PALLADIUM-CATALYZED AMINE SYNTHESIS: CHEMOSELECTIVITY AND REACTIVITY UNDER AQUEOUS CONDITIONS

by

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DALHOUSIE UNIVERSITY

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For Mom and Dad

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ABSTRACT

The palladium-mediated cross-coupling of aryl electrophiles and amines (Buchwald-Hartwig amination) has become a widely used method of constructing arylamine frameworks. A crucial aspect of the advancement of this chemistry has been the design of ancillary ligands that are able to promote enhanced reactivity in challenging amination reactions. Despite significant ligand development within the field, challenges in this chemistry remain.

Chemoselective aminations, wherein one amine substrate undergoes preferential arylation in the presence of multiple reactive amines has remained an underexplored area of Buchwald-Hartwig amination chemistry. This thesis describes the use of $[Pd(cinnamyl)Cl]_2$ and N-[2-di(1-adamantylphosphino)phenyl]morpholine (Mor-DalPhos) in an extensive study of chemoselective Buchwald-Hartwig aminations, with 62 examples of structurally diverse di-, tri-, and tetraamines obtained in synthetically useful yields at reasonable catalyst loadings (1-5 mol % Pd). The coordination chemistry of [(Mor-DalPhos)Pd] species was also explored, as were complementary chemoselective aminations with the isomeric *p*-Mor-DalPhos ligand, leading to divergent product formation in some instances. The same $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system used in the chemoselectivity study was also employed in a series of Buchwald-Hartwig aminations conducted under aqueous and solvent-free conditions, another underexplored area of this chemistry. A total of 52 amine products were isolated using these methodologies, moderate catalyst loadings (3 mol % Pd), and without the use of any additional additives, co-solvents, or rigorous exclusion of air.

The synthesis of low-coordinate palladium complexes featuring both NHC and dialkylchlorophosphine ligands is also discussed herein. These complexes are prepared via a previously unreported and straightforward methodology involving an unusual net P-Cl bond reductive elimination, and represent a potential new class of pre-catalysts for palladium-mediated reactions.

LIST OF ABBREVIATIONS AND SYMBOLS USED

Å	angstrom
δ	chemical shift *or* partial charge
η	hapticity (contiguous donor atoms)
κ	hapticity (non-contiguous donor atoms)
1-Ad	1-adamantyl
Amphos	(di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline
Anal. Calcd.	analysis calculated
App.	apparent
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
br	broad
BrettPhos	dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine
Conv.	conversion
COSY	homonuclear shift correlation spectroscopy
Cy	cyclohexyl
d	doublet(s)
dba	dibenzylideneacetone
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
DavePhos	2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

DiPPF	1,1'-bis(diisopropylphosphino)ferrocene
DPPF	bis(diphenylphosphino)ferrocene
DPCB	diphosphinidenecyclobutene
ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
h	hour(s)
Hex	hexane
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrometry
Hz	hertz
IAPU	2,8,9-triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo
IPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene
JