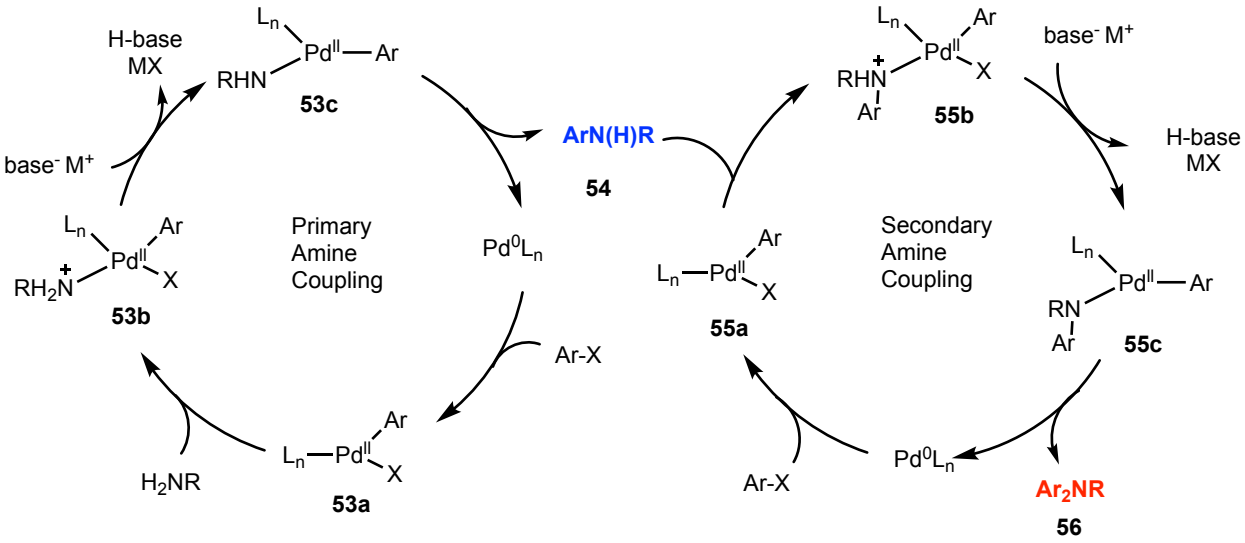


Figure 13. Mechanism of mono and diarylation of primary alkyl amines.

There is a significant difference in nucleophilicity of the primary alkyl amine and the corresponding monoaryl amine (aniline) product. The primary alkyl amine with its much greater nucleophilicity has a greater affinity in binding to the OA intermediate than the monoarylated amine, which of course is beneficial for desired monoarylation.[35] That said, the pK_a of the corresponding palladium ammonium complex (**53b**) is greater by several (~ 10) orders of magnitude compared to the palladium anilinium complex **55b**, which results from the attack of monoarylated amine to the OA intermediate (**55a**). Therefore, deprotonation of the anilinium complex by mild bases such as carbonate is more facile compared to the alkylammonium complex. Consequently, even if RE of the arylpalladium amide to form the monoarylated product is facile, only a limited amount of desired product might be formed due to the sluggish deprotonation step. Owing to the greater acidity of the aniline competitor, once successive binding to the OA intermediate takes place, the cycle continues smoothly to furnish the (undesired) diarylated product

(**56**). Confounding things is that one must consider steady-state kinetics in this over-arylation problem. That is, as the reaction progresses, the concentration of the starting amine (the desired nucleophile) decreases while that of the aniline product (the unwanted nucleophile) necessarily increases. If one wants to avoid using large excesses of the starting amine to compensate for this, especially if it is expensive or took many steps to prepare, one either has to engineer a process to favour the desired reaction, such as adding the coupling solution slowly to the starting amine, or design a catalyst (*vide infra*) that, overall, favours the first arylation.[93] In addition to enhancing reaction efficiency, this affords practical benefits in product isolation by minimizing the amounts of excess starting amine and undesired diarylated product, all of which are now amine-containing. Adding to the complexity of reaction-process and catalyst design is that there is a high substrate diversity that can work contrary to mono arylation. That is, the nature of substrate can greatly impact monoarylation selectivity. For example, an electron-poor and/or sterically encumbered aryl halide (e.g., *ortho*-substituted) will render the resultant aniline product less nucleophilic and diminish its ability to re-enter another cycle by coordinating to **55a**.[94]

As mentioned above, drastically increasing the amount of the starting amine partner relative to the aryl halide certainly would improve monarylation selectivity to some degree, but this is not desirable, or practical for many reasons.[94] The proper choice of pre-catalyst, solvent, and base would also be expected to play a crucial role in achieving high levels of selectivity with pre-catalyst being the most influential parameter. To this end, the steric and electronic properties of ancillary ligands have been tuned with the aim of improving the mono selectivity of the reaction, many successful ligand systems have been reported to date.

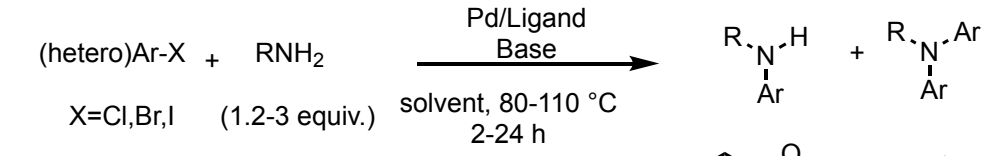
1.4.1.1. State-of-the-art ligands in selective monoarylation of primary alkyl amines

The use of primary alkyl amines in BHA reactions was first reported in 1996 by Buchwald and co-workers, who demonstrated that the coupling of aryl bromides to both primary alkyl amines and secondary amines could proceed in the presence of $Pd_2(dba)_3$/BINAP catalyst system and NaO*t*Bu as the base (Scheme 12a).[48] In 2000, Buchwald and co-workers revealed that a variety of amines including primary alkyl amines, could be successfully coupled with aryl chlorides using (*o*-biphenyl)P(*t*Bu)$_2$ ligand (Scheme 12a).[95] This method provided access to the corresponding monoaryl amine in moderate to good yields, however, it required high reaction temperatures (100-110 °C) and could not accommodate substrates with base-sensitive functionality. Following Buchwald's report, efforts were directed towards the development of catalyst systems capable of improving the selectivity, efficiency, and substrate scope of these cross-coupling reactions. Hartwig and co-workers reported the superior activity of *JosiPhos* ligand (**24**) in the cross-coupling of a variety of (hetero)aryl chlorides and (hetero)aryl tosylates with primary alkyl amines in good to excellent yield and excellent selectivity for the monoarylation product (Scheme 12b).[24,96] However, elevated temperatures (70-100 °C) and extended reaction times (>48 h) were required and in most cases high ratios of mono- to di-arylated products could not be obtained unless 3 equivalents of the amine were used. In 2008, Buchwald and co-workers established a new catalyst system based on the *BrettPhos* ligand (**22**) for selective monoarylation of aryl chlorides (Scheme 12a).[97] While the new catalyst system allowed the coupling of simple primary aliphatic amines with aryl halides to take place with high levels of selectivity, the use of a strong base such as *tert*-butoxide and very high temperatures of the reaction curtailed the efficiency and utility of the system. In a subsequent publication, Buchwald's group further explored the reactivity of this

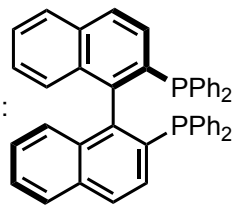
catalyst system and showed that a broad range of simple and functionalized primary alkyl amines can be coupled with a variety of functionalized aryl and heteroaryl halides in moderate to excellent yields, albeit at high temperatures (≥ 100 °C).[52] It is noteworthy that one drawback of this protocol was the need for different reaction conditions (e.g., solvent, base and temperatures) with different substrate combinations, that is, the reaction conditions were not general, but rather substrate specific.

In 2010, Stradiotto and co-workers reported that [Pd (allyl)Cl]$_2$ or [Pd (cinnamyl)Cl]$_2$) in conjunction with *DalPhos* ligands **59** and **60** led to highly reactive catalysts capable of coupling a variety of aryl and heteroaryl halides and primary alkyl amine in good to excellent yield (Scheme 12c). That said, this protocol suffered from two drawbacks - the need for high temperatures (≥ 100 °C) and low functional group tolerance.[98] In 2013, Stradiotto's group reported on the use of the *MorDalPhos* ligand in a similar coupling of alkyl amines and aryl mesylates at high temperatures (e.g., 110 °C) (Scheme 12c).[99] Later that year, Stradiotto and co-workers synthesized a phosphine-functionalized NHC ligand (**61**) and investigated the utility of such ligand in BHA. The authors reported **61** to be very effective in coupling a range of aryl chlorides with primary alkyl amines using LiHMDS as the base (Scheme 12c).[100] In 2015, César and co-workers revealed that the backbone-modified *Pd-PEPPSI-IPr$^{(NMe_2)_2}$* (**62**) is capable of catalyzing the reaction between various aryl chlorides and amine nucleophiles such as secondary amines, primary alkyl amines and primary aryl amines under mild conditions using Cs_2CO_3 as the base (Scheme 12d).[70] Although the reaction proceeded to completion in the five primary alkyl amine substrates that were screened, the selectivity of the transformation was not satisfactory and substantial amount of diarylated product was formed.

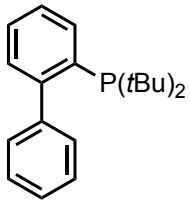
a) Buchwald, et al. (Ref. 48, 52, 95, 97):



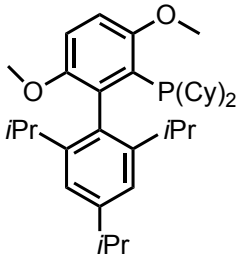
Ligands:



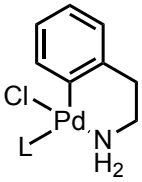
BINAP **17**



(*o*-biphenyl)P(*t*Bu)$_2$ **57**

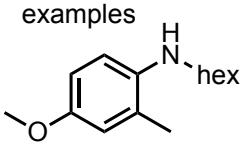


BrettPhos **22**

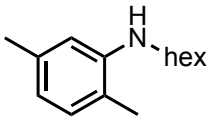


58 (L=22)

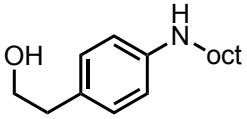
Representative examples



$Pd_2(dba)_3$/ **17**
NaO*t*Bu (1.4 equiv.),
toluene, 80 °C, 24h
95%

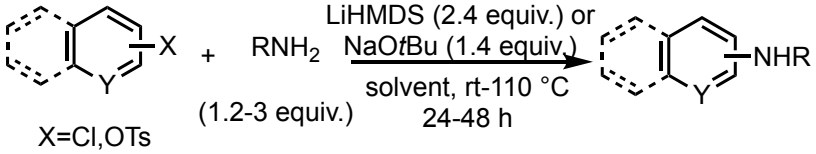


$Pd_2(dba)_3$/ **57**
NaO*t*Bu (1.4 equiv.),
dioxane, 100 °C, 24h
70%

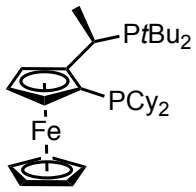


58
LiHMDS (1.4 equiv.),
dioxane, 100 °C, 20min
84%

b) Hartwig, et al. (Ref. 24, 96):

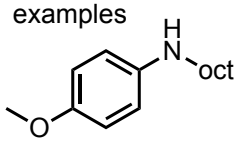


X=Cl,OTs
Y=CH, N

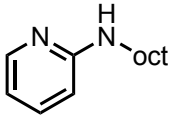


JosiPhos **24**

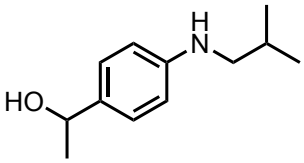
Representative examples



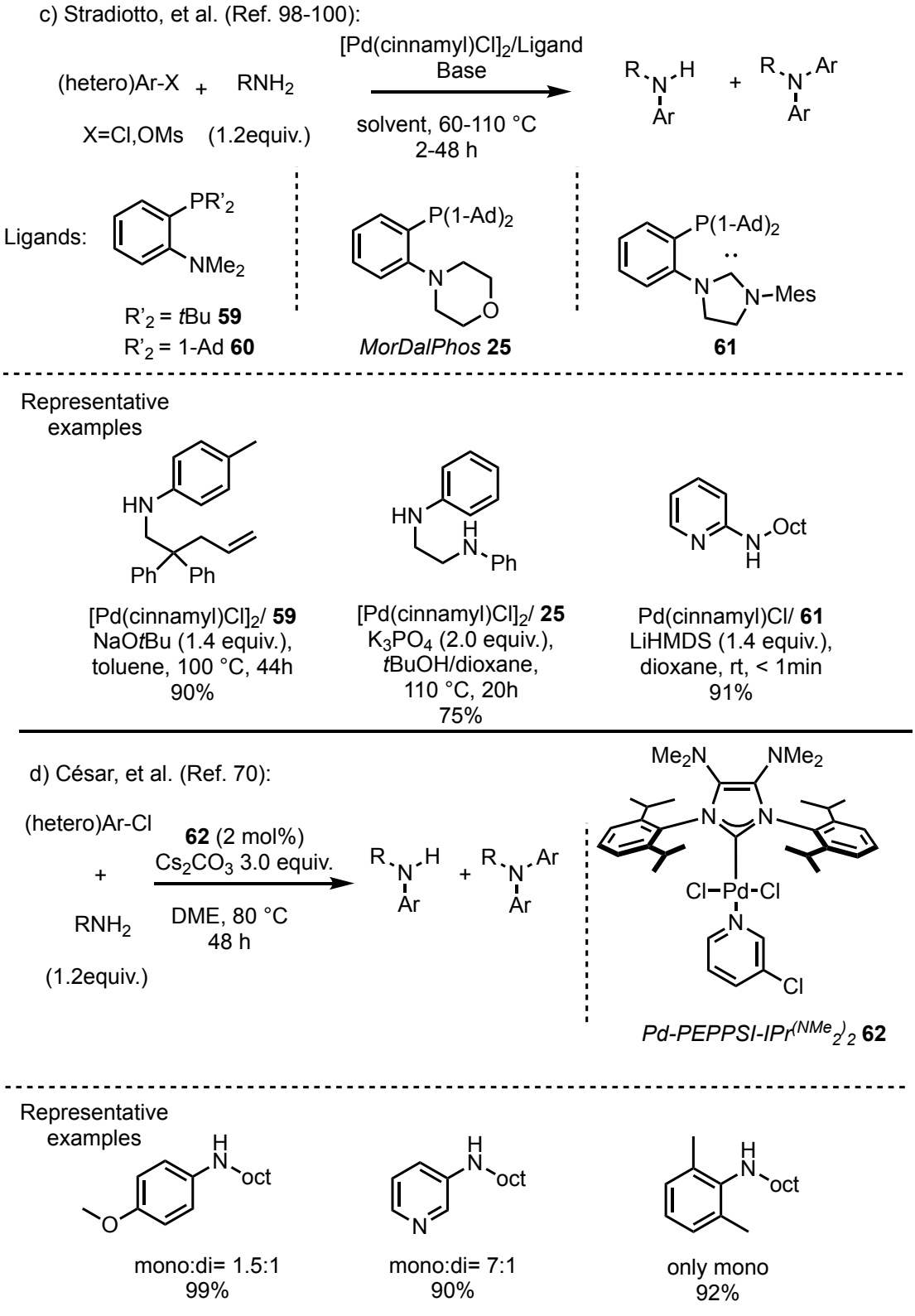
$Pd(OAc)_2$/ **24**
NaO*t*Bu (1.4 equiv.),
DME, 100 °C, 48h
92%



$Pd(OAc)_2$/ **24**
NaO*t*Bu (1.4 equiv.),
toluene, 100 °C, 24h
98%



$Pd(OAc)_2$/ **24**
LHMDS (2.4 equiv.),
DME, 100 °C, 18h
90%



Scheme 12. Selected examples of state-of-the-art ligands used in BHA with primary alkyl amines.

1.4.2. Enantioretentive N-arylation of α-amino (acids)esters

Another challenge in BHA is the enantioretentive *N*-arylation of α-amino esters. Among the reported syntheses of enantiopure aromatic amines, the approach toward optically enriched *N*-(hetero)aryl α-amino acids(esters) has proven to be among the most challenging.[101] This is due to the lower pKa value of the racemizable (~ 20 in DMSO) α proton of chiral α-amino acids (esters) relative to simpler chiral amines. Consequently, the former chiral amines are more prone to undergo racemization even under mildly basic reaction conditions. Racemization of α-chiral amines can occur through BHE during catalysis and it has been studied in great detail by Buchwald and others (Figure 14).[102] After OA and the amine coordination/deprotonation step, the Pd^{II}-amido complex **63a** forms and can undergo RE to generate the product. Alternatively, if **63a** contains β-hydrogens, it can undergo reversible BHE to form the π-coordinated imine **64a**, which is in equilibrium with its the σ-coordinated counterpart (**65**). Further equilibration between the π and σ-coordinated complexes provide access to π-coordinated imine **64b**. Then, migratory insertion of either π-coordinated prochiral imines **63b** and **64b** into the palladium-hydride bond generates the enantiomeric Pd^{II}-amido complexes **63a** and **63b**, respectively. These complexes then undergo RE to produce the racemic mixture of products (**66a** and **66b**).

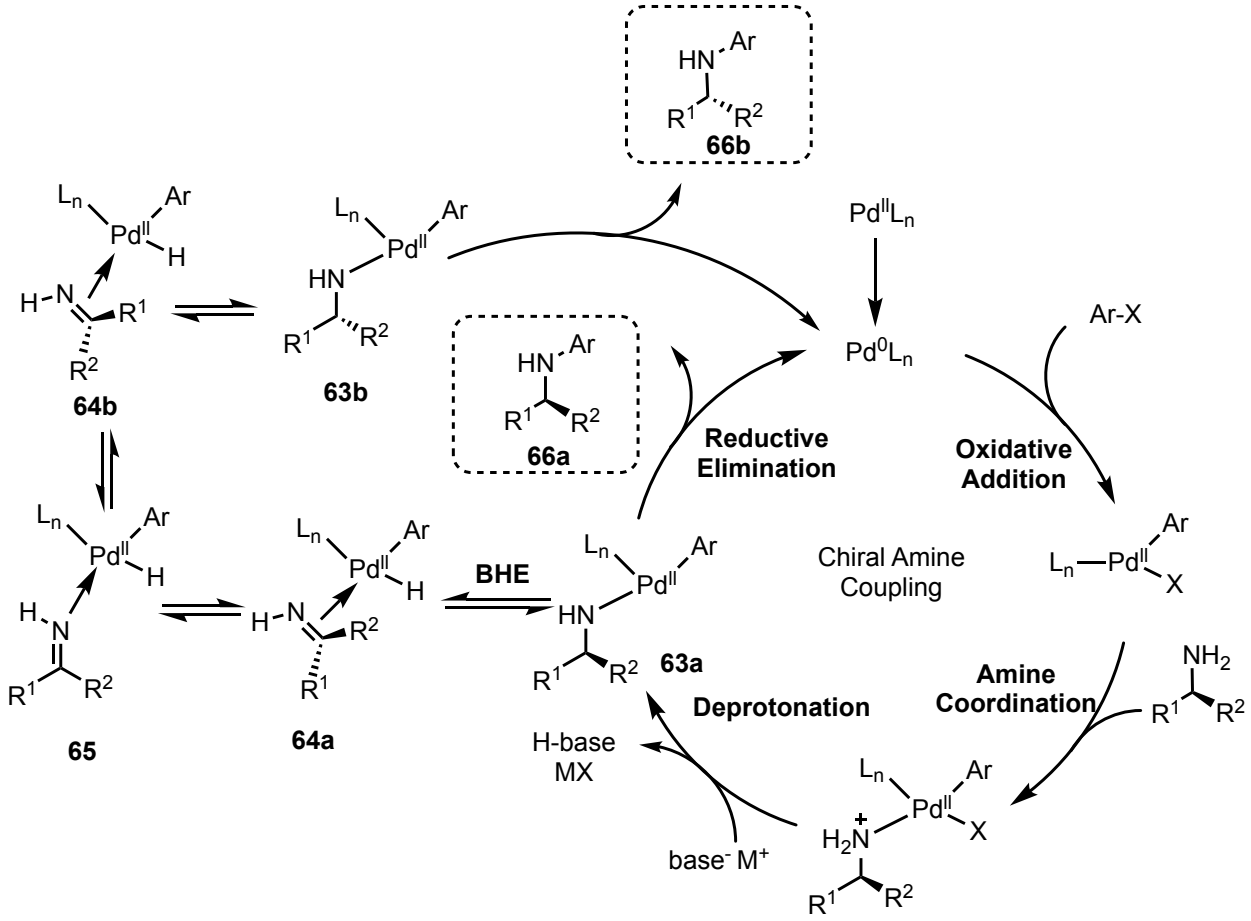


Figure 14. Mechanism of Pd-mediated racemization of α-amino (acids)esters.

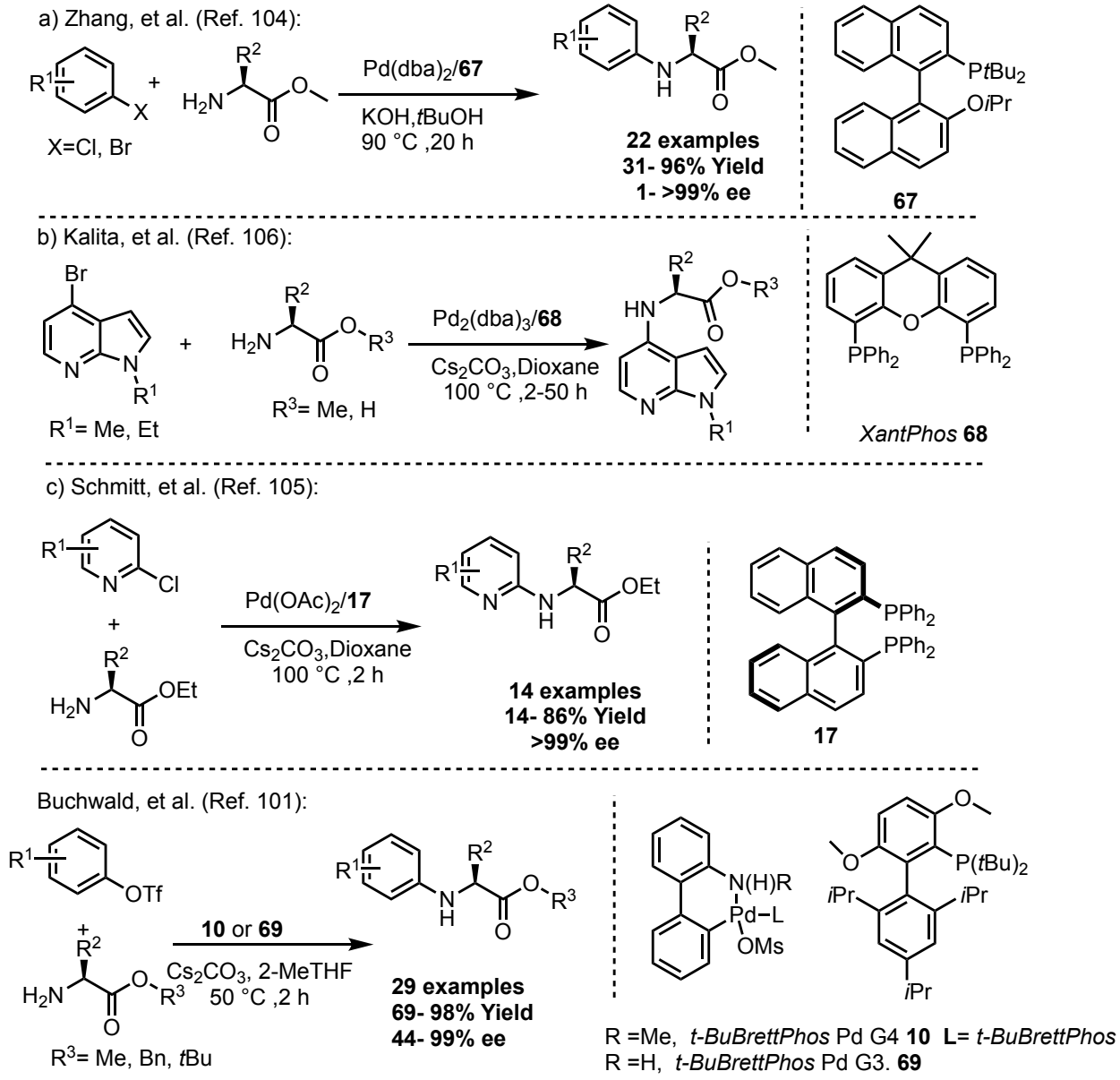
Moreover, similar to primary alkyl amines, primary α-amino esters (i.e., $RO_2CCH(NH_2)R'$), when arylated using metal catalysis, also have the monoarylation selectivity concern as the diarylated product ($RO_2CCH(NAr_2)R'$) can be obtained from over-arylation of the desired mono-arylated product as discussed in section 1.4.1. For instance, it has been shown that the use of α-amino esters with relatively less bulky alkyl group at the α carbon (e.g., methyl and benzyl vs. isopropyl and sec-butyl) results in the formation of significant amounts of diarylated product.[103] Also, in the case of the relatively less bulky α-amino esters stereochemical integrity of the α-amino esters was not preserved.[104] These challenges are typically overcome through ligand design and a number of

ligands have been rationally designed for the coupling of a variety of (hetero)aryl halides with α-amino acids(esters), with moderate-to-excellent enantio-retention.[101,104–106]

1.4.2.1. Ancillary ligands used in enantioretentive N-arylation of α-amino ester

Despite the prevalence of *N*-aryl amino esters in the structure of medicinal and biologically active compounds, there exist only a few reports on Pd-catalyzed *N*-(hetero)arylation of optically pure α-amino esters. An early report by Zhang and co-workers employed **67** as catalyst and KOH as base to couple various optically pure α-and β-amino acids with aryl chlorides in moderate-to excellent yields (Scheme 13a).[104] The enantioretention of the product was found to be dependent on the structure of the α–amino ester, and that those with a bulky alkyl group at the α-carbon (e.g., isopropyl) gave a high level of enantioretention, whereas those with less bulky groups at α-carbon (e.g., methyl) showed a poor level of enantioretention. In 2012, Kalita and co-workers reported a procedure for the cross-coupling of *N*-substituted 4-bromo-7-azaindoles with amino acid esters using *Xantphos* (**68**) as the supporting ligand and Cs_2CO_3 as the base (Scheme 13b).[105] Unfortunately, the substrate scope was limited to azaindoles. Additionally, Schmitt and co-workers developed a protocol for *N*-heteroarylation of chiral α-aminoesters in which BINAP and Cs_2CO_3 were employed as the supporting ligand and the base, respectively (Scheme 13c).[106] Using this protocol, Schmitt showed that a wide variety of six-membered heterocycles could be coupled with α-aminoesters to generate the desired product in moderate to good yields and excellent levels of enantioretention. However, under these conditions, the use of α-amino acids(esters) with relatively less bulky alkyl groups at the α-carbon proved to be challenging as significant amounts of di-*N*-arylated products were formed. More recently, Buchwald and co-workers developed a method for the *N*-arylation of amino esters with aryl triflates using palladacycle pre-catalysts **10** and **69** and

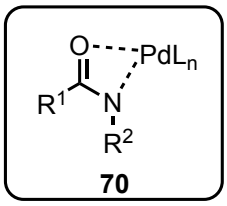
Cs_2CO_3 as base. This method provided access to a wide variety of *N*-arylated amino acid esters in moderate to good yield with high to excellent enantiopurity, however, the scope of the electrophile was limited to aryl triflates and the method was unsuccessful with the more desirable aryl bromides and chlorides (Scheme 13d).[101]



Scheme 13. State-of-the-art ligands used in BHA with α-amino acids(esters)

1.4.3. Pd-mediated arylation of amides

While palladium-catalyzed C-N bond formation reactions have been well developed for the cross-coupling of a wide range of nitrogen nucleophiles with (hetero)aryl halides, the use of amides as nucleophilic partner remains particularly challenging.[107] This is a result of the lower nucleophilicity of amides relative to other amines, which is well reflected in their pK_a values. The pK_a of alkyl amine is ~43 and an aniline is ~30, whereas an amide has a pK_a of ~23 (all values in DMSO). Thus, within a catalytic cycle, the relative binding affinity of these amines to OA complexes dramatically decreases in the same order. While the lower nucleophilicity of the amides appears to be problematic in the amine-coordination step, it is advantageous in the deprotonation step. If the amide coordinates to the metal, the resultant palladium-amide complex will be deprotonated more easily than those derived from alkyl amines. Moreover, amide nucleophiles are capable of binding to the palladium center at both the nitrogen and oxygen atoms simultaneously and form a κ^2-amidate complex (Figure 15).[107]



70

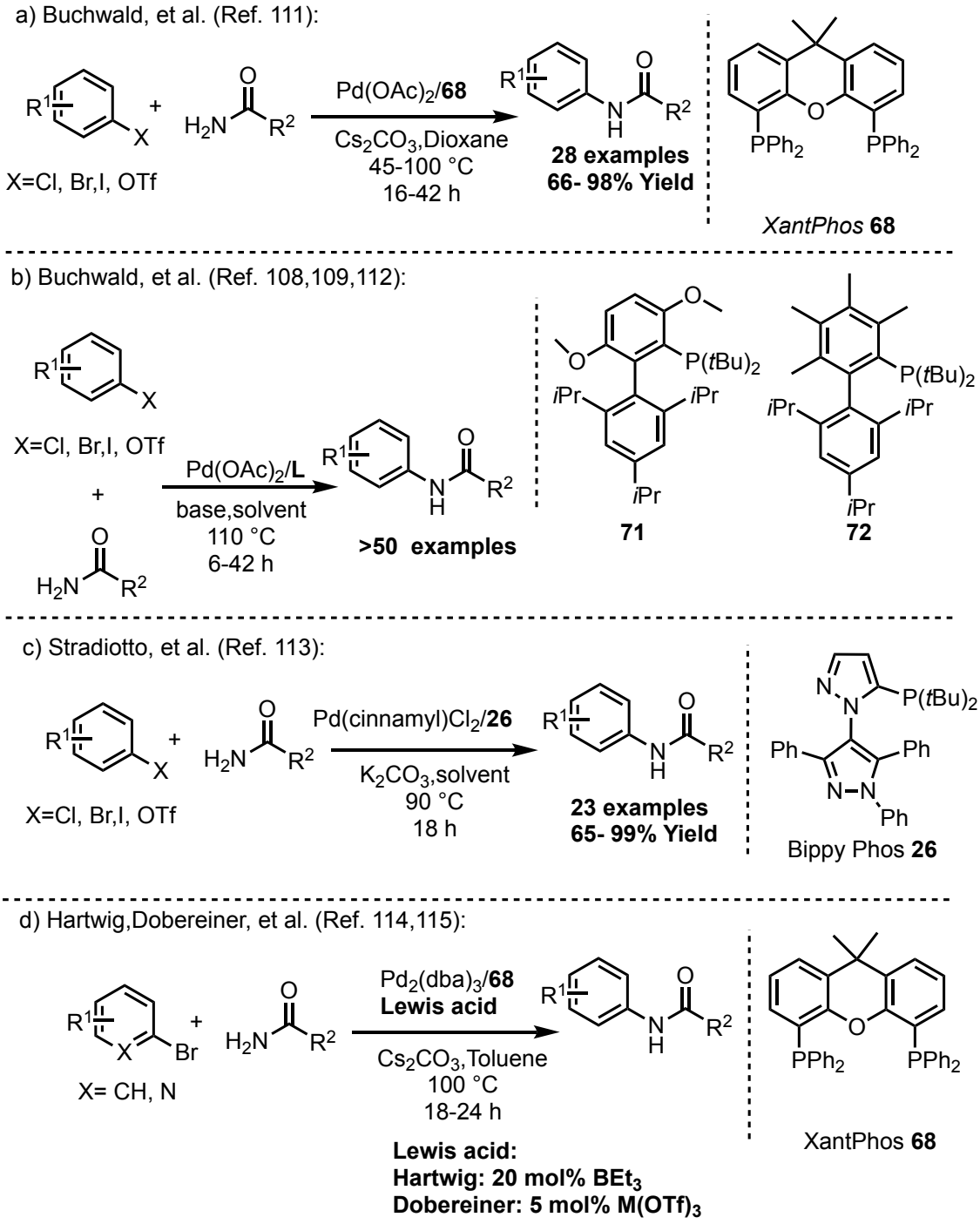
Figure 15. κ^2-amidate complex

Complex **70** with its bidentate metal-amide complexation is a non-productive Pd^{II}-amidate resting state and is expected to inhibit the RE step. Therefore, only those catalyst systems capable of resisting the formation of κ^2-amidate complex will be successful and lead to the formation of the desired product in high yield. The main strategy to overcome this challenge is through ligand

design and over the past decade many ligands have been successfully designed with the aim of inhibiting the amide coordination to Pd in a κ^2-fashion.[49,108–110]

1.4.3.1. Ancillary ligands in Pd-mediated aryl amidation reactions

In 2000, Buchwald and co-workers reported the first Pd-mediated intermolecular cross-coupling of aryl halides with primary and secondary amides and sulfonamides in which *Xantphos* and Cs_2CO_3 were employed as the ancillary ligand and base, respectively (Scheme 14a).[111]. This method provided access to the corresponding aryl amide in good to excellent yields, however, it required high reaction temperatures (100 °C) and long reaction times. In a series of publications, Buchwald and co-workers reported that biaryl monophosphine ligands such as **71** and **72** are useful for the coupling of a wide variety of aryl and heteroaryl chlorides and aryl mesylates with amide nucleophiles (Scheme 14b).[108,109,112] Despite the important advances made with these class of phosphine ligands, temperatures in excess of 110 °C were still required to achieve full conversion. Additionally, BippyPhos/$[Pd(cinnamyl)Cl]_2$ has been reported as a useful catalyst system for (hetero)aryl amidation with primary amides (Scheme 14c).[113] Hartwig[114] and Dobereine[115] independently reported that catalytic amounts of Lewis acid additives accelerate the Pd-mediated aryl amidation reactions. In both studies, *XantPhos*/$Pd_2(dba)_3$ was employed as the catalyst system and elevated temperatures (e.g., 110 °C) were necessary to achieve full conversions to product (Scheme 14d). In Hartwig's report which was the first example of the Lewis acid promoted aryl amidation, boron-based Lewis acids were used as the promoter, and the scope of electrophile was limited to heteroaryl bromides. Dobereine employed metal triflates as the promoter and a broad scope of aryl and heteroaryl halides were coupled to amide nucleophiles in moderate to excellent yields.



Scheme 14. State-of-the-art ligands used in BHA with primary amide

1.5. **Plan of study**

Despite the significant advances made by phosphine ligands in challenging C–N bond forming reactions, the majority of protocols employing such ligands still suffer from a number of limitations. With respect to selective mono arylation of primary alkyl amines the majority of current catalytic systems utilize aggressive bases such as NaO*t*Bu, which is incompatible with base-sensitive functional groups, and/or require high temperatures. Furthermore, there has been no universal catalyst system to allow selective coupling of a truly wide selection of aryl halides as well as six- and five-membered heteroaryl halides with simple or functionalized primary amines. In the case of arylation of α-amino esters, the reported methods suffer from restricted substrate scope and loss of optical purity during the formation of the product. For the arylation of primary amides, the majority of the reported protocols typically employ harsh reaction conditions and only a few reports exist on the incorporation of sterically demanding coupling partners, and those require high temperatures (i.e., 150 °C). Therefore, development of protocols capable of overcoming these limitations in such challenging Buchwald-Hartwig aminations would be highly desirable and would be a useful addition to current methods.

While NHC ligands have emerged as useful alternatives to phosphine ligands, there have been very few reports on the application of these ligands in challenging Pd-catalyzed aryl amination reactions. The main objective of this research was to investigate the reactivity of Pd-NHC pre-catalysts, in particular *Pd-PEPPSI* complexes, in such challenging BHA reactions. We set out to establish a mild and general set of reaction conditions for mono-selective C–N cross-coupling of a broad spectrum of aryl and heteroaryl halides with primary alkyl amines using *Pd-PEPPSI* complexes.

Once a set of conditions were developed for the highly selective monoarylation of primary alkyl amines, the objective of this research would expand to encompass the creation of a single, mild set of coupling conditions for the enantioretentive arylation of α-amino acids(esters). The last objective of this research is to develop a mild set of Pd-catalyzed aryl amidation conditions that make use of Pd-NHC pre-catalysts where sterically demanding coupling partners could be accommodated.

Chapter 2- Selective Monoarylation of Primary Alkyl Amines Using *Pd-PEPPSI-IPent^{Cl}*

2.1. **Background**

Secondary aromatic amines are found in the structure of a variety of useful compounds, including natural and pharmaceutical products and organic materials (Figure 16).[4,116–118] Traditional methods to prepare these moieties include nucleophilic aromatic substitution (S_NAr) of aryl halides with amines and reductive alkylation of primary aromatic amines with carbonyl compounds in the presence of a reducing agent,[119,120] however both of these methods suffer from a number of limitations. For instance, for S_NAr-type reactions, elevated temperatures are usually required to achieve an acceptable level of conversion and the reaction only works on electron-poor arenes or heterocycles.[119] With respect to reductive alkylation, the choice of reducing agent is critical to the success of the reaction.[120] Copper-mediated methods including Ullmann-type reaction[121] and reaction of arylboronic acids with amines (Chan-Lam amination)[122,123] serve as an alternative to these traditional methods. The major limitation with Ullmann coupling is the need for stoichiometric amounts of copper and high temperatures are often required.[121] While catalytic amounts of copper are required in Chan-Lam amination, the formation of side products such as reduced product, diaryl ether, and phenols is the main drawback of this method.[122] Recently, palladium-catalyzed amination of aryl-(pseudo)halides with primary alkyl amines has emerged as a general methodology for the preparation such moieties. The main challenge in this transformation is to produce the secondary aniline selectively and avoid the formation of tertiary aniline product resulting from diarylation of the primary alkyl amine. Although several catalyst systems reported for this transformation have proven to be remarkably successful, no single

universal catalyst system exists that can selectively couple a wide selection of aryl halides as well as six- and five-membered heteroaryl halides with simple or functionalized primary amines.

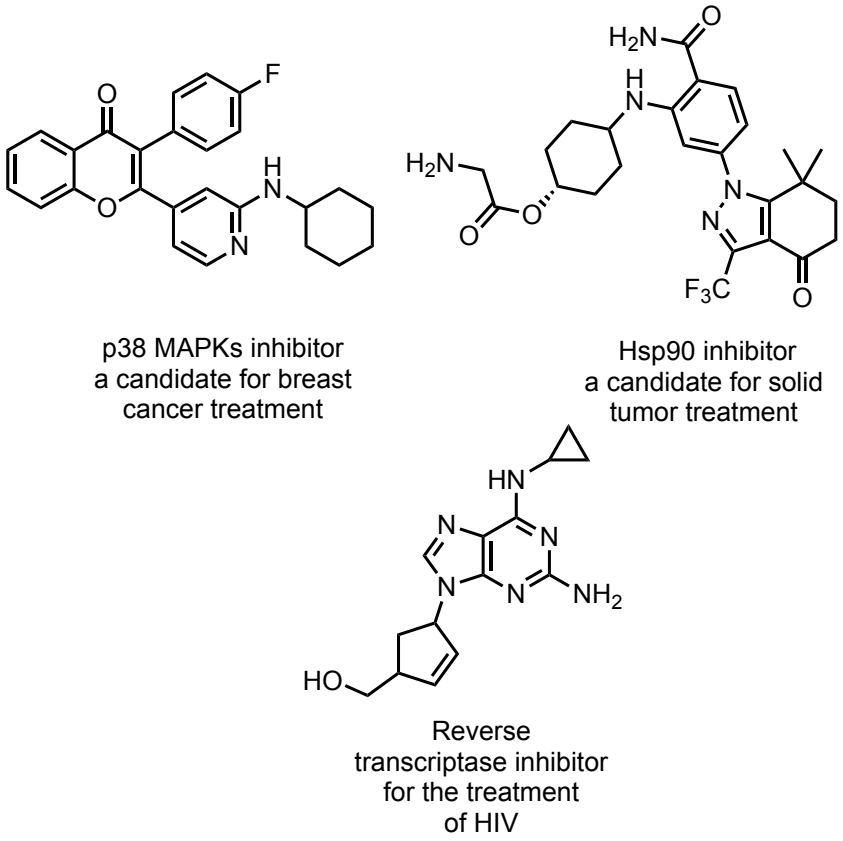


Figure 16. Useful compounds containing secondary aromatic amines motif.[116–118]

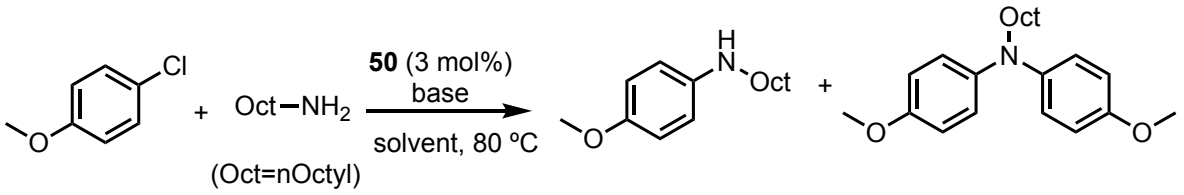
This chapter of the thesis describes the significant improvements made by *Pd-PEPPSI-IPent*^{Cl} (**50**) in selective monoarylation of primary alkyl amines.

2.2. **Investigating the reactivity of *Pd-PEPPSI-IPent*^{Cl}**

Given the superior reactivity of *Pd-PEPPSI-IPent*^{Cl} (**50)** in challenging BHA with deactivated anilines[91] we opted to evaluate the reactivity of **50** in the cross-coupling of aryl halides and primary alkyl amines. To this end, the cross-coupling of 4-chloroanisole (**73**) with octylamine (**74**) using Cs_2CO_3 as the base was chosen as the model reaction. This particular aryl chloride was selected because electron-rich aryl halides are known to undergo OA slowly and also lead to a more difficult

RE step. Further, the resulting cross-coupled product (**75**) is sufficiently electron rich to enter another cycle to generate the diarylamine product (**76**). Therefore, this particular OA partner is a 'worst case scenario' for conversion to the desired monoaryl amine product in high yield and selectivity, so the method developed around it should be applicable to a wide range of aryl halides. The initial experiment was conducted at 80 °C with 3 mol% of **50** in DME as solvent (Table 1, Entry 1), based upon conditions developed in our group for the successful arylation of secondary amines.[91] The reaction proceeded to completion, however with low selectivity for the desired mono-coupled product. Decreasing the concentration of the OA partner from 0.5 M to 0.25 M resulted in a slight increase in selectivity for the monoarylated product (Entry 2). The use of other inorganic bases such as $K_3PO_4 \cdot H_2O$ resulted in incomplete consumption of the aryl halide as well as diminished selectivity (Entry 3). With Li*O*^{i}Pr as the base, the reaction went to 25% completion with a moderate 5:1 ratio of **75** to **76** (Entry 4). Switching to K*O*^{t}Bu, enabled the reaction to proceed to 89% conversion with no significant improvement in selectivity (Entry 5). However, with 1.3 equivalents of Na*O*^{t}Bu, which has been used extensively by others is BHA reactions,[7] the reaction reached 100% conversion with much improved selectivity for the mono-arylated product (Entry 6). Finally, decreasing the concentration of the OA partner from 0.5 M to 0.1 M, had no deleterious impact on the reaction (Entry 7).

Table 1. Evaluation of *Pd-PEPPSI-IPent*^{Cl} (**50**) in selective monoarylation of octyl amine [a]



73 (1.0 equiv.) **74** (1.3 equiv.) **75** **76**

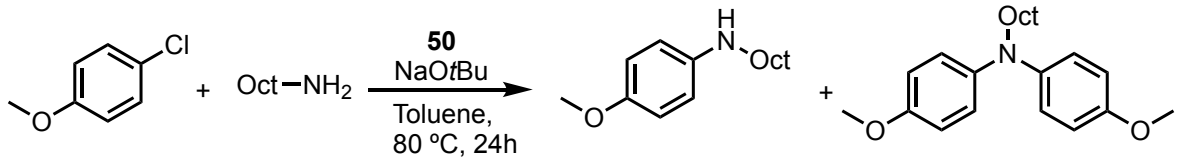
Entry	Base (equiv.)	solvent	**75**/**76**[b,c]	% Conv. of **73**[c]	%Yield (**75**)[d]
1	Cs_2CO_3 (3.0)	DME	3.3:1	100	71
2[e]	Cs_2CO_3 (3.0)	DME	5.3:1	100	77
3	K_3PO_4 (3.0)	DME	2.9:1	96	78
4	LiO*i*Pr (1.3)	Toluene	5:1	25	12
5	KO*t*Bu (1.3)	Toluene	3:1	89	34
6	NaO*t*Bu (1.3)	Toluene	15.9:1	100	68
7[f,g]	NaO*t*Bu (1.3)	Toluene	15.9:1	100	68

[a] Reactions were conducted on a 0.5 mmol scale where concentration of [**73**] = 0.5 M; [b] **75**/**76** is the ratio of the desired monoarylation to the undesired diarylation. [c] Determined using ^{1}H NMR spectral analysis of the crude reaction mixture. [d] Isolated yields are reported on products purified by flash chromatography and are averaged over two runs. [e] Reaction was conducted at a concentration of 0.25 M. [f] Reaction was conducted at a concentration of 0.1 M. [g] 1.1 equiv. of **74** was used.

Having identified NaO*t*Bu as the optimal base, attention was then focused on further optimizing the reaction conditions with the aim of improving the selectivity for the mono-arylated product (Table 2). In the first attempt, reducing the amount of base from 1.3 to 1.1 equivalents resulted in marginally improved selectivity (Entries 1-2). Next, decreasing the catalyst loading from 3 to 2 mol% while keeping the amount of the base the same also saw a slight improvement in selectivity (Entry 3). Further decreasing the catalyst loading resulted in a significant improvement in selectivity, with 0.5 mol% providing the best selectivity (Entries 4 and 5). Lastly, decreasing the

reaction temperature to 60 °C had no impact on the reaction (Entry 6). Of note, when using NaO*t*Bu as the base, prolonged heating is not required and in most cases, the reaction reaches completion within 2h.

Table 2. Effect of pre-catalyst loading on selectivity[a]



73 (1.0 equiv.) **74** (1.1 equiv.) **75** **76**

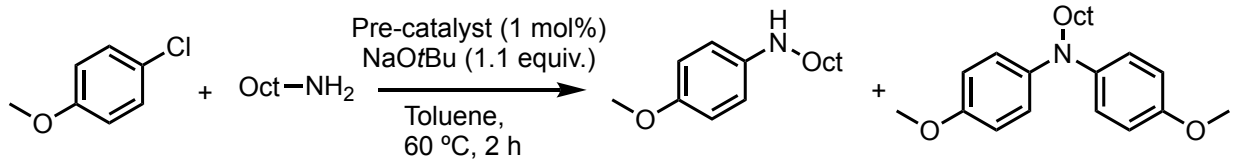
Entry	NaO*t*Bu (equiv.)	**50** (mol%)	**75**/**76**[b,c]	% Conv. of **73**[c]	%Yield (**75**)[d]
1	(1.3)	3	15.9:1	100	68
2	(1.1)	3	18.3:1	100	90
3	(1.1)	2	20.1:1	100	93
4	(1.1)	1	28:1	100	93
5	(1.1)	0.5	40:1	100	92
6[e]	(1.1)	0.5	43:1	100	90

[a] Reactions were conducted on a 0.5 mmol scale where concentration of [**73**] = 0.5 M. [b] **75**/**76** is the ratio of the desired monoarylation to the undesired diarylation. [c] Determined using ^{1}H NMR spectral analysis of the crude reaction mixture. [d] Isolated yields are reported on products purified by flash chromatography and are averaged over two runs. [e] Reaction was conducted at 60 °C.

The last thing to probe was the impact of the steric bulk of the NHC ligand on selectivity. To this end, a series of experiments were conducted with *Pd-PEPPSI-IPent* (**48**) and *Pd-PEPPSI-IHept* (**49**) and their chlorinated analogues *Pd-PEPPSI-IPent*^{Cl} (**50**) and *Pd-PEPPSI-IHept*^{Cl} (**51**) (Table 3). The impact of the alkyl chain size on selectivity is evident when comparing those results obtained from **48** and **49**. With **48** the reaction proceeded with moderate selectivity, which

improved only slightly with **49** (Entries 1 and 3). Conversely, the chlorinated analogues were shown to be much more selective than their non-chlorinated counterparts (compare entries 1 vs. 2 and 3 vs. 4).

Table 3. Effect of steric bulk of pre-catalyst on selectivity [a]



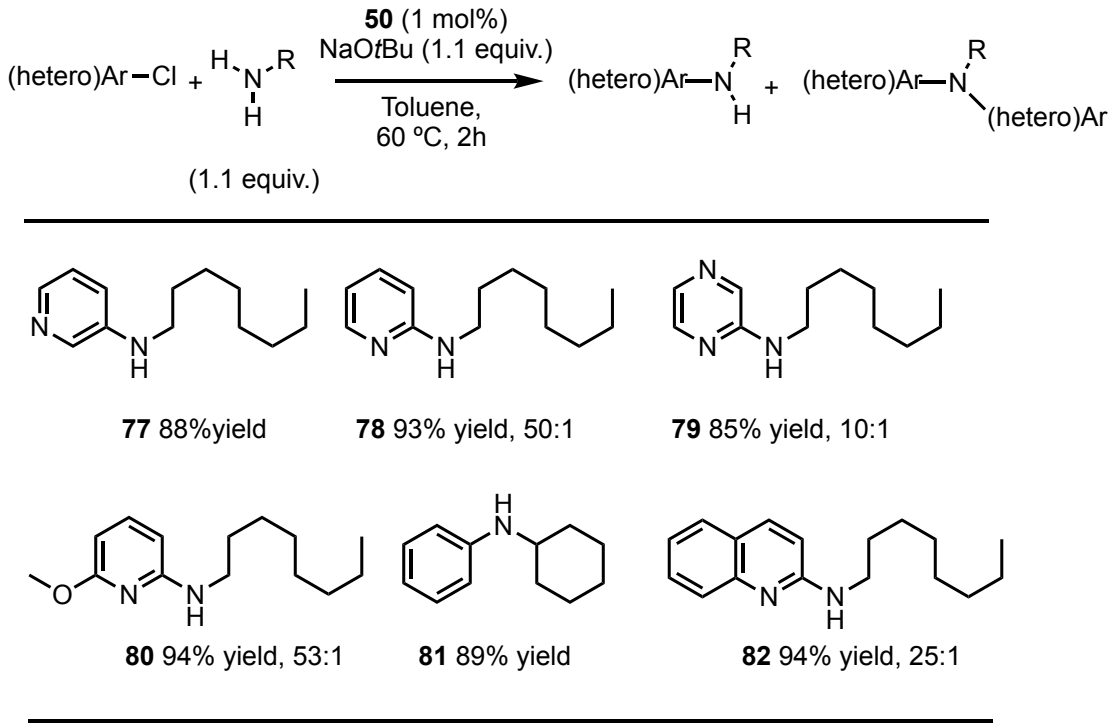
73 (1.0 equiv.) **74** (1.1 equiv.) **75** **76**

Entry	Pre-catalyst	**75**/**76**[b,c]	% Conv. of **73**[c]	%Yield (**75**)[d]
1	*Pd-PEPPSI-IPent* (**48**)	8:1	75	72
2	*Pd-PEPPSI-IPent*^{Cl} (**50**)	28:1	100	93
3	*Pd-PEPPSI-IHept* (**49**)	10:1	100	77
4	*Pd-PEPPSI-IHept*^{Cl} (**51**)	19:1	100	88

[a] Reactions were conducted on a 0.5 mmol scale at where concentration of [**73**] = 0.5 M. [b] **75**/**76** is the ratio of the desired monoarylation to the undesired diarylation. [c] Determined using ^{1}H NMR spectral analysis of the crude reaction mixture. [d] Isolated yields are reported on products purified by flash chromatography and are averaged over two runs.

With the optimization complete, the reactivity and selectivity of **50** was evaluated in the mono-arylation of primary alkyl amines with various aryl and heteroaryl halides (Table 4). In all cases, the reactions proceeded smoothly under the optimized conditions to yield the desired monoarylated product in very high yield and excellent selectivity. It is worth noting that all reactions went to completion within 2-4 h.

Table 4. Substrate scope of aryl aminations catalyzed by *Pd-PEPPSI-IPent*^{Cl} (**50**)[a]



[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel and are averaged over two runs.

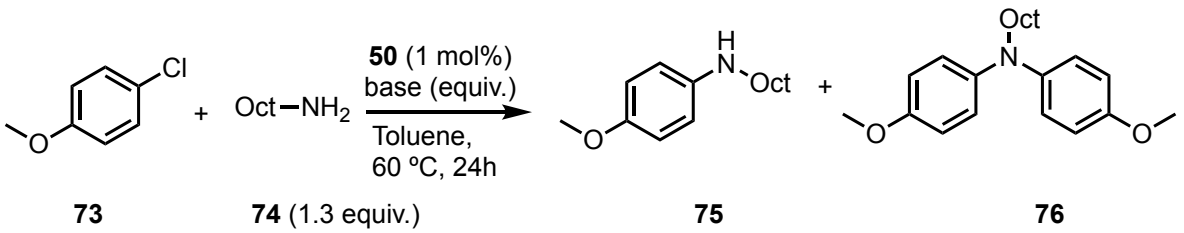
2.3. **Phenolate derivatives as a milder alternative to *tert*-butoxide**

While the vast majority of C-N cross-coupling methods in the literature utilize aggressive bases such as *tert*-butoxide, there is a strong desire to move away from them. This is mainly because such bases are incompatible with functional groups such as carbonyl groups, nitriles, amides, alcohols and amines that are prevalent in the core structure many desirable target molecules (e.g., drug candidates and novel materials). Accordingly, we opted to find a milder alternative to *tert*-butoxide in this reaction in order to improve the functional group compatibility of the developed method. In 2007, Tweedie and co-workers reported a general method for Pd-catalyzed cross-coupling of heteroaryl amines and aryl halides utilizing sodium phenolate NaOPh as the base.[124] The scope and functional group compatibility of soluble NaOPh was well demonstrated in this

report and coupling partners bearing base-sensitive functionality such as nitrile, nitro, and ester moieties were successfully coupled. In 2012, Organ's group disclosed a rational design of a base that is useful in Pd-catalyzed amination reactions.[125] The base, potassium 2,2,5,7,8-pentamethyl-6-chromanoxide (**83**), was demonstrated to be basic enough (pK_a of corresponding phenol ca.11.4) to deprotonate the corresponding aryl palladium ammonium complexes in the catalytic cycle, yet was mild enough to not destroy the base-sensitive functional groups. Moreover, in 2013, Erdélyi and co-workers reported a procedure for Buchwald–Hartwig aryl amination of protected azamacrocycles in which sodium 2,4,6-tri-*tert*-butyl-phenolate was employed as the base. This bulky phenolate base with its diminished nucleophilicity was shown to be compatible with the base sensitive functional groups.[126] Intrigued by these studies, we opted to evaluate the reactivity of phenolate bases in the model reaction using pre-catalyst **50** (Table 5). With **83**, the reaction reached full conversion, albeit with very poor selectivity for the desired product (Entry 1). Disappointed by this result, attention was focused on using 2,6-di-*tert*-butyl-4-methylphenolate as the base. Under otherwise similar reaction conditions, with KBHT (**84**) as the base, the reaction proceeded to completion to furnish the desired product with an enhanced selectivity of 7.4:1 (Entry 2). Increasing the amount of base to 1.25 equivalents doubled the selectivity (Entry 3). Finally, increasing the base amount to 1.5 equivalents gave a selectivity of 20:1 for the desired monoarylated product (Entry 4). To determine whether the counter ion of the base has any impact upon selectivity, the sodium salt of BHT was prepared. Under similar reaction conditions to entry 2, NaBHT (**85**) a notable improvements in selectivity and yield of the desired product was observed (Entry 5). Similar to **84**, increasing the amount of **85** also resulted in a jump in selectivity (Entry 6). Of note, in all instances, the phenolate base was prepared, isolated and stored in a glove box prior to the cross-coupling reaction. In the last attempt (Entry 7), when the base was prepared *in*

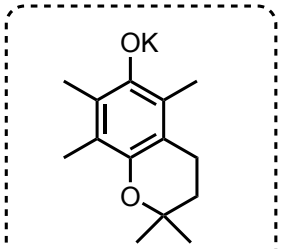
situ, rather than using that stored in the glove box, a significant increase in isolated yield of product **73** to 95% was recorded.

Table 5. Optimization study- phenolate bases screening[a]

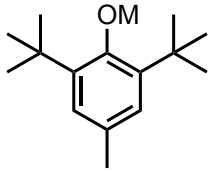


73 **74** (1.3 equiv.) **75** **76**

Entry	Base (equiv.)	**75**/**76**[b,c]	% Conv. of **73**[c]	%Yield (**75**)[d]
1	**83** (1.1)	1.7:1	100	32
2	**84** (1.1)	7.4:1	100	63
3	**84** (1.25)	15.4:1	100	66
4	**84** (1.5)	20:1	100	69
5	**85** (1.25)	25:1	100	81
6	**85** (1.5)	28.6:1	100	83
7[e]	**85** (1.5)	25:1	100	95



K-Chromanoxide **83**



M= K, KBHT **84**
M= Na, NaBHT **85**

[a] Reactions were conducted on a 0.5 mmol scale at a concentration of 0.1 M; [b] **75**/**76** is the ratio of the desired monoarylation to the undesired diarylation. [c] Determined using a using ^{1}H NMR spectral analysis of the crude reaction mixture. [d] Isolated yields are reported on products purified by flash chromatography and are averaged over two runs. [e] Using phenolate salt prepared *in situ*.

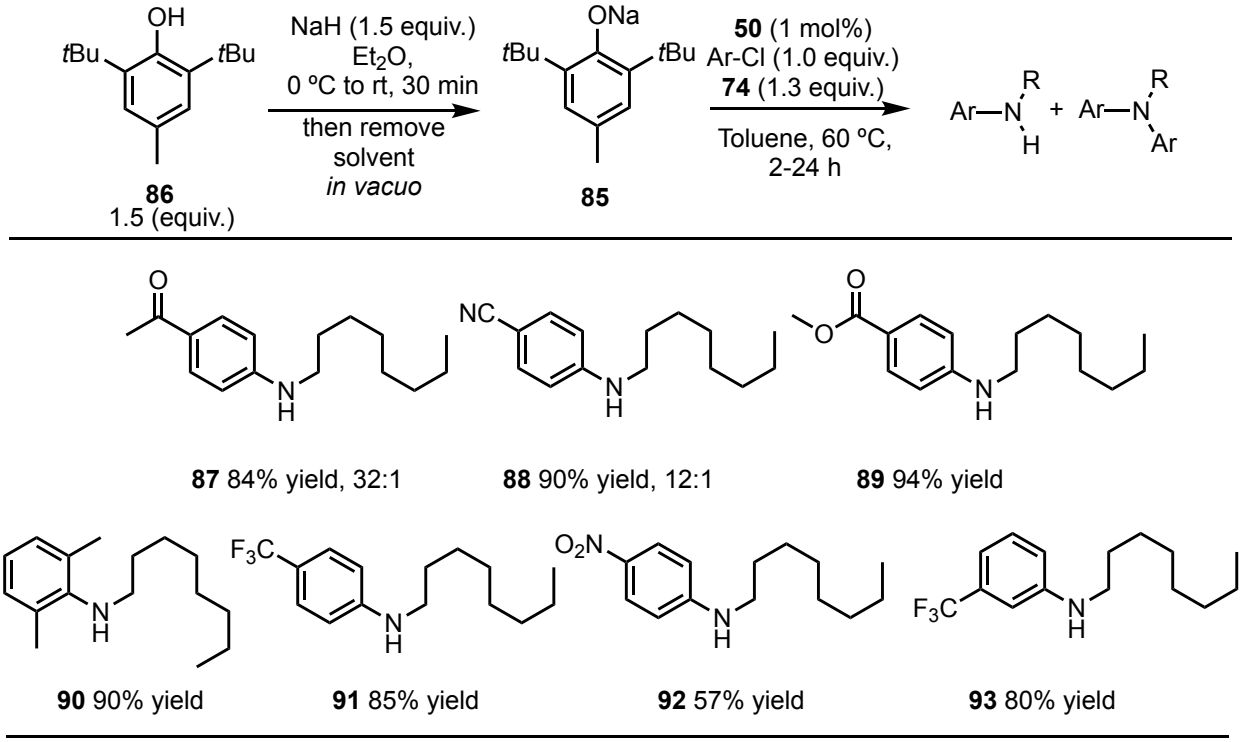
While phenoxide derivates are capable of undergoing coupling with aryl halides to generate the ether product,[127,128] we were pleased to note that the potential etherification product was not observed to any appreciable extent. BHT not only has a similar pK_a as the acids of carbonate and phosphate bases but, more importantly, it is much more soluble in organic solvents. In case of inorganic bases such as carbonate with their limited solubility in organic solvents, it has been

repeatedly shown that particle size, hence surface area of the base, is critical to the success of amination reactions.[7] With soluble phenoxides, problems associated with particle size could be circumvented. Despite these advantages, a quick survey in literature reveals that there are only a few reports where phenoxide bases are employed as basic additives in palladium-catalyzed C-N bond forming reactions.

2.4. **Substrate scope study of primary alkyl amine coupling**

With NaBHT proving to be a highly efficient base, a robust method was established for the cross-coupling of (hetero)aryl halides with primary alkyl amines. Using the final conditions outlined at the top of Table 6, a wide selection of interesting aryl chlorides possessing keto (**87**), cyano (**88**), carbomethoxy (**89**), di-*ortho* methyl substituted (**90**), trifluoromethyl (**91** and **93**) and 4-nitro (**92**) groups were successfully coupled with octylamine in very high yields and selectivity for the mono-aryl product, further demonstrating that this procedure is highly mono-selective and broadly functional-group tolerant. In those cases where traces of di-aryl products were formed, purification and isolation of the desired mono-aryl product were achieved by column chromatography on silica gel.

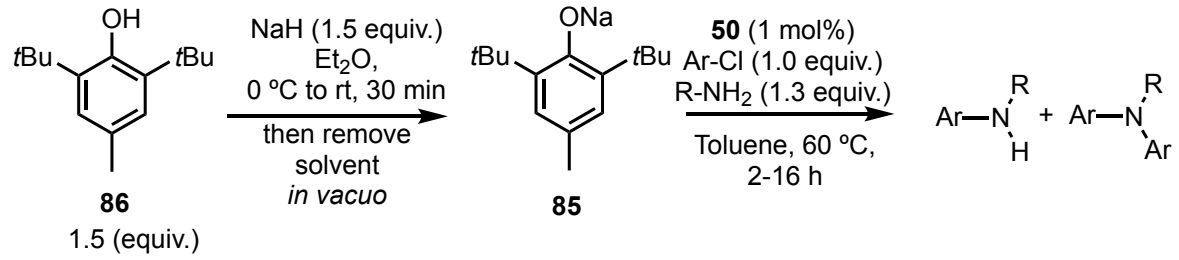
Table 6. Selective amination of aryl chlorides by **74** to give secondary aniline products[a]



[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel and are averaged over two runs.

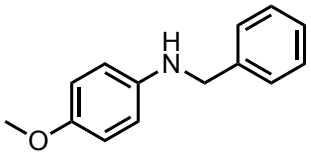
With these promising results in hand, the scope of nucleophilic partner was then investigated, with the aim of incorporating more elaborate amines. Under standard reaction conditions, benzylic, phenethyl, 2-furylmethyl, and 2-thiophenethyl derivatives were all competent nucleophiles and could be coupled with activated and deactivated *ortho*-, *meta*-, and *para*-substituted electrophiles (Table 7, products **94**-**101**). In all instances, exclusive or excellent selectivity for the desired mono-aryl product was obtained.

Table 7. Coupling of functionalized primary alkyl amines with simple aryl halides using **50** [a]

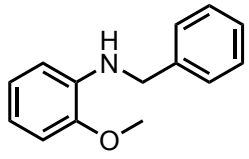


86
1.5 (equiv.)

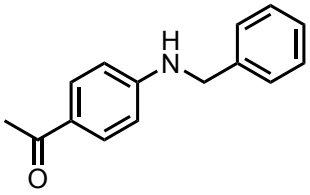
85



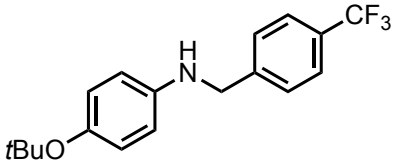
94 85% yield



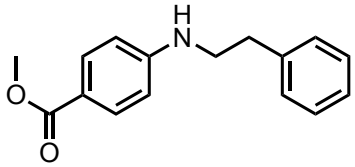
95 95% yield



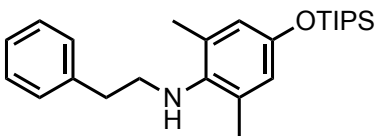
96 86% yield, 22:1



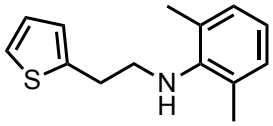
97 70% yield, 20:1



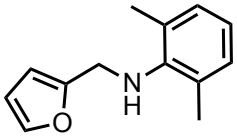
98 88% yield



99 85% yield



100 90% yield



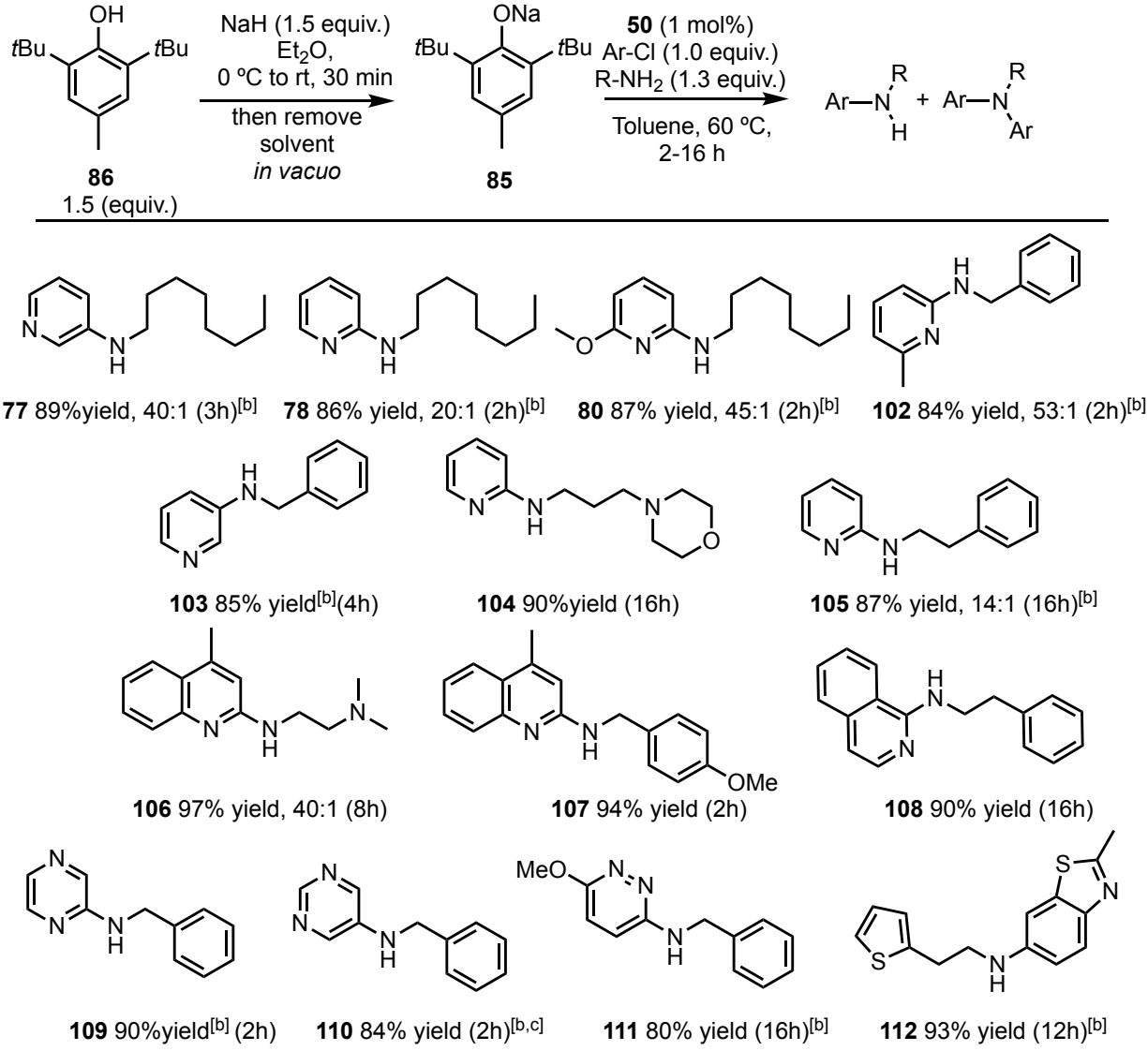
101 71% yield

[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel are averaged over two runs.

The scope and functional group compatibility of these conditions allowed for the effective coupling of six-membered heterocyclic chlorides, including 2- and 3-chloropyridines (**77**, **78**, **80**, **102**-**105**, Table 8), 2-chloro-4-methylquinoline (**106** and **107**), and 1-chloroisoquinoline (**108**) with both simple and functionalized primary aliphatic amines. Using a simple extractive workup, products possessing tertiary alkyl amine functionality (**104** and **106**) were successfully isolated in high purity. Further, under this single set of conditions, OA partners possessing multiple

heteroatoms such as 2-chloropyrazine (**109**), 5-bromopyrimidine (**110**), as well as pyridazine (**111**) and benzothiazole (**112**) were also successfully coupled to generate the desired mono-arylated product in very good yield.

Table 8. Coupling of primary alkyl amines with six-membered heteroaryl halides using **50** [a]

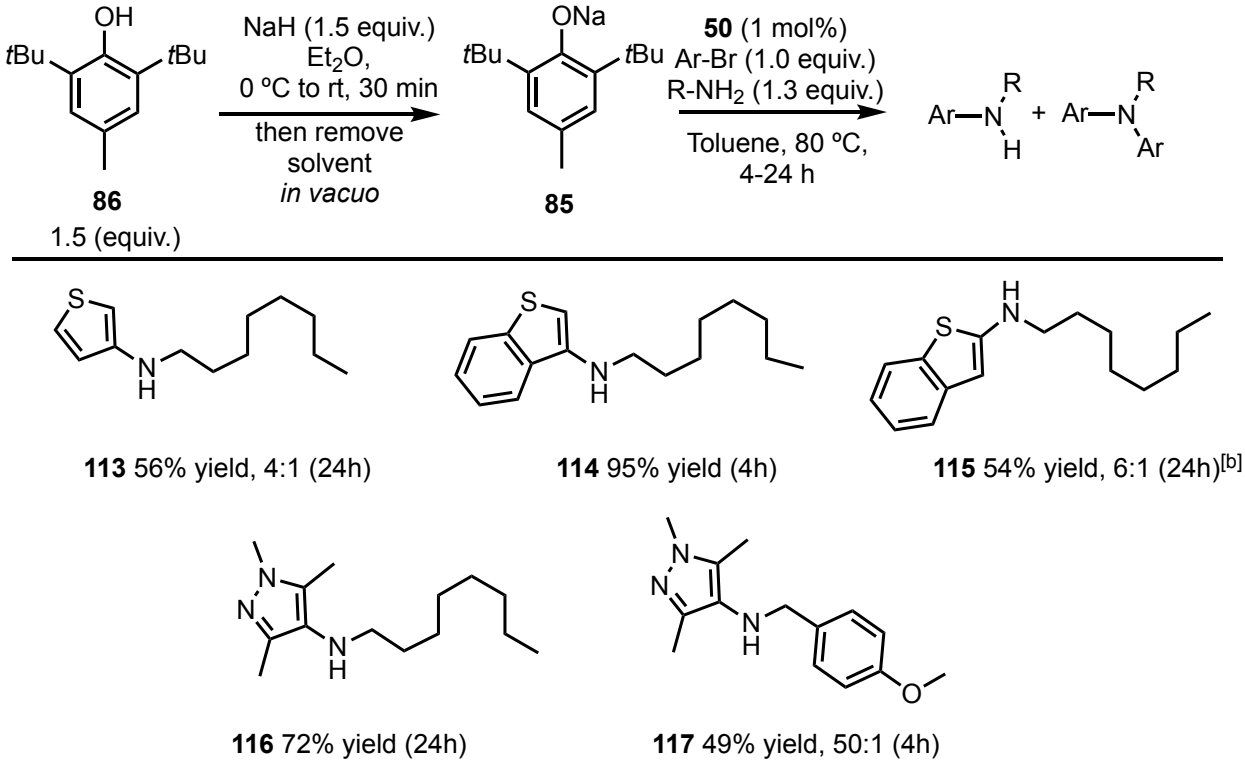


[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel are averaged over two runs. [b] 50 °C. [c] Using Ar-Br.

With pre-catalyst **50** exhibiting excellent reactivity and selectivity with six-membered heteroaryl halides, attention was turned to five-membered heteroaryl halide substrates as these substrates have

been repeatedly shown to be more challenging coupling partners.[129,130]As shown in Table 9, by simply increasing the temperature to 80 °C, five-membered heteroaryl halides including 3-bromothiophene (**113**), 3-bromobenzothiophene (**114**), 2-bromobenzothiophene (**115**), and 4-bromo-1,3,5-trimethyl-1H-pyrazole (**116** and **117**) were found to couple smoothly to primary alkyl amines with excellent mono-selectivity.

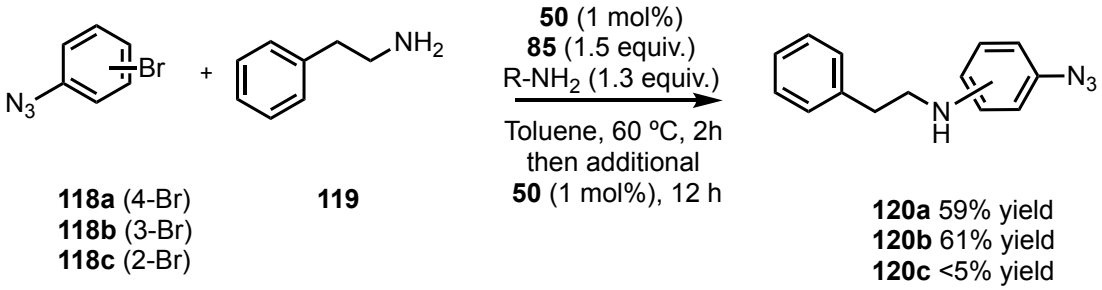
Table 9. Coupling of primary alkyl amines with five-membered heteroaryl bromides using **50** [a]



[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel are averaged over two runs. [b] Using 3 mol% of **50**.

Given the success of the developed protocol which results from the combination of the highly reactive and selective pre-catalyst **50** with soluble and nonaggressive NaBHT base **85**, we wondered if it would be possible to use halo-(azido)benzene electrophiles in this amination reaction. To the best of our knowledge, there is no report in the literature on utilizing such

electrophiles in any palladium- or nickel-catalyzed amination reactions. In approaching this challenge, *ortho*, *para* and *meta*-azidobromobenzene derivatives were prepared and reacted with amine **119** under the conditions outlined in Scheme 15. Both *para* and *meta*-substituted halo-(azido)benzene underwent coupling to furnish the desired mono-aryl products **120a** and **120b** in very good yield. In these reactions, the desired mono-aryl product was formed exclusively and no sign of over arylation was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. However, for *ortho*-substituted compound very poor conversion, and low yield of product was observed.

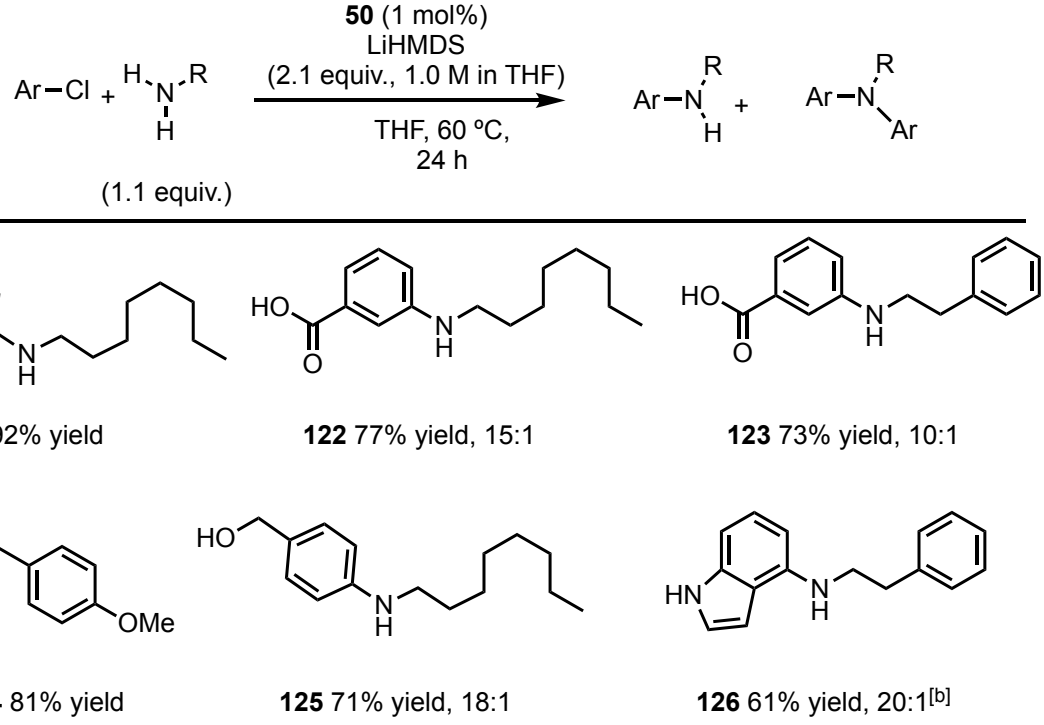


Scheme 15. Selective monoarylation of primary amines with azide- containing oxidative addition partners.

The last remaining electrophiles to be examined in this selective amination study were those bearing acidic functional groups. 3-Chlorobenzoic acid was reacted with **119** under the general reaction conditions using 2.2 equivalents of NaBHT (**85**), but no product was formed (**123**) and only starting materials were recovered. This might not be surprising, as the first equivalents of the base would remove the most acidic proton of the functional group and the resultant anion could bind to the palladium and remove it from the catalytic cycle. In approaching this problem, Buchwald's group disclosed a protocol for coupling of amines with aryl halides containing hydroxyl, amide, or enolizable keto groups in which LiHMDS (2 equivalents) was used as base.[131] In that report, the authors proposed that following deprotonation of the acidic functionality of the

substrate, the corresponding lithium-derived aggregate could act as a protecting group and prevent the coordination of the anion to the palladium center.[131,132] Intrigued by this study, cross-coupling of primary alkyl amines with electrophiles bearing acidic functionality was attempted using 1 mol% of **50** and 2.1 equivalent of LiHMDS (Table 10). To our delight, the reaction of benzoic acid and cyclopropanecarboxylic acid derivatives with primary alkyl amines reached full conversion and generated the desired mono arylated amine in very high yield and excellent selectivity (**121**-**123**). Phenol and benzylic-alcohol-containing electrophiles were also investigated and in both cases full conversion along with excellent selectivity was obtained (**124**, **125**). Lastly, free, unprotected indole was found to be a competent electrophile and coupled readily with **119** to afford the desired monoarylated product in high yield (**126**).

Table 10. Amination of electrophiles bearing acidic functional groups using *Pd-PEPPSI-IPent*^{Cl} (**50**) in conjunction with LiHMDS[a]



[a] Unless otherwise indicated, only the monoaryl product was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields are those of the products isolated after purification by column chromatography on silica gel are averaged over two runs. [b] The corresponding Ar-Br was used.

2.5. **Conclusion**

In conclusion, a robust protocol for the selective monoarylation of primary aliphatic amines was developed in which sterically bulky *Pd-PEPPSI-IPent*^{Cl} (**50**) was shown to be extremely reactive and selective in this transformation. The high level of selectivity that was exhibited by **50** is assured by the use of the mild, soluble and sterically demanding sodium salt of butylated hydroxytoluene (NaBHT; **85**). The functional group compatibility of the developed conditions facilitates the coupling of aryl halides bearing base sensitive functional groups such as ketones, esters, nitro and nitrile derivatives. In all instances, excellent selectivity along with very high yield for the desired mono-arylated compound was observed. Using pre-catalyst **50** in combination with NaBHT, allowed for the cross-coupling of a wide variety of five and six-membered electrophiles with primary aliphatic amines, leading to the formation of the desired mono-coupled heteroaromatic amines in good yield. Lastly, by switching the base to LiHMDS, oxidative addition partners bearing acidic functional groups were coupled to primary alkyl amines with ease to furnish the desired mono-coupled product with remarkable selectivity.

Chapter 3- *N*-(Hetero)arylation of α-Amino Esters Using *Pd-PEPPSI-IPent^{Cl}-o-picoline*

3.1. **Background**

Many biologically and pharmaceutically active molecules have an aromatic amine bearing stereocenter α to the nitrogen embedded in their structure (Figure 17).[133–136] Since the properties of different stereoisomers can differ remarkably,[137] much attention has been focused on the development of enantioselective methods for the preparation of intermediates used to synthesis such targets.

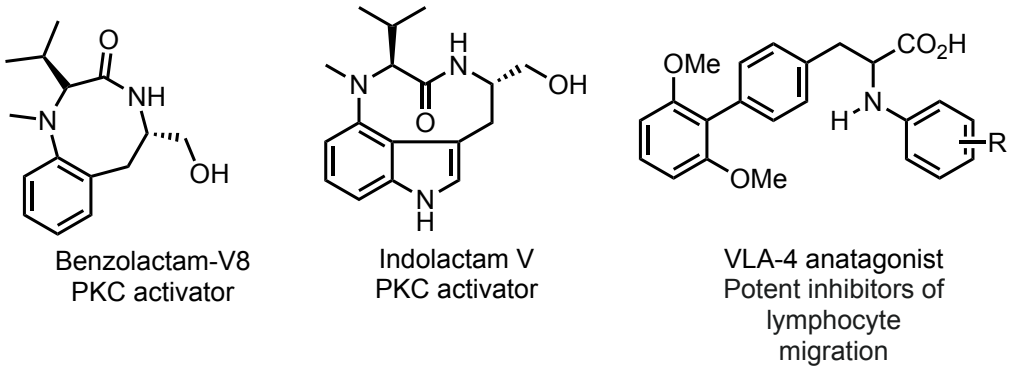


Figure 17. Useful compounds containing an *N*-aryl amino acid core[134–136]

Most typically these compounds are prepared via nucleophilic aromatic substitution (S_NAr), however, the substrate scope is limited to activated aryl halides and elevated temperatures (usually> 100 °C) are often required.[138,139] Transition metal-catalyzed amination of (hetero)aryl halides has emerged as a more mild and general protocol for the preparation of aromatic amines. Many of the existing catalytic processes for the preparation of enantioenriched *N*-arylated α-amino acids(esters) are based on copper-catalyzed Ullmann-type reaction. That said, the scope of OA partners is limited to aryl bromides and iodides, and the use of heteroaryl halides or aryl chlorides has been not reported to date. Additionally, high temperature (usually >80° C) and prolonged

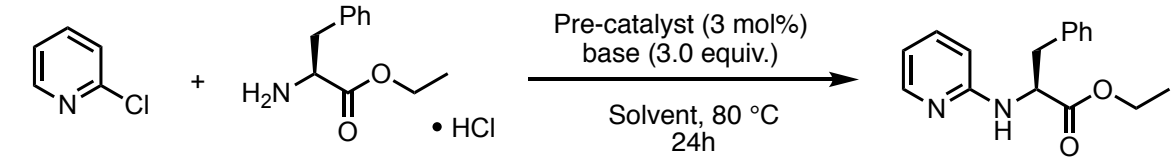
reaction times are usually required.[140–143] Although the advent of Pd-catalyzed amination reactions has obviated the substrate scope limitation associated with the copper-catalyzed reactions, only a few Pd-catalyzed methods have been developed for the coupling of optically pure α-amino esters. This chapter is focused on the development of an efficient protocol for *N*-(heteroarylation) of optically pure α-amino acids(esters) using *Pd-PEPPSI* complexes.

3.2. **Investigating the reactivity of *Pd-PEPPSI* complexes in *N*-heteroarylation of α-amino esters**

In light of the superior reactivity and selectivity of *Pd-PEPPSI-IPent*^{Cl} (**50**) in the selective monoarylation of primary amines, attention was then focused on using this bulky NHC pre-catalyst in the selective coupling of (hetero)aryl halides with optically pure α-amino esters.[144] We postulated that the use of bulky NHC catalysts such as **50**, would improve the stereochemical integrity of the product by increasing the rate of RE relative to BHE, assuming that this was the cause of racemization. The coupling of 2-chloropyridine (**127**) with L-phenyl alanine ethyl ester hydrochloride (**128**) was first explored, using the protocol developed for monoarylation of primary amines (Table 11). It was envisioned that the use of a mild, sterically hindered base such as NaBHT (**85**)[145] would suppress the base-mediated racemization pathway. However, the desired product was only formed in 15% yield with significant erosion of optical purity (Entry 1). It should be noted that in this study % ee reflects the retention of optical purity of the product. The use of less sterically encumbered phenolate bases such as the sodium 2,4-dimethyl phenolate and sodium phenolate did not significantly improve the yield nor the % ee of the product (Entries 2 and 3). In 2005, Hartwig and co-workers reported that, zinc trimethylsilylamide $Zn(HMDS)_2$ in the presence of LiCl, could serve as a mild and functional group tolerant base in Pd-catalyzed amination of aryl

halides and triflates.[146] During the course of this study, Hartwig found that similar to K_3PO_4, $Zn(HMDS)_2$ is also a non-racemizing base. Of note, ZnHMDS can be easily prepared *in situ* by combining $ZnCl_2$ with LiHMDS. Unfortunately, when ZnHMDS was used as the base in the model reaction, conversion to the desired product was very low and resulted in the recovery of starting material (Entry 4).

Table 11. Influence of basic additives and pre-catalysts on the enantio-retention and conversion of **127** and **128** into **129**[a]



127 (1.0 equiv.) **128**(1.3 equiv.) **129**

Entry	Base	solvent	Pre-catalyst	Conv. of **127** [%][b]	Yield [%],[c] (ee [%])[d]
1	NaBHT	toluene	**50**	20	15 (0)
2	Na-2,4-dimethyl phenolate	toluene	**50**	45	38 (10)
3	Na-phenolate	toluene	**50**	48	39 (13)
4	$Zn(HMDS)_2$	DME	**50**	10	-
5	K_3PO_4	DME	**50**	28	21 (54)
6	Cs_2CO_3	DME	**50**	100	73 (58)
7[e]	Cs_2CO_3	DME	**52**	100	83 (76)
8[f]	Cs_2CO_3	DME	**52**	100	81 (76)

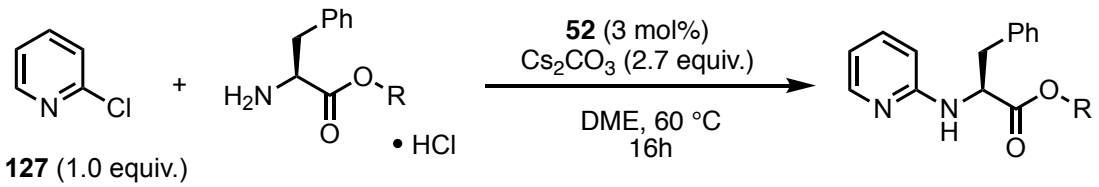
[a] Reactions were conducted on a 0.25 mmol scale at a concentration of 0.5 M [b] Percent conversion of **127** to **129** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel. [d] The percent ee of **129** was determined by chiral HPLC analysis. For a full description of the method, see the Experimental. [e] Reaction was carried out at 60 °C. [f] Concentration of **127**=0.125M.

In the case of K_3PO_4, the coupled product was obtained in 21% yield with 54 ee% (Entry 5). Disappointed by these results, attention was focused on using other inorganic bases such as cesium carbonate which had been extensively used in *Pd-PEPPSI* catalyzed BHA.[37,91] Full conversion of aryl halides was recorded at 80 °C, but with a poor enantiomeric excess (Entry 6). This poor observed enantio-retention could be attributed in some way to the high temperature of the reaction. To test this assumption, the reaction needed to be carried out at lower temperatures. To this end, *PEPPSI-IPent^{Cl}-o-Picoline* (**52**) was employed as the pre-catalyst as it had been previously reported by Organ's group to be highly effective in room temperature coupling of poorly reactive electron-rich aryl halides with electronically deactivated anilines using a mild carbonate base.[91] With **52** the coupling could be carried out at a lower temperature (60 °C instead of 80 °C) and the cross-coupled product was obtained in 83% yield with a better enantio-retention (76% ee) (Entry 6). Under the similar reaction conditions to entry 6, this time at a lower concentration of the aryl halide (e.g., 0.125 M), the stereochemical retention of the coupled product did not improve (Entry 7).

While trying to understand the origin of the observed racemization, a correlation was found between the steric bulk of the ester moiety of amino ester and the enantio-retention of the cross-coupled product where an increase in the size of the ester moiety, resulted in higher enantio-retention of the product (Table 12). For instance, when L-phenyl alanine methyl ester hydrochloride was used instead of ethyl ester analog, the % ee of the cross-coupled product decreased from 75% to 58% (Entry 2 vs. 1). When the ester bulk was further increased to *tert*-butyl, the desired product was obtained in very high yield with complete sterioretention (98% ee) (Entry 3). Furthermore, it was found that with the free base amino ester, the reaction could be carried out with 1.5 equivalents of the Cs_2CO_3 to furnish the product in high yield while still

retaining the stereocenter (>99% ee) (Entry 4). Of note, *tert*-butyl esters of the amino acids have significant advantages over their ethyl and the methyl congeners. For example, the free-base *tert*-butyl esters of amino acids have longer shelf lives and as a carboxylic acid protecting group *tert*-butyl can be more readily cleaved off under mild conditions.[147]

Table 12. Influence of sterics of the ester moiety of the amino ester on %enantio-retention[a]



Entry	R	Conv. of **127** [%][b]	Product	Yield [%][d]	ee [%][c]
1	Me (**130**)	100	**132**	83	53
2	Et (**128**)	100	**129**	93	76
3	*t*Bu (**131**)	100	**133**	95	98
4[d,e]	*t*Bu (**131**)	100	**133**	95	>99

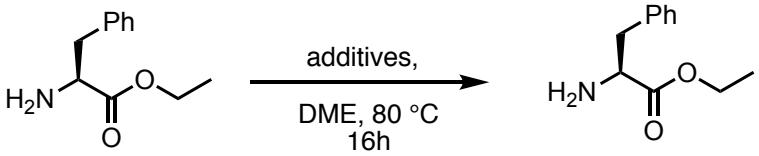
[a] Reactions were conducted on a 0.25 mmol scale at a concentration of 0.5 M [b] Percent conversion of **127** to product was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel. [d] The percent ee of product was determined by chiral HPLC analysis. For a full description of the method, see the Experimental. [d] free base amino ester was used. [e] 1.5 equiv. of Cs_2CO_3 was used.

3.3. **Investigating the source of racemization in *N*-heteroarylation of α-amino esters**

A number of control experiments were designed to understand the racemization process. In the initial experiment when optically enriched (>99% ee) **128** was subjected to the optimized reaction conditions (e.g., (3 mol% catalyst, Cs_2CO_3 (3.0 equiv.), 80 °C), the chiral integrity of the amino ester remained high (Table 13, Entry 1). A similar result was obtained when **128** was treated under similar reaction conditions, this time in the absence of the base (Entry 2). Lastly, when **128**, was

treated only with base (e.g., Cs_2CO_3 (3.0 equiv.)), the enantio-purity of the amino ester did not erode (Entry 3). These results demonstrate that under the optimized conditions the primary amino ester remains intact and does not undergo racemization.

Table 13. Investigating the source of racemization- starting primary amino ester [a]



128 **128**

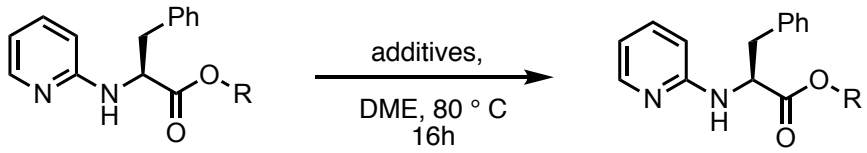
Entry	Initial ee [%]	additives	Final ee [%]
1	>99	**52** (3 mol%), Cs_2CO_3 (3.0 equiv.)	>99
2	>99	-	>99
3	>99	**52** (3 mol%)	>99

[a] Initial and final percentage ee of the substrate were determined by chiral HPLC analysis. For a full description of the method, see the Experimental.

Having identified that racemization does not occurs with the starting primary amino ester, attention was then focused to product. Similar control experiments were carried out with **129** and the results are summarized in Table 14. Subjecting optically enriched **129** (84% ee) to the optimized reaction conditions (e.g., 3 mol% catalyst, Cs_2CO_3 (3.0 equiv.), 80 °C) resulted in a significant decrease in the enantio-retention (Table 13, Entry 1). Thus, it can be said with certainty that it is the product that isomerizes under reaction conditions. In order to ensure that the stereocenter is thermally stable, **129** was stirred in DME at 80 °C for 24 h and no change to enantio-purity was observed (Entry 2). Next, treating **129** under similar reaction conditions to enrtry1, this time in the absence of the base, resulted in no degradation of stereocenter (Entry 3). This result reveals that *Pd-PEPPSI-IPent^{Cl}-o-picoline* (**52**) does not result in BHE of the amine product, which is consistent

with the results disclosed by Organ's group on selective cross-coupling of secondary alkyl zinc reagents where *Pd-PEPPSI-IPent*^{Cl} (**50**) was shown to resist BHE.[148] However, when compound **129** was treated with only the base (e.g., Cs_2O_3) the enantio-purity diminished drastically from 84% ee to 8% ee, suggesting that racemization is base-dependent (Entry 4). When **133** was treated with Cs_2O_3 (Entry 5), predictably, racemization occurred to a lesser extent than with **129** (Entry 4). This result confirms the hypothesis that increasing the steric bulk of the ester moiety suppresses the base-mediated racemization pathway.

Table 14. Investigating the source of racemization-*N*-heteroarylated product [a]



R= Et **129**
R=*t*Bu **133**

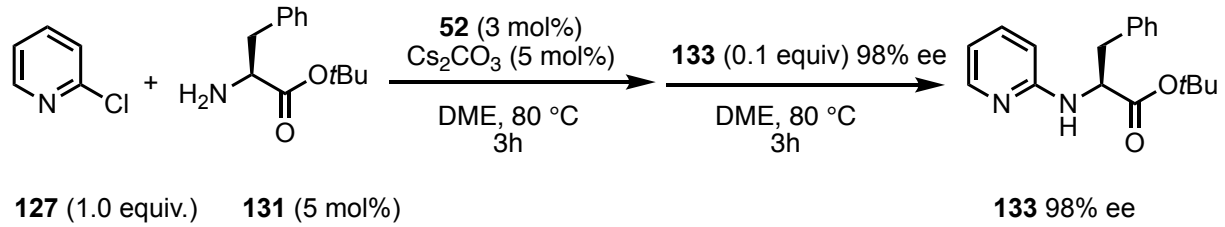
R= Et **129**
R=*t*Bu **133**

Entry	R	Initial ee [%]	additives	Final ee [%]
1	Et	84	**52** (3 mol%), Cs_2CO_3 (3.0 equiv.)	8
2	Et	84	-	84
3	Et	84	**52** (3 mol%)	84
4	Et	84	Cs_2CO_3 (3.0 equiv.)	8
5	*t*Bu	98	Cs_2CO_3 (3.0 equiv.)	61

[a] Initial and final percentage ee of the substrate were determined by chiral HPLC analysis. For a full description of the method, see the Experimental.

To further confirm that BHE is is not responsible for the observed racemization, we had to ensure that the pre-catalyst is activated prior to the control experiment employing **52**. To this end, a reaction was performed in which 1.0 equivalent of **127** was reacted with 5 mol% of free base L-

phenylalanine *tert*-butyl ester **131**, in presences of 5 mol% cesium carbonate and 3 mol% of **52** at 80° C. Since these are the cross-coupling conditions, activation of **52** is certain. Three hours later 0.1 equivalents of **133** was added and after stirring for an additional 20h, no notable change was observed in enantio-purity of **133**, suggesting that BHE is not operative. (Scheme 16).

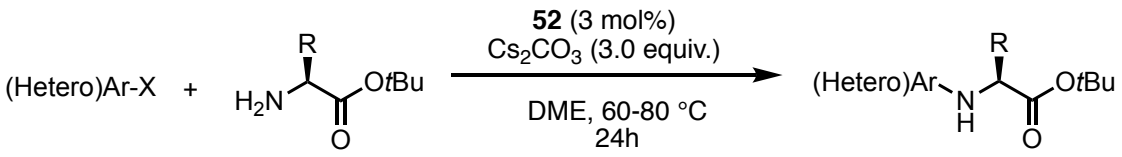


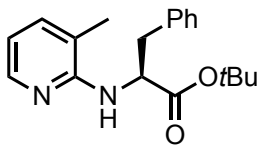
Scheme 16. Further investigation into the possibility of BHE-mediated racemization.

3.4. **Substrate scope study of α-amino esters couplings with six-membered heterocycles**

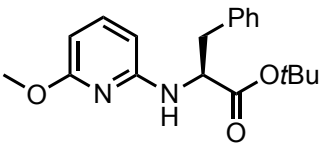
With reaction optimization completed, the substrate scope of this transformation was explored. A wide variety of 6-membered heterocyclic chlorides were efficiently coupled with the *tert*-butyl ester of l-alanine, l-valine, l-phenylalanine, l-isoleucine, and l-proline in very high yield with excellent enantiopurity (Table 15, products **134**-**142**). The generality of these conditions allowed for the successful coupling of oxidative addition partners possessing multiple heteroatoms, including 2-chloropyrazine (**143**), 5-bromopyrimidine (**144**), and 2-chloro-6- methoxypyridazine (**145** and **146**) with a variety of amino esters, generating the arylated product in excellent yield and very high enantio-purity (Table 15). It is important to note that exclusive monoarylation was observed in all cases. Of note, the scalability of the reaction was also investigated by synthesizing **133** on a 10 mmol scale where the desired product was isolated in 93% yield with excellent enantio-retention (>99% ee).

Table 15. Scope of amination of six-membered heteroaryl halides using optically pure α–amino esters [a,b]

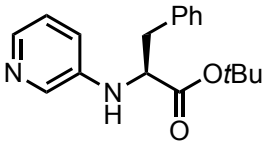




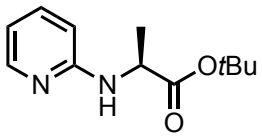
134 85% Yield, 90% ee



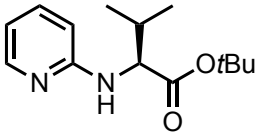
135 89% Yield, 90% ee



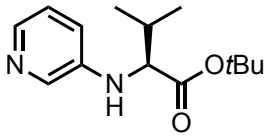
136 74% Yield, 80% ee



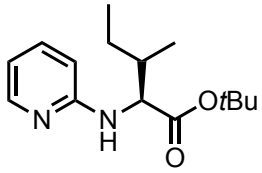
137 87% Yield, 99% ee



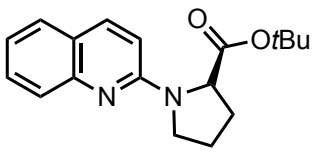
138 95% Yield, >99% ee



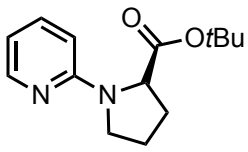
139 92% Yield, >99% ee



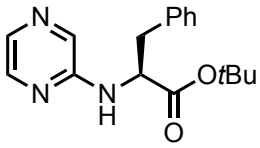
140 83% Yield, >99% ee



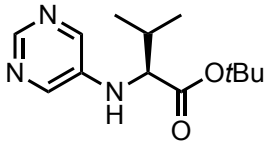
141 85% Yield, >99% ee



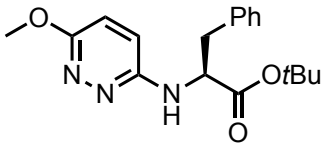
142 76% Yield, 95% ee



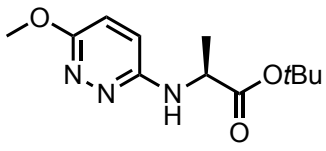
143 87% Yield, >99% ee



144 89% Yield, 98% ee[c]



145 90% Yield, >99% ee



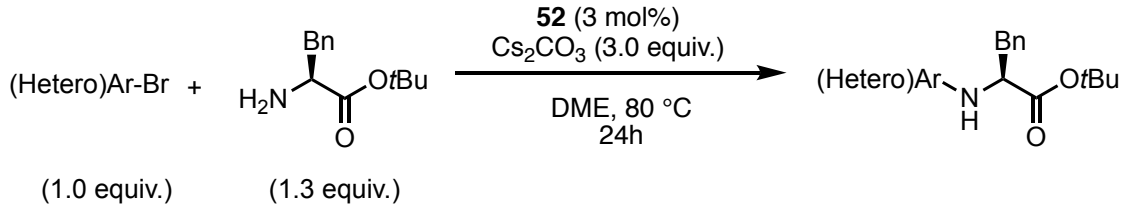
146 96% Yield, 90% ee

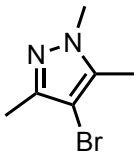
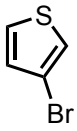
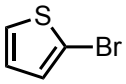
[a] Yields are reported on isolated product following purification by column chromatography using silica gel. [b] Percentage ee of product was determined by chiral HPLC analysis. [c] Ar-Br was used.

3.5. **Substrate scope study of α-amino esters couplings with five-membered heterocycles**

With a protocol developed for coupling of six-membered heterocycles with *tert*-butyl amino esters, attention was then focused on using five-membered heterocycles as oxidative addition partner. Using **52**, the coupling of **147** with **131** was first investigated under the optimized conditions. Unfortunately, this resulted in an incomplete conversion of oxidative addition partner with significant erosion of the stereocenter at the product (Table 16, Entry 1). Decreasing the concentration of the oxidative addition partner from 0.5 M to 0.25 M, while keeping all other parameters the same, did not significantly improve the enantio-purity of the aryl aminated product (Entry 2). Switching to NaO*t*Bu as the base, resulted in complete erosion of the stereocenter (Entry 3). The outcome of this reaction was found to be independent of the type of heteroatom or position in the five-membered ring that underwent the coupling. For example, with both 3-bromo and 2-bromo thiophene the coupling did not proceed to completion (e.g., 55% and 39% respectively) (Entries 4 and 5). Five-membered heterocyclic halide electrophiles have been repeatedly reported as notoriously difficult coupling partner in BHA.[130] This is mainly due to their altered electronic and steric properties that lead to a more difficult reductive elimination step in the catalytic cycle relative to six-membered heteroarenes.[130] Since all attempts to optimize conditions for the coupling of five-membered heterocycles failed, this pursuit was terminated.

Table 16. Scope of amination of five-membered heteroaryl halides with optically pure α–amino esters[a]



Entry	Ar-Br	Base (equiv.)	Conv. of Ar-Br [%][b]	ee [%][c]
1	 **147**	Cs_2CO_3 (1.5 equiv.)	79	72
2[d]		Cs_2CO_3 (1.5 equiv.)	68	80
3[d]		NaO*t*Bu (0.99 equiv.)	77	0
4	 **148**	Cs_2CO_3 (1.5 equiv.)	55	-
5	 **149**	Cs_2CO_3 (1.50 equiv.)	39	-

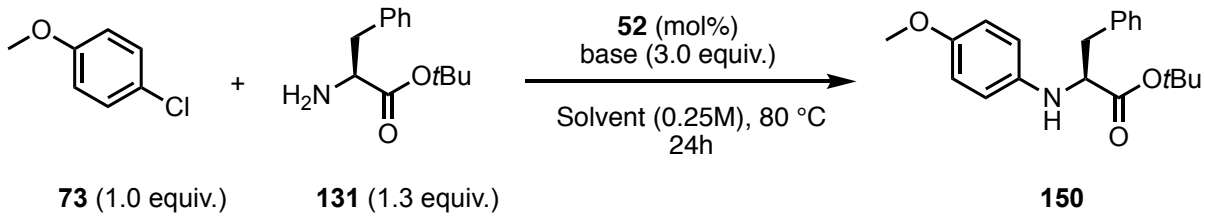
[a] Reactions were conducted on a 0.25 mmol scale at a concentration of 0.5 M [b] Percent conversion of Ar-Br was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] The percent ee of product was determined by chiral HPLC analysis. For a full description of the method, see the Experimental [d] Reaction was conducted at a concentration of 0.25M.

3.6. **Investigating the reactivity of *Pd-PEPPSI* complexes in *N*-arylation of α-amino esters**

Moving forward, attention was focused on expanding the scope of this chemistry to the use of aryl chlorides. To this end, the coupling of 4-chloroanisole (**73**) with **131** was first investigated (Table

17). Beginning with previously optimized conditions for the coupling of six-membered heterocycles with amino esters, conversion to the desired product (**150**) was low with mostly starting material recovered (Entry 1). maintaining Cs_2CO_3 as the base while increasing the equivalents from 1.5 to 3.0 and the reaction time to 48 hours resulted in a moderate increase in conversion to the desired product, but with complete erosion of the stereocenter (Entry 2). Increasing the catalyst loading to 5 mol% did result in better conversion to the desired product (67%) along with better enantio-purity (28%) respectively (Entry 3). While a marked improvement in conversion to **150** was observed by increasing the concentration of the OA partner twofold, no apparent change in enantio-purity of the desired product was observed (Entry 4). Recalling that in the case of the six-membered heterocyclics racemization was solely base-mediated, attention was then focused on studying other bases. The use of sodium phenolate resulted in the little formation of the desired product with full erosion of stereocenter (Entry 4). With potassium chromanoxide (**83**) as the base, the reaction went to 60% completion, however, the stereocenter again fully racemized (Entry 5).

Table 17. Influence of basic additives on the enantio-retention and conversion of **73** and **131** into **150** [a]



73 (1.0 equiv.) **131** (1.3 equiv.) **150**

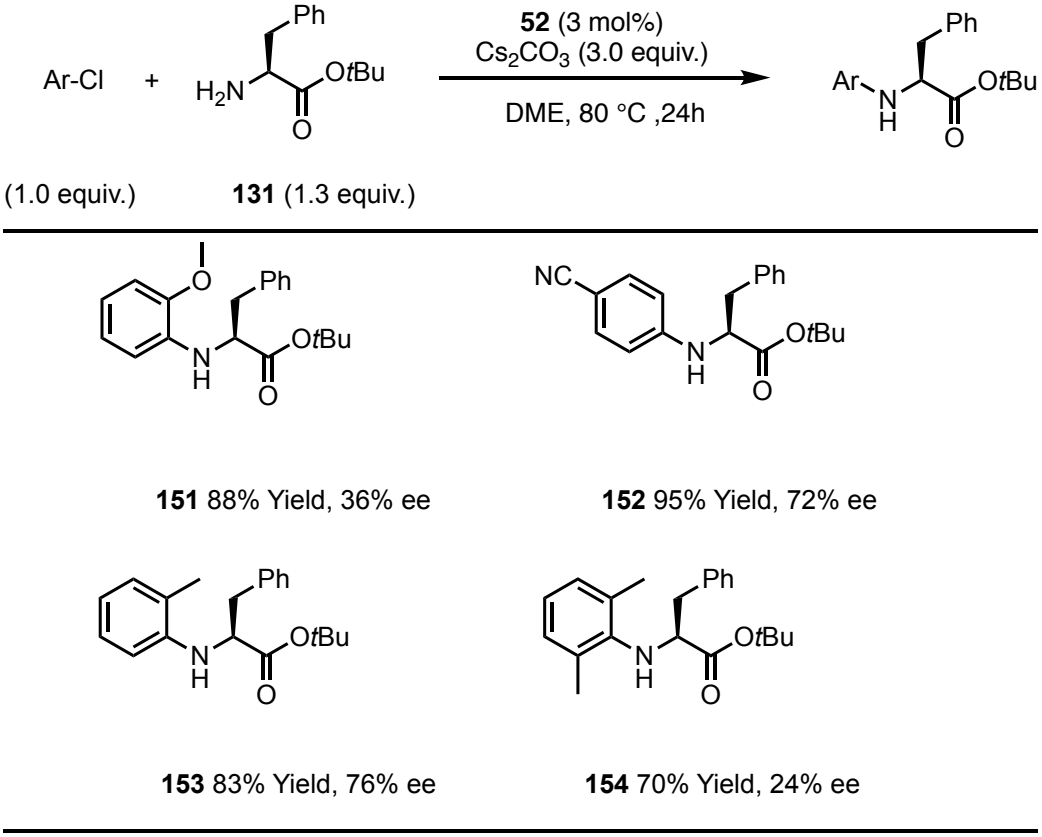
Entry	Base (equiv.)	**52** (mol%)	Conv. of **73** [%][b]	Yield [%][c]	ee [%][d]
1	Cs_2CO_3 (1.5 equiv.)	3	10	-	
2[e]	Cs_2CO_3 (3.0 equiv.)	3	31	27	0
3	Cs_2CO_3 (3.0 equiv.)	5	63	57	28
4	Na-phenolate	5	15	10	0
5	K-Chromonaxide	5	60	50	0

[a] Reactions were conducted on a 0.25 mmol scale [b] Percent conversion of **73** to **150** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel. [d] The percent ee of **150** was determined by chiral HPLC analysis. For a full description of the method, see the Experimental. [e] Reaction was conducted for 48h.

In an attempt to determine the extent to which racemization is influenced by the structure of the electrophile, coupling of **131** with OA halides with different steric and electronic properties was next examined (Table 18). The results reveal that racemization is dependent to a large extent on the electronic nature of the aryl halide. While reactions with both electron-rich and electron-deficient aryl halides proceeded to completion, interestingly, only those with electron-deficient partners retained higher levels of enantio-purity (**151**, **152**). Since the pK_a of the racemizable α-proton in (**152**) is lower than (**151**), deprotonation by carbonate base would have been expected to occur more readily. However, as previously reported by Organ's group for the arylation of alkyl amines with *Pd-PEPPSI* complexes, electron-deficient aryl halides have overall higher reaction rates than electron-rich aryl halides. In other words, if the rate of catalyst turnover is high in this

study, the consequent consumption of base is also high. So, after the product is formed there may not be enough available base to carry out the racemization which may be exacerbated by the heterogeneous nature of Cs_2CO_3.

Table 18. Influence of electronic and steric properties of aryl halide on the enantio-retention of the product[a]



[a] Reactions were conducted on a 0.25 mmol scale. Yields are reported on isolated product following purification by column chromatography on silica gel. The percent ee of the products was determined by chiral HPLC analysis. For a full description of the method, see the Experimental.

The degree of racemization also appeared to be dependent on the steric properties of the aryl chloride. In the case of 2-chlorotoluene, the cross-coupled product (**153**) was formed in good yield with an acceptable level of enantio-purity (76%). However, with more sterically encumbered electrophilic halide, the coupled product was obtained with a low level of enantio-purity (24% ee) (product **154**). Since all attempts to optimize the reaction conditions for better retention of the

stereocenter during the cross-coupling of substituted aromatic substrates, this part of the project was also abandoned.

3.7. **Conclusion**

In summary, a mild, robust and efficient protocol using *Pd-PEPPSI-IPent^{Cl}-o-picoline* (**52**) for *N*-heteroarylation of α-amino esters was developed. Using this protocol, a variety of six-membered heterocyclic electrophiles were successfully coupled with a selection of α-amino esters to prepare products in high yield and excellent enantio-purity (i.e., enantio-retention). Extensive control experiments support that racemization only occurs with the cross-coupled product and not the starting primary amino ester, and that this event is base-mediated. Also, control experiments revealed that **52** does not undergo BHE of the amine product. Key to this transformation is the use of *tert*-butyl amino acid esters, which are both readily available and easily deprotected to liberate the free acids. Attempts to expand the scope of this protocol to five-membered heterocycles and aryl chlorides as OA partners have, thus far, proven unsuccessful. These coupling partners were found to be recalcitrant, furnishing the cross-coupled products but with unacceptable levels of enantio-purity.

Chapter 4- Cross-Coupling of Primary Amides to Aryl and Heteroaryl Partners Using *(DiMeIHept^{Cl})Pd* Promoted by Trialkylboranes or $B(C_6F_5)_3$

4.1. Background

One of the most commonly performed transformations in organic chemistry is amide bond formation, simply because the amide linkages constitute the backbone of all peptides/ proteins and are ubiquitous in numerous natural products and biomedically important compounds, such as therapeutics (see Figure 18 for examples).[149] Indeed, a statistical analysis of all pharmaceuticals on the market revealed that 25% of them contain an amide bond.[150,151] One of the most common synthetic approaches to prepare such moieties is to react a carboxylic acid with an amine in the presence of a coupling reagent (e.g., EDC, HOBt, CDI, HATU, BOP).[152,153] However, this classic coupling route is not atom economical and generates stoichiometric quantities of by-product. As a result, in 2007, "amide formation avoiding poor atom economy reagents" was chosen as a featured area of research by the American Chemical Society Green Chemistry Institute.[154]

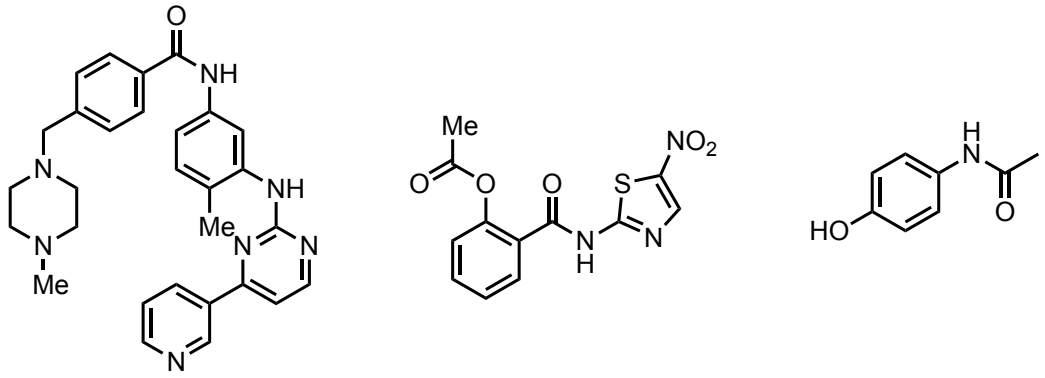
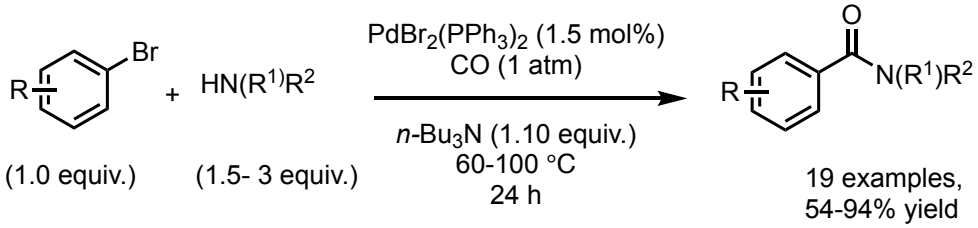


Figure 18. Examples of marketed drugs containing the *N*-aryl amide moiety.[149]

In response to this challenge, several metal-catalyzed approaches for the formation of amides have been developed.[155] With respect to Pd catalysis, aminocarbonylation of aryl halides and vinyl halides, which have been developed over 35 years ago (Scheme 17),[156] proved to be a convenient method for constructing amide bonds and many successful methods have been reported to date.[157–160]

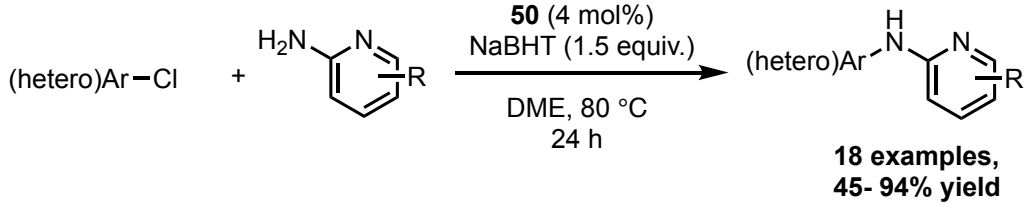


Scheme 17. First example of Pd-catalyzed aminocarbonylation of aryl halides[156]

While Pd-catalyzed C-N bond formation reactions have been widely developed for the coupling of a variety of nitrogen-based nucleophiles with (hetero)aryl halides, the use of amides as nucleophiles is significantly more challenging due to the reduced nucleophilic nature of the amides, as well as the formation of unproductive Pd^{II}-amidate resting states (see Figure 15 in Chapter 1).[107] The focus of this chapter is the development of an efficient method for the construction of *N*-aryl amide bonds using Pd-NHC complexes.

4.2. **Investigating the reactivity of Pd-NHC complexes in aryl amidation**

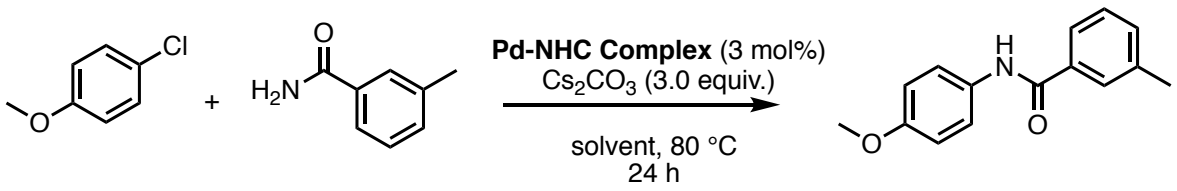
In 2017, Organ and co-workers reported conditions for coupling of 2-aminopyridine derivatives with aryl halides using the bulky *Pd-PEPPSI-IPent^{Cl}* (**50**) catalyst (Scheme 18).[161] In this study, it was demonstrated that the steric bulk of the catalyst facilitates RE within the catalytic cycle, and perhaps more importantly, it resists the formation of the aminopyridine-Pd resting states that inhibit the catalyst from starting the cycle.



Scheme 18. Coupling of 2-aminopyridne derivatives to aryl chlorides using *Pd-PEPPSI-IPent*^{Cl} (**50**) pre-catalyst.[161]

Using this as a starting point, we rationalized that this bulky NHC catalyst might be also suited for the aryl amidation chemistry by resisting the κ^2-coordination of the amide to Pd. To this end, the cross-coupling of 4-chloroanisole (**71**) with 3-methyl benzamide (**155**) in the presence of Cs_2CO_3 as the base was chosen as the model reaction (Table 19). With pre-catalyst **50**, which had demonstrated excellent reactivity and selectivity in amination of aryl halides with deactivated anilines,[91] primary alkyl amines,[145] ammonia,[87,162] and sterically hindered amines,[88] the reaction did not proceed at all and starting materials were recovered (Entry 1). Switching to a bulkier NHC ligand, *Pd-PEPPSI-IHept*^{Cl} (**51**) led to similar result with no conversion to the cross-coupled product (Entry 2). Applying *(DiMeIHept*^{Cl}*)Pd(cinammyl)Cl* (**11**), the bulkiest NHC developed by the Organ group to date, resulted in the best initial conversion to the product (Entry 3). Changing the solvent to a coordinating one like DME improved the percentage conversion of **71** to **156** by 17% (Entry 4).

Table 19. Optimization of amide coupling using Pd-NHC pre-catalysts[a]



73 (1.0 equiv.) **155** (1.3 equiv.) **156**

Entry	Pd-NHC complex	solvent	Conv. of **73** [%][b] (yield [%])[c]
1	*Pd-PEPPSI-IPent^{Cl}* (**50**)	toluene	0
2	*Pd-PEPPSI-IHept^{Cl}* (**51**)	toluene	0
3	*(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**)	toluene	21 (15)
4	*(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**)	DME	38 (32)

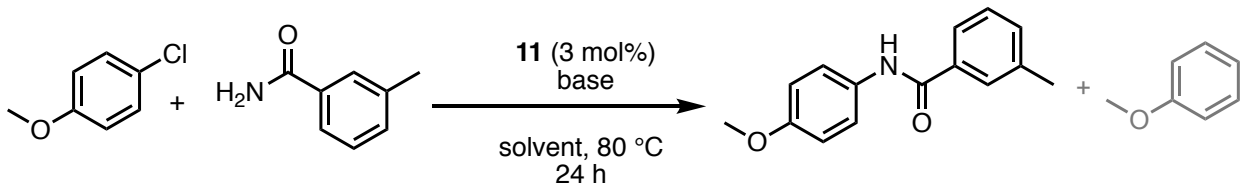
[a] Reactions were conducted on a 0.25 mmol scale at a concentration of 0.5 M of **73** [b] Percent conversion of **73** to **156** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs.

4.3. **Optimization study in aryl amidation using *(DiMeIHept^{Cl})Pd(cinammyl)Cl***

Having identified **11** as the most reactive catalyst in the model reaction, attention was then focused on finding the optimal base for the reaction (Table 20). The use of NaO*t*Bu, one of the most commonly used bases in BHA, led to a poor conversion to product (Entry 1). Switching to $Zn(HMDS)_2$ which has been previously reported by Hartwig to be a mild and effective base in amination reactions,[146] resulted in no conversion to the product (Entry 2). Then, attention was focused on using sodium BHT (BHT= 2,6-di-*tert*-butyl hydroxytoluene) (**85**), which has been previously reported by Organ and co-workers to be a mild and highly efficient base in selective BHA reactions including monoarylation of primary amines and coupling of 2-aminopyridines.[145,161] In the initial experiment with **85** coupling proceeded to 26% (Entry 3) and increasing the concentration of the aryl halide significantly increased conversion to the cross-coupled product (Entry 4). It should be noted that in these reactions, depending on the percentage

conversion to the product, between 15-50% of the reduced product (**157**) was obtained. Similar results were obtained when the solvent was changed to ethereal solvents such as DME and 1,4-dioxane (Entries 5 and 6). Surprisingly, increasing the equivalents of the base appeared to have a deleterious effect and resulted in exclusive formation of **157** (Entry 7), implying that hydrodehalogenation outcompetes the desired cross-coupling reaction if the coupling process is relatively slow. A more in-depth discussion on the origin of the observed phenolate-mediated hydrodehalogention is the subject of the next chapter of the thesis.

Table 20. Influence of basic additives on the conversion of **73** into **156**[a]



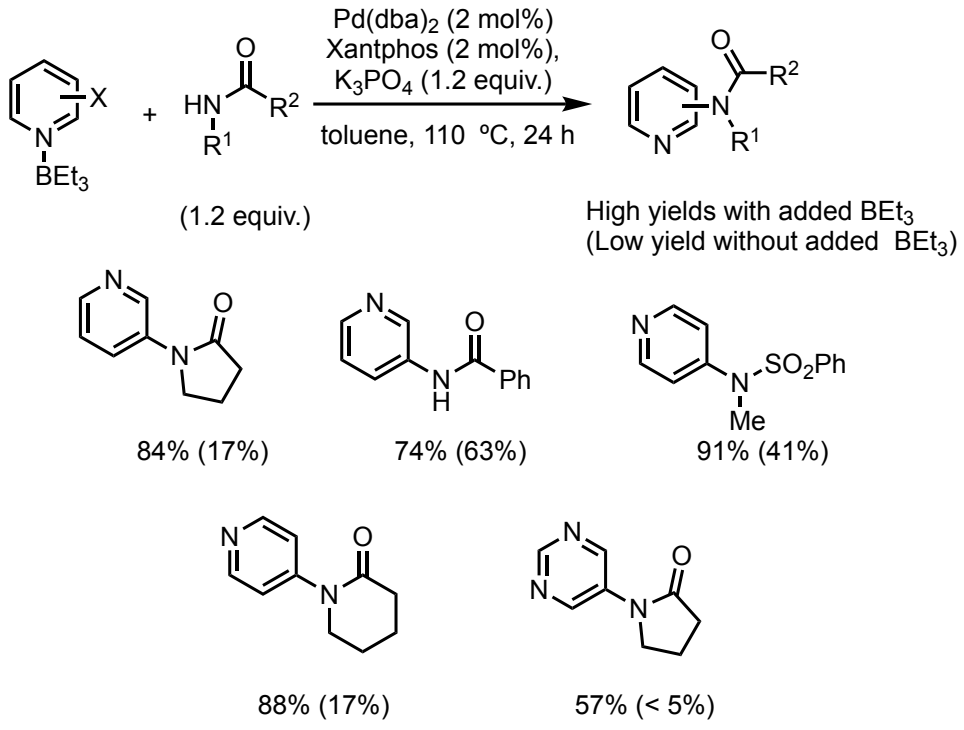
73 (1.0 equiv.) **155** (1.3 equiv.) **156** **157**

Entry	base (equiv.)	Solvent (M)[b]	Conv. of **73** [%][c] (yield [%])[d]
1	NaO*t*Bu (1.1)	toluene (0.5)	10
2	$Zn(HMDS)_2$ (1.5)	THF:toluene (0.5)	0
3	NaBHT (1.5)	toluene (0.25)	26
4	NaBHT (1.5)	toluene (0.5)	83 (78)
5	NaBHT (1.5)	DME (0.5)	81 (76)
6	NaBHT (1.5)	1,4-dioxane (0.5)	84 (80)
7	NaBHT (3.0)	toluene (0.5)	0

[a] Reactions were conducted on a 0.25 mmol scale. [b] Reported concentrations are based on **73**. [c] Percent conversion of **73** to **156** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [d] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs.

4.4. **Investigating the impact of Lewis acids in aryl amidation**

Since it appeared to be difficult to inhibit the hydrodehalogenation pathway in the presence of **85**, we opted to explore another set of reaction conditions in which the hydrodehalogenation pathway was not operative. In 2007, Hartwig and co-workers reported the cross-coupling of heteroaromatic reagents with amides in the presence of a boron-based Lewis acid (e.g., BEt_3, BPh_3 and $B(C_6F_5)_3$) that was shown to dramatically improve conversion to the desired amide (Scheme 19).[114]. It was suggested that coordination of the Lewis acid to the to the heteroatom of OA partner could make it more electron-poor and hence lower the barrier for RE.

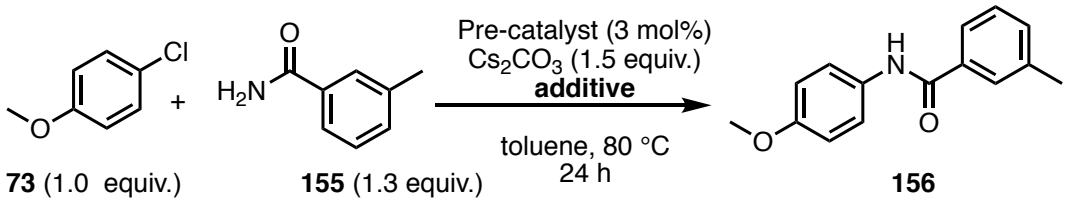


Scheme 19. First report of Pd-catalyzed amidation of heteroaryl halides in the presence of Lewis acids.[114]

Inspired by these results, we evaluated the impact of Lewis acid on the model reaction using pre-catalyst **11** and Cs_2CO_3 as the base (Table 21). In the presence of 20 mol% of triethylborane (Et_3B) (**B1**), the cross-coupled product was formed in 86% yield (Entry 1). Other boron-based Lewis

acids were also examined. Under similar reaction conditions with *tri-sec*-butyl borane ((*sec*Bu)$_3$B) (**B2**) and B(C_6F_5)$_3$ (BCF) (**B4**), the reactions also proceeded well (Entries 2 and 3). Borate ester (EtO)$_3$B (**B3**), which is what one might expect to be in the reaction in entry 1 following the presumably rapid autoxidation of Et_3B was less catalytically proficient (Entry 4). Furthermore, other Lewis acids such as $ZnCl_2$ and Et_2AlCl were found to be less effective for this reaction (Entries 5 and 6). When **155** and **73** were mixed together under the similar reaction conditions to entry 2 but without Pd, no conversion to the product was observed (Entry 7), confirming that the process is catalyzed. Lastly, pre-catalyst **51**, which had failed to show any activity on its own, started to see notable conversion (55%) with Et_3B (Entry 8).

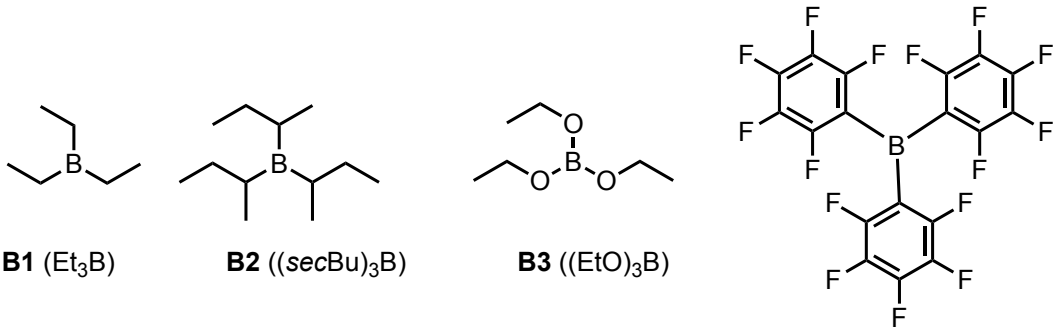
Table 21. Influence of Lewis acid additives on the conversion of **73** into **156**[a]



73 (1.0 equiv.) **155** (1.3 equiv.) **156**

Entry	additive (20 mol%)	pre-catalyst	Conv. of **73** [%][b]	Yield [%] [c]
1	Et_3B (**B1**)	**11**	100	86
2	(*sec*Bu)$_3$B (**B2**)	**11**	100	92
3	B(C_6F_5)$_3$ (**B4**)	**11**	100	70
4	(EtO)$_3$B (**B3**)	**11**	53	-
5	$ZnCl_2$	**11**	20	15
6	Et_2AlCl	**11**	26	19
7	Et_3B	none	0	-
8	Et_3B	**51**	55	47

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **156** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs.

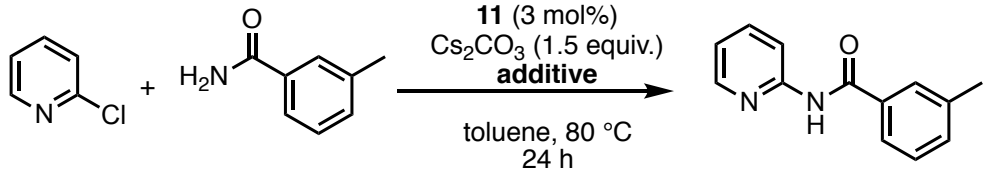


B1 (Et_3B) **B2** ($(sec Bu)_3B$) **B3** ($(EtO)_3B$) **B4** ($B(C_6F_5)_3$)

Figure 19. Boron based-Lewis acids used in amide coupling using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**).

Similar trends were also observed when 2-chloropyridine (**127**) was used as the electrophilic partner and results are summarized in Table 22. Again, with alkylboranes and BCF, the reaction proceeded in very good yield (Entries 2-4), while other Lewis acids appeared to have little effect on this reaction (Entries 5 and 6). Again, now in the absence of pre-catalyst no conversion to the product was observed (Entry 7).

Table 22. Influence of Lewis acid additives on the conversion of **127** into **158**[a]

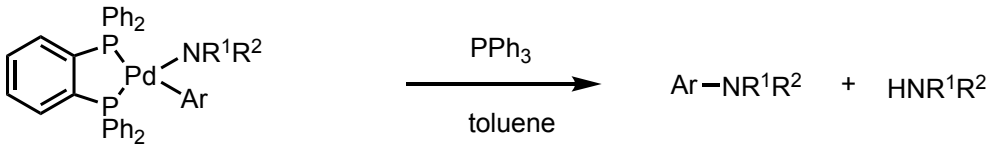


127 (1.0 equiv.) **155** (1.3 equiv.) **158**

Entry	additive (20 mol%)	pre-catalyst	Conv. of **127** [%][b]	Yield [%][c]
1	none	**11**	0	-
2	Et_3B	**11**	100	77
3	$(sec Bu)_3B$	**11**	100	92
4	$B(C_6F_5)_3$	**11**	100	94
5	$ZnCl_2$	**11**	0	-
6	Et_2AlCl	**11**	20	17
7	Et_3B	none	0	-

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **127** to **158** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs.

As mentioned previously, Hartwig reported that Lewis acids promoted both amination and amidation of heteroaryl bromides by binding to the OA partner and forming an electron-poor aryl group (Scheme 20a and 20b) .[114] With OA partners lacking heteroatoms no acceleration of C-N reductive elimination by the Lewis acid was observed (Scheme 20c). This observation led Hartwig group to conclude that the Lewis acid can accelerate the reaction only if the OA partner contains a heteroatom. It should be noted that the intermediate Hartwig studied in case of OA partner lacking heteroatom was not derived from amides, but diarylamines with an assumption that the same trends would hold for amide nucleophiles (Scheme 20c).

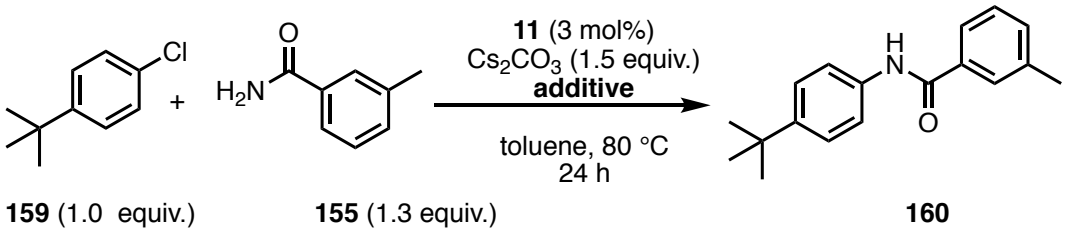


a) Ar= 4-py, R^1=R^2= *p*-*t*-BuC_6H_4	without Lewis acid, 90 °C, 10h	0%	100%
	with BEt_3 (1.0 equiv.), rt, 30min	90%	< 5%
b) Ar= 4-py, R^1=Me, R^2=SO_2Ph	without Lewis acid, 110 °C, 24h	0%	100%
	with BEt_3 (1.0 equiv.),110 °C, 1h	81%	19%
c) Ar= *p*-tol, R^1=R^2= *p*-*t*-BuC_6H_4	without Lewis acid, 90 °C, 8h	50%	50%
	with BEt_3 (1.0 equiv.),110 °C, 1h	0%	95%

Scheme 20. Studying the effect of Lewis acids on Pd-catalyzed aryl amination/amidation reactions.[114]

While amidation using pre-catalyst **11** and a Lewis acid proceeds well for **73** and **127**, an interesting question arises keeping Hartwig's proposal in mind: does the same trend hold for OA partners that do not contain any heteroatoms? To address this question, 1-*tert*-butyl-4-chlorobenzene (**159**) was reacted with the amide **155** first in the absence and the in the presence of a Lewis acid (Table 23). In the absence of the Lewis acid, the reaction proceeded only to 26% conversion (Entry 1), whereas in the presence of a Lewis acid, excellent yields of **160** were obtained (Entries 2 and 3). Importantly, this indicates a role for the Lewis acid that is independent of the nature of the OA partner and casts doubt on Hartwig's suggestion, at least under our reaction conditions. These mechanistic features are further considered in section 4.6 below.

Table 23. Amide coupling to *tert*butyl-4-chlorobenzene[a]



Entry	additive (20 mol%)	Conv. of **159** [%][b]	Yield [%][c]
1	-	0	-
2	(*sec*Bu)$_3$B	100	87
3	$(C_6F_5)_3B$	100	82

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **159** to **160** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs.

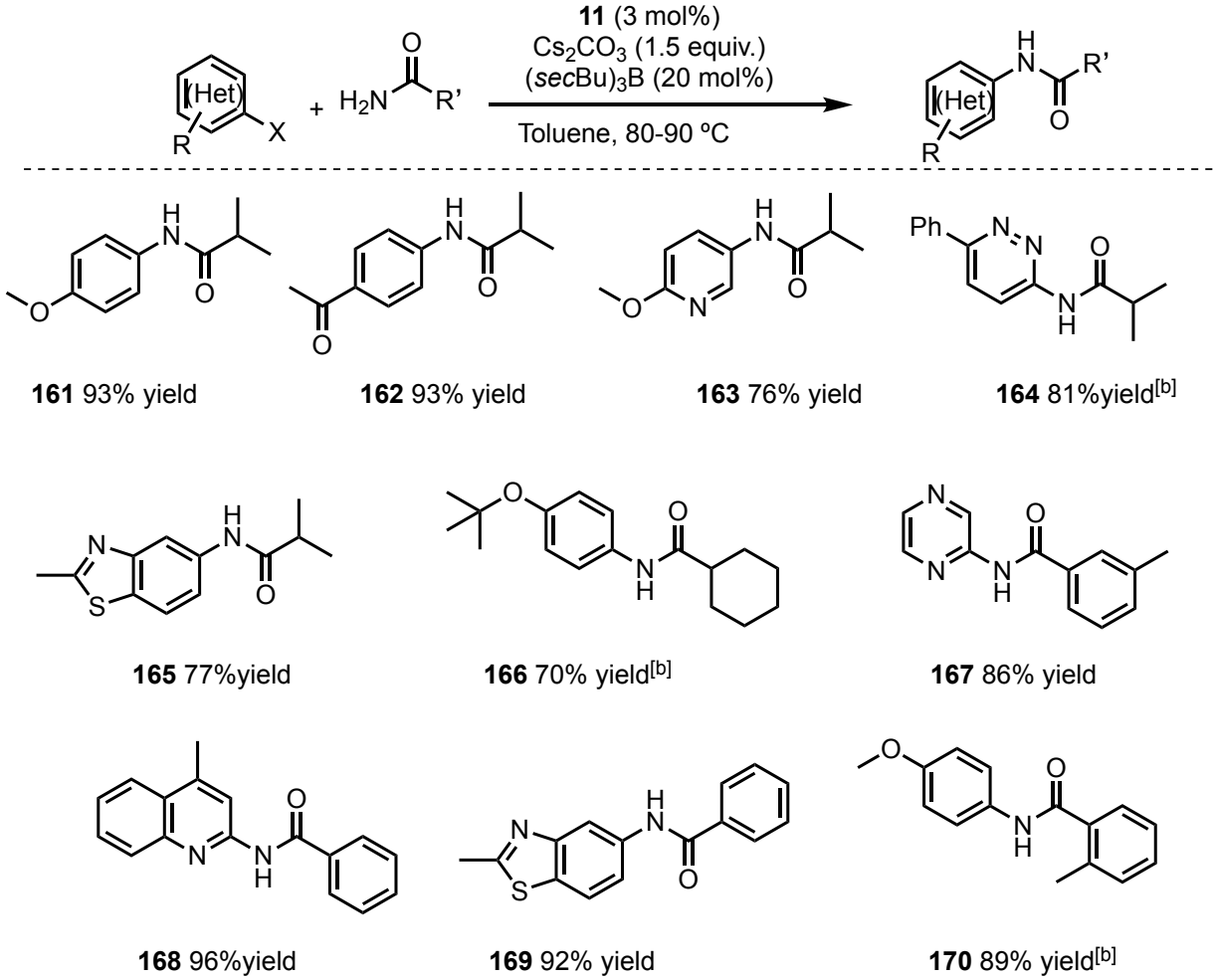
4.5. **Substrate scope study of aryl amidation**

With these promising results in hand, the substrate scope of this transformation using **11** was then investigated, with the aim of preparing a broad range of functionalized *N*-(hetero)aryl amides (Table 24). Tri-*sec*-butylborane was used as the Lewis acid, as it is generally more stable and easier to store and handle than Et_3B. The scope and functional group compatibility of these conditions allowed for the successful coupling of electrophiles containing base-sensitive functionality such as nitrile (**173**), ketone (**162**, **174**), nitro (**172**) groups, with both alkyl or aryl amides. While coupling of various amides with six-membered nitrogen-containing heterocycles furnished the desired product in excellent yield (**163**, **164**, **167**, **168**, **171**), all attempts to couple five-membered heterocycles were unsuccessful.

Based on these promising results, attention was then focused on coupling of sterically hindered electrophiles with amide nucleophiles. There is only one other example in the literature where

sterically congested electrophilic partners were coupled with primary amides. However, in this example, temperatures in excess of 150 °C have been required to make such coupling work. Again, under the standard conditions the coupling proceeded smoothly and hindrance on the amide (**170**, **171**, **173**, **174**), OA partner (**178-180**) or both (**181**) was well tolerated.

Table 24. Scope of amide coupling using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) and (*sec*Bu)$_3$B (**B2**)[a]



161 93% yield

162 93% yield

163 76% yield

164 81%yield[b]

165 77%yield

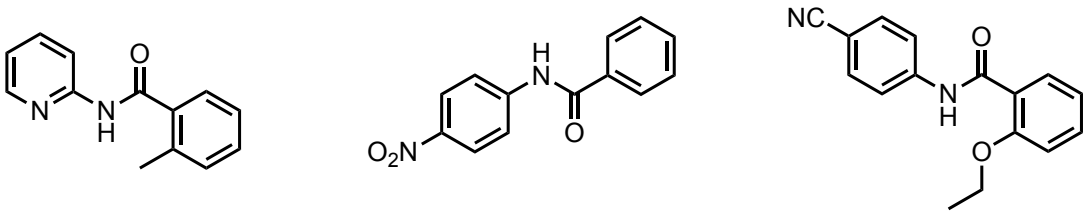
166 70% yield[b]

167 86% yield

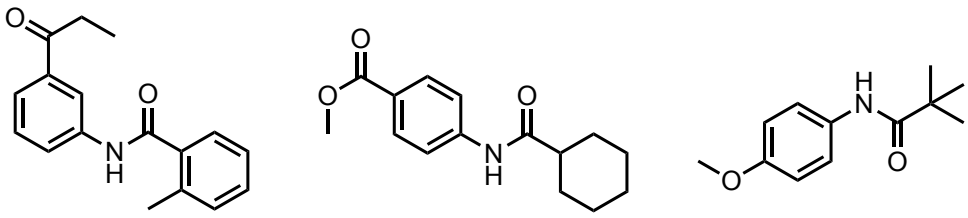
168 96%yield

169 92% yield

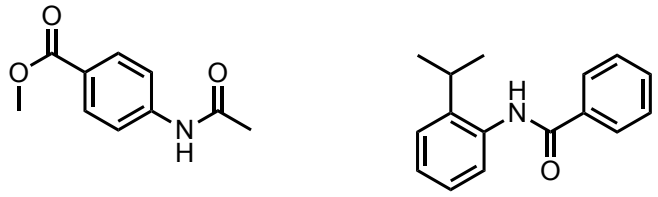
170 89% yield[b]



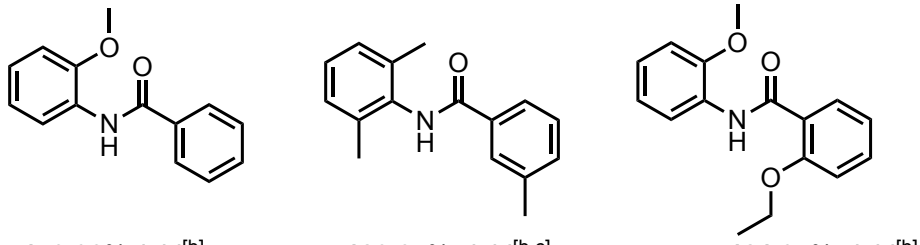
171 92%yield **172** 85% yield **173** 57% yield[b]



174 55%yield[b] **175** 76% yield [b] **176** 96% yield



177 80%yield **178** 42% yield[b]



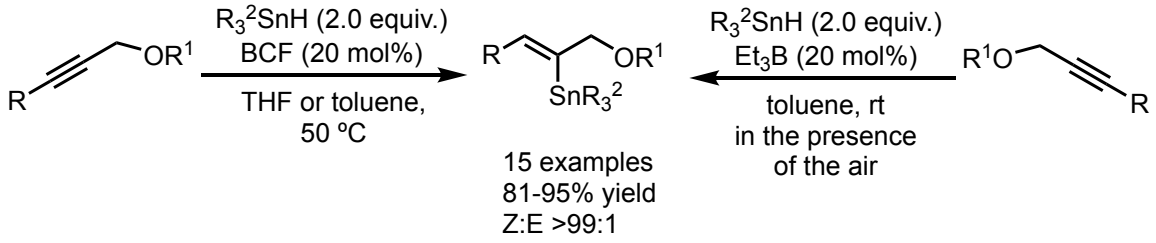
179 96%yield[b] **180** 67% yield[b,c] **181** 95% yield[b]

[a] Yields are reported on isolated product following purification by column chromatography on silica gel and are averaged over two runs. [b] Reaction run at 90 °C. [c] Reaction run with 1.0 equiv. of (*sec*Bu)$_3$B.

4.6. **Mechanistic considerations**

By taking a cursory glance at the outcome of all three boron-derived Lewis acids used in this study, it is tempting to suggest that they are all promoting the coupling by the same mechanism. However, this may not to be the case. In 2012, Organ and co-workers investigated the mechanism of BCF-catalyzed hydrostannylation of propargylic alcohol derivatives.[163] One year later, in 2013, the same

group published a detailed mechanistic study on the hydrostannylation of alkynes using Et_3B/O_2 as the promoter (Scheme 21).[164] During the course of their mechanistic investigations, they found that although the use of both BCF and Et_3B led to the formation of the product with identical regio- and stereoselectivity, the mechanisms of the two transformations are completely unrelated.

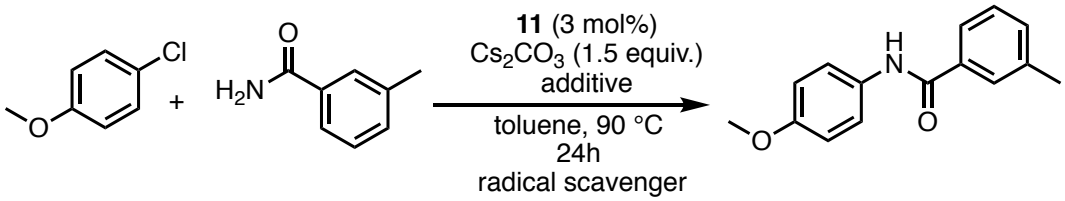


Scheme 21. Hydrostannylation of propargylic alcohol derivatives using Et_3B or BCF as a promoter.[163,164]

The Organ group[164–166] and others[167,168] have previously shown that triethylborane autoxidizes instantaneously in air leading to the formation of free radicals, importantly, even when the reactions are carried out with what are believed to be O_2-free conditions. Furthermore, in 2016, Buchwald and McMillan developed a protocol for arylamination using nickel^{II} salts where the RE from the nickel^{II}-amido complex was induced by a photoredox-catalyzed electron transfer event.[169] It is therefore reasonable to speculate that a redox shuttle might be operative with alkylboranes in the current aryl amidation chemistry given their propensity to readily generate radicals. To test this assumption, a series of coupling reactions were performed in the presence of radical scavengers and the results from those experiments are described in Table 25. In the case of (*sec*Bu)$_3$B, increasing the equivalents of TEMPO from 0 to 1.0 resulted in a significant decrease in conversions to product from 100% to 27% (Entries 1-6). However, with Et_3B, adding TEMPO into the reaction mixture appeared to have no significant impact on conversion to the product (Entries 7-12). Similar results were also obtained when galvinoxyl was used with Et_3B (Entry 13).

It is important to know whether the radical scavengers are impacting the chemistry in other ways that might lead to a misinterpretation of these control experiments. While the results from entries 12 and 13 showed that coupling was less impacted with Et_3B (i.e., 80% and 100% conversion was attained with 1.0 equivalent of TEMPO and galvinoxyl, respectively), it supports the notion that the scavengers are not just otherwise interfering in the case of (*sec*Bu)$_3$B. Considering that the coupling was not completely shut down when a radical scavenger was used with either alkylborane reagents, it is reasonable to propose that a redox pathway is not the primary pathway by which this chemistry is proceeding, if it is involved at all. That said, at this time it is not clear why there is such a clear and repeatable difference between Et_3B or (*sec*Bu)$_3$B promotors when the radical scavenger is present.

Table 25. Effect of radical scavengers TEMPO and galvinoxyl on amide coupling using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) with Et_3B or (*sec*Bu)$_3$B promotors.

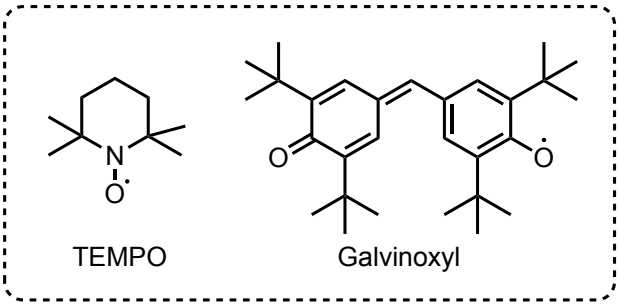


73 (1.0 equiv.) **155** (1.3 equiv.) **156**

Entry	additive (20 mol%)	radical scavenger (equiv.)	Conv. of **73** [%][a] (Yield [%]) [b]
1	(*sec*Bu)$_3$B	-	100 (92)
2	(*sec*Bu)$_3$B	TEMPO (0.1)	94 (88)
3	(*sec*Bu)$_3$B	TEMPO (0.2)	75 (68)
4	(*sec*Bu)$_3$B	TEMPO (0.3)	65 (52)
5	(*sec*Bu)$_3$B	TEMPO (0.4)	55 (52)
6	(*sec*Bu)$_3$B	TEMPO (1.0)	27 (24)

7	Et_3B	-	100 (86)
8	Et_3B	TEMPO (0.1)	100 (88)
9	Et_3B	TEMPO (0.2)	100 (92)
10	Et_3B	TEMPO (0.3)	100 (92)
11	Et_3B	TEMPO (0.4)	100 (90)
12	Et_3B	TEMPO (1.0)	80 (71)
13	Et_3B	Galvinoxyl (1.0)	100 (97)

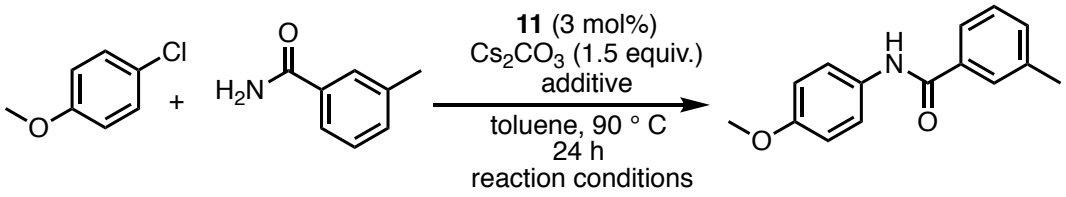
[a] Percent conversion of **73** to **156** was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.
[b] Yields are reported on isolated product following purification by column chromatography on silica gel.



Knowing that triethylborane rapidly autoxidizes to the corresponding boronate ester(s) in the presence of even a trace amount of oxygen that could be present in the reaction mixture, despite all best efforts to exclude it using Schlenk techniques, the impact of oxygen on these amide coupling was then investigated (Table 26). First, the amide couplings with both akylboranes were set up in an argon-filled glovebox where the solvents were degassed via the freeze-pump-thaw method and all glassware, syringes and reagents were scrubbed free of oxygen in a glovebox for 7 days prior to being used so as to ensure the meticulous exclusion of oxygen (Entries 2a and 2b). The Organ group has shown that this handling of the reaction is suitable to remove all oxygen to eliminate the autoxidation of triethylborane.[163] In both cases excellent conversions to the expected products were obtained despite the rigorous exclusion of oxygen, again implying that radicals are

not involved in this coupling reaction. Next, using standard Schlenk technique all reagents were premixed, stirred for 5 min. at ambient temperature, exposed to air for 5 min., and finally the mixture was allowed to stir at 90 °C for 24h. With (*sec*Bu)$_3$B the reaction proceeded well (Entry 3b), and with Et$_3$B, which ignites upon exposure to the air, similar result was obtained (Entry 3a). Following this, both akylboranes were first dissolved in toluene, stirred open to air for 10 min., then all other reagents were added to the borane solution and the mixture heated for 24h. With (*sec*Bu)$_3$B the coupling proceeded to give **156** with 100% conversion which implies that (*sec*Bu)$_3$B is not sensitive to the oxygen at all (Entry 4b). However, with Et$_3$B, no conversion into **156** occurred (Entry 4a). This would suggest that there is something in the reaction mixture that '*protects*' the Et$_3$B from the impact of oxygen.

Table 26. Effect of oxygen on coupling of **73** with **155** using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) and Et$_3$B or (*sec*Bu)$_3$B as promotors.



73 (1.0 equiv.) **155** (1.3 equiv.) **156**

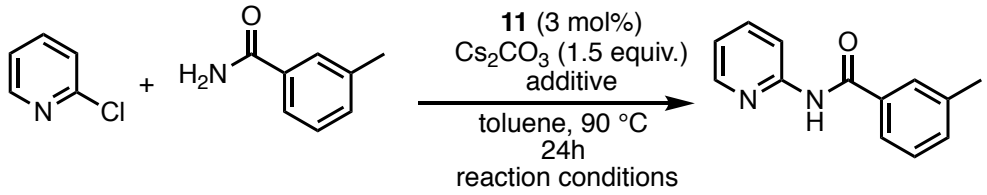
Entry	additive (20 mol%)	Reaction procedure	Conv. of **73** [%][a]
1a	Et$_3$B	standard Schlenk technique[b]	100
1b	(*sec*Bu)$_3$B		100
2a	Et$_3$B	set up reaction in glovebox with stringent removal of oxygen and degassed solvents, and heat for 24 h	93
2b	(*sec*Bu)$_3$B		78

3a	Et_3B	premix reagents using standard Schlenk technique, stir for 5 min., expose to air for 5min., and heat for 24 h	100
3b	(*sec*Bu)$_3$B		100
4a	Et_3B	dissolve borane in toluene, stir open to air for 10 min, add all other reagents, and heat for 24 h	0
4b	(*sec*Bu)$_3$B		100
5	Et_3B	using standard Schlenk technique, stir Et_3B (1.0 equiv.) and **155** together for 1 h, add base, **73**, and **11**, and heat for 24 h	100

[a] Percent conversion of **73** to **156** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.
[b] For a detailed reaction procedure using standard Schlenk technique see Chapter 6.

To examine whether these observations are unique to this OA partner, 2-chloropyridine was also examined. Results obtained from those experiments are summarized in Table 27. Again, (*sec*Bu)$_3$B showed no sensitivity to oxygen (Entries 1b, 2b and 3b). However, in the case of Et_3B when the autoxidation process occurred prior to adding the rest of the reaction mixture, the reaction proceeded to only 30% conversion (compare entries 1a, 2a and 3a). As the effect of oxygen on reactions with Et_3B are similar for both OA partners it would be reasonable to assume this is general across all couplings using these reaction conditions.

Table 27. Effect of oxygen on the coupling of **127** with **155** using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) and Et_3B or (*sec*Bu)$_3$B



127 (1.0 equiv.) **155** (1.3 equiv.) **158**

Entry	additive (20 mol%)	Reaction procedure	Conv. of **127** [%][a]
1a	Et_3B	standard Schlenk technique[b]	100
1b	(*sec*Bu)$_3$B		100
2a	Et_3B	premix reagents using standard Schlenk technique, stir for 5 min, expose to air for 5 min., and heat for 24 h	100
2b	(*sec*Bu)$_3$B		100
3a	Et_3B	dissolve borane in toluene, stir open to air for 10 min, add all other reagents, and heat for 24 h	30
3b	(*sec*Bu)$_3$B		100

[a] Percent conversion of **127** to **158** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [b] For a detailed reaction procedure using standard Schlenk technique see Chapter 6.

To rationalize the observed results, it came to mind that, irrespective of the coupling per se, coordination of the boron-based Lewis acid to the Lewis-basic amide coupling partner, however reversibly, likely occurs. If this does occur prior to the introduction of oxygen into the flask, it is conceivable that the amide serves to mitigate the effects of oxygen on the borane. To probe any possible interactions between the Lewis acid and the amide, a series of NMR experiments were conducted (Figure 20). A sample of Et_3B in C_6D_6 that was prepared with rigorous exclusion of air inside the glovebox and its corresponding ^{11}B spectrum is shown in Figure 18d. When the same sample was exposed to air for 5 min. the typical alkylborane resonance at 85 ppm diminished and

two other resonance appeared at approximately 55 and 35 ppm (Figure 20e). This is consistent with Organ's group observations where they showed that, on contact with air, alkylboranes (R_3B) autoxidize instantaneously to commence the formation of the corresponding borinate (R_2B-OR), boronate ($RB(OR)_2$), and borate ($B(OR)_3$) species.[164] Next, the amide and Et_3B were mixed in C_6D_6 with careful exclusion of air and monitored by ^{11}B and ^{13}C NMR spectroscopy. In the ^{11}B spectrum, the alkylborane peak at 85 ppm diminishes while the peak at 55 ppm intensifies (Figure 20f). At the same time, comparison of the spectra in (Figure 20a and 20b) reveals that the amide carbonyl peak that comes near 168.6 ppm, upon mixing with Et_3B gives rise to three new signals, the most prominent of which is a broad peak at 169.5 ppm. In a last attempt to determine more details about the interaction between the amide and Et_3B, the NMR sample of mixed amide-Et_3B from figure 20b was subjected to an aqueous workup followed by extraction. As seen in figure 20c, the single amide peak re-appears highlighting that nothing untoward happened to **155** stemming from Et_3B. These results suggest that the amide coordinates to Et_3B and forms a boron-amidonium complex (**182**) that is deprotonated under the basic reaction conditions to furnish cesium boron amidate salt **183** (Scheme 22). Referring back to Table 27, when all reagents were premixed and then exposed to air (Table 27, Entry 2a), the species generated from mixing of amide with Et_3B (e.g., **182**), is likely to be a stable boron amidate complex which resist autoxidation. Presumably, this coordination must not be reversible on the time scale of this transformation (i.e., Et_3B has a huge k_{off} from the amide) which in turn explains how no decomposition of the Et_3B occurs when the reaction mixture is exposed to air for extended periods of time prior to addition of the remaining reaction components.

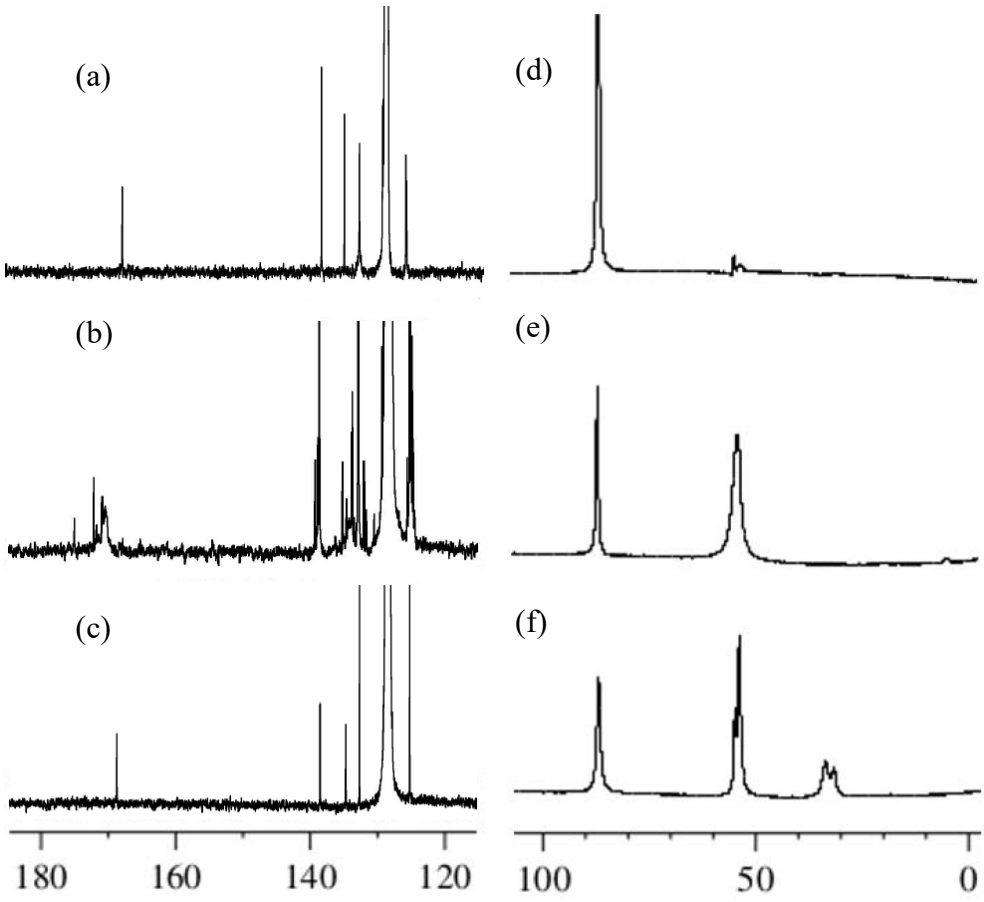
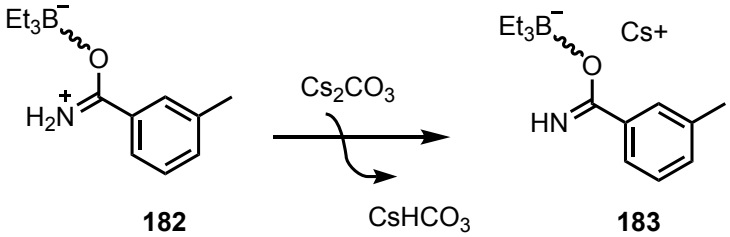


Figure 20. NMR spectra for Et_3B and amide **155**. Spectra are all run in benzene-d_6 at 75 °C. (a) ^{13}C NMR spectrum of amide **155**. (b) ^{13}C NMR spectrum of amide **155** plus Et_3B (1:1). (c) ^{13}C NMR spectrum of sample in b) following aqueous extraction. (d) ^{11}B NMR spectrum of Et_3B prepared with rigorous exclusion of air. (e) ^{11}B NMR spectrum amide **155** plus Et_3B. (f) ^{11}B NMR spectrum of Et_3B sample from panel (a) after brief exposure to air.



Scheme 22. Formation of the cesium boron amidate salt (**183**)

When the same series of experiments were conducted with (*sec*Bu)$_3$B changes to both the ^{11}B and ^{13}C NMR spectra were less notable. Mixing (*sec*Bu)$_3$B with the amide **155** led to no significant

changes in both ^{11}B and ^{13}C NMR spectra (Figure 21a-21d), implying that complexation with this alkylborane is weaker than Et_3B.

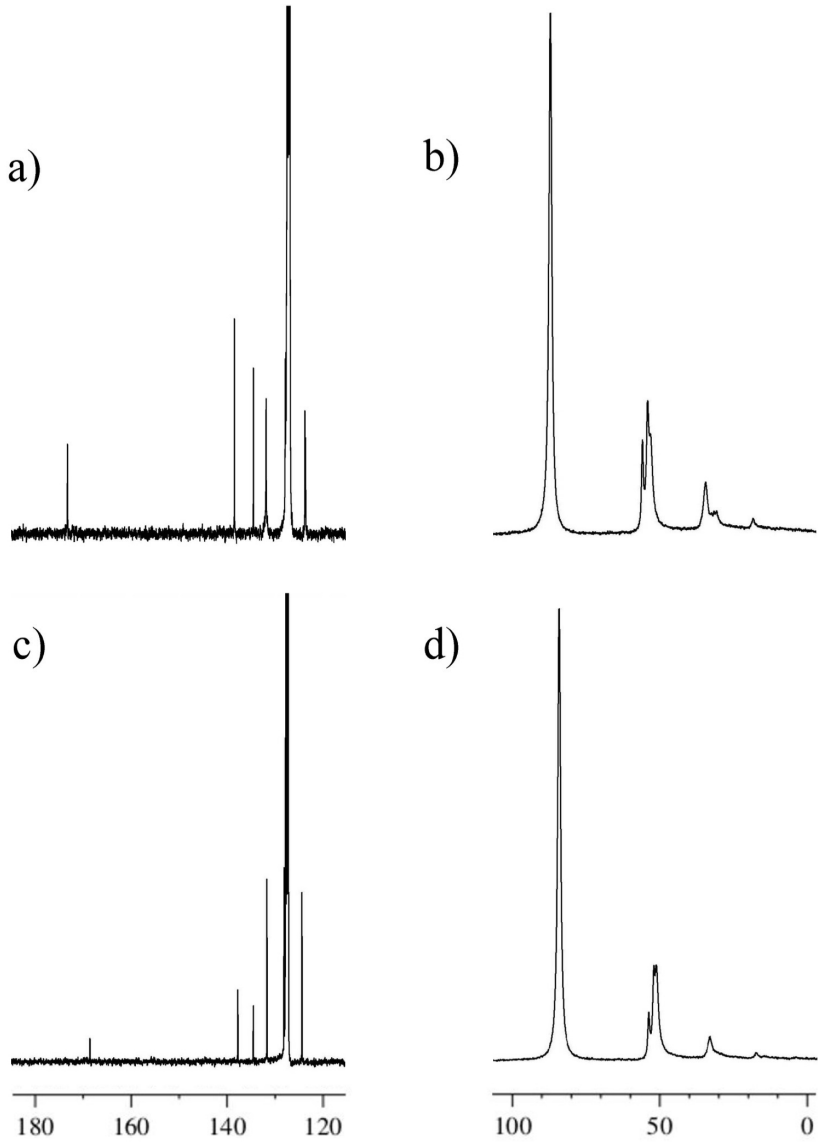


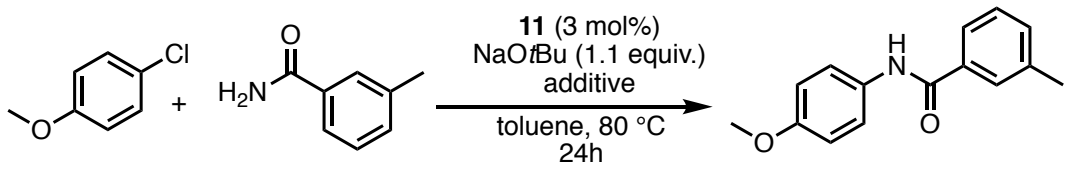
Figure 21. NMR spectra for (*sec*Bu)$_3$B and amide **155**. Spectra are all run in benzene D_6 at 75 °C. (a) ^{13}C NMR spectrum of amide **155**. (b) ^{11}B NMR spectrum of (*sec*Bu)$_3$B prepared with rigorous exclusion of air. (c) ^{13}C NMR spectrum of amide **155** plus (*sec*Bu)$_3$B (1:1). (d) ^{11}B NMR spectrum amide **155** plus (*sec*Bu)$_3$B.

With strong sigma-donating NHC ligands, it has been shown that the OA is facile, while the large size of bulky NHCs used in this thesis dramatically drives RE forward. This means that the rate-

limiting step of Pd-NHC catalyzed amination is believed to be closely associated with amine coordination (in the case of aniline nucleophiles) and/or deprotonation (in the case of alkyl amines). For example, Organ and co-workers published detailed rate and computational studies on amination with aniline derivatives using *Pd-PEPPSI* complexes where they identified amine-coordination to Pd^{II} as the rate limiting step.[170] In 2014, the same group disclosed that with the bulky *Pd-PEPPSI-IPent^{Cl}-o-picoline* pre-catalyst (**52**) both the OA and RE steps in the amination of deactivated anilines and aryl halides are spontaneous at room temperatures.[91] With the more electron-poor amide nucleophilic partners, as in the case of anilines, amine coordination is almost assuredly the rate-limiting step. Recalling that this amide coupling proceeded very well in the absence of a coordinating group on either coupling partners further moves the attention away from boron promoting the RE step as suggested by Hartwig,[114] at least with NHC ligands. Under the basic reaction conditions of these couplings it is reasonable to propose that the Lewis acid forms a boron-amidate complex (e.g., **183**) that boosts the amide's nucleophilicity thereby facilitating the amide coordination step. With Et_3B, amide complexation is rapid and complete, hence the lack of oxygen sensitivity for Et_3B. Conversely, (*sec*Bu)$_3$B, due to its additional steric bulk and lower Lewis acidity, only forms weak amide complexes that may very well be part of an equilibrium favouring the dissociated complex (i.e., small k_{on} and k_{off} rates), which is supported by the NMR spectroscopic study in Figure 19. In support of these hypotheses, when the Et_3B- amidate complex (100 mol%) was pre-formed by stirring equimolar Et_3B and amide for 1h, followed by addition of the remaining reaction components, the reaction proceeded to full conversion (Table 28, Entry 5). When the coupling was performed with NaO*t*Bu in the absence of any Lewis acids (Table 28, Entry 1), no conversion to the product was obtained. There is no successful report of this coupling with NaO*t*Bu in the literature, presumably because not only is the base not strong enough to

deprotonate the amide prior to binding to Pd^{II}, but also it outcompetes the amide for the metal-center thus taking the metal off cycle. However, in the presence of 20 mol% of Et_3B, the amide coupling proceeded to completion, presumably because the amidate now can be formed due to the enhanced pK_a of the coordinated amide and, once formed, the amidate preferentially coordinates to the metal over *tert*-butoxide (Entry 2).

Table 28. Effect of Lewis-acid additive on amide coupling using NaO*t*Bu and *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**)



73 (1.0 equiv.) **155** (1.3 equiv.) **156**

Entry	additive (20 mol%)	Conv. of **73** [%][a]
1	none	0
2	Et_3B	100

[a] Percent conversion of **73** to **156** was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture.

Based on the experience that the Organ group have had in hydrostannylation, it is reasonable to assume that something different could be happening in the case of BCF. Jordan and co-workers, demonstrated that BCF has the ability to abstract anion ligands from Pd^{II}, thus generating cationic Pd species.[171] In 2017, Becica and Dobereiner reported a very detailed mechanistic study on the use of metal triflate Lewis acids in Pd-catalyzed cross-coupling of amides and aryl halides using *xantphos* (**68**) as the ligand[115]. They proposed that the metal triflate additives promote halide abstraction from the OA intermediate to form $[(xant)Pd(Ph)]^+$. The formation of such cationic Pd species was evidenced by stoichiometric ^{31}P NMR studies and this intermediate with its increased

electrophilicity was postulated to bind to the weak amide nucleophile more readily, hence facilitating the rate-limiting amide-binding step. Taken together, one might attribute the observed acceleration effect in amide coupling using BCF as the promoter (in the presence of **11** as the pre-catalyst) to the anion abstracting ability of this particular Lewis acid.

4.7. **Conclusion**

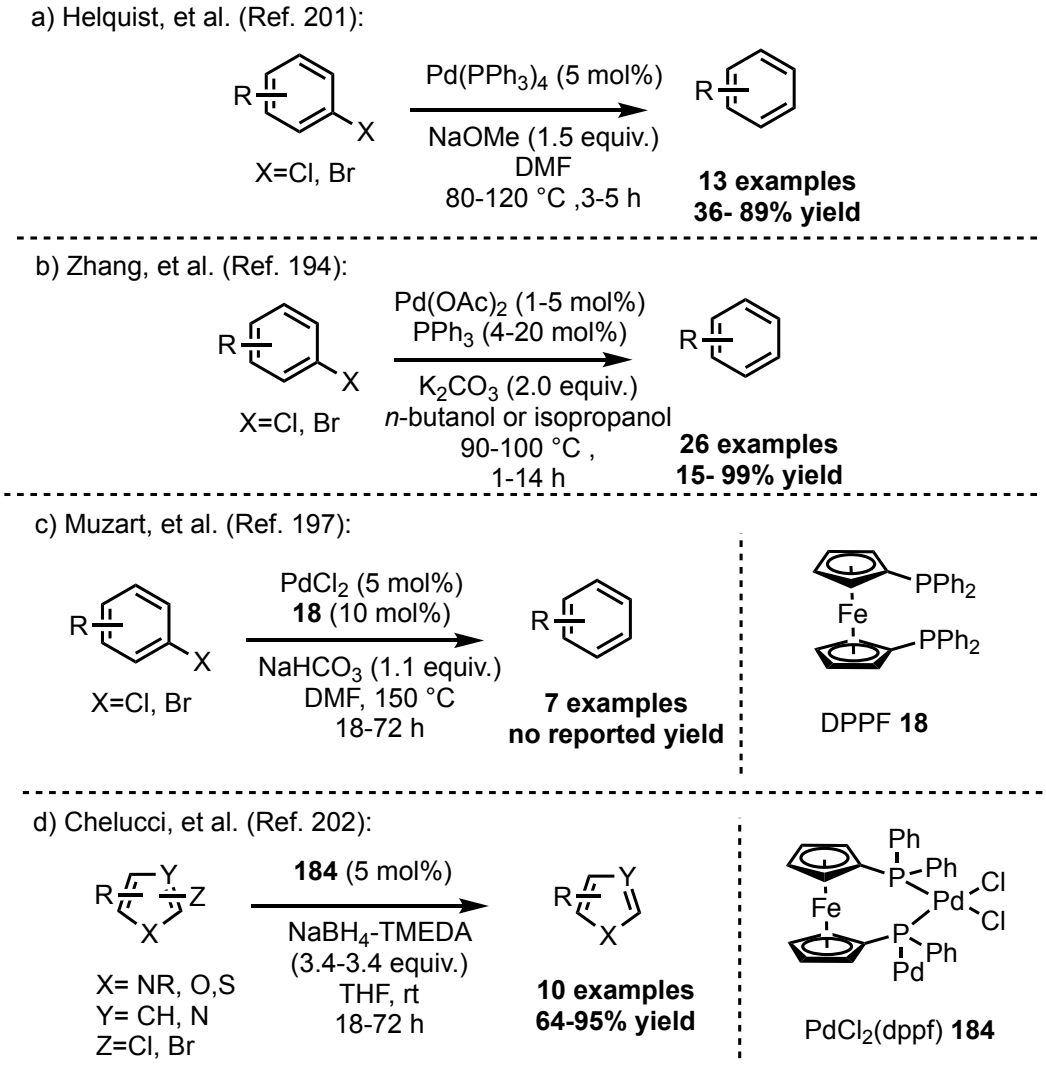
A series of bulky of Pd-NHC catalyst were evaluated in *N*-aryl amidation reactions. The initial screening results revealed that the steric bulk of the catalyst governs the success of the coupling, with the bulkiest NHC ligand *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) showing the best initial results. Following an earlier study by Hartwig and co-workers, the impact of Lewis acids on this coupling was then investigated. Boron-based Lewis acids such as (*sec*Bu)$_3$B, Et$_3$B, and BCF were demonstrated to be excellent promotors in this coupling and (*sec*Bu)$_3$B was chosen as the promotor for application studies of this new method due to its ease of use and low cost. The couplings are easy to set up and do not require careful exclusion of air. The scope and functional group compatibility of these condition allowed for the efficient coupling of wide variety of electrophiles bearing base ketone, nitrile, and nitro groups under very mild conditions (e.g., carbonate base). Additionally, using this method, sterically congested aryl halides, which had proven to be challenging coupling partners, were readily coupled with wide range of amides. In order to better understand the acceleration effect imparted by the Lewis acids in this reaction, a series of control experiments and detailed NMR studies were performed. Based on the results, it appears that under basic reaction conditions, alkylboranes form a boron-amidate complex that assists the amide binding to Pd^{II} that, in turn, pushes the coupling forward.

Chapter 5- BHT-Mediated Hydrodehalogenation of Aryl Halides Using Pd-NHC Complexes

5.1. Background

Aryl halides are very important substrates in organic chemistry with broad applications such as starting materials for metal-mediated cross-coupling reactions as we have seen in this thesis. Halides are also prevalent is the core structure of many natural products, pharmaceuticals and agrochemicals.[172–174] Additionally, halide functionalities can serve as useful protecting and directing groups in organic synthesis.[175] For instance, they have been frequently employed as protecting groups in regioselective synthesis of *ortho*-substituted benzenes.[175] On the other hand, many of aryl halides are considered as persistent organic pollutants with adverse effect on human health and the environment.[176] Therefore, hydrodehalogenation of aryl halides has received considerable attention from the environmental perspective. After fulfilling their obligations, reductive removal of the halide functionality (hydrodehalogenation) is usually necessary for completing the synthetic route. Also addressing the environmental concern over halogenated organics in waste streams, hydrodehalogenation of aryl halides has received considerable attention to address that problem and many methods have been developed over the years. Usually these protocols are transition-metal mediated and metals such as iron,[177,178] rhodium,[179,180] palladium,[181–187] and nickel[188,189] have catalyzed this transformation. Among these metals, Pd has become the metal of choice since it has shown very good reactivity in numerous aryl halide transformations and many systems based on homogenous and heterogeneous Pd-catalysts have been developed to date.[190] A variety of hydride sources have been employed in this transformation such as molecular hydrogen,[191,192] metal hydrides,[193] hydride transfer agents including alcohols,[13,19] alkoxides,[184,185] formic acid and its salts,[195,196] DMF,[197] silane,[198] hydrazine,[199] and paraformaldehyde.[200]

Phosphine and NHC ligands have been used as ancillary ligands in these Pd-catalyzed hydrodehalogenation reactions. The first example of hydrodehalogenation of aryl halides catalyzed by $Pd(PPh_3)_4$ was reported by Helquist in 1978, where sodium methoxide was employed as the source of hydride (Scheme 23a). Using this method, a variety of aryl bromides and chlorides were reduced to the corresponding arene in moderate to excellent yield, albeit at high temperatures (e.g., 120°C).[201]

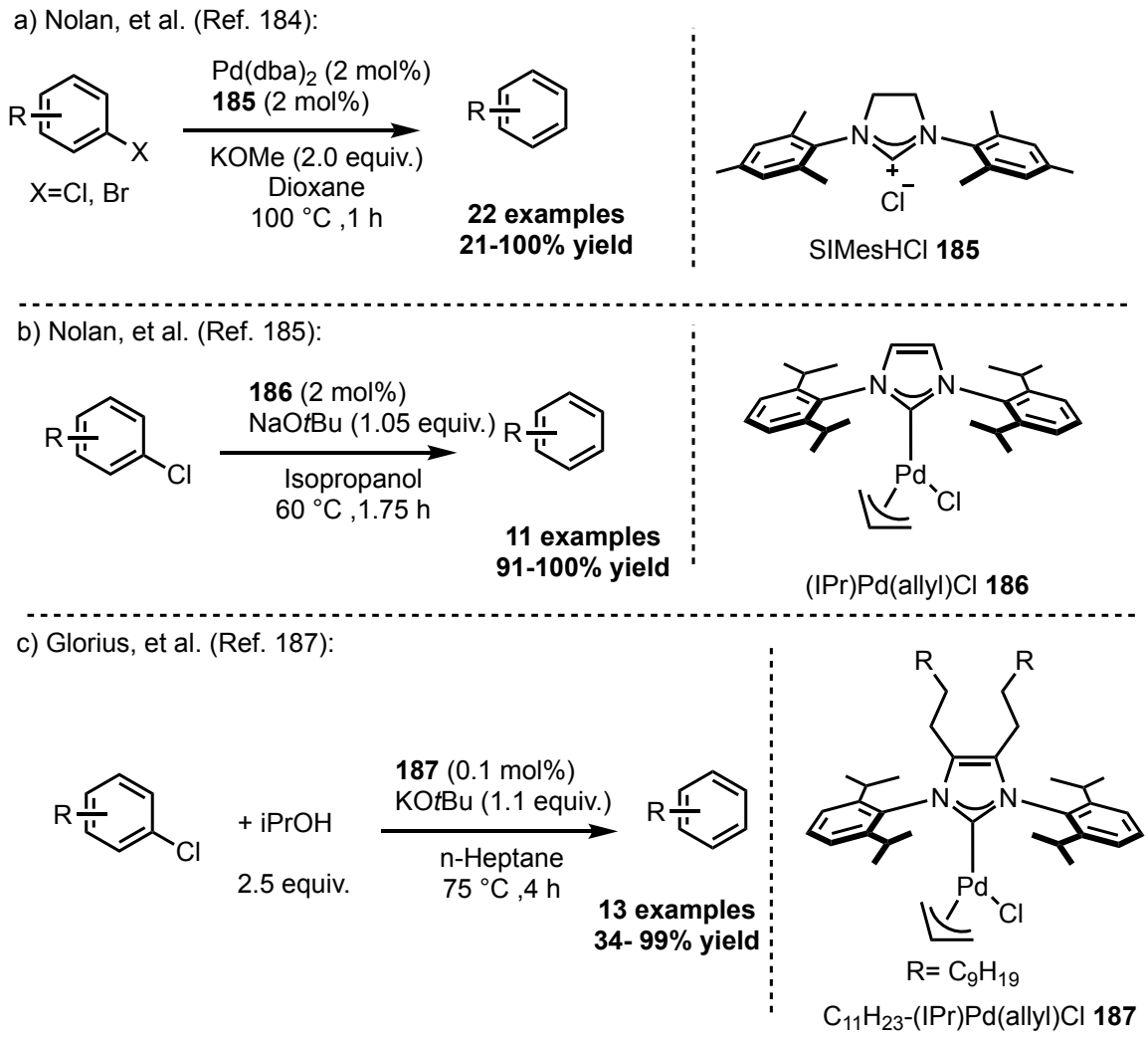


Scheme 23. Selected example of Pd-catalyzed hydrodehalogenation of aryl halides using phosphine ligands.

Following Helquist's report, a number of other methods have been developed for hydrodehalogenation of aryl halides using phosphine ligands. For example, in 2007 Zhang and co-workers reported a useful catalyst system based on $Pd(OAc)_2/PPh_3$ where K_2CO_3 and either isopropanol or n-butanol were used as the base and the hydride source, respectively.[194] Using this catalyst system, a variety of aryl halide bearing various functional groups were reduced to their corresponding arene in moderate to excellent yields (Scheme 23b). Shortly after, Muzart found the catalyst derived from $PdCl_2$ and dppf to be effective in hydrodehalogenating of aryl bromides and iodides with DMF as the source of hydride and sodium bicarbonate as the base (Scheme 23c).[197] However, temperatures in excess of 150 °C and prolonged reaction times in excess of 48 h were required to achieve full conversion. In 2012, Chelucci reported that the $PdCl_2$/dppf system in combination with $NaBH_4$-TMEDA can serve as an efficient system for hydrodehalogenation of wide variety of five-membered heterocycles in moderate to excellent yields (Scheme 23d).[202] Of note, a large excess of the $NaBH_4$-TMEDA pair (e.g., 3.4 equivalents) was needed to achieve full substitution of the halogen atom with hydrogen.

The use of NHCs as ancillary ligand in hydrodehalogenation of aryl halides was first reported in 2001 by Nolan and co-workers. Using $Pd(dba)_2$/*SIMesHCl* as the catalytic system in combination with potassium methoxide (KOMe) as the hydride source, a variety of aryl chlorides and bromides were reduced to their corresponding arene products in moderate to excellent yields, albeit at high temperatures (e.g., 100 °C) (Scheme 24a).[184] In 2004, Nolan and co-workers, while studying the Suzuki-Miyaura cross-coupling of aryl chlorides with phenylboronic acids using *(IPr)Pd(allyl)Cl* (**186**), found the corresponding reduced arene as a side product.[185] Using **186** they developed a set of conditions for hydrodehalogenation of aryl chlorides where *in situ*-generated isopropoxide served as the hydride source (Scheme 24b). This method provided access to variety of arenes in

excellent yields, however, aryl chlorides bearing base sensitive functional groups could not be accommodated. More recently, Glorius and co-workers developed a protocol for hydrodehalogenation of aryl chlorides using *$C_{11}H_{23}$-(IPr)Pd(allyl)Cl* (**187**) pre-catalyst in the presence of isopropanol as the source of hydride and n-Heptane as the solvent.[187] Using this protocol, aryl chlorides including those bearing ester and ketone functionalities were converted to their corresponding arenes (Scheme 24c).



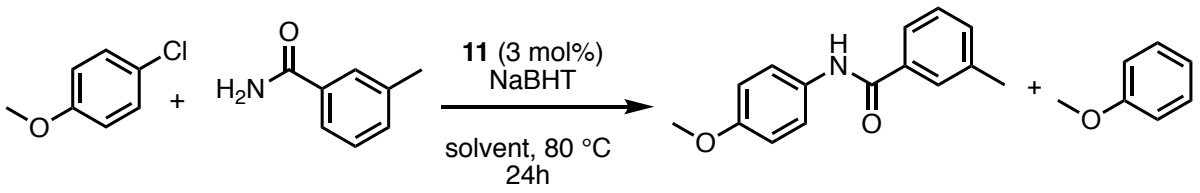
Scheme 24. Selected example of Pd-catalyzed hydrodehalogenation of aryl halides using phosphine ligands.

While the above-mentioned methodologies have proven successful in many instances, the majority still require temperature in excess of 100 °C to achieve acceptable conversions and employ harsh bases that are incompatible with base-sensitive functional groups. Therefore, development of a mild and general protocol for hydrodehalogenation of (hetero)aryl halides in the presence of a mild, cheap and readily available hydride source is still of great importance. During the course of optimization of aryl amidation using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**), we found the hydrodehalogenated arene as the side product when NaBHT (**85**) was employed as base. In light of these observations, it was wondered if **85** is serving as a hydride source in the hydrodehalogenation pathway, and if so how this occurs. Consequently, the aim of this project is to understand the role of **85** in hydrodehalogenation of aryl halides using Pd-NHC complexes.

5.2. **Investigating the reactivity of Pd-NHC complexes in hydrodehalogenation of aryl halides**

During the optimization study of C-N coupling of aryl halides with primary amides, when NaBHT (**85**) was used as the base between 15-50% of the reduced product was formed as the side product (Table 29, Entries 1-3). Increasing the amount of base to 3.0 equivalents, while keeping the other parameters constant, led to exclusive formation of the reduced arene (Entry 4).

Table 29. Aryl amidation using NaBHT (**85**) and *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**)



73 (1.0 equiv.) **155** (1.3 equiv.) **156** **157**

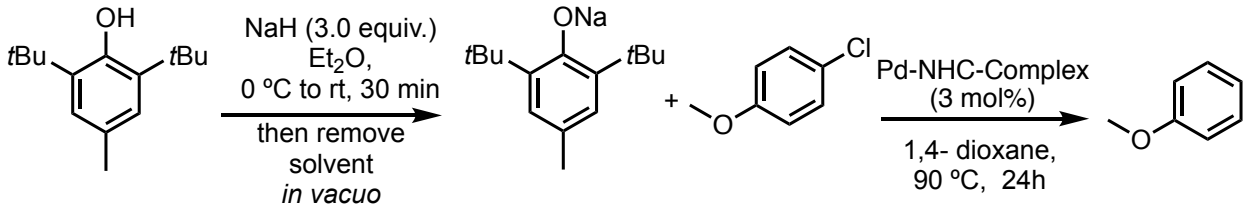
Entry	NaBHT (equiv.)	Solvent (M)	Conv. [%][b] to **156**	Conv. [%][b] to **157**
1	(1.5)	toluene (0.25)	26	50
2	(1.5)	toluene (0.5)	83	15
3	(1.5)	dioxane (0.5)	81	15
4	(3.0)	toluene (0.5)	0	100

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **156** and **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

Interestingly, when the same base was used in combination with *Pd-PEPPSI-IPent^{Cl}* (**50**) in the coupling of primary alkyl amines none of the reduced product was observed (see Chapter 2). It might have been easier to rationalize where the hydride was coming from with alkyl amines as nucelophiles. Given that reduction was not observed, it was even less clear how hydrodehalogenation was occurring in the case of primary amides arylation. To shed light on this, a few questions need to be considered first: 1) does the amide play a role in hydrodehalogenation, 2) is the process catalyzed, and if so, 3) is hydrodehalogenation unique to pre-catalyst **11**? To address these questions, a number of experiments were designed and the results are shown in Table 30. When the reaction was conducted in the absence of the amide nucleophile, the only product observed was the reduced product **157**, which confirms that the amide is not necessary/involved in the hydrodehalogenation process. When the reaction was conducted with other bulky Pd-NHC complexes (*Pd-PEPPSI-IHept^{Cl}* (**51**), *Pd-PEPPSI-IPent^{Cl}* (**50**) or *Pd-PEPPSI-IPent* (**48**)) full

reduction was also observed (Entries 2-4) whereas with *Pd-PEPPSI-IPr* (**46**) the reaction only progressed to 48% conversion (Entry 5). When the reaction was conducted without Pd, no reduction was observed at all (Entry 6) confirming that the hydrodehalogenation process is catalyzed and occurs with any Pd-NHC complex.

Table 30. Impact of Pd-NHC complex on the hydrodehaloneation of **73**[a]



86 (3.0 equiv.) **85** (3.0 equiv.) **73** (1.0 equiv.) **157**

Entry	Pd-NHC Complex	Conv. [%][b]
1	*(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**)	100
2	*Pd-PEPPSI-IHept^{Cl}* (**51**)	100
3	*Pd-PEPPSI-IPent^{Cl}* (**50**)	100
4	*Pd-PEPPSI-IPent* (**48**)	100
5	*Pd-PEPPSI-IPr* (**46**)	48
6	none	0

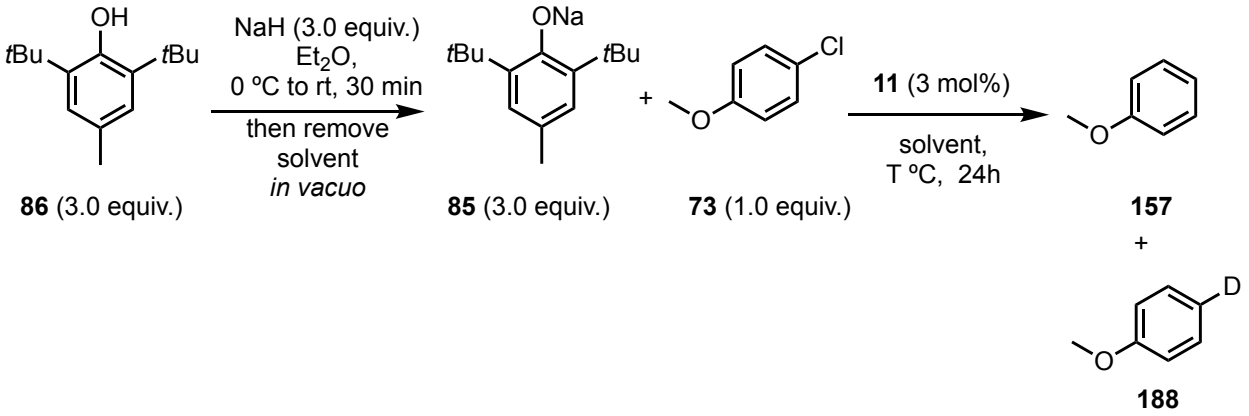
[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and is averaged over two runs.

5.3. **Investigating the impact of solvent in hydrodehalogenation of aryl halides**

Moving forward, to determine whether the solvent has any impact on hydrodehalogenation, a solvent screen was then conducted (Table 31). The course of the reduction did not vary with either ethereal solvents, such as DME and THF (Entries 1 and 2), or aromatic solvents, such as benzene (Entry 3) or toluene (Entry 4). There was no sign of deuterium incorporation when the reaction

was conducted in benzene-d_6 or THF-d_8 (Entries 5 and 6), implying that solvent is not the source of hydride in this reaction.

Table 31. Effect of solvent on hydrodehalogenation of **73**[a]



Entry	solvent	T °C	Conv. [%][b]
1	DME	80	100
2	THF	60	100
3	toluene	90	100
4	benzene	80	100
5[c]	benzene-d_6	80	100
6[c]	THF-d_8	60	100

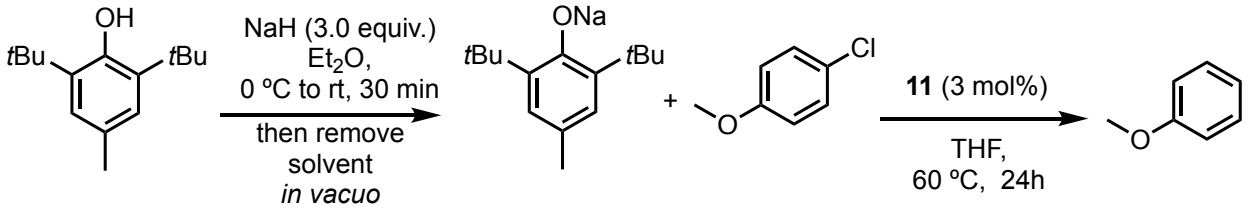
[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and is averaged over two runs. [c] product **188** was not observed.

5.4. **Investigating the source of hydride in hydrodehalogenation of aryl halides**

Next, attention was focused on determining the minimum amount of **85** required for the reaction to proceed to completion (Table 32). With 1.5 equivalents of **85** the reaction proceeded to 56% conversion (Entry 1) and further increasing **85** to 2.0 equivalents resulted in a 14% jump in

conversion to **157** (Entry 2). Full conversion to **157** could be achieved with 2.5 equivalents of **85** (Entry 3). Moreover, diluting the reaction was found to have no significant impact on conversion (Compare entries 4 and 5). Lastly, when LiBHT was used in place of NaBHT, the reaction went to full conversion, implying that the counter ion of phenolate does not have an appreciable effect on the reaction (Entry 6). It is noteworthy that in all cases where the reaction reached completion, 80% of BHT was recovered after workup followed by purification.

Table 32. Influence of amounts of **85** on the conversion of **73** into **157**[a]



86 **85** **73** (1.0 equiv.) **157**

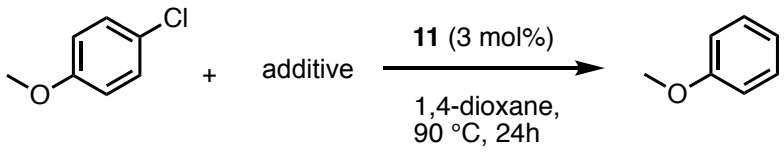
Entry	**85** (equiv.)	[**73**] M	Conv. [%][b]
1	1.5	0.5	56
2	2	0.5	70
3	2.5	0.5	100
4	3.0	0.5	100
5	3.0	0.25	90
6[c]	3.0	0.5	100

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and is averaged over two runs. [c] LiBHT was used instead of NaBHT.

To further investigate the source of hydride in this process a number of experiments were designed and the results from those experiments are described in Table 33. In an initial experiment when the reaction was performed in the absence of NaBHT (**85**), no conversion to the reduced arene was

observed, confirming that a basic additive is required to promote the transformation (Entry 1). When other basic additives (e.g., Cs_2CO_3 and NaO*t*Bu) were employed in place of **85**, no conversion to **157** occurred (Entries 2 and 3). Of note, in all instances, NaBHT (**85**) was prepared *in situ* by stirring equimolar BHT and NaH in diethyl ether for 30 min., followed by *in vacuo* removal of diethyl ether. Therefore, it is possible that any trace amounts of unreacted BHT and/or NaH might be involved in hydrodehalogenation reaction. To shed light on this hypothesis, BHT and NaH were used separately as additives in this reaction. With 3.0 equivalents of BHT, no conversion to product was observed (Entry 4), whereas with 3.0 equivalents of NaH there was 25% conversion to product (Entry 5), which is interesting as NaH is not thought of as a hydride source. To confirm that NaH is not serving as the source of hydride in the hydrodehalogenation $NaNH_2$ was examined. NaBHT was prepared in the usual way employing $NaNH_2$ in diethyl ether for 30 min., followed by *in vacuo* removal of diethyl ether (Entry 6). Full reduction of **73** was observed supporting that NaH could not be the source of hydride in this reaction under the usual conditions (e.g., Table 32, Entry 4).

Table 33. Influence of different base additives on the conversion of **73** into **157**[a]



73 (1.0 equiv.) **157**

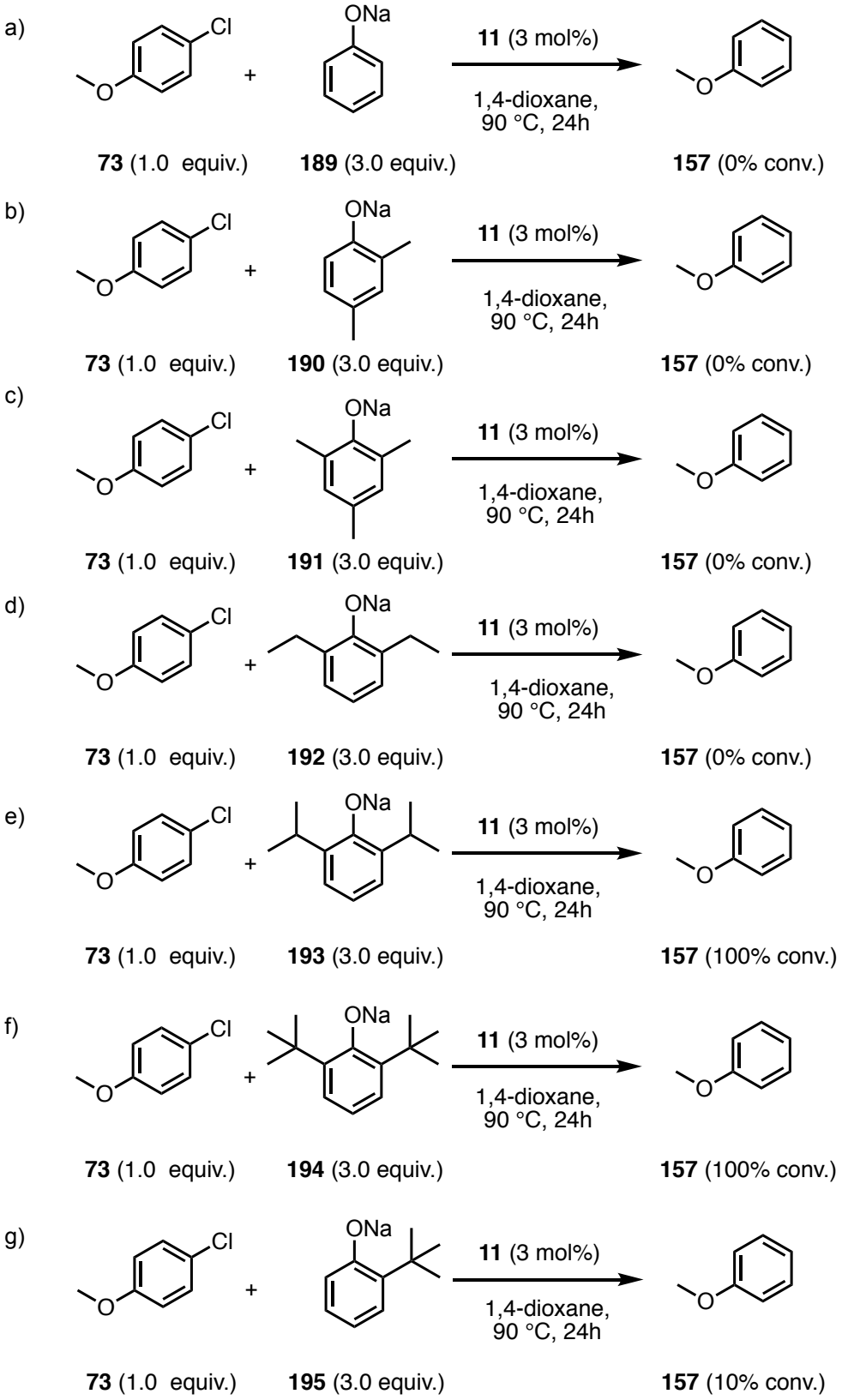
Entry	additive (equiv.)	Conv. [%][b]
1	-	0
2	Cs_2CO_3 (3.0)	0
3	NaO*t*Bu (3.0)	0
4	BHT (3.0)	0
5	NaH (3.0)	25
6[c]	NaBHT (3.0)	100

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and are averaged over two runs. [c] BHT was deprotonated with $NaNH_2$.

5.5. **Investigating the impact of phenolate structure on hydrodehalogenation of aryl halides**

At this point, it was wondered whether there is a correlation between the structure of phenolate additive and its activity as a hydride source. To this end, substituents on the phenolate were varied systematically to determine their effect on the hydride donor activity of NaBHT during the hydrodehalogenation of **73** in the presence of pre-catalyst **11**. When Na-phenolate (**189**), the least bulky phenolate, was used no reduction occurred at all (Scheme 25a) confirming that the *ortho* substituent(s) on the phenolate are crucial for this reaction. With sodium 2,4-dimethyl phenolate (**190**), no reaction occurred and only starting material was recovered (Scheme 25b). In light of these observations, it was speculated that di-*ortho* substituents on phenolate are likely required for

it to act as a hydride source. To examine this assumption, sodium-2,4,6-tri-methyl phenolate (**191**) was employed in the model reaction and again no conversion to product was observed (Scheme 25c). In order to determine whether steric bulk of the *ortho*-substituents has any impact on activity of phenolate as hydride source, sodium 2,6-diethyl phenolate (**192**) was prepared and used in the reaction, and once again no arene was formed (Scheme 25d). With sodium 2,6-di-*iso*propyl phenolate (**193**) featuring more sterically bulky *ortho*-substituents, the reaction proceeded to completion and **157** was formed exclusively (Scheme 25e). So, while it may not be 'bulk' per se that leads to the hydride donor capability to commence, it is possible that the additional methyl groups on **193** vs. **192** cause the terminal hydride now to enter a more reactive conformation, causing it to become susceptible to being transferred.



Scheme 25. Effect of phenolate substituents on the conversion of **73** into **157**.

Full conversion to **157** was obtained with 2,6-di-*tert*-butyl phenolate (**194**) (Scheme 25f), which not only highlights the importance of the bulky substituents at the *ortho* position of the phenolate it shows that the hydride need not come from the activated benzylic (i.e., 4-methyl) position of BHT (Scheme 25f). Lastly, with 2-*tert*-butyl phenolate (**195**) the reaction only proceeded to 10% completion, further emphasizing that bulk at both *ortho* positions is necessary for ready hydride transfer.

5.6. **Investigating the mechanism of hydrodehalogenation of aryl halides by NaBHT**

As mentioned previously, after the reaction had proceeded to completion, 2.4 equivalents (80%) of BHT (**86**) could be recovered. Assuming that each molecule of NaBHT can only deliver one hydride, theoretically no more than 66% of BHT could be recovered after the reaction is over. Further puzzling is that if the majority of BHT is recovered, why 2.5 or more equivalents are required to get the reduction to proceed efficiently to product? That 80% of BHT being recovered after the reaction, two possible scenarios come to mind: 1) each molecule of BHT is delivering more than one hydride; or 2) a BHT-based intermediate is being formed during the reaction that upon workup reverts back to BHT. To examine these scenarios, the progress of reaction of **73** with NaBHT (**85)** in the presence of pre-catalyst **11** was monitored by ^{1}H NMR spectroscopy (Figure 22). Figure 22a shows the ^{1}H NMR spectrum of the reaction mixture 2 min. after the addition of **73** and no significant changes to ^{1}H NMR spectrum were observed after 1h (Figure 22b). After 3h, a broad singlet peak at 5.50 ppm started to emerge (Figure 22c). More notable changes to ^{1}H NMR spectrum of the reaction mixture were noticed after 24h (Figure 22d). When comparing Figure 22a with 22d, a significant downfield shift for aromatic protons of BHT could be noticed. Second, the

peak at 5.50 ppm dramatically intensified, 3) few other resonances appeared at aromatic region, the two most prominent of which are the singlet peaks at 9.90 and 6.58 ppm.

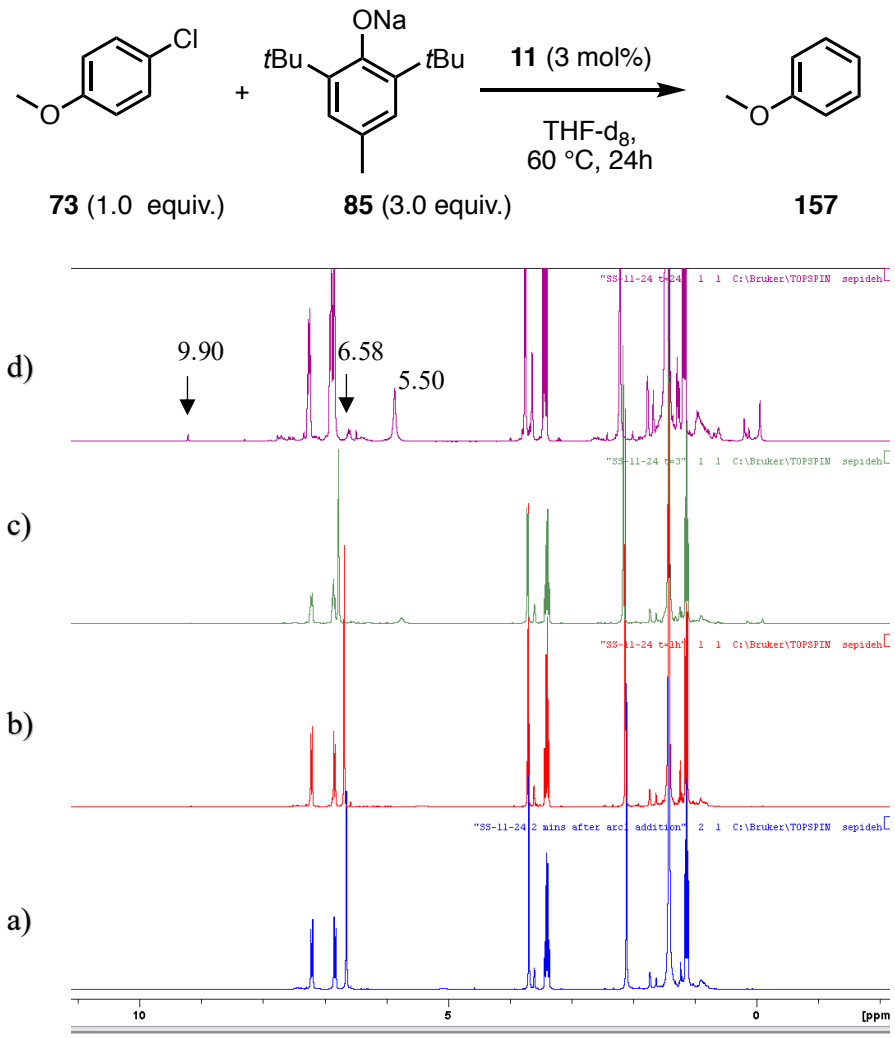
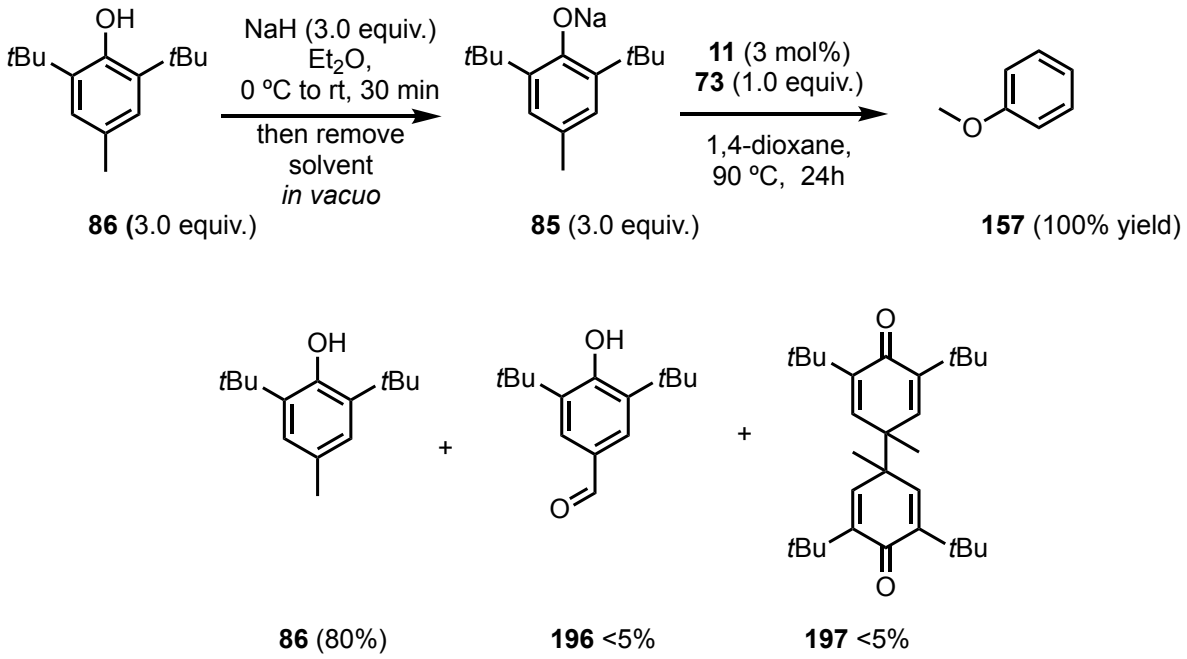


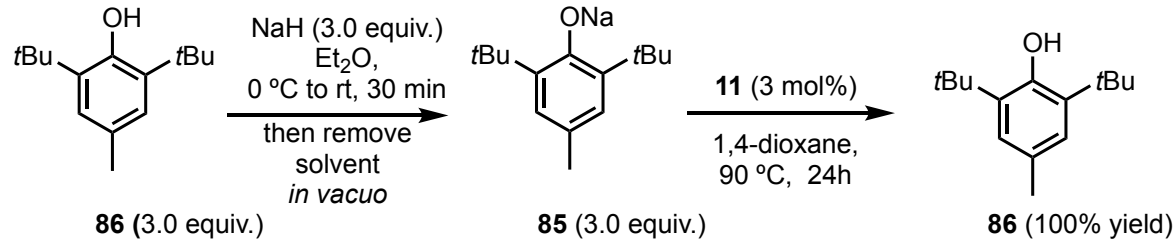
Figure 22. ^{1}H NMR spectra of the reaction mixture after a) 2min, b) 1h, c) 3h, d) 24h.

Of note, careful ^{1}H NMR spectroscopic analysis of the crude reaction mixture of the previously run hydrodehalogenation of **73** using **85** and **11**, revealed the presence of the same resonances at 9.90 and 6.57 ppm. Attempts to isolate any by-product(s) formed during the reaction led to isolation of trace amounts of 3,5-di-*t*-butyl-4-hydroxybenzaldehyde (**196**) and dimerized BHT (**197**) (Scheme 26). Both **196** and **197** were fully characterized by ^{1}H NMR, ^{13}C NMR and HRMS.



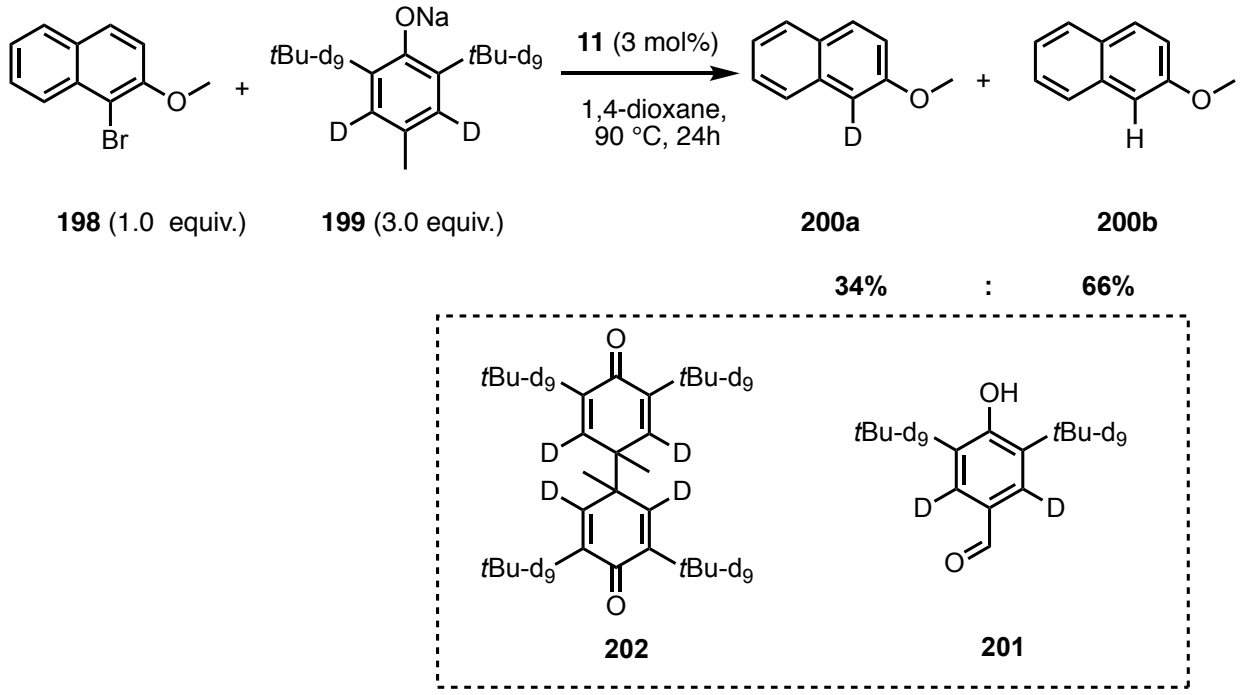
Scheme 26. By-products of the dehalogenation reaction of **73** with **11**.

While the formation of **196** supports the idea of one molecule of BHT is delivering more than one molecule of hydride, it clearly cannot be the only source of hydride, assuming that the aldehyde is the product of hydride delivery from NaBHT. To further examine whether **196** and **197** are the by-products of the hydrodehalogenation reaction and not the products of degradation of **85** under reaction conditions, an experiment was conducted in which NaBHT (**85**) and 1 mol% of **11** were mixed in dioxane and allowed to stir at 90 °C for 24h. No trace amounts of **196** and **197** were detected and 100% of **86** was recovered (Scheme 27).



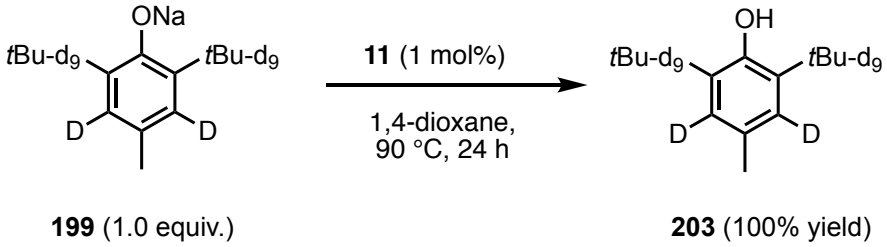
Scheme 27. Investigation of the stability of **85** under reaction conditions.

To gain more insight on the reaction mechanism and further confirm that NaBHT is serving as a hydride delivering agent in this hydrodehlagenation chemistry, BHT-d_{21} was employed in the reaction (Scheme 28). For the ease of purification and isolation purposes, it was decided to use aryl halide **198** for this reaction. The hydrodebromination of **198** by **199** resulted in deuterium incorporation of 34% in the reduced product. Of note, trace amounts of **201** and **202** by-products were observe in the crude mixture. The observed partial deuterium incorporation implies that 66% of the reduced product (**200b**) likely originates from a pathway which involves the *para*-methyl group in **199** and the other 34% (**200a**) likely comes from a different pathway involving any of the deuterated sites (this assumes no deuterium isotope effect). Furthermore, formation of by-product **201** confirms that the *para*-methyl group in **199** can deliver two molecules of hydride in the process.



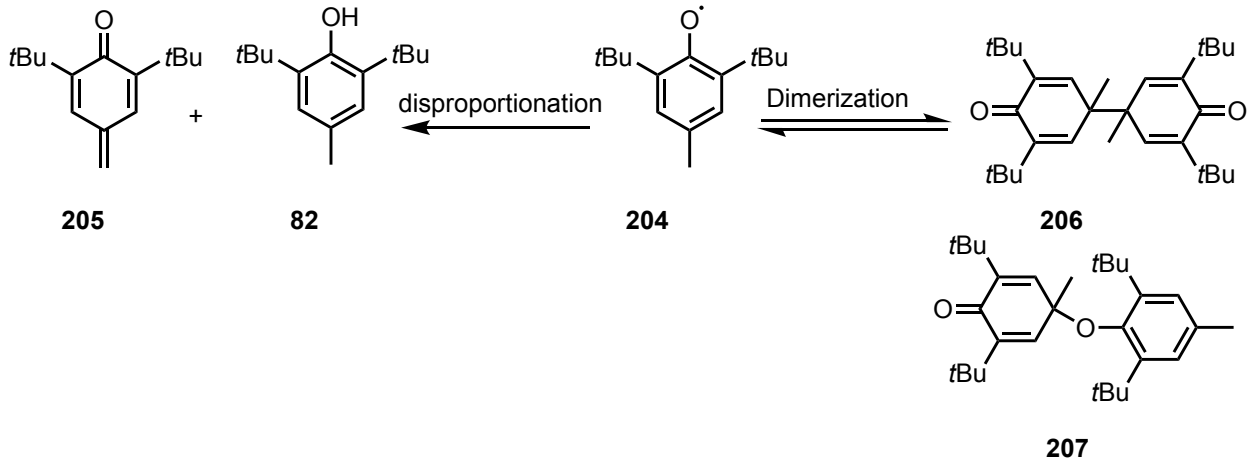
Scheme 28. Determination of deuterium incorporation in hydrodehalogenation of **198** with **199** and pre-catalyst **11**.

That said, this proposal that two different pathways are operative would be true only if no scrambling occurred in the reaction. When **199** was mixed with catalytic amount of **11** (e.g., 1 mol%) (Scheme 29), no H/D exchange was observed by ^{1}H NMR spectroscopy further supporting the possibility of having two different pathways in this hydrodehalogenation chemistry.



Scheme 29. Investigation the possibility of H/D scrambling in **199** under reaction conditions.

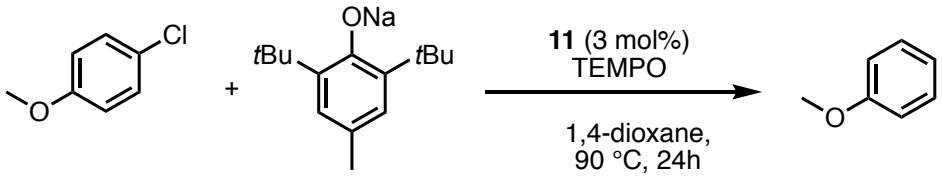
BHT is known to react with trace oxygen to generate radicals[203,204] and it has been shown that phenoxy radicals such as **204**, disproportionate very rapidly in solution to form **86** and quinone methide **205** which is labile and degrades in solution (Scheme 30).[203] Phenoxy radicals can also dimerize reversibly to form BHT-dimer **206** (Scheme 30); it has been shown that dimerization through C-O coupling (i.e., **207**) cannot occur due to steric restrictions.[203]



Scheme 30. Disproportionation and dimerization of phenoxy radical **204**.[203]

That said, it is might be reasonable to expect that BHT-mediated hydrodehalogenation to proceed through a radical pathway. To examine whether radicals are involved, the reaction was conducted in the presence of a radical scavenger and the results are presented in Table 34. In parallel reactions, the amount of TEMPO was increased from 0 to 0.5 equivalents and the impact is clear (Entries 1-5). With 0.5 equivalents of TEMPO the reaction was completely shut down and no conversion to **157** was observed.

Table 34. Effect of radical scavenger on hydrodehalogenation of **73** using **85** and **11**[a]

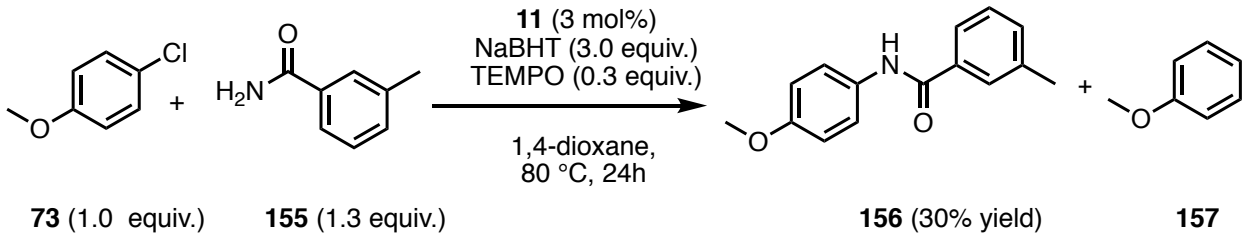


73 (1.0 equiv.) **85** (3.0 equiv.) **157**

Entry	TEMPO (equiv.)	Conv. [%][b]
1	0	100
2	0.1	26
3	0.2	15
4	0.3	8
5	0.5	0

[a] Reactions were conducted on a 0.25 mmol scale. [b] Percent conversion of **73** to **157** was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and is averaged over two runs.

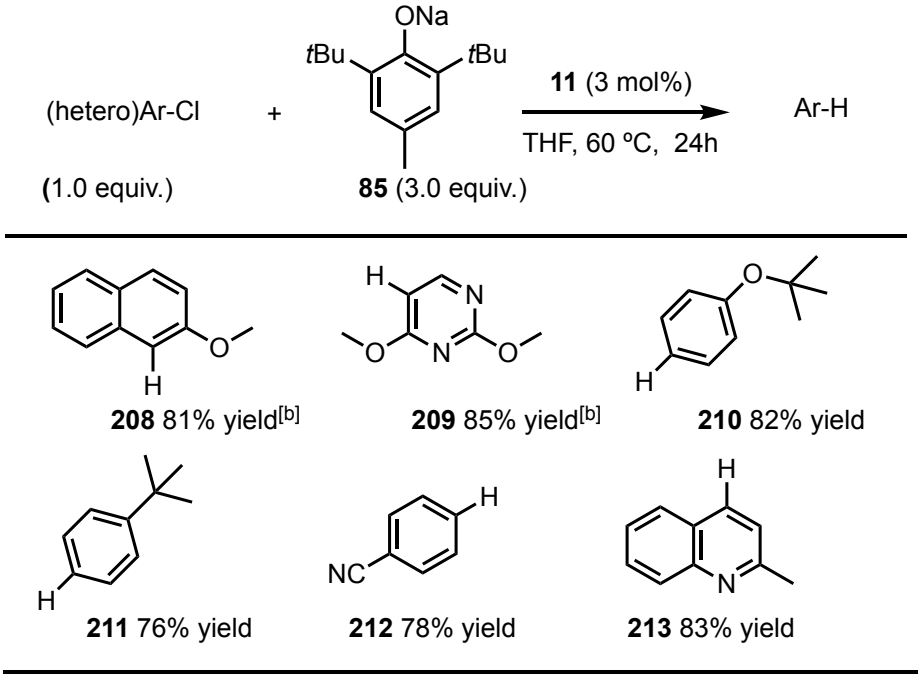
Recall, in our aryl amidation with Pd-NHC complexes, the use of 3.0 equivalents of NaBHT as base led exclusively to the formation of **157**. Now, when the same reaction was conducted in the presence of 0.3 equivalent of TEMPO we started to see some conversion to the desired product and we were able to isolate **156** in 30% yield (Scheme 31).



Scheme 31. Effect of TEMPO on aryl amidation with **85**.

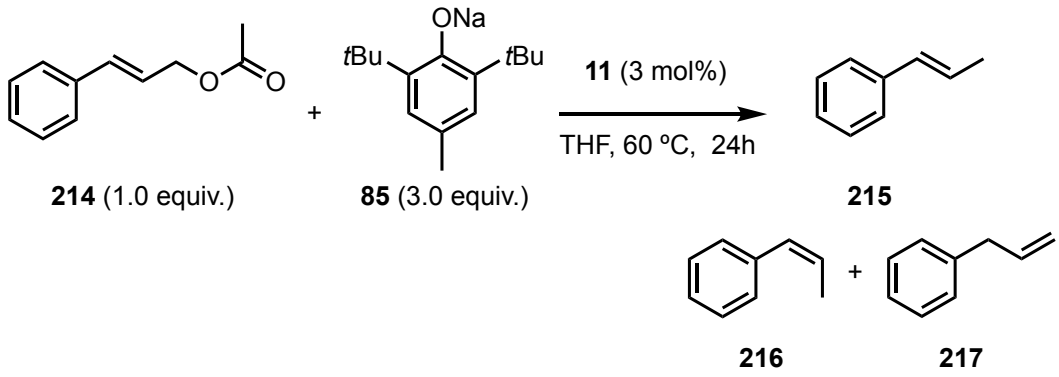
Taken together, these results corroborate the proposal that a redox pathway might be operative in this chemistry, however, the mechanism by which this transformation is proceeding in not clear. Despite this, the substrate scope for this reduction is quite broad (Table 35) and in all instances complete conversion to reduced (hetero)arene were achieved along with 80% recovery of **86** in all instances.

Table 35. Scope of hydrodehalogenation using *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (**11**) and NaBHT[a]



[a] Yields are those of the products isolated after purification by column chromatography on silica gel. [b] The corresponding Ar-Br was used.

Lastly, in light of great reactivity of NaBHT (**85**) in hydrodehalogenation of aryl halides we thought it worthwhile to investigate the use of **85** in reduction of allylic esters. When **214** was reacted with 3.0 equivalents of **85** in the presences of pre-catalyst **11**, the reaction proceeded to completion within 24 h and **215** along with its other regioisomers (**216** and **217**) were formed (Scheme 32).



Scheme 32. Reduction of allylic esters using **85** and pre-catalyst **11**.

5.7. **Conclusion**

In conclusion, it has been shown for the first time that NaBHT (**85**) can serve as a hydride delivering agent in Pd-catalyzed hydrodehalogenation of (hetero)aryl halides. During the course this study, it was found that the hydrodehalogenation is independent of the structure of Pd-NHC complexes and the solvent of the reaction. However, the structure of the phenolate was found to be critical to the success of this protocol, that is, bulky di-*ortho*- substituents on phenolate are required to achieve optimal results. Although the definitive mechanism(s) for this hydrodehalogenation have yet to be firmly elucidated, control experiments reveal that the reaction completely shuts down in the presence of 0.5 equivalents of TEMPO, hinting at radical involvement. Lastly, using pre-catalyst **11** in combination with NaBHT as the source of hydride,

a variety of aryl and heteroaryl halides were successfully reduced to their corresponding arene. NaBHT was also found as an efficient hydride delivering agent in reduction of allylic esters.

Chapter 6- Experimental Procedures

6.1. General experimental

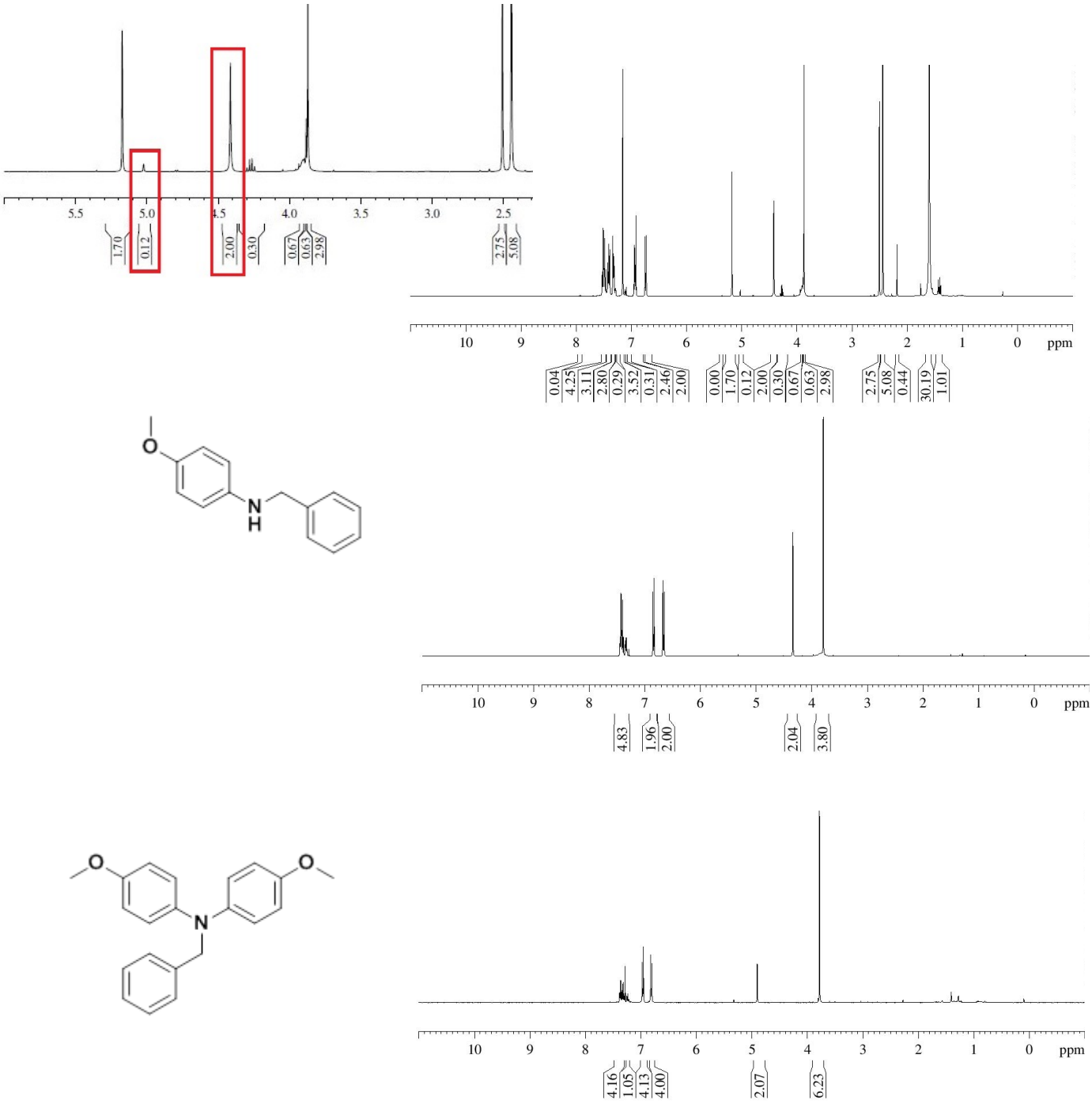
All experiments were conducted under an atmosphere of dry argon in oven-dried glassware using standard Schlenk techniques unless noted otherwise. Experiments performed in an oil bath were done using Fisher Scientific silicone oil in a Pyrex crystallizing dish on top of an IKA RCT basic model magnetic hotplate stirrer with an ETS-D5 electronic contact thermometer. Glovebox manipulations were performed in an MBraun Unilab glove-box under an atmosphere of dry argon. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification unless noted otherwise. Pre-catalysts were acquired from Total Synthesis Ltd., Toronto, Canada. All reaction vials (screw-cap threaded, caps attached, 15x45 mm) were purchased from Fisher Scientific. Analytical thin layer chromatography (TLC) was performed 61 on EMD 60 F254 pre-coated glass plates and spots were visualized with UV light (254 nm). Column chromatography purifications were carried out using either the flash technique on EMD silica gel 60 (230 – 400 mesh) or the Biotage Isolera Four with 25 g SNAP cartridges. NMR spectra were recorded on Bruker 300 AVANCE and Bruker 400 AVANCE spectrometers. The chemical shifts for ^{1}H NMR spectra are given in parts per million (ppm) referenced to the residual proton signal of the deuterated solvent; coupling constants are expressed in Hertz (Hz). ^{13}C NMR spectra were referenced to the carbon signal(s) of the deuterated solvent. ^{19}F NMR Spectra were referenced to (trifluoromethyl)benzene. The ^{11}B NMR spectra were recorded at 128 MHz, using $BF_3.OEt_2$ (0.0 ppm) as the reference standard. The following abbreviations are used to describe peak multiplicities: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quint= quintet, dd = doublet of doublets, tt = triplet of triplets, qt = quartet of triplets, qd = quartet of doublets, and m = multiplet. High Resolution Mass Spectrometry (HRMS) analysis was performed by the

Mass Spectrometry and Proteomics Unit at Queen's University in Kingston, Ontario. The enantiomeric excesses (ee) of the products were determined by High-Performance Liquid Chromatography (HPLC) analysis performed on Agilent 1200 series chromatographs using a Daicel chiral column (25 cm) as noted for each compound.

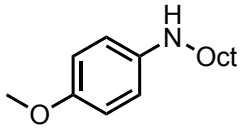
6.2. **Compound characterization data for arylation of primary alkyl amines**

General amination procedure A: In a glovebox, a 10 mL round-bottom flask equipped with magnetic stir bar was charged with 18 mg of 95% purity NaH (0.75 mmol, 1.5 equiv.) and then the flask was sealed with a rubber septum prior to removal from the glovebox. Then, in air, 165.2 mg of 2,6-di-tert-butyl-4-methylphenol (BHT, 0.75 mmol, 1.5 equiv.) was added after which the septum was replaced and the round-bottom flask was evacuated and backfilled with Ar (x3). The flask was then cooled to 0°C and Et_2O (3 mL) was added. After stirring for 15 min at 0°C, the solution was warmed up to rt and allowed to stir for an additional 15 min. The solvent was then removed under high vacuum to yield an off-white solid. To the flask was added 4.2 mg of *Pd-PEPPSI-IPent*^{Cl} (0.005 mmol, 1 mol%) then the vial was evacuated and backfilled with Ar (x2), followed by addition of toluene (5mL). The contents were allowed to stir at rt for 5 min, then the aryl halide (0.5 mmol, 1.0 equiv.) and amine (0.65 mmol, 1.3 equiv.) were added by syringe. Alternatively, if the aryl halide or amine were solids at room temperature, they were added to the vial with *Pd-PEPPSI-IPent*^{Cl} prior to evacuation. The round-bottom flask was placed in a pre-heated 60 °C oil bath, and stirred under argon at 1150 – 1200 rpm for 2 h (or for the indicated period of time). The reaction mixture was cooled to rt, diluted with CH_2Cl_2, filtered through a plug of silica or Celite, and the filtrate concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel (unless noted otherwise) to yield product of >95% purity. Where

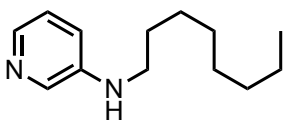
applicable, the ratio of desired product (monoarylamine) to diarylamine product was readily determined by ^{1}H NMR analysis of the crude mixture (for example (**97**) (Table 7)).



General amination procedure B :(for reaction partners with alcohol, phenol, carboxylic acid, or indole functionality): To a 10 mL round bottom flask equipped with a stir bar was added Pd-*PEPPSI-IPent*^{Cl} (1 mol%, 0.005 mmol, 4.2 mg) and the aryl halide (1.0 equiv, 0.5 mmol). The flask was evacuated and back-filled with Ar (3X). 3.9 mL of THF was added followed by the amine (1.1 equiv, 0.55 mmol) and LiHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol). The reaction was vigorously stirred at 60 °C under Ar. Upon consumption of the electrophile, the reaction was allowed to cool to rt, and the vigorously-stirred reaction mixture was acidified to *p*H = 4 using 1.0 M aqueous HCl. The contents of the flask were then transferred to a 60 mL separatory funnel and extracted using 15 mL of CH_2Cl_2 (3X). The organic layer was then dried over anhydrous Na_2SO_4. Filtration and subsequent concentration under reduced pressure yielded the crude reaction mixture, which was then further purified using silica gel column chromatography.

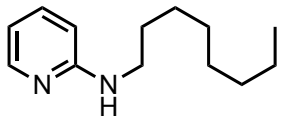


4-methoxy-*N*-octylaniline (**75**) (Table 1). Following general amination procedure A, 105.9 mg of **75** were isolated by flash chromatography (2.5% EtOAc/hexanes, Rf = 0.3) as a yellow oil (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, J = 9.0 Hz, 2H), 6.63 (d, J = 9.0 Hz, 2H), 3.78 (s, 3H), 3.57 (bs, 1H), 3.10 (t, J = 7.2 Hz, 2H), 1.64 (quint, J = 7.2 Hz, 2H), 1.34-1.45 (m, 10 H), 0.94 (t, J = 6.4, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 151.9, 142.6, 114.8, 114.0, 55.7, 45.0, 31.7, 29.5, 29.4, 29.2, 27.1, 22.6, 14.0. The spectral data of the major mono-alkylated product are in accordance with those reported in the literature.[24] The ratio of monoaryl amine to diaryl amine product was determined to be 22:1 by 1H NMR spectroscopic analysis of the crude reaction mixture.

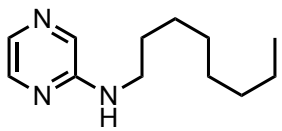


***N*-octylpyridin-3-amine** (**77**) (Table 4). Following general amination procedure A, 89.1 mg of **77** were isolated by flash chromatography (20%

EtOAc/hexanes, R_f = 0.38) as a white solid (86% yield). Mp: 32-35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 6.4 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H),4.57 (bs, 1H), 3.24 (t, *J* = 7.2 Hz, 2H), 1.62 (quint, *J* = 7.2 Hz, 2H), 128-1.42 (m, 10 H), 0.94 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 148.1, 137.2, 112.4, 106.1, 42.2, 31.7, 29.4, 29.2, 29.1, 26.9, 22.5, 13.9. The spectral data of the major product are in accordance with those reported in the literature.[24] The ratio of monoaryl amine to diaryl amine product was determined to be 15:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

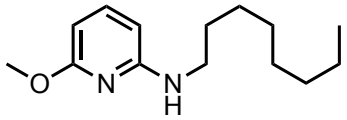


***N*-octylpyridin-2-amine** (**78**) (Table 4). Following general amination procedure, 91.6 mg of **78** were isolated by flash chromatography (30→50% EtOAc/Hexanes, R_f = 0.4) as a light green solid (89% yield). Mp: 46-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.8 Hz, 1H), 7.93 (d, *J* = 4.0 Hz, 1H), 7.04-7.08 (m, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.78 (bs, 1H), 3.10 (q, *J* = 6.4 Hz, 2H), 1.62 (quint, *J* = 7.2 Hz, 2H), 128-1.40 (m, 10 H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.5, 138.3, 136.7, 123.4, 117.1, 43.1, 31.9, 29.4, 29.3, 29.2, 27.0, 22.7, 14.0. The spectral data of the product are in accordance with those reported in the literature.[24] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

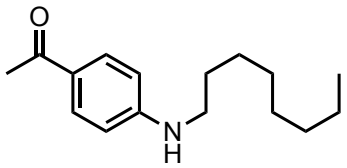


***N*-octylpyrazin-2-amine** (**79**) (Table 4). Following general amination procedure A, 80.7 mg of **79** were isolated by flash chromatography (20% EtOAc/pentane, R_f = 0.32) as an orange solid (87% yield). Mp: 55 - 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.8 Hz, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 2.8 Hz, 1H), 7.28-7.37

(m, 5H), 5.26 (bs, 1H), 4.56 (d, J = 5.6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 141.9, 138.4, 132.9, 132.0, 128.6, 127.5, 127.4, 45.4. The ratio of monoaryl amine to diaryl amine product was determined to be 14:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{11}H_{11}N_3$, 185.0953; found 185.0959.

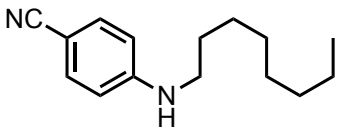


6-methoxy-*N*-octylpyridin-2-amine (**80**) (Table 4). Following general amination procedure A, 102.8 mg of **80** were isolated by flash chromatography (step gradient 2.5% Et_2O/pentane followed by 5% Et_2O/pentane, R_f = 0.5 in 5% Et_2O/pentane) as a colorless oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.0, 7.6 Hz, 1H), 6.02 (d, J = 7.6 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 4.41 (bs, 1H), 3.86 (s, 3H), 3.23 (quart, J = 6.8 Hz, 2H), 1.62 (quint, J = 7.2 Hz, 2H), 1.30-1.42 (m, 10 H), 0.93 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 157.8, 139.8, 97.1, 96.9, 52.9, 42.3, 31.7, 29.5, 29.3, 29.2, 27.0, 22.5, 14.0. The spectral data of the product are in accordance with those reported in the literature.[24] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

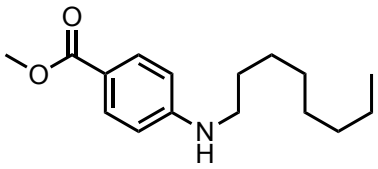


1-(4-(octylamino)phenyl)ethan-1-one (**87**) (Table 6). Following the general amination procedure A, 104.1 mg of **87** were isolated by flash chromatography (20% EtOAc/hexanes, R_f = 0.4) as a white solid (84% yield). Mp: 68-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 4.34 (bs, 1H), 3.17 (dt, J = 6.8, 5.6 Hz, 2H), 2.50 (s, 3H), 1.64 (quint, J = 7.2 Hz, 2H), 1.29-1.40 (m, 10 H), 0.90 (t, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 152.4, 130.8, 126.3, 111.2, 43.3, 31.8, 29.4, 29.3, 29.2, 27.1, 25.9, 22.7, 14.1. The spectral data of the major product are in accordance with those reported in the literature. [24] The ratio of monoaryl

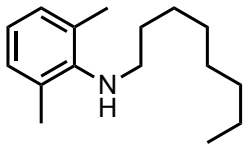
amine to diaryl amine product was determined to be 32:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



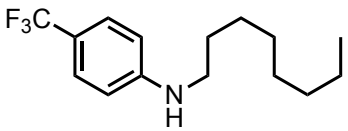
4-(octylamino)benzonitrile (**88**) (Table 6). Following general amination procedure A, 105.0 mg of **88** were isolated by flash chromatography (5% EtOAc/hexanes, R_f = 0.17) as a white solid (90% yield). Mp: 31-33 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.28 (bs, 1H), 3.14 (t, *J* = 6.4 Hz, 2H), 1.63 (quint, *J* = 7.2 Hz, 2H), 1.24-1.40 (m, 10H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 133.5, 120.6, 111.9, 97.9, 43.1, 31.7, 29.2, 29.1, 29.0, 26.9, 22.5, 14.0. The spectral data of the major product are in accordance with those reported in the literature.[205] The ratio of monoaryl amine to diaryl amine product was determined to be 12:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



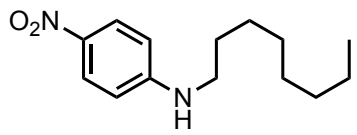
(methyl 4-(octylamino)benzoate) (**89**) (Table 6). Following general amination procedure A, 121.6 mg of **89** were isolated by flash chromatography (0→30% EtOAc/hexanes gradient, R_f = 0.53 in 20% EtOAc/hexanes) as a white solid (92% yield). Mp: 82-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.10 (bs, 1H), 3.87 (s, 3H), 3.17 (quart, *J* = 6.8 Hz, 2H), 1.62 (quint, *J* = 7.2 Hz, 2H), 1.30-1.42 (m, 10 H), 0.91 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 152.1, 131.4, 117.8, 111.2, 51.4, 43.3, 31.7, 29.3, 29.2, 29.1, 27.0, 22.5, 14.0. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{16}H_{15}NO_2$, 263.1885; found 263.1875.



2,6-dimethyl-*N*-octylaniline (**90**) (Table 6). Following general amination procedure A, 105.0 mg of **90** were isolated by flash chromatography (2.5% Et_2O/pentane, R_f = 0.43) as a yellow oil (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.2 Hz, 2H), 6.86 (t, *J* = 7.2 Hz, 1H), 3.04 (t, *J* = 7.2 Hz, 3H), 2.35 (s, 6H), 1.65 (quint, *J* = 7.2 Hz, 2H), 1.36-1.46 (m, 10H), 0.96 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 129.0, 128.7, 121.4, 48.6, 31.8, 31.2, 29.4, 29.2, 27.1, 22.6, 18.5, 14.0. The spectral data of the product are in accordance with those reported in the literature.[24] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

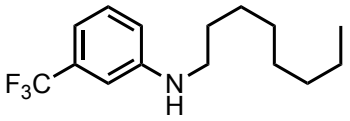


***N*-octyl-4-(trifluoromethyl)aniline** (**91**) (Table 6). Following general amination procedure A, 116.3 mg of **91** were isolated by flash chromatography (1% Et_2O/pentane, R_f = 0.51) as light-yellow oil (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 6.61 (d, *J* = 8.4 Hz, 2H), 3.97 (bs, 1H), 3.16 (quart, *J* = 6.8 Hz, 2H), 1.65 (quint, *J* = 7.2 Hz, 2H), 1.33-1.47 (m, 10 H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 150.7, 126.4, 123.6 (quart, $^1J_{CF}$ = 268 Hz), 118.4 (quart, $^2J_{CF}$ = 32 Hz) , 111.5, 43.4, 31.7, 29.3, 29.2, 29.1, 26.9, 22.5, 13.9; ^{19}F-NMr (376 MHz, $CDCl_3$) δ -60.8 (s, 3F). The spectral data of the major product are in accordance with those reported in the literature.[205] The ratio of monoaryl amine to diaryl amine product was determined to be 12:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

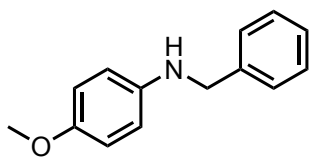


4-nitro-*N*-octylaniline (**92**) (Table 6). Following general amination procedure A, 69.7 mg of **92** were isolated by flash column

chromatography (step gradient, 5% EtOAc/hexanes followed by 10% EtOAc/hexanes, R_f = 0.36 in 10% EtOAc/hexanes) as a yellow solid (57% yield). Mp: 42-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 2H), 6.52 (d, *J* = 9.2 Hz, 2H), 4.63 (bs, 1H), 3.21 (quart, *J* = 6.8 Hz, 2H), 1.66 (quint, *J* = 7.2 Hz, 2H), 1.22-1.41 (m, 10H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 137.5, 126.3, 110.8, 43.3, 31.6, 29.2, 29.1, 29.0, 26.9, 22.5, 14.0. The spectral data of the product are in accordance with those reported in the literature.[53] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

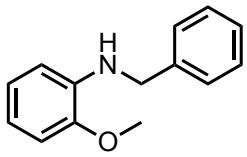


***N*-octyl-3-(trifluoromethyl)aniline (93)** (Table 6). Following general amination procedure A, 108.9 mg of **93** were isolated by flash chromatography (0→10% EtOAc/hexanes, R_f = 0.45 in 5 %EtOAc/Hexanes) as a yellow oil (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.79 (bs, 1H), 3.11 (t, *J* = 7.0 Hz, 2H), 1.62 (quint, *J* = 7.1 Hz, 2H), 1.40-1.28 (m, 11H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 131.5 (q, *J*= 31.4 Hz), 129.5, 124.4 (q, *J* = 199.0 Hz), 115.6, 113.3 (q, *J* = 3.8 Hz), 108.6 (q, *J* = 3.8 Hz), 43.7, 31.8, 29.4, 29.3, 29.2, 27.1, 22.7, 14.1. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{15}H_{22}F_3N$, 273.1711; found 273.1704.

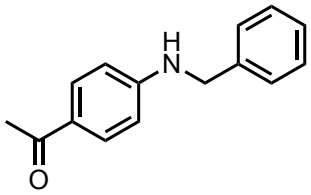


***N*-benzyl-4-methoxyaniline (94)** (Table 7). Following general amination procedure A, 90.0 mg of **94** were isolated by flash chromatography (step gradient 2% Et_2O/pentane followed by 10% Et_2O/pentane, R_f = 0.48 in 10% Et_2O/pentane) as a yellow oil, (85% yield). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.31-7.44 (m, 5H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.66 (d, *J* = 8.0 Hz, 2H), 4.43 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 142.4, 139.6, 128.5, 127.5, 127.1, 114.8, 114.0, 55.7, 49.1. The spectral data of the major product are in accordance with those reported in the literature.[97] The ratio of monoaryl amine to diaryl amine product was determined to be 17:1 by ^1H NMR spectroscopic analysis of the crude reaction mixture.

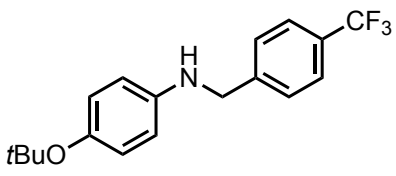


***N*-benzyl-2-methoxyaniline** (**95**) (Table 7). Following general amination procedure A, 105.0 mg of **95** were isolated by flash chromatography (5% Et_2O/pentane, R_f = 0. 46) as a light-yellow oil (98% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.47 (m, 5H), 6.91 (t, *J* = 8.4 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.75 (t, *J* = 8.4 Hz, 1 H), 6.66 (d, *J* = 8.0 Hz, 1 H), 4.70 (bs, 1H), 4.42 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 139.5, 138.1, 128.5, 127.4, 127.0, 121.2, 116.5, 110.0, 109.3, 55.3, 48.0. The spectral data of the product are in accordance with those reported in the literature.[24] No diaryl amine product was detected by ^1H NMR spectroscopic analysis of the crude reaction mixture.

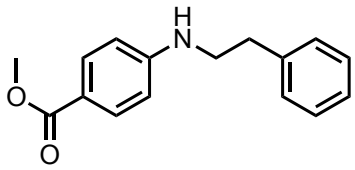


1-(4-(benzylamino)phenyl)ethanone (**96**) (Table 7). Following general amination procedure A, 96.1 mg of **96** were isolated by flash chromatography (20% EtOAc/hexanes, R_f = 0.3) as a yellow solid (86% yield). Mp: 88-90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.6 Hz, 2H), 7.32-7.38 (m, 5H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.85 (bs, 1H), 4.42 (d, *J* = 5.6 Hz, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 152.0, 138.2, 130.7, 128.7, 127.4, 127.2, 126.7, 111.5, 47.4, 25.9. The spectral data of the major product are in accordance with those reported in the literature.[96] The ratio of

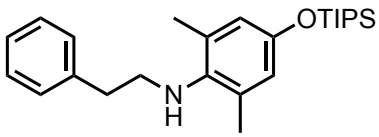
monoaryl amine to diaryl amine product was determined to be 20:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



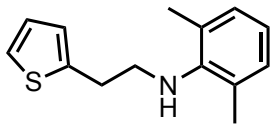
4-(*tert*-butoxy)-*N*-(3-(trifluoromethyl)benzyl)aniline (**97**) (Table 7). Following general amination procedure A, 113.2 mg of **97** were isolated by flash column chromatography (5% EtOAc/hexanes, R_f = 0.27) as a light-brown oil (70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.55-7.60 (m, 2H), 7.46-7.50 (m, 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 2H), 4.37 (s, 2H), 3.98 (bs, 1H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7, 144.0, 140.7, 130.9 (quart, $^2J_{CF}$ = 32 Hz), 130.7, 128.9, 125.4, 124.1(quart, $^3J_{CF}$ = 4 Hz), 123.9 (quart, $^3J_{CF}$ = 4 Hz), 122.7 (quart, $^1J_{CF}$ = 271 Hz) , 113.0, 77.7, 48.4, 28.6; ^{19}F-NMR (376 MHz, $CDCl_3$) δ -62.49 (s, 3F). The ratio of monoaryl amine to diaryl amine product was determined to be 20:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{18}H_{20}F_3NO$, 323.1497; found 323.1491.



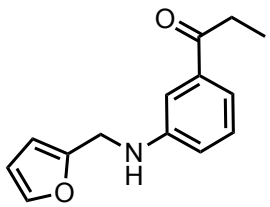
methyl 4-(phenethylamino)benzoate (**98**) (Table 7). Following general amination procedure A, 112.9 mg of **98** were isolated by flash chromatography (5% EtOAc/hexanes, R_f = 0.14) as a light-yellow oil (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.8 Hz, 2H), 7.23 – 7.38 (m, 5H), 6.58 (d, J = 8.8 Hz, 2H), 4.24 (bs, 1H), 3.88 (s, 3H), 3.46 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 151.6, 138.6, 131.5, 128.7,128.6, 126.5, 118.3, 111.5, 51.4, 44.3, 35.1. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.



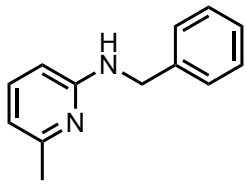
2,6-dimethyl-*N*-phenethyl-4-((triisopropylsilyl)oxy)aniline (**99**) (Table 7). Following general amination procedure A, 169.8 mg of **99** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.54 in 20% EtOAc/hexanes as a colorless oil (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23-7.35 (m, 5H), 6.53 (s, 2H), 3.16 (t, *J* = 7.2 Hz, 2H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 6H), 1.19-1.31 (m, 3H), 1.11 (d, *J* = 2.8 Hz, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 139.8, 139.2, 131.2, 128.8, 128.5, 126.3, 119.6, 50.0, 37.0, 18.2, 18.0, 12.7. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{25}H_{39}NOSi$, 397.2801; found 397.2810.



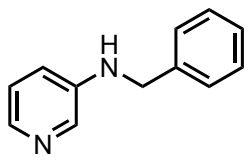
2,6-dimethyl-*N*-(2-(thiophen-2-yl)ethyl)aniline (**100**) (Table 7). Following general amination procedure A, 104.4 mg of **100** were isolated by flash chromatography (2% Et_2O/pentane, R_f = 0.38) as a yellow oil (90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 5.2 Hz, 1H), 7.02-7.06 (m, 3H), 6.95 (d, *J* = 3.2 Hz, 1H), 6.89 (t, *J* = 7.2 Hz, 1H), 3.37 (t, *J* = 6.8 Hz, 2H), 3.24 (bs, 1H), 3.17 (t, *J* = 6.8, 2H), 2.26 (s, 6H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 142.0, 129.2, 128.8, 126.9, 125.4, 123.8, 121.8, 49.4, 31.1, 18.3. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{14}H_{17}NS$, 231.1082; found 231.1089.



1-(3-((furan-2-ylmethyl)amino)phenyl)propan-1-one (**101**) (Table 7). Following general amination procedure A, 81.4 mg of **101** were isolated by flash chromatography (10% EtOAc/hexanes, R_f = 0.28) as a light-brown solid (71% yield). Mp: 32-34 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.38 (m, 4H), 6.85 (dd, *J* = 1.6, 2.0 Hz, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.26 (d, *J* = 2.4 Hz, 1H), 4.37 (s, 2H), 4.28 (bs, 1H), 2.97 (quart, *J* = 7.2 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 152.1, 147.7, 142.0, 137.8, 129.2, 117.7, 117.5, 111.7, 110.3, 107.1, 41.1, 31.7, 8.2. No diaryl amine product was detected by by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{14}H_{15}NO_2$, 231.1082; found 231.1089.

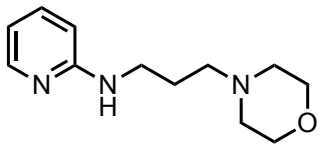


***N*-benzyl-3-methylpyridin-2-amine** (**102**) (Table 8). Following general amination procedure A, 88.7 mg of **102** were isolated by flash chromatography (5% Et_2O/pentane, R_f = 0.19) as a yellow oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 4.8 Hz, 1H), 7.27-7.44 (m, 6H), 6.60 (t, *J* = 5.2 Hz, 1H), 4.74 (d, *J* = 5.2 Hz, 2H), 4.42 (bs, 1H), 2.12 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 145.4, 139.9, 136.8, 128.5, 127.8, 127.1, 116.4, 112.8, 45.74, 16.9. The spectral data of the product are in accordance with those reported in the literature.[206] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

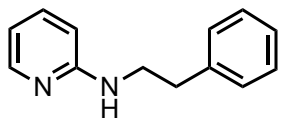


***N*-benzyl-3-aminopyridin** (**103**) (Table 8). Following general amination procedure A, 79.0 mg of **103** were isolated by flash chromatography (step gradient 30% EtOAc/hexanes followed by 50% EtOAc/hexanes, R_f = 0.28 in 50% EtOAc/hexanes) as an orange solid (86% yield). Mp: 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.09 (d, *J* = 2.4 Hz, 1H), 7.95 (d, *J* = 4.4 Hz, 1H), 7.29-7.38 (m, 5H), 7.08 (dd, *J* = 4.8, 2.8 Hz, 1H), 6.88 (dd, *J* = 5.6, 2.4 Hz, 1H), 4.36 (d, *J* = 5.2 Hz, 2H), 4.31 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.8, 138.4, 136.1, 128.7, 127.4, 127.3, 123.6, 118.4, 47.7. The spectral data of the product are in accordance with those reported in the literature.[24] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

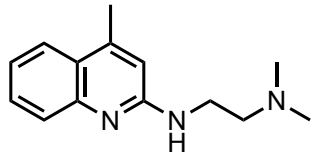


***N*-(3-morpholinopropyl)pyridin-2-amine** (**104**) (Table 8). Following general amination procedure A, 99.9 mg of **104** were isolated by acid-base extraction as a yellow solid (90% yield). Mp: 46-48 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 4.4 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.52 (t, *J* = 6.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 5.28 (bs, 1H), 3.72 (t, *J* = 4.8 Hz, 4H), 3.35 (q, *J* = 6.0 Hz, 2H), 2.46 (d, *J* = 6.4 Hz, 6H), 1.78 (quint, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 146.1, 137.1, 112.4, 106.7, 66.9, 57.1, 53.6, 41.0, 25.6. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{12}H_{19}N_3O$, 221.1528; found 221.1520.

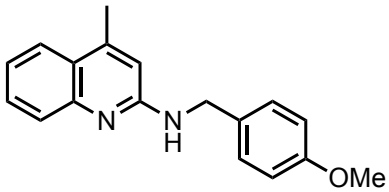


***N*-phenethylpyridin-2-amine** (**105**) (Table 8). Following general amination procedure A, 86.4 mg of **105** were isolated by flash chromatography (20% EtOAc/hexanes, R_f = 0.33) as a clear, colorless oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 4.8 Hz, 1H), 7.45 (t, *J* = 7.2, Hz, 1H), 7.25-7.36 (m, 5H), 6.96 (t, *J* = 7.2Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 4.67 (bs, 1H), 3.58 (q, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 148.1, 139.2, 137.3, 128.7, 128.5, 126.3, 112.8, 106.7, 43.2, 35.6. The spectral data of the major product are in accordance with those reported in

the literature.[207] The ratio of monoaryl amine to diaryl amine product was determined to be 45:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

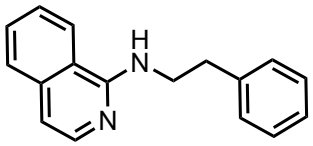


***N*^{1},*N*^{1}-dimethyl-*N*^{2}-(4-methylquinolin-2-yl)ethane-1,2-diamine** (**106**) (Table 8). Following general amination procedure A, 108.9 mg of **106** were isolated by acid-base extraction as a pale yellow oil (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 8.0 Hz, 2H), 7.53 (dt, *J* = 9.1 ,1.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 6.48 (s, 1H), 5.34 (bs, 1H), 3.59 (quart, *J* = 5.4 Hz, 2H), 2.57 (quart, *J* = 6.0 Hz, 2H), 2.51 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 148.0, 144.3, 128.9, 126.4, 123.6, 123.4, 121.4, 112.1, 58.0, 45.0, 38.5, 18.5. The ratio of monoaryl amine to diaryl amine product was determined to be 40:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{14}H_{19}N_3$, 229.1579; found 229.1585.

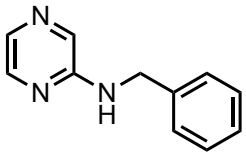


***N*-(4-methoxybenzyl)-4-methylquinolin-2-amine** (**107**) (Table 8). Following general amination procedure A, 132.0 mg of **107** were isolated by flash column chromatography (step gradient, 5% EtOAc/hexanes followed by 20% EtOAc/hexanes, R_f = 0.24 in 20% EtOAc/hexanes) as a light-yellow solid (94% yield). MP: 92-94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.46 (s, 1H), 5.13 (bs, 1H), 4.65 (d, *J* = 3.2 Hz, 2H), 3.80 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.6, 147.9, 145.0, 131.4, 129.2, 128.9, 126.5, 123.8, 123.5, 121.8, 113.9, 111.4, 55.2, 45.1, 18.7; HRMS (EI) [M+] calcd. for C18H18N2O 278.1419; found 278.1409. The

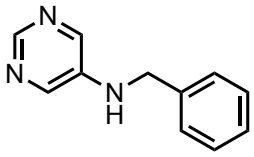
No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{18}H_{18}N_2O$, 278.1419; found 278.1409.



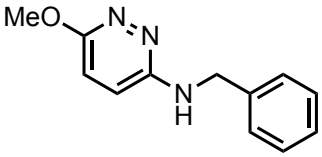
***N*-phenethylisoquinolin-1-amine** (**108**) (Table 8). Following general amination procedure A, 111.4 mg of **108** were isolated by flash chromatography (0→40% EtOAc/hexanes gradient, R_f = 0.24 in 20% EtOAc/hexanes) as a white solid (90% yield). Mp: 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 6.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.57-7.62 (m, 2H), 7.26-7.45 (m, 6H), 6.97 (d, *J* = 6.0 Hz, 1 H), 5.32 (bs, 1H), 3.93 (quart, *J* = 6.8 Hz, 2H), 3.08 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 141.5, 139.7, 137.1, 129.6, 129.0, 128.7, 127.2, 126.4, 125.9, 121.3, 118.2, 110.9, 42.8, 35.5. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{17}H_{16}N_2$, 248.1313; found 248.1320.



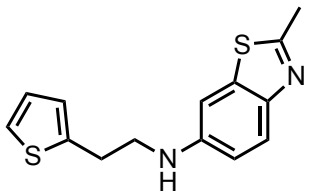
***N*-benzylpyrazin-2-amine** (**119**) (Table 8). Following general amination procedure A, 80.7 mg of **109** were isolated by flash chromatography (20% EtOAc/pentane, R_f = 0.32) as an orange solid (87% yield). Mp: 55 - 58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.8 Hz, 1H), 7.88 (d, *J* = 1.2 Hz, 1H), 7.80 (d, *J* = 2.8 Hz, 1H), 7.28-7.37 (m, 5H), 5.26 (bs, 1H), 4.56 (d, *J* = 5.6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 141.9, 138.4, 132.9, 132.0, 128.6, 127.5, 127.4, 45.4. The ratio of monoaryl amine to diaryl amine product was determined to be 14:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{11}H_{11}N_3$, 185.0953; found 185.0959.



***N*-benzylpyrimidin-5-amine** (**110**) (Table 8). Following general amination procedure A, 77.7 mg of **110** were isolated by flash chromatography (40% EtOAc/hexanes, R_f = 0.23) as an off-white solid (84% yield). Mp: 102-104 °C, (lit. Mp: 99-100)[8]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.10 (s, 2H), 7.29-7.38 (m, 5H), 4.55(bs, 1H), 4.34 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 141.6, 140.8, 137.4, 128.8, 127.7, 127.3, 47.3, 29.6. The spectral data of the product are in accordance with those reported in the literature.[206] No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

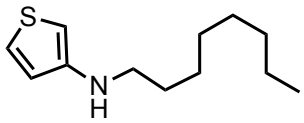


***N*-benzyl-6-methoxypyridazin-3-amine** (**111**) (Table 8). Following general amination procedure A, 85.9 mg of **111** were isolated by flash column chromatography (30% EtOAc/pentan, R_f = 0.28) as a light-yellow solid (80% yield). Mp: 101-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.39 (m, 5H), 6.76 (d, *J* = 9.2 Hz, 1H), 6.70 (d, *J* = 9.2 Hz, 1H), 4.79 (bs, 1H), 4.59 (d, *J* = 5.6 Hz, 2H), 4.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.8, 139.0, 128.5, 127.7, 127.2, 119.6, 119.3, 54.1, 46.3. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{12}H_{13}N_3O$, 215.1059; found 215.1065.

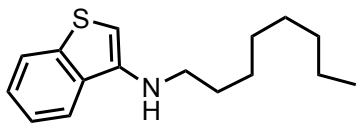


2-methyl-*N*-(2-(thiophen-2-yl)ethyl)benzo[d]thiazol-5-amine (**112**) (Table 8). Following general amination procedure A, 128.2 mg of **112** were isolated by flash chromatography (0→60% EtOAc/hexanes gradient, R_f = 0.15 in 20% EtOAc/hexanes) as a light-yellow solid (92% yield). Mp: 69-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.8 Hz, 1H), 7.18-7.22 (m, 2H), 6.98 (t, *J* = 5.2 Hz, 1H),

6.88 (d, *J* = 3.2 Hz, 1 H), 6.70 (dd, J = 2.4, 2.0 Hz, 1H), 3.98 (bs, 1H), 3.51 (t, *J* = 6.8 Hz, 2H), 3.18 (t, *J* = 6.8 Hz, 2H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 155.1, 146.8, 141.6, 127.0, 125.4, 124.3, 124.0, 121.6, 113.7, 104.3, 45.4, 29.4, 20.1. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{14}H_{14}N_2S_2$, 274.0598; found 274.0591.

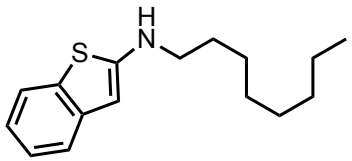


***N*-octylthiophen-3-amine** (**112**) (Table 9)**.** Following general amination procedure A, 121.6 mg of **112** were isolated by flash chromatography (0→100% toluene/hexanes gradient, R_f = 0.60 in 20% EtOAc/hexanes) as a light-yellow oil (56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06-7.18 (m, 1H), 6.52-6.54 (m, 1H), 5.86-5.87 (m, 1H), 3.49 (bs, 1H), 2.98 (t, *J* = 7.2 Hz, 2H), 1.50-1.57 (quint, *J* = 7.2 Hz, 2H), 1.21-1.32 (m, 10H), 0.81 (t, *J* = 6.8 Hz, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 125.1, 119.9, 95.3, 46.4, 31.7, 29.6, 29.5, 29.3, 27.2, 22.7, 14.1. The ratio of monoaryl amine to diaryl amine product was determined to be 4:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{12}H_{21}NS$, 211.1395; found 211.1404.

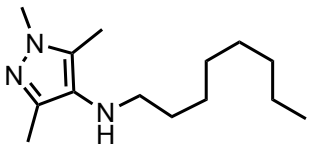


***N*-octylbenzo[b]thiophen-3-amine** (**114**) (Table 9). General amination procedure A was followed except that the reaction was conducted using 0.25 mmol of 3-bromobenzothiophene (53.3 mg, 1.0 equiv) and 0.325 mmol of octyl amine (1.3 equiv, 42.0 mg, 53.7 µL). Following this procedure, 62.5 mg of **114** were isolated by flash chromatography (0→30% EtOAc/hexanes gradient, R_f = 0.65 in 20% EtOAc/hexanes) as a red oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68-7.80 (m, 1H), 7.45-7.48 (m, 1H), 7.16-7.26 (m, 2H), 5.94 (s, 1H), 3.70 (bs, 1H), 3.13 (t, *J* = 7.2 Hz, 2H), 1.64 (quint, *J* = 7.2 Hz, 2H),

1.19-1.42 (m, 10 H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 139.2, 132.8, 124.6, 123.4, 123.2, 119.3, 94.1, 45.9, 31.9, 29.4, 29.5, 29.3, 27.4, 22.7, 14.1. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{16}H_{23}NS$, 261.1551; found 261.1547.

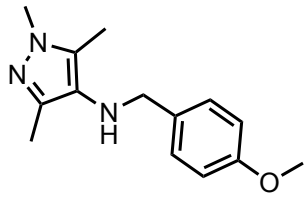


***N*-octylbenzo[b]thiophen-2-amine** (**115**) (Table 9). General amination procedure A was followed except that the reaction was conducted using 3 mol% of *Pd-PEPPSI-IPent^{Cl}* (0.0075 mmol, 6.5 mg), 0.25 mmol of 2-bromobenzothiophene (53.3 mg, 1.0 equiv) and 0.325 mmol of octyl amine (1.3 equiv, 42.0 mg, 53.7 μL). Following this procedure, 34.9 mg of **115** were isolated by flash chromatography (0→30% Et_2O/hexane gradient, R_f = 0.51 in 20% EtOAc/hexanes) as a red oil (53% yield). Mp: 43-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.6 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.20-7.25 (m, 1 H), 5.22 (s, 1H), 3.58 (t, J = 6.8 Hz, 2H), 1.80 (quint, J = 7.2 Hz, 2H), 1.15-1.36 (m, 10 H), 0.80 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.2, 156.4, 143.6, 136.8, 128.3, 127.4, 126.4, 124.9, 60.0, 31.7, 29.7, 29.2, 29.1, 27.5, 22.5, 14.0. The ratio of monoaryl amine to diaryl amine product was determined to be 6:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{16}H_{23}NS$, 261.1551; found 261.1559.

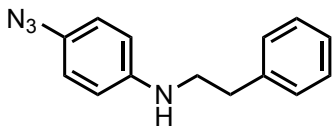


1,3,5-trimethyl-*N*-octyl-1*H*-pyrazol-4-amine (**116**) (Table 9). Following general amination procedure A, 85.4 mg of **116** were isolated by flash column chromatography (5% MeOH/CH_2Cl_2, R_f = 0.52) as a light-pink liquid (72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.82 (t, J = 7.2 Hz, 2H),

2.26 (bs, 1H), 2.15 (d, J = 9.2 Hz, 6H), 1.46 (quint, J = 7.2 Hz, 2H), 1.27-1.34 (m, 10H), 0.88 (t, J = 6.8Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1, 1312, 126.4, 50.9, 36.0, 31.7, 30.4, 29.4, 29.2, 27.0, 22.5, 14.0, 11.0, 8.9. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. For $C_{14}H_{27}N_3$, 237.2205; found 237.2208.

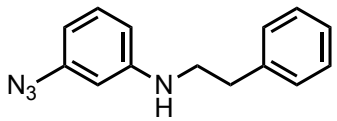


***N*-(4-methoxybenzyl)-1,3,5-trimethyl-1*H*-pyrazol-4-amine** (**117**) (Table 9). Following general amination procedure A, 60.4 mg of **117** were isolated by flash column chromatography (0% → 5% MeOH/CH_2Cl_2, R_f = 0.38 in 5% MeOH/CH_2Cl_2) as a pale yellow oil (49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 3.9 (s, 2H), 3.80 (s, 3H), 3.66 (s, 2H), 2.52 (bs, 1H), 2.10 (s, 3 H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 132.5, 132.0, 129.5, 125.7, 113.6, 55.2, 54.5, 36.1, 34.2, 30.2, 11.0, 8.8. The ratio of monoaryl amine to diaryl amine product was determined to be 50:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{14}H_{19}N_3O$, 245.1528; found 245.1521.

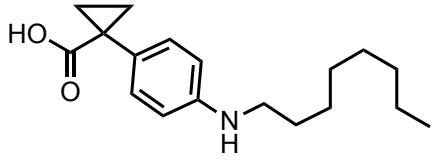


4-azido-*N*-phenethylaniline (**120a**). General amination procedure A was followed except that after 4 h of reaction time at 60 °C, the heat was removed, an additional 1 mol% of *Pd-PEPPSI-IPent*^{Cl} (0.005 mmol, 4.2 mg) was added quickly, and the reaction allowed to proceed for an additional 12h at 60 °C. Following this procedure, 70.5 mg of **120a** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.38 in 20% EtOAc/hexanes) as a pale-yellow oil (59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.26 (m, 5H), 6.78 (d, J = 14.4 Hz, 2H), 6.50 (d, J = 14.4 Hz, 2H), 3.58 (bs, 1H),

3.29 (t, J = 7.2 Hz, 2H), 2.82 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 139.1, 129.0, 128.8, 128.7, 126.6, 120.0, 114.1, 45.3, 35.4. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The product was obtained in *ca.* 95% purity as estimated by ^{1}H NMR spectroscopic analysis. HRMS (EI) [M+] calcd. for $C_{14}H_{14}N_4$, 238.1218; found 238.1222.

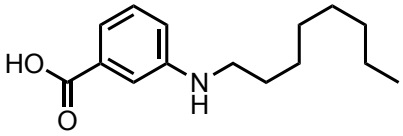


3-azido-*N*-phenethylaniline (**120b**). General amination procedure A was followed except that after 4 h of reaction time at 60 °C, the heat was removed, an additional 1 mol% of *Pd-PEPPSI-IPent^{Cl}* (0.005 mmol, 4.2 mg) was added quickly, and the reaction allowed to proceed for an additional 12h at 60 °C. Following this procedure, 73.2 mg of **120b** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.57 in 20% EtOAc/hexanes) as a pale-yellow oil (61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 6.0 Hz, 2H), 7.27-7.22 (m, 3H), 7.14 (t, J = 6.0 Hz, 1H), 6.39 (t, J = 6.0 Hz, 2H), 6.23 (s, 1H), 3.79 (bs, 1H), 3.40 (t, J = 6.0 Hz, 2H), 2.92 (t, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.3, 141.1, 139.0, 130.4, 128.8, 128.7, 126.6, 109.9, 107.8, 103.0, 44.8, 35.4. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The product was obtained in *ca.* 95% purity as estimated by ^{1}H NMR spectroscopic analysis. HRMS (EI) [M+] calcd. for $C_{14}H_{14}N_4$, 238.1218; found 238.1211.

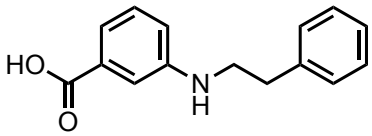


1-(4-(octylamino)phenyl)cyclopropanecarboxylic acid (**121**) (Table 10). Following general amination procedure B, 133.9 mg of **121** were isolated by flash chromatography

(0→100% EtOAc/hexanes gradient, R_f = 0.31 in 33% EtOAc/hexanes) as a white solid (92% yield). Mp: 64-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (bs, 2H), 718 (d, *J* = 8.0 Hz, 2H), 6.58 (d, *J* = 8.0 Hz, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 1.61-1.68 (m, 4H), 1.35-1.43 (m, 10H), 1.22-1.25 (m, 2H), 0.95 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.9, 142.6, 131.2, 127.1, 112.3, 44.0, 31.7, 29.4, 29.3, 29.2, 28.0, 27.1, 22.6, 17.4, 14.0. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{18}H_{27}NO_2$, 289.2042; found 289.2049.

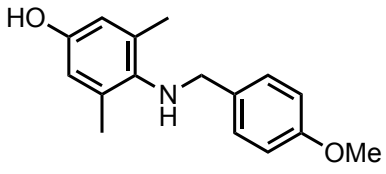


4-(phenethylamino)benzoic acid (**122**) (Table 10). Following general amination procedure B, 96.2 mg of **122** were isolated by flash chromatography (0→100% EtOAc/hexanes, R_f = 0.58 in 66% EtOAc/hexanes) as a white solid (77% yield). Mp: 75-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (bs, 2H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.14-7.24 (m, 2H), 6.74 (d, *J* = 7.6 Hz, 1H), 3.05 (t, *J* = 6.8 Hz, 2H), 1.54 (quint, *J* = 6.8 Hz, 2H), 1.20-1.32 (m, 10H), 0.81 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 172.7, 148.6, 129.9, 129.1, 118.3, 117.8, 113.3, 43.7, 31.7, 29.3, 29.2, 29.1, 27.0, 22.5, 13.7. The spectral data of the major product are in accordance with those reported in the literature. The ratio of monoaryl amine to diaryl amine product was determined to be 15:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

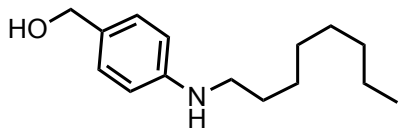


3-(phenethylamino)benzoic acid (**123**) (Table 10). Following general amination procedure B, 87.9 mg of **123** were isolated by flash chromatography (0→100% EtOAc/hexanes, R_f = 0.51 in 50% EtOAc/hexanes) as a white solid (73% yield). Mp: 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (bs, 1H), 7.51 (d, *J* = 7.6

Hz, 1H), 7.26-7.39 (m, 7H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.49 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 147.9, 138.9, 130.2, 129.2, 128.7, 128.6, 126.5, 119.2, 118.3, 113.8, 44.8, 35.2. The ratio of monoaryl amine to diaryl amine product was determined to be 10:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{15}H_{15}NO_2$, 241.1103; found 241.1111.

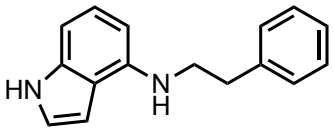


4-((4-methoxybenzyl)amino)-2,6-dimethylphenol (**124**) (Table 10) Following general amination procedure B, 104.2 mg of **124** were isolated by flash chromatography (0→50% EtOAc/hexanes gradient, R_f = 0.50 in 33% EtOAc/hexanes) as a white solid (81% yield). Mp: 112-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.49 (s, 2H), 4.2 (bs, 1H), 3.96 (s, 2H), 3.84 (s, 3H), 2.22 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 151.1, 138.3, 132.3, 132.2, 129.3, 115.2, 113.8, 55.2, 52.8, 18.2. No diaryl amine product was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{16}H_{19}NO_2$, 257.1416; found 257.1409.



(4-(octylamino)phenyl)methanol (**125**) (Table 10). Following general amination procedure B, 84.1 mg of **125** were isolated by flash chromatography (0→66% EtOAc/hexanes, R_f = 0.48 in 33% EtOAc/hexanes) as a white solid (71% yield). Mp: 35-36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 8.0 Hz, 2H), 4.54 (s, 2H), 3.12 (t, *J* = 7.2 Hz, 2H), 1.64 (quint, *J* = 7.2 Hz, 2H), 1.32-1.42 (m, 10H), 0.93 (t , *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.1, 129.4, 128.7, 112.6, 65.2, 44.0, 31.7, 29.4, 29.3, 29.2, 27.1, 22.6, 14.0. The ratio of monoaryl amine to diaryl amine product

was determined to be 18:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{15}H_{25}NO$, 235.1936; found 235.1942.

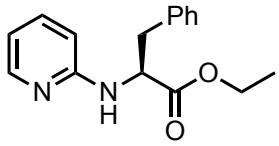


***N*-phenethyl-1*H*-indol-5-amine** (**126**) (Table 10). Following general amination procedure B, 71.6 mg of **126** were isolated by flash chromatography (0→75% EtOAc/hexanes gradient, R_f = 0.39 in 33% EtOAc/hexanes) as a brown oil (61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (bs, 1H), 7.30-7.41 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 2.8 Hz, 1H), 6.95 (s, 1H), 6.66 (dd, *J* = 2.4, 1.6 Hz, 1H), 6.46 (s, 1H), 3.51 (t, *J* = 6.8 Hz, 3H), 3.01 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.6, 130.1, 128.8, 128.7, 128.5, 126.2, 124.4, 112.4, 111.6, 102.6, 101.6, 46.4, 35.5. The ratio of monoaryl amine to diaryl amine product was determined to be 20:1 by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. HRMS (EI) [M+] calcd. for $C_{16}H_{16}N_2$, 236.1313; found 236.1320.

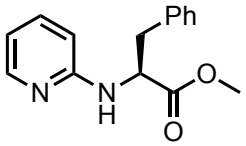
6.3. **compound characterization data for *N*-heteroarylation of α-amino esters**

General amination procedure: In a glovebox, a 10 mL round-bottom flask equipped with magnetic stir bar was charged with 122.1 mg of Cs_2CO_3 (0.375 mmol, 1.5 equiv.) and then the flask was sealed with a rubber septum prior to removal from the glovebox. To the flask was added 6.4 mg of *Pd-PEPPSI-IPent^{Cl}*-o-picoline (0.005 mmol, 1 mol%) then the vial was evacuated and backfilled with Ar (x3), followed by the addition of aryl halide (0.25 mmol, 1.0 equiv.) and amine (0.325 mmol, 1.3 equiv.) by syringe. Alternatively, if the aryl halide or amine were solids at room temperature, they were added to the vial with *Pd-PEPPSI-IPent^{Cl}*-o-picoline prior to evacuation. Then DME (1mL) was added by syringe and the round-bottom flask was placed in a pre-heated 80 °C oil bath, and stirred under argon at 1150 – 1200 rpm for 24 h (or for the indicated period of time if different). The reaction mixture was cooled to rt, diluted with CH_2Cl_2, filtered through a

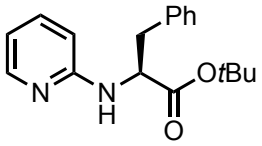
plug of silica or Celite, and the filtrate concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel (unless noted otherwise) to yield the desired product.



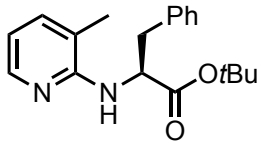
(S)-ethyl 3-phenyl-2-(pyridin-2-ylamino)propanoate (**129**) (Table 11). Following general amination procedure A, 62.7 mg of **129** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.43 in 20% EtOAc/hexanes) as a yellow solid (93% yield). Mp: 70-72 °C ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 4.2 Hz, 1H), 7.39 (t, *J* = 8.4 Hz, 1H), 7.18-7.31 (m, 5H), 6.61 (t, *J* = 5.4 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 4.89 (bs, 1H), 4.18 (q, *J* = 6.9 Hz, 1H), 3.14-3.28 (m, 2H), 1.23 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 157.1, 147.9, 137.2, 136.5, 129.4, 128.4, 126.8, 113.6, 108.7, 61.1, 55.2, 38.2, 14.1; HPLC analysis (IC, hexanes:*i*PrOH = 97:3, 1.0 mL/min, 245 nm) indicated 75% ee: t_R (major) = 9.07 min, t_R (minor) = 9.35 min. The spectral data of the product are in accordance with those reported in the literature.[106]



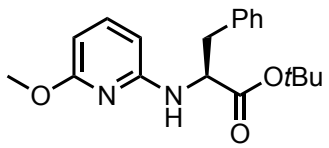
(S)-methyl 3-phenyl-2-(pyridin-2-ylamino)propanoate (**132**) (Table 11). Following general amination procedure A, 52.8 mg of **132** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.35 in 20% EtOAc/hexanes) as a yellow solid (83% yield). Mp: 86-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 4.5 Hz, 1H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.16-7.33 (m, 5H), 6.62 (t, *J* = 6.0 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 4.93 (bs, 1H), 3.72 (s, 3H), 3.14-3.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 157.1, 147.7, 137.3, 136.5, 129.3, 128.5, 126.9, 113.6, 108.7, 55.2, 52.1, 38.1; HPLC analysis (IC, hexanes:*i*PrOH = 90:10, 0.7 mL/min, 245 nm) indicated 58% ee: t_R (major) = 10.34 min, t_R (minor) = 9.90 min.



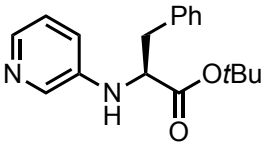
(S)-*tert*-butyl 3-phenyl-2-(pyridine-2-ylamino)propanoate (**133**) (Table 11). Following general amination procedure A, 70.7 mg of **133** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.42 in 10% EtOAc/hexanes) as a light-orange oil (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 4.8 Hz, 1H), 7.41 (t, *J* = 4.4 Hz, 1H), 7.22-7.31 (m, 5H), 6.60 (t, *J* = 6.0 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 4.94 (d, *J* = 7.2 Hz, 1H), 4.77 (q, *J* = 6.0 Hz, 1H), 3.18 (qq, *J* = 6.0 Hz, *J* = 3.2 Hz, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 157.3, 147.7, 137.1, 136.8, 129.5, 128.2, 126.6, 113.3, 108.4, 81.5, 55.7, 38.2, 27.8; HRMS (EI) [M+] calcd. for $C_{18}H_{22}N_2O_2$, 298.1681; found 298.1686. HPLC analysis (IC, hexanes:*i*PrOH = 97:3, 1.0 mL/min, 245 nm) indicated 98% ee: t_R (major) = 6.20 min, t_R (minor) = 5.80 min.



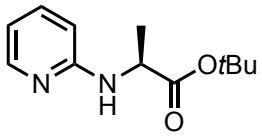
(S)-*tert*-butyl 2-((3-methylpyridin-2-yl)amino)-3-phenylpropanoate (**134**) (Table 15). Following general amination procedure A, 65.9 mg of **134** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.45 in 10% EtOAc/hexanes) as a light pink solid (85% yield). Mp: 44-46 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 4.4 Hz, 1H), 7.21-7.32 (m, 6H), 6.571 (t, *J* = 5.2 Hz, 1H), 5.01 (quint, *J* = 6.0 Hz, 1H), 4.66 (d, *J* = 7.6 Hz, 1H), 3.23 (ddd, *J* = 13.6, 6.4, 5.6 Hz, 2H), 2.07 (s, 3H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 155.5, 145.1, 137.0, 136.8, 129.5, 128.1, 126.6, 116.9, 113.2, 81.3, 55.1, 37.9, 27.9, 16.6; HRMS (EI) [M+] calcd. for $C_{19}H_{24}N_2O_2$, 312.1838; found 312.1832. HPLC analysis (IC, hexanes:*i*PrOH = 95:5, 1.0 mL/min, 245 nm) indicated > 99% ee: t_R (major) = 4.24 min, t_R (minor) =4.43 min.



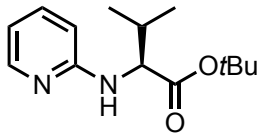
(S)-*tert*-butyl 2-((6-methoxypyridin-2-yl)amino)-3-phenylpropanoate (**135**) (Table 15). Following general amination procedure A, 73.0 mg of **135** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.49 in 10% EtOAc/hexanes) as a light brown oil (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.35 (m, 6H), 6.06 (d, *J* = 7.8 Hz, 1H), 6.01 (d, *J* = 7.8 Hz, 1H), 4.76-4.79 (m, 2H), 3.89 (s, 3H), 3.18 (d, *J* = 5.2 Hz, 2H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 163.4, 156.2, 139.7, 136.8, 129.4, 128.2, 126.6, 99.4, 97.7, 81.4, 55.8, 52.9, 38.3, 27.8; HRMS (EI) [M+] calcd. for $C_{19}H_{24}N_2O_3$, 328.1787; found 328.1779. HPLC analysis (IC, hexanes:*i*PrOH = 95: 5, 1.0 mL/min, 245 nm) indicated 90% ee: t_R (major) = 4.9 min, t_R (minor) = 5.4 min.



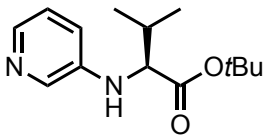
(S)-*tert*-butyl 3-phenyl-2-(pyridin-3-ylamino)propanoate (**136**) (Table 15). Following general amination procedure A, 55.2 mg of **136** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.47 in 40% EtOAc/hexanes) as a light orange solid (74% yield). Mp: 69-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.8 Hz, 1H), 7.99 (d, *J* = 4.4 Hz, 1H), 7.21-7.33 (m, 5H), 7.05-7.08 (m, 1H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.22-4.31 (m, 2H), 3.13 (ddd, *J* = 13.6, 6.0, 6.0 Hz, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 142.5, 139.5, 136.5, 136.1, 129.3, 128.3, 126.9, 123.5, 119.4, 81.1, 57.6, 38.3, 27.8; HRMS (EI) [M+] calcd. for $C_{18}H_{22}N_2O_2$, 298.1681; found 298.1688. HPLC analysis (IB, hexanes:*i*PrOH = 90:10, 1.0 mL/min, 245 nm) indicated 80% ee: t_R (major) = 8.54 min, t_R (minor) = 10.63 min.



(S)-*tert*-butyl 3-methyl-2-(pyridin-2-ylamino)butanoate (**137**) (Table 4). Following general amination procedure A, 45.8 mg of **137** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.38 in 10% EtOAc/hexanes) as a yellow oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 3.9 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 6.60 (t, *J* = 5.7 Hz, 1H), 6.43 (d, *J* = 8.4 Hz, 1H), 4.91 (d, *J* = 6.3 Hz, 1H), 4.45 (quint, *J* = 7.2 Hz, 1H), 1.46-1.48 (m, 12H) ; ^{13}C NMR (100MHz, $CDCl_3$) δ 173.7, 157.5, 147.9, 137.2, 113.3, 108.2, 81.3, 50.6, 27.9, 17.8; HRMS (EI) [M+] calcd. for $C_{12}H_{18}N_2O_2$, 222.1368; found 222.1360. HPLC analysis (IC, hexanes:*i*PrOH = 95:5, 1.0 mL/min, 245 nm) indicated 99% ee: t_R (major) = 8.33 min, t_R (minor) = 8.85 min.

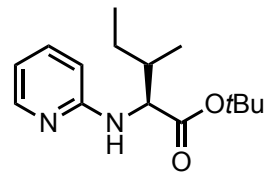


(S)-*tert*-butyl 3-methyl-2-(pyridin-2-ylamino)butanoate (**138**) (Table 15). Following general amination procedure A, 59.7 mg of **138** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.42 in 10% EtOAc/hexanes) as a light yellow solid (95% yield). Mp: 62-64 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, *J* = 4.8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.58 (t, *J* = 6.0 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 4.91 (d, *J* = 8.4 Hz, 1H), 4.34 (q, *J* = 5.6 Hz, 1H), 2.19 (dqq, *J* = 6.8, 6.8, 6.0 Hz, 1H), 1.46 (s, 9H), 1.02 (t, *J* = 5.6 Hz, 6H) ; ^{13}C NMR (100MHz, $CDCl_3$) δ 172.4, 158.1, 147.7, 137.1, 113.2, 108.0, 81.2, 59.9, 31.2, 27.9, 18.9, 18.2; HRMS (EI) [M+] calcd. for $C_{14}H_{22}N_2O_2$, 250.1681; found 250.1688. HPLC analysis (IA, hexanes:*i*PrOH = 75:25, 1.5 mL/min, 250 nm) indicated > 99% ee: t_R (major) = 4.70 min, t_R (minor) = 3.63 min.

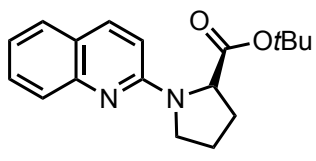


(S)-*tert*-butyl 3-methyl-2-(pyridin-3-ylamino)butanoate (**139**) (Table 15). Following general amination procedure A, 58.0 mg of **139** were

isolated by flash chromatography (30→50% EtOAc/hexanes gradient, R_f = 0.47 in 50% EtOAc/hexanes) as a light brown solid (92% yield). Mp: 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.7 Hz, 1H), 7.97 (d, *J* = 4.2 Hz, 1H), 7.05-7.09 (m, 1H), 6.88-6.91 (m, 1H), 4.24 (d, *J* = 9.0 Hz, 1H), 3.74 (t, *J* = 5.6 Hz, 1H), 2.19 (dqq, *J* = 6.9, 6.6, 6.6 Hz, 1H), 1.44 (s, 9H), 1.02 (t, *J* = 6.4 Hz, 6H), ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 143.5, 139.3, 136.6, 123.6, 119.4, 81.9, 62.4, 31.4, 28.0, 18.9, 18.5; HRMS (EI) [M+] calcd. for $C_{14}H_{22}N_2O_2$, 250.1681; found 250.1675. HPLC analysis (IC, hexanes:*i*PrOH = 95: 5, 1.0 mL/min, 245 nm) indicated >99% ee: t_R (major) = 7.55 min, t_R (minor) = 8.50 min.

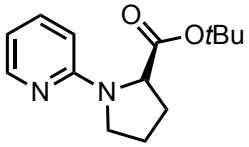


(2S,3S)-*tert*-butyl 3-methyl-2-(pyridin-2-ylamino)pentanoate (**140**) (Table 4). Following general amination procedure A, 48.7 mg of **140** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.48 in 10% EtOAc/hexanes) as a light yellow solid (83% yield). Mp: 43-45 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 4.4 Hz, 1H), 7.39 (t, *J* = 6.8 Hz, 1H), 6.57 (t, *J* = 6.8 Hz, 1H), 6.42 (d, *J* = 8.4 Hz, 1H), 4.90 (d, *J* = 8.0 Hz, 1H), 4.35-4.39 (m, 1H), 1.88-1.94 (m, 1H), 1.55-1.70 (m, 1H), 1.45 (s, 9H), 1.28-1.33 (m, 1H), 0.96-1.00 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.0, 147.8, 137.1, 113.1, 107.8, 81.2, 59.0, 37.9, 27.9, 25.6, 15.3, 11.6; HRMS (EI) [M+] calcd. for $C_{15}H_{24}N_2O_2$, 264.1838; found 264.1845. HPLC analysis (IC, hexanes:*i*PrOH = 95:5, 1.0 mL/min, 245 nm) indicated >99% ee: t_R (major) = 4.17 min, t_R (minor) = 3.88 min.

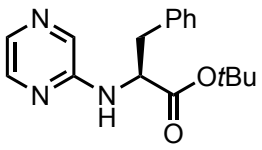


(R)-*tert*-butyl 1-(4-methylquinolin-2-yl)pyrrolidine-2-carboxylate (**141**) (Table 15). Following general amination procedure A, 66.6 mg of **141** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.45 in 20% EtOAc/hexanes) as a yellow solid (85% yield). Mp: 86-88 °C. ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.63 (s, 1H), 4.62 (d, *J* = 2.7 Hz, 3H), 3.74-3.81 (m, 1H), 3.63-3.70 (m, 1H), 2.61 (s, 1H), 2.10-2.4 (m, 4H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 154.8, 148.1, 144.6, 128.9, 126.9, 123.5, 123.3,121.3,110.2, 80.4, 60.5, 47.2, 30.0, 28.0, 24.3, 19.1; HRMS (EI) [M+] calcd. for $C_{19}H_{24}N_2O_2$, 312.1838; found 312.1830. HPLC analysis (IC, hexanes:*i*PrOH = 95:5, 1.0 mL/min, 245 nm) indicated 97% ee: t_R (major) = 4.17 min, t_R (minor) = 3.88 min.

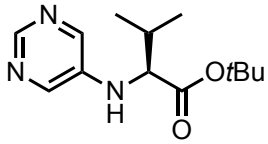


(R)-*tert*-butyl 1-(pyridin-2-yl)pyrrolidine-2-carboxylate (**142**) (Table 15). Following general amination procedure A, 47.2 mg of **142** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.28 in 10% EtOAc/hexanes) as a yellow oil (76% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (d, *J* = 4.2 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 6.56 (t, *J* = 6.3 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 4.42 (d, *J* = 8.4 Hz, 1H), 3.48-3.61 (m, 2H), 2.02-2.3 (m, 4H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 156.5, 147.8, 136.8, 111.9, 106.4, 80.1, 60.4, 47.0, 30.1, 27.8, 23.9; HRMS (EI) [M+] calcd. for $C_{14}H_{20}N_2O_2$, 248.1525; found 248.1515. HPLC analysis (IA, hexanes:*i*PrOH = 50:50, 0.7 mL/min, 245 nm) indicated> 99% ee: t_R (major) = 6.20 min, t_R (minor) = 6.00 min.

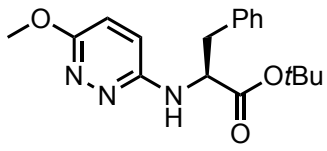


(S)-*tert*-butyl 3-phenyl-2-(pyrazin-2-ylamino)propanoate (**143**) (Table 15). Following general amination procedure A, 64.8 mg of **143** were isolated by flash chromatography (10→40% EtOAc/pentane gradient, R_f = 0.43 in 40% EtOAc/pentane) as a white solid (87% yield). Mp: 119-121 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 1.9 Hz, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 1.9 Hz, 1H), 7.19-7.33 (m, 5H), 5.18

(d, *J* = 7.5 Hz, 1H), 4.79 (q, *J* = 6.3 Hz, 1H), 3.19 (ddd, *J* = 13.8, 6.0, 6.0 Hz, 2H), 1.42 (s, 9H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 153.5, 141.6, 136.4, 133.3, 133.2, 129.5, 128.4, 126.9, 82.1, 55.0, 37.9, 27.9; HRMS (EI) [M+] calcd. for $C_{17}H_{21}N_3O_2$, 299.1634; found 299.1639. HPLC analysis (IC, hexanes:*i*PrOH = 95:5, 1.0 mL/min, 245 nm) indicated >99% ee: t_R (major) = 7.98 min, t_R (minor) = 9.38 min.

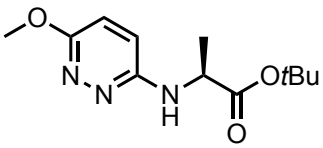


(S)-*tert*-butyl 3-methyl-2-(pyrimidin-5-ylamino)butanoate (**144**) (Table 15). Following general amination procedure A, 55.5 mg of **144** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.34 in 50% EtOAc/hexanes) as a light-yellow solid (89% yield). Mp: 91-92 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.14 (s, 1H), 4.37 (d, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 5.4 Hz, *J* = 5.4 Hz, 1H), 2.14 (dqq, *J* = 6.6, 6.6, 6.3 Hz, 1H)1.45 (s, 9H), 1.03 (m, 6H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 148.9, 141.5, 141.3, 82.4, 61.7, 31.3, 28.0, 18.9, 18.3; HPLC analysis (IA, hexanes:*i*PrOH = 90:10, 1.5 mL/min, 250 nm) indicated >99% ee: t_R (major) =5.53 min, t_R (minor) = 4.76 min. The spectral data of the product are in accordance with those reported in the literature.[106]



(S)-*tert*-butyl 2-((6-methoxypyridazin-3-yl)amino)-3-phenylpropanoate (**145**) (Table 15). Following general amination procedure A, 73.9 mg of **145** were isolated by flash chromatography (0→40% EtOAc/hexanes gradient, R_f = 0.48 in 40% EtOAc/hexanes) as a white solid (89% yield). Mp: 162-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19-7.27 (m, 5H), 6.76 (d, *J* = 9.2 Hz, 1H), 6.66 (d, *J* = 9.2 Hz, 1H), 5.00 (q, *J* = 6.0 Hz, 1H), 4.84 (d, *J* = 7.6 Hz, 1H), 4.02 (s, 3H), 3.24 (ddd, *J* = 13.6, 6.0, 5.6 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 160.0,

154.4, 136.7, 129.5, 128.1, 126.7, 120.2, 119.7, 81.8, 55.2, 54.1, 37.5, 30.8; HRMS (EI) [M+] calcd. for $C_{18}H_{23}N_3O_3$, 329.1739; found 329.1748. HPLC analysis (IC, hexanes:*i*PrOH = 85:15, 0.7 mL/min, 245 nm) indicated 96% ee: t_R (major) = 17.56 min, t_R (minor) = 18.59 min.

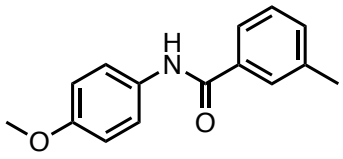


(S)-*tert*-butyl 2-((6-methoxypyridazin-3-yl)amino)propanoate (**146**) (Table 4). Following general amination procedure A, 61.2 mg of **22** were isolated by flash chromatography (0→40% EtOAc/hexanes gradient, R_f = 0.47 in 40% EtOAc/hexanes) as a white solid (96% yield). Mp: 107–109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69-6.80 (m, 2H), 4.83 (bs, 1H), 4.66 (quint, *J* = 6.9 Hz, 1H), 4.01 (s, 3H), 1.48-150 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 160.0, 154.5, 120.1, 119.7, 81.5, 54.1, 50.4, 27.9, 18.5; HRMS (EI) [M+] calcd. for $C_{12}H_{19}N_3O_3$, 253.1426; found 253.1422. HPLC analysis (IA, hexanes:*i*PrOH = 85:15, 1.5 mL/min, 250 nm) indicated 90% ee: t_R (major) = 8.86 min, t_R (minor) = 3.99 min.

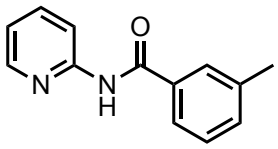
6.4. **Compound characterization data for aryl amidation reactions**

General amidation procedure: In a glovebox, a 15x45 mm 1-dram vial equipped with magnetic stir bar and Teflon-lined screw-cap was charged with 122.1 mg of Cs_2CO_3 (0.375 mmol, 1.5 equiv.) and then vial was removed from the glovebox. Then, in air, 7.8 mg of *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (0.0075 mmol, 3 mol%) and amide (0.325 mmol, 1.3 equiv.) were added after which the vial was evacuated and backfilled with Ar (x3). The aryl halide (0.25 mmol, 1.0 equiv.) and alkylborane (0.05 mmol, 0.2 equiv.) were then added via microliter syringe followed by Toluene (0.5 mL). Alternatively, if the aryl halide was solid at room temperature, it was added to the vial with other solids prior to evacuation. If $B(C_6F_5)_3$ (BCF) was used, in the

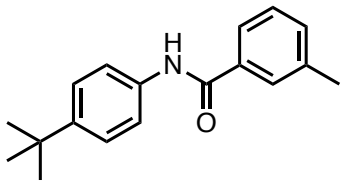
glovebox 25.5 mg of it (0.05 mmol, 0.2 equiv.) was added to the vial with Cs_2CO_3. The vial was then sealed, immersed in a pre-heated 80-90°C oil bath, and allowed to stir under a static Ar atmosphere at 1150 –1200 rpm. After 24 h, the reaction mixture was cooled to rt, diluted with EtOAc, filtered through a plug of silica and the filtrate was concentrated *in vacuo*. The residue thus obtained was purified using Biotage Isolera Four to yield pure coupled product.



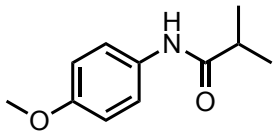
***N*-(4-Methoxyphenyl)-4-methylbenzamide** (**156**) (Table 21). Following general amidation procedure A, 55.5 mg of **156** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.58 in 30% EtOAc/hexanes) as an off-white solid (92% yield). Mp: 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (bs, 1H), 7.68 (s,1H), 7.64 (s,1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 4.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H), 2.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 156.4, 138.4, 134.9, 132.3, 131.0, 128.4, 127.7, 123.9, 122.1, 114.0, 55.4, 21.2. The spectral data of the product are in accordance with those reported in the literature.[208]



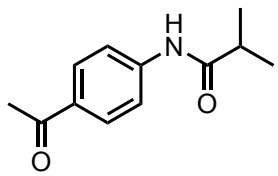
3-Methyl-*N*-(pyridin-2-yl)benzamide (**158**) (Table 22). Following general amidation procedure A, 48.9 mg of **158** were isolated by flash chromatography (20→40% EtOAc/hexanes gradient, R_f = 0.6 in 40% EtOAc/hexanes) as a yellow solid (92% yield). Mp: 42-44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (bs, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 8.17 (d, *J* = 4.4 Hz, 1H), 7.71-7.78 (m, 3H), 7.37 (d, *J* = 4.4 Hz, 2H), 7.03-7.06 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 151.6, 147.7, 138.6, 138.4, 134.2, 132.8, 128.5, 127.9, 124.2, 119.7, 114.1, 21.2. The spectral data of the product are in accordance with those reported in the literature.[209]



***N*-(4-(*tert*-Butyl)phenyl)-3-methylbenzamide** (**160**) (Table 23). Following general amidation procedure A, 58.1 mg of **160** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.46 in 40% EtOAc/hexanes) as a yellow oil (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37-7.42 (m, 4H), 2.45 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 147.4, 138.6, 135.2, 134.9, 132.4, 128.5, 127.7, 125.8, 123.8, 119.8, 34.3, 31.3, 21.3; HRMS (EI) [M+] calcd. for $C_{18}H_{21}NO$, 267.1623; found 267.1630.

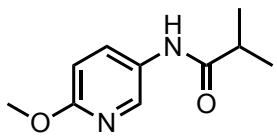


***N*-(4-Methoxyphenyl)isobutyramide** (**161**) (Table 24). Following general amidation procedure A, 44.8 mg of **161** were isolated by flash chromatography (20→40% EtOAc/hexanes gradient, R_f = 0.64 in 40% EtOAc/hexanes) as a light yellow solid (93% yield). Mp: 106-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.8 Hz, 2H), 7.32 (bs, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 2.50 (sept, *J* = 6.8 Hz, 1H), 1.25 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 156.1, 131.1, 121.6, 113.9, 55.4, 36.3, 19.5. The spectral data of the product are in accordance with those reported in the literature.[210]

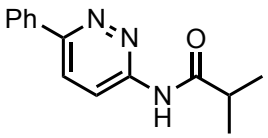


***N*-(4-Acetylphenyl)isobutyramide** (**162**) (Table 24). Following general amidation procedure A, 42.8 mg of **162** were isolated by flash chromatography (20→40% EtOAc/hexanes gradient, R_f = 0.4 in 40% EtOAc/hexanes) as a light yellow solid (83% yield). Mp: 125-127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (bs, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 2H), 2.56-2.63 (m, 4H), 1.26 (d, *J* =

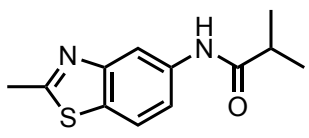
6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ197.2, 175.8, 142.6, 132.5, 129.6, 118.9, 36.6, 26.3, 19.4. The spectral data of the product are in accordance with those reported in the literature.[211]



***N*-(6-Methoxypyridin-3-yl)isobutyramide** (**163**) (Table 24). Following general amidation procedure A, 36.4 mg of **163** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.62 in 40% EtOAc/hexanes) as a light yellow solid (76% yield). Mp: 41-43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.67 (bs, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 3H), 2.56 (sept, *J* = 6.8 Hz, 1H) , 1.28 (d, *J* = 6.8 Hz, 6H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2, 162.7, 149.0, 140.8, 105.5, 105.3, 53.3, 36.7, 19.4; HRMS (EI) [M+] calcd. for $C_{10}H_{14}N_2O_2$, 194.1055; found 194.1060.

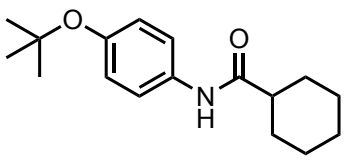


***N*-(6-Phenylpyridazin-3-yl)isobutyramide** (**164**) (Table 24). Following general amidation procedure A, 48.4 mg of **164** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.68 in 50% EtOAc/hexanes) as a light orange solid (81% yield). Mp: 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.74 (d, *J* = 9.6 Hz, 1H), 8.06 (d, *J* = 7.2 Hz , 2H), 7.96 (d, *J* = 9.6 Hz, 1H), 7.50-7.57 (m, 3H), 3.83 (sept, *J* = 6.8 Hz, 1H), 1.35 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 156.1, 154.6, 135.9, 129.6, 128.9, 126.4, 125.9, 119.3, 36.3, 19.4; HRMS (EI) [M+] calcd. for $C_{14}H_{15}N_3O$, 214.1215; found 214.1219.

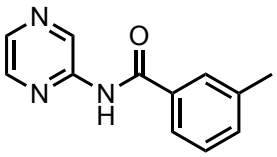


***N*-(2-Methylbenzo[d]thiazol-5-yl)isobutyramide** (**165**) (Table 24). Following general amidation procedure A, 45.1 mg of **165** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.68 in 50% EtOAc/hexanes)

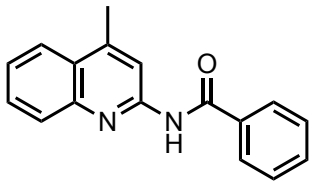
as a light orange solid (77% yield). Mp: 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.69-7.4 (m, 2H), 7.59 (bs, 1H), 2.83 (s, 3H), 2.57 (sept, *J* = 6.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 168.1, 153.7, 136.5, 130.9, 121.3, 117.9, 113.1, 36.6, 20.1, 19.5; HRMS (EI) [M+] calcd. for $C_{12}H_{14}N_2OS$, 234.0827; found 234.0821.



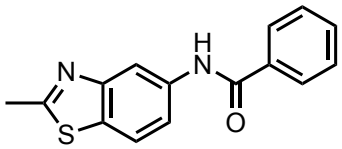
***N*-(4-(*tert*-Butoxy)phenyl)cyclohexanecarboxamide** (**166**) (Table 24). Following general amidation procedure A, 48.2 mg of **166** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.68 in 50% EtOAc/hexanes) as a white solid (70% yield). Mp: 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 2H), 2.20-2.27 (m, 1H), 1.94-1.97 (m, 2H), 1.83-1.85 (m, 2H), 1.70-1.73 (m, 1H), 1.53-1.56 (m, 2H), 1.27-1.33 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ174.1, 151.4, 133.6, 124.6, 120.4, 78.4, 46.3, 29.6, 28.6, 25.6 (two coincidental overlapping carbons); HRMS (EI) [M+] calcd. for $C_{17}H_{25}NO_2$, 275.1885; found 275.1889.



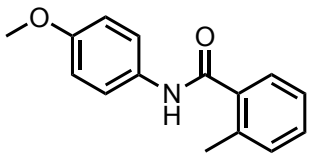
3-Methyl-*N*-(pyrazin-2-yl)benzamide (**167**) (Table 24). Following general amidation procedure A, 47.5 mg of **167** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.37 in 40% EtOAc/hexanes) as a yellow solid (86% yield). Mp: 98-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.82 (bs, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 8.21 (s, 1H), 7.72-7.77 (m, 2H), 7.38- 7.42 (m, *2*H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 148.3, 141.9, 140.2, 138.8, 137.2, 133.3, 133.2, 128.7, 127.9, 124.2, 21.6; HRMS (EI) [M+] calcd. for $C_{12}H_{11}N_3O$, 213.0902; found 213.0909.



***N*-(4-Methylquinolin-2-yl)benzamide** (**168**) (Table 24). Following general amidation procedure A, 63.4 mg of **168** were isolated by flash chromatography (10→50% EtOAc/hexanes gradient, R_f = 0.75 in 50% EtOAc/hexanes) as a light yellow solid (96% yield). Mp: 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (bs, 1H), 8.48 (bs, 1H), 7.84-8.00 (m, 3H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.59 (d, *J* = 7.2 Hz, 1H), 7.47-7.52 (m, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ166.0, 150.8, 147.2, 146.3, 134.1, 132.2, 129.6, 128.7, 127.7, 127.2, 126.4, 124.9, 123.8, 114.6, 19.1; HRMS (EI) [M+] calcd. for $C_{17}H_{14}N_2O$, 262.1106; found 262.1113.

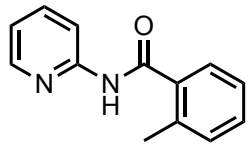


***N*-(2-Methylbenzo[d]thiazol-5-yl)benzamide** (**169**) (Table 24). Following general amidation procedure A, 61.7 mg of **169** were isolated by flash chromatography (20→40% EtOAc/hexanes gradient, R_f = 0.24 in 40% EtOAc/hexanes) as a white solid (92% yield). Mp: 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 8.14 (s, 1H), 7.91 (d, *J* = 7.6 Hz , 2H), 7.79 (s, 2H), 7.55-7.59 (m, 1H), 7.48-7.51 (m, 2H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 165.8, 153.8, 136.3, 134.7, 131.8, 131.4, 128.7, 127.0, 121.5, 118.2, 113.7, 20.1; HRMS (EI) [M+] calcd. for $C_{15}H_{12}N_2OS$, 268.0670; found 268.0677.

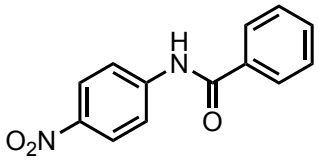


***N*-(4-Methoxyphenyl)-2-methylbenzamide** (**170**) (Table 24). Following general amidation procedure A, 53.4 mg of **170** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.27 in 20% EtOAc/hexanes) as a light yellow solid (92% yield). Mp: 136-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.43 (bs, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25-7.29 (m, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 3.84 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz,

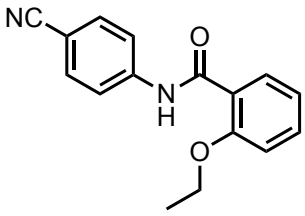
$CDCl_3$) δ 167.8, 156.5, 136.4, 136.3, 131.1, 130.9, 130.1, 126.5, 125.8, 121.6, 114.1, 55.4, 19.7. The spectral data of the product are in accordance with those reported in the literature.[212]



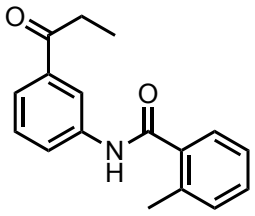
2-Methyl-*N*-(pyridin-2-yl)benzamide (**171**) (Table 24). Following general amidation procedure A, 48.9 mg of **171** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.6 in 40% EtOAc/hexanes) as a light yellow solid (92% yield). Mp: 96-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (bs, 1H), 8.41 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 4.4 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.22-7.27 (m, 2H), 6.91 (t, *J* = 4.4 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 151.7, 147.5, 138.5, 136.2, 136.1, 131.1, 130.3, 126.9, 125.8, 119.6, 114.2, 19.7. The spectral data of the product are in accordance with those reported in the literature.[209]



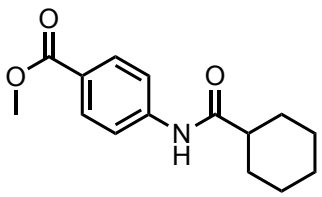
***N*-(4-Nitrophenyl)benzamide** (**172**) (Table 24). Following general amidation procedure A, 51.4 mg of **172** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.65 in 40% EtOAc/hexanes) as a yellow solid (85% yield). Mp: 194-196 °C; ^{1}H NMR (300 MHz, Acetone-d6)) δ 10.08 (bs, 1H), 8.28 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.56 (dd, *J* = 7.6, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, Acetone-d6) δ165.9, 145.4, 143.0, 134.5, 131.9, 128.4, 127.6, 124.5, 119.5; HRMS (EI) [M+] calcd. for $C_{13}H_{10}N_2O_3$, 242.0691; found 242.0696.



***N*-(4-Cyanophenyl)-2-ethoxybenzamide** (**173**) (Table 24). Following general amidation procedure A, 32.0 mg of **173** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.5 in 50% EtOAc/hexanes) as a light yellow solid (57% yield). Mp: 142-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (bs, 1H), 8.29 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 4.32 (q, *J* = 6.8 Hz, 2H), 1.67 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 156.6, 142.5, 133.8, 133.2, 132.5, 121.7, 120.7, 119.7, 118.9, 112.4, 106.6, 65.1, 14.9; HRMS (EI) [M+] calcd. for $C_{16}H_{14}N_2O_2$, 266.1055; found 266.1059.

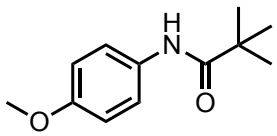


2-Methyl-*N*-(3-propionylphenyl)benzamide (**174**) (Table 24). Following general amidation procedure A, 36.73 mg of **174** were isolated by flash chromatography (20→40% EtOAc/hexanes gradient, R_f = 0.6 in 40% EtOAc/hexanes) as a light yellow solid (55% yield). Mp: 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 8.03 (d, *J* = 3.6 Hz, 1H), 7.94 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.47-7.50 (m, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.24-7.27 (m, 2H), 2.99 (q, *J* = 7.2 Hz, 2H), 2.51 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 168.2, 138.4, 137.5, 136.4, 135.9, 131.2, 130.4, 129.3, 126.6, 125.8, 124.2, 123.8, 119.0, 31.8, 19.7, 8.1; HRMS (EI) [M+] calcd. for $C_{17}H_{17}NO_2$, 267.1259; found 267.1249.

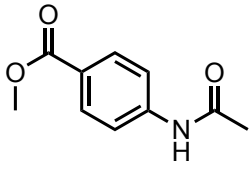


Methyl 4-(cyclohexanecarboxamido)benzoate (**175**) (Table 24). Following general amidation procedure A, 48.6 mg of **175** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient,

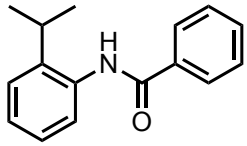
R_f = 0.60 in 40% EtOAc/hexanes) as a white solid (76% yield). Mp: 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.4 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.47 (bs, 1H), 3.91 (s, 3H), 2.24-2.31 (m, 1H), 1.96-1.99 (m, 2H), 1.84-1.87 (m, 2H), 1.72-1.74 (m, 1H), 1.52-1.67 (m, 2H), 1.27-1.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 166.5, 142.2, 130.7, 125.5, 118.6, 51.9, 46.5, 29.5, 25.7; HRMS (EI) [M+] calcd. for $C_{15}H_{19}NO_3$, 261.1365; found 261.1371.



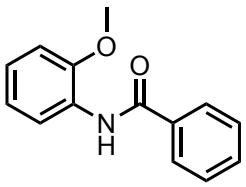
***N*-(4-Methoxyphenyl)pivalamide** (**176**) (Table 24). Following general amidation procedure A, 49.5 mg of **176** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.46 in 30% EtOAc/hexanes) as a yellow solid (96% yield). Mp: 120-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.8 Hz, 2H), 7.41 (bs, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ176.4, 156.2, 131.0, 121.8, 113.9, 55.4, 39.3, 27.5. The spectral data of the product are in accordance with those reported in the literature.[213]



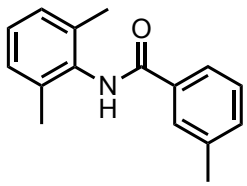
Methyl 4-acetamidobenzoate (**177**) (Table 24). Following general amidation procedure A, 38.2 mg of **177** were isolated by flash chromatography (20→50% EtOAc/hexanes gradient, R_f = 0.25 in 50% EtOAc/hexanes) as a white solid (80% yield). Mp: 130-132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (bs, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 3.91 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 166.6, 142.2, 130.7, 125.3, 118.7, 51.9. 24.6. The spectral data of the product are in accordance with those reported in the literature.[109]



***N*-(2-isoPropylphenyl)benzamide** (**178**) (Table 24). Following general amidation procedure A, 25.7 mg of **178** were isolated by flash chromatography (10→40% EtOAc/hexanes gradient, R_f = 0.60 in 40% EtOAc/hexanes) as a light yellow solid (42% yield). Mp: 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 1H), 7.79 (s, 1H), 7.51-7.61 (m, 2H), 7.36 (d, *J* = 6.8 Hz, 2H), 7.23-7.35 (m, 2H), 3.14 (sept, *J* = 6.8 Hz, 1H), 1.31 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 140.4, 134.9, 134.0, 131.7, 128.7, 126.9, 126.4, 126.1, 125.6, 124.6, 28.1, 22.9; HRMS (EI) [M+] calcd. for $C_{16}H_{17}NO$, 239.1310; found 239.1315.

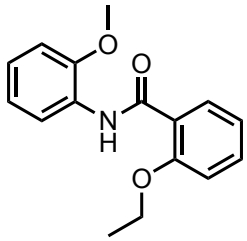


***N*-(2-Methoxyphenyl)benzamide** (**179**) (Table 24). Following general amidation procedure A, 55.4 mg of **179** were isolated by flash chromatography (0→20% EtOAc/hexanes gradient, R_f = 0.35 in 20% EtOAc/hexanes) as an yellow oil (96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 8.56 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 2H), 7.50-7.59 (m, 3H), 7.03-7.13 (m, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 148.0, 135.2, 131.6, 128.7, 127.7, 126.9, 123.8, 121.1, 119.7, 109.8, 55.7. The spectral data of the product are in accordance with those reported in the literature.[212]



***N*-(2,6-Dimethylphenyl)-3-methylbenzamide** (**180**) (Table 24). Following general amidation procedure A, 40.1 mg of **180** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.60 in 30% EtOAc/hexanes) as a light yellow solid (67% yield). Mp: 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (bs, 1H), 7.72 (s, 1H), 7.39-7.43 (m, 3H), 7.12-7.19 (m, 3H), 2.46 (s, 3H), 2.30 (s, 6H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 165.9, 138.6, 135.4, 134.4, 133.8, 132.4, 128.5, 128.2, 127.9, 127.3, 123.9, 21.3, 18.4; HRMS (EI) [M+] calcd. for $C_{16}H_{17}NO$, 239.1310; found 239.1316.

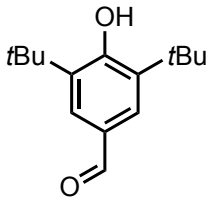


2-Ethoxy-*N*-(2-methoxyphenyl)benzamide (**181**) (Table 24). Following general amidation procedure A, 65 mg of **181** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.45 in 30% EtOAc/hexanes) as a white solid (95% yield). Mp: 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.46 (bs, 1H), 8.71 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.01-7.14 (m, 4H), 6.93 (d, *J* = 8.4 Hz, 1H), 4.28 (q, *J* = 6.8 Hz, 2H), 3.92 (s, 3H), 1.61 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 156.7, 148.3, 132.9, 132.4, 128.4, 123.4, 122.1, 121.1, 120.9, 120.7, 112.2, 109.8, 64.9, 55.3, 14.8; HRMS (EI) [M+] calcd. for $C_{16}H_{17}NO_3$, 271.1208; found 271.1211.

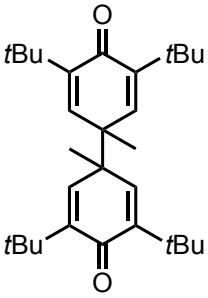
6.5. **Compound characterization data for hydrodehalogenation of aryl halides**

General hydrodehalogenation procedure: In a glovebox, a 10 mL round-bottom flask equipped with magnetic stir bar was charged with 18 mg of 95% purity NaH (0.75 mmol, 3.0 equiv.) and then the flask was sealed with a rubber septum prior to removal from the glovebox. Then, in air, 165.2 mg of 2,6-di-*tert*-butyl-4-methylphenol (BHT, 0.75 mmol, 3.0 equiv.) was added after which the septum was replaced and the round-bottom flask was evacuated and backfilled with Ar (x3). The flask was then cooled to 0°C and Et_2O (3 mL) was added. After stirring for 15 min at 0°C, the solution was warmed up to rt and allowed to stir for an additional 15 min. The solvent was then removed under high vacuum to yield an off-white solid. To the flask was added 7.8 mg of *(DiMeIHept^{Cl})Pd(cinammyl)Cl* (0.0075 mmol, 3 mol%) then the vial was evacuated and backfilled with Ar (x2), followed by addition of THF (0.5 mL). Then the aryl halide (0.25 mmol, 1.0 equiv.)

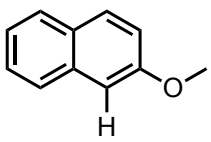
was added by syringe. Alternatively, if the aryl halide was a solid at room temperature, it was added to the vial with *(DiMeIHept^{Cl})Pd(cinammyl)Cl* prior to evacuation. The round-bottom flask was placed in a pre-heated 60 °C oil bath, and stirred under argon at 1150 – 1200 rpm for 24 h. The reaction mixture was cooled to rt, diluted with CH_2Cl_2, filtered through a plug of silica or Celite, and the filtrate concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel (unless noted otherwise) to yield product.



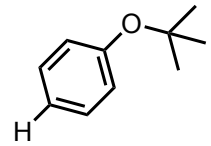
3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**196**). Following general hydrodehalogenation procedure, 5.0 mg of **196** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.25 in 5% EtOAc/hexanes) as a yellowe solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.75 (s, 2H), 5.87 (s, 1H), 1.50 (s, 18 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 158.3, 136.5, 127.7, 34.4, 30.1; HRMS (EI) [M+] calcd. for $C_{15}H_{22}O_2$, 234.1613; found 234.0889.



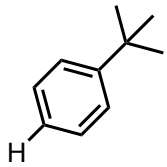
3,3',5,5'-tetra-*tert*-butyl-1,1'-dimethyl-[1,1'-bi(cyclohexane)]-2,2',5,5'-tetraene-4,4'-dione (**197**). Following general hydrodehalogenation procedure, 5.0 mg of **197** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.34 in 5% EtOAc/hexanes) as a yellowe solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 4H), 1.44 (s, 6H), 1.24 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.0, 145.4, 143.1, 67.3, 34.5, 29.4, 28.0; HRMS (EI) [M+] calcd. for $C_{30}H_{46}O_2$, 438.6921; found 437.3756.



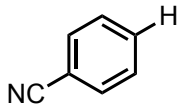
2-Methoxynaphthalene (**208**) (Table 24). Following general hydrodehalogenation procedure, 31.2 mg of **208** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.45 in 5% EtOAc/hexanes) as a white solid (81% yield). Mp: 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.72 (m, 3H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 12.2 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 134.7, 129.5, 129.1, 127.8, 126.8, 126.5, 123.7, 118.8, 105.8, 55.3. The spectral data of the product are in accordance with those reported in the literature.[214]



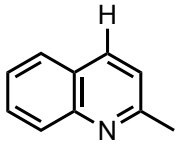
***t*ert-Butoxybenzene** (**210**) (Table 35). Following general hydrodehalogenation procedure, 30.7 mg of **210** were isolated by flash chromatography (0→10% EtOAc/hexanes gradient, R_f = 0.36 in 5% EtOAc/hexanes) as a colorless oil (76% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 7.5 Hz, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 128.8, 124.2, 123.3, 78.3, 28.9. The spectral data of the product are in accordance with those reported in the literature.[94]



***t*-Butylbenzene** (**211**) (Table 35). Following general hydrodehalogenation procedure A, 25.1 mg of **211** were isolated by flash chromatography (0→5% EtOAc/hexanes gradient, R_f = 0.34 in 5% EtOAc/hexanes) as a colorless oil (76% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 6.8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 6.8 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 128.2, 125.6, 125.4, 34.8, 31.5. The spectral data of the product are in accordance with those reported in the literature.[214]



Benzonitrile (**212**) (Table 35). Following general hydrodehalogenation procedure A, 20.1 mg of **211** were isolated by flash chromatography (0→5% EtOAc/hexanes gradient, R_f = 0.36 in 5% EtOAc/hexanes) as a yellow solid (78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61-7.51 (m, 3H), 7.45-7.37 (m, 2H); ^{13}C NMR (100 MHz, CDCl3) δ 132.5, 131.8, 128.8, 118.5, 112.0 The spectral data of the product are in accordance with those reported in the literature.[214]



2-Methylquinoline (**213**) (Table 35). Following general hydrodehalogenation procedure A, 31.2 mg of **213** were isolated by flash chromatography (10→30% EtOAc/hexanes gradient, R_f = 0.45 in 5% EtOAc/hexanes) as a colorless oil (81% yield); ^{1}H NMR (400 MHz, $CDCl_3$) 8.02 (dd, J = 8.4, 4.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 1H), 7.69-7.65 (m, 1H), 7.48-7.44 (m, 1H), 7.25 (d, J = 8.4 Hz, 1H), 2.74 (s, 3H); 13C NMR (100 MHz, CDCl3): δ 158.9, 147.8, 136.0, 129.3, 128.5, 127.4, 126.4, 125.6, 121.9, 25.3. The spectral data of the product are in accordance with those reported in the literature. [215]

Chapter 7- References

1 C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085.

2 J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347.

3 S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451–3479.

4 X.-G. Li, M.-R. Huang, W. Duan, Y.-L. Yang, *Chem. Rev.* **2002**, *102*, 2925–3030.

5 P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649.

6 I. P. Beletskaya, A. V Cheprakov, *Organometallics* **2012**, *31*, 7753–7808.

7 D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50.

8 Rylan J. Lundgren and Mark Stradiotto, *Aldrichimia ACTA* **2012**, *45*, 59–69.

9 T. M. M. Kosugi, M. Kameyama, *Chem. Lett.* **1983**, 927–928.

10 N. M. . Kondratenko, N. W.; Kolomeitsev, A. A.; Mogilevskaya, V. O.; Varlamova, L. M. Yagupol'skii, *J. Org. Chem. USSR* **1986**, *22*, 1547–1554.

11 S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem. Int. Ed.* **1995**, *34*, 1348–1350.

12 J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609–3612.

13 M. Torborg, C.; Beller, *adv. Synth. Catal.* **2009**, *351*, 3027–3043.

14 S. Shekhar, P. Ryberg, J. F. Hartwig, J. S. Mathew, D. G. Blackmond, E. R. Strieter, S. L. Buchwald, *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.

15 J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157.

16 J. Muzart, *J. Mol. Catal. A Chem.* **2009**, *308*, 15–24.

17 C. Amatore, E. Carre, A. Jutand, M. A. M'Barki, *Organometallics* **1995**, *14*, 1818–1826.

18 J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158–1174.

19 M. D. Charles, P. Schultz, S. L. Buchwald, *Org. Lett.* **2005**, *7*, 3965–3968.

20 M. S. Viciu, R. A. K. Iii, E. D. Stevens, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479–

1482.

21 M. Sayah, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 16196–16199.

22 F. Barrios-landeros, B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2009**, *131*, 8141–8154.

23 A. H. Roy, J. F. Hartwig, *Organometallics* **2004**, *23*, 194–202.

24 T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848–13849.

25 Y. Zhang, G. Lavigne, V. César, *J. Org. Chem.* **2015**, *80*, 7666–7673.

26 Jens Ahman and StephenL.Buchwal, *Tetrahedron Lett.* **1997**, *38*, 6363–6366.

27 L. M. Alcazar-Roman, J. F. Hartwig, *Organometallics* **2002**, *21*, 491–502.

28 J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.* **1977**, *10*, 434–442.

29 Z. Li, Y. Fu, Q.-X. Guo, L. Liu, *Organometallics* **2008**, *27*, 4043–4049.

30 B. U. W. Maes, S. Verbeeck, T. Verhelst, A. Ekomié, N. von Wolff, G. Lefèvre, E. A. Mitchell, A. Jutand, *Chem. Eur. J.* **2015**, *21*, 7858–7865.

31 R. A. Widenhoefer, S. L. Buchwald, **1996**, *7333*, 3534–3542.

32 R. A. Widenhoefer, H. A. Zhong, S. L. Buchwald, *Organometallics* **1996**, *15*, 2745–2754.

33 G. Mann, J. F. Hartwig, M. S. Driver, C. Fernández-Rivas, *J. Am. Chem. Soc.* **1998**, *120*, 827–828.

34 F. G. Bordwell, D. J. Algrim, *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968.

35 M. R. Biscoe, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 7232–7235.

36 K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145–151.

37 K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 3086–3090.

38 J. F. Hartwig, *Inorg. Chem.* **2007**, *46*, 1936–1947.

39 M. Yamashita, J. V Cuevas Vicario, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 16347–16360.

40 P. L. Arrechea, S. L. Buchwald, *J. Am. Chem. Soc.* **2016**, *138*, 12486–12493.

41 J. L. Klinkenberg, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 11830–11833.

42 M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245.

43 C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2956–2965.

44 C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2953–2956.

45 C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313–348.

46 E. Negishi, T. Takahashi, K. Akiyoshi, *J. Organomet. Chem.* **1987**, *334*, 181–194.

47 R. Tonner, G. Frenking, *Organometallics* **2009**, *28*, 3901–3905.

48 J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216.

49 B. R. Rosen, J. C. Ruble, T. J. Beauchamp, A. Navarro, *Org. Lett.* **2011**, *13*, 2564–2567.

50 A. Ehrentraut, A. Zapf, M. Beller, *J. Mol. Catal. A* **2002**, *182–183*, 515–523.

51 N. P. Reddy, M. Tanaka, *Tetrahedron Lett.* **1997**, *38*, 4807–4810.

52 D. Maiti, B. P. Fors, J. L. Henderson, Y. Nakamura, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 57–68.

53 Q. Shen, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 4109–4112.

54 J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544.

55 R. J. Lundgren, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 8686–8690.

56 R. J. Lundgren, B. D. Peters, P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2010**, *49*, 4071–4074.

57 R. A. Singer, M. Doré, J. E. Sieser, M. A. Berliner, *Tetrahedron Lett.* **2006**, *47*, 3727–3731.

58 G. Organ, G. A. Chass, D. Fang, A. C. Hopkinson, *Synthesis.* **2008**, *17*, 2776–2797.

59 H. W. Wanzlick, *Angew. Chem. Int. Ed.* **1962**, *1*, 75–80.

60 K. Öfele, . *Organomet. Chem* **1968**, *12*, 42–43.

61 A. J. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361–363.

62 W. A. Herrmann, M. Elison, J. Fischer, C. Köcher, G. R. J. Artus, *Angew. Chem. Int. Ed.* **1995**, *34*, 2371–2374.

63 G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.

64 A. J. Arduengo, R. Krafczyk, R. Schmutzler, H. A. Craig, J. R. Goerlich, W. J. Marshall,

M. Unverzagt, *Tetrahedron* **1999**, *55*, 14523–14534.

65 G. Altenhoff, S. Würtz, F. Glorius, *Tetrahedron Lett.* **2006**, *47*, 2925–2928.

66 C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180–190.

67 X. Luan, R. Mariz, M. Gatti, C. Costabile, A. Poater, L. Cavallo, A. Linden, R. Dorta, *J. Am. Chem. Soc.* **2008**, *130*, 6848–6858.

68 L. Wu, E. Drinkel, F. Gaggia, S. Capolicchio, A. Linden, L. Falivene, L. Cavallo, R. Dorta, *Chem. Eur. J.* **2011**, *17*, 12886–12890.

69 G. Berthon-Gelloz, M. A. Siegler, A. L. Spek, B. Tinant, J. N. H. Reek, I. E. Markó, *Dalt. Trans.* **2010**, *39*, 1444–1446.

70 Y. Zhang, V. César, G. Lavigne, *Chem. Eur. J.* **2015**, 2042–2050.

71 A. R. Chianese, X. Li, M. C. Janzen, J. W. Faller, R. H. Crabtree, *Organometallics* **2003**, *22*, 1663–1667.

72 A. R. Chianese, A. Kovacevic, B. M. Zeglis, J. W. Faller, R. H. Crabtree, *Organometallics* **2004**, *23*, 2461–2468.

73 R. A. Kelly III, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202–210.

74 A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, *2009*, 1759–1766.

75 M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749–4755.

76 C. Valente, S. Baglione, D. Candito, C. J. O. Brien, M. G. Organ, *Chem. Commun.* **2008**, 735–737.

77 M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *13*, 150–157.

78 M. G. Organ, M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, *Chem. Eur. J.* **2008**, *14*, 2443–2452.

79 E. A. B. Kantchev, C. J. O. Brien, M. G. Organ, *Chem. Eur. J.* **2007**, *12*, 2768–2813.

80 G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201.

81 S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem. Int. Ed.* **2010**, *49*, 2014–2017.

82 S. Çalimsiz, M. G. Organ, *Chem. Commun.* **2011**, *47*, 5181–5183.

83 J. L. Farmer, H. N. Hunter, M. G. Organ, *J. Am. Chem. Soc.* **2012**, *134*, 17470–17473.

84 M. Dowlut, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 4279–4283.

85 M. Sayah, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 11719–11722.

86 K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2012**, *19*, 843–845.

87 C. Lombardi, D. Mitchell, M. J. Rodriguez, M. G. Organ, *Chem. Eur. J.* **2016**, *2017*, 1510–1513.

88 A. Khadra, S. Mayer, D. Mitchell, M. J. Rodriguez, M. G. Organ, *Organometallics* **2017**, *36*, 3573–3577.

89 M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354–11357.

90 B. Atwater, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, M. Pompeo, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, *54*, 9502–9506.

91 M. Pompeo, J. L. Farmer, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2014**, *53*, 3223–3226.

92 Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596.

93 R. D. J. Froese, C. Lombardi, M. Pompeo, R. P. Rucker, M. G. Organ, *Acc. Chem. Res.* **2017**, *50*, 2244–2253.

94 N. Kataoka, Q. Shelby, J. P. Stambuli, J. F. Hartwig, *J. Org. Chem.* **2002**, *67*, 5553–5566.

95 M. H. Ali, S. L. Buchwald, *J. Org. Chem.* **2001**, *66*, 2560–2565.

96 Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2005**, *44*, 1371–1375.

97 B. P. Fors, D. A. Watson, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.

98 R. J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, *Chem. Eur. J.* **2010**, *16*, 1983–1991.

99 P. G. Alsabeh, M. Stradiotto, *Angew. Chem. Int. Ed.* **2013**, *52*, 7242–7246.

100 C. A. Wheaton, J.-P. J. Bow, M. Stradiotto, *Organometallics* **2013**, *32*, 6148–6161.

101 S. M. King, S. L. Buchwald, *Org. Lett.* **2016**, *18*, 4128–4131.

102 S. Wagaw, R. a Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458.

103 H. Hammoud, M. Schmitt, E. Blaise, F. Bihel, J. J. Bourguignon, *J. Org. Chem.* **2013**, *78*, 7930–7937.

104 F. Ma, X. Xie, L. Ding, J. Gao, Z. Zhang, *Tetrahedron* **2011**, *67*, 9405–9410.

105 R. Surasani, D. Kalita, A. V. Dhanunjaya Rao, K. B. Chandrasekhar, *Beilstein J. Org. Chem.* **2012**, *8*, 2004–2018.

106 H. Hammoud, M. Schmitt, E. Blaise, F. Bihel, J.-J. Bourguignon, *J. Org. Chem.* **2013**, *78*, 7930–7937.

107 K. I. Fujita, M. Yamashita, F. Puschmann, M. M. Alvarez-Falcon, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9044–9045.

108 K. Dooleweerdt, B. P. Fors, S. L. Buchwald, *Org. Lett.* **2010**, *12*, 2350–2353.

109 T. Ikawa, T. E. Barder, M. R. Biscoe, S. L. Buchwald, *J. Am. Chem. Soc.* **2007**, *129*, 13001–13007.

110 J. D. Hicks, A. M. Hyde, A. M. Cuezva, S. L. Buchwald, *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734.

111 J. Yin, S. L. Buchwald, *Org. Lett.* **2000**, *2*, 1101–1104.

112 B. P. Fors, K. Dooleweerdt, Q. Zeng, S. L. Buchwald, *Tetrahedron* **2009**, *65*, 6576–6583.

113 H. Amination, S. M. Crawford, C. B. Lavery, M. Stradiotto, *Chem. Eur. J.* **2013**, *19*, 16760–16771.

114 Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2007**, *129*, 7734–7735.

115 J. Becica, G. E. Dobereiner, *ACS Catal.* **2017**, *7*, 5862–5870.

116 H. F. Olivo, J. Yu, *J. Chem. Soc. Perkin Trans. 1* **1998**, 391–392.

117 C. Dyrager, L. N. Möllers, L. K. Kjäll, J. P. Alao, P. Dinér, F. K. Wallner, P. Sunnerhagen, M. Grøtli, *J. Med. Chem.* **2011**, *54*, 7427–7431.

118 S. Duan, S. Venkatraman, X. Hong, K. Huang, L. Ulysse, B. I. Mobele, A. Smith, L. Lawless, A. Locke, R. Garigipati, *Org. Process Res. Dev.* **2012**, *16*, 1787–1793.

119 J. F. Bunnett, R. E. Zahler, *Chem. Rev.* **1951**, *49*, 273–412.

120 R. N. Salvatore, H. Yoon, K. Woon, *Tetrahedron* **2001**, *57*, 7785–7811.

121 J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456.

122 D. M. T. Chan, K. L. Monaco, R. P. Wang, M. P. Winters, *Tetrahedron Lett.* **1998**, *39*, 2933–2936.

123 P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941–2944.

124 James P. Schulte II, S. R. Tweedie, *Synlett* **2007**, *15*, 2331–2337.

125 K. H. Hoi, M. G. Organ, *Chem. Eur. J.* **2011**, *18*, 804–807.

126 A. X. Veiga, S. Arenz, M. Erdélyi, *Synthesis (Stuttg).* **2013**, *45*, 777–784.

127 A. Aranyos, D. W. Old, A. Kiyomori, J. P. Wolfe, J. P. Sadighi, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 4369–4378.

128 S. Harkal, K. Kumar, D. Michalik, A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, M. Beller, *Tetrahedron Lett.* **2005**, *46*, 3237–3240.

129 M. Su, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2012**, *51*, 4710–4713.

130 M. W. Hooper, J. F. Hartwig, *Organometallics* **2003**, *22*, 3394–3403.

131 M. C. Harris, X. Huang, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 2885–2888.

132 B. L. Lucht, D. B. Collum, *Acc. Chem. Res.* **1999**, *32*, 1035–1042.

133 K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843–845.

134 G. A. Doherty, T. Kamenecka, E. McCauley, G. Van Riper, R. A. Mumford, S. Tong, W. K. Hagmann, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 729–731.

135 A. P. Kozikowski, S. Wang, D. Ma, J. Yao, S. Ahmad, R. I. Glazer, K. Bogi, P. Acs, S. Modarres, N. E. Lewin, et al., *J. Med. Chem.* **1997**, *40*, 1316–1326.

136 J. Quick, B. Saha, P. E. Driedger, *Tetrahedron Lett.* **1994**, *35*, 8549–8552.

137 L. A. Nguyen, H. He, C. Pham-Huy, *Int. J. Biomed. Sci.* **2006**, *2*, 85–100.

138 M. G. Bursavich, S. Lombardi, A. M. Gilbert, *Org. Lett.* **2005**, *7*, 4113–4116.

139 P. M. Chandrika, T. Yakaiah, A. R. R. Rao, B. Narsaiah, N. C. Reddy, V. Sridhar, J. V. Rao, *Eur. J. Med. Chem.* **2008**, *43*, 846–852.

140 S. Wagaw, R. a Rennels, S. L. Buchwald, G. W. Anderson, F. M. Callahan, H. Hammoud, M. Schmitt, E. Blaise, F. Bihel, J. J. Bourguignon, et al., *J. Am. Chem. Soc.* **2009**, *8*, 5159–5161.

141 Z. Lu, R. J. Twieg, *Tetrahedron Lett.* **2005**, *46*, 2997–3001.

142 N. Narendar, S. Velmathi, *Tetrahedron Lett.* **2009**, *50*, 5159–5161.

143 K. K. Sharma, S. Sharma, A. Kudwal, R. Jain, *Org. Biomol. Chem.* **2015**, *13*, 4637–4641.

144 S. Sharif, R. P. Rucker, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, *54*, 9507–9511.

145 S. Sharif, R. P. Rucker, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2015**, *54*, 9507–9511.

146 D. Y. Lee, J. F. Hartwig, *Org. Lett.* **2005**, *7*, 1169–1172.

147 G. W. Anderson, F. M. Callahan, *J. Am. Chem. Soc.* **1960**, *82*, 3359–3363.

148 M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 11354–11357.

149 V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471.

150 N. Schneider, D. M. Lowe, R. A. Sayle, M. A. Tarselli, G. A. Landrum, *J. Med. Chem.* **2016**, *59*, 4385–4402.

151 A. K. Ghose, V. N. Viswanadhan, J. J. Wendoloski, *J. Comb. Chem.* **1999**, *1*, 55–68.

152 E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631.

153 J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, *20*, 140–177.

154 D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. Leazer Johnnie L., R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, et al., *Green Chem.* **2007**, *9*, 411–420.

155 C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3415.

156 A. Schoenberg, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3327–3331.

157 J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463.

158 K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Böttcher, M. Arlt, M. Beller, *Org. Lett.* **2004**, *6*, 7–10.

159 S.-M. Lu, H. Alper, *J. Am. Chem. Soc.* **2008**, *130*, 6451–6455.

160 E. Takács, C. Varga, R. Skoda-Földes, L. Kollár, *Tetrahedron Lett.* **2007**, *48*, 2453–2456.

161 A. Khadra, S. Mayer, M. G. Organ, *Chem. Eur. J.* **2017**, *23*, 3206–3212.

162 C. Lombardi, J. Day, N. Chandrasoma, D. Mitchell, M. J. Rodriguez, J. L. Farmer, M. G.

Organ, *Organometallics* **2017**, *36*, 251–254.

163 M. S. Oderinde, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 9834–9837.

164 M. S. Oderinde, R. D. J. Froese, M. G. Organ, *Angew. Chem. Int. Ed.* **2013**, *52*, 11334–11338.

165 M. S. Oderinde, H. N. Hunter, R. D. J. Froese, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10821–10824.

166 M. S. Oderinde, H. N. Hunter, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 10817–10820.

167 C. Ollivier, P. Renaud, *Chem. Rev.* **2001**, *101*, 3415–3434.

168 Z.-C. Zhang, T. C. M. Chung, *Macromolecules* **2006**, *39*, 5187–5189.

169 E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. Dirocco, I. W. Davies, S. L. Buchwald, D. W. C. Macmillan, *Science.* **2016**, *353*, 279–283.

170 K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145–151.

171 N. D. Contrella, R. F. Jordan, *Organometallics* **2014**, *33*, 7199–7208.

172 G. W. Gribble, *Chem. Soc. Rev.* **1999**, *28*, 335–346.

173 R. Wilcken, M. O. Zimmermann, A. Lange, A. C. Joerger, F. M. Boeckler, *J. Med. Chem.* **2013**, *56*, 1363–1388.

174 M. Z. Hernandes, S. M. T. Cavalcanti, D. R. M. Moreira, W. F. de A. J. and A. C. L. Leite, *Curr. Drug Targets* **2010**, *11*, 303–314.

175 C. Ramanathan, L. S. Jimenez, *Synthesis (Stuttg).* **2010**, 217–220.

176 G. Cagnetta, J. Robertson, J. Huang, K. Zhang, G. Yu, *J. Hazard. Mater.* **2016**, *313*, 85–102.

177 W. M. Czaplik, S. Grupe, M. Mayer, A. J. von Wangelin, *Chem. Commun.* **2010**, *46*, 6350–6352.

178 H. Guo, K. Kanno, T. Takahashi, *Chem. Lett.* **2004**, *33*, 1356–1357.

179 K. Fujita, M. Owaki, R. Yamaguchi, *Chem. Commun.* **2002**, 2964–2965.

180 M. L. Buil, M. A. Esteruelas, S. Niembro, M. Oliván, L. Orzechowski, C. Pelayo, A. Vallribera, *Organometallics* **2010**, *29*, 4375–4383.

181 S. H. Leung, D. G. Edington, T. E. Griffith, J. J. James, *Tetrahedron Lett.* **1999**, *40*, 7189–7191.

182 O. Navarro, N. Marion, Y. Oonishi, R. A. Kelly, S. P. Nolan, *J. Org. Chem.* **2006**, *71*, 685–692.

183 A. Arcadi, G. Cerichelli, M. Chiarini, R. Vico, D. Zorzan, *European J. Org. Chem.* **2004**, *2004*, 3404–3407.

184 M. S. Viciu, G. A. Grasa, S. P. Nolan, *Organometallics* **2001**, *20*, 3607–3612.

185 O. Navarro, H. Kaur, P. Mahjoor, S. P. Nolan, *J. Org. Chem.* **2004**, *69*, 3173–3180.

186 S. Akzinnay, F. Bisaro, C. S. J. Cazin, *Chem. Commun.* **2009**, 5752–5753.

187 A. Rühling, L. Rakers, F. Glorius, *ChemCatChem* **2017**, *9*, 547–550.

188 S. Kuhl, R. Schneider, Y. Fort, *Adv. Synth. Catal.* **2003**, *345*, 341–344.

189 M. Weidauer, E. Irran, C. I. Someya, M. Haberberger, S. Enthaler, *J. Organomet. Chem.* **2013**, *729*, 53–59.

190 F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2002**, *102*, 4009–4092.

191 A. Kume, Y. Monguchi, K. Hattori, H. Nagase, H. Sajiki, *Appl. Catal. B Environ.* **2008**, *81*, 274–282.

192 Y. Monguchi, A. Kume, K. Hattori, T. Maegawa, H. Sajiki, *Tetrahedron* **2006**, *62*, 7926–7933.

193 G. Chelucci, *Tetrahedron Lett.* **2010**, *51*, 1562–1565.

194 J. Chen, Y. Zhang, L. Yang, X. Zhang, J. Liu, L. Li, H. Zhang, *Tetrahedron* **2007**, *63*, 4266–4270.

195 N. A. Cortese, R. F. Heck, *J. Org. Chem.* **1977**, *42*, 3491–3494.

196 X. Wang, L. Zhang, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2009**, *11*, 5026–5028.

197 A. M. Zawisza, J. Muzart, *Tetrahedron Lett.* **2007**, *48*, 6738–6742.

198 N. Iranpoor, H. Firouzabadi, R. Azadi, *J. Organomet. Chem.* **2010**, *695*, 887–890.

199 P. P. Cellier, J.-F. Spindler, M. Taillefer, H.-J. Cristau, *Tetrahedron Lett.* **2003**, *44*, 7191–7195.

200 A. Pyo, S. Kim, M. R. Kumar, A. Byeun, M. S. Eom, M. S. Han, S. Lee, *Tetrahedron Lett.* **2013**, *54*, 5207–5210.

201 P. H. Arie Zask, *J. Org. Chem.* **1978**, *43*, 1619–1620.

202 G. Chelucci, S. Baldino, A. Ruiu, D. Agraria, U. Sassari, V. Italia, I.- Sassari, *J. Org. Chem.* **2012**, *77*, 9921–9925.

203 K. Omura, *J. Org. Chem.* **1991**, *56*, 921–927.

204 W. A. Yehye, N. A. Rahman, A. Ariffin, S. B. Abd Hamid, A. A. Alhadi, F. A. Kadir, M. Yaeghoobi, *Eur. J. Med. Chem.* **2015**, *101*, 295–312.

205 S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627.

206 N. Dastbaravardeh, M. Schnürch, M. D. Mihovilovic, *Org. Lett.* **2012**, *14*, 1930–1933.

207 M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774.

208 Y.-C. Teo, F.-F. Yong, I. K. Ithnin, S.-H. T. Yio, Z. Lin, *European J. Org. Chem.* **2013**, *2013*, 515–524.

209 K. Yan, D. Yang, W. Wei, G. Li, M. Sun, Q. Zhang, L. Tian, H. Wang, *RSC Adv.* **2015**, *5*, 100102–100105.

210 C. G. McPherson, K. Livingstone, C. Jamieson, I. Simpson, *Synlett* **2016**, *27*, 88–92.

211 A. M. Whittaker, V. M. Dong, *Angew. Chem. Int. Ed.* **2015**, *54*, 1312–1315.

212 Y. Qiao, G. Li, S. Liu, Y. Yangkai, J. Tu, F. Xu, *Synthesis.* **2017**, *49*, 1834–1838.

213 T. T. Nguyen, K. L. Hull, *ACS Catal.* **2016**, *6*, 8214–8218.

214 A. Bhattacharjya, P. Klumphu, B. H. Lipshutz, *Org. Lett.* **2015**, *17*, 1122–1125.

215 K. H. He, F. F. Tan, C. Z. Zhou, G. J. Zhou, X. L. Yang, Y. Li, *Angew. Chem. Int. Ed.* **2017**, *56*, 3080–3084.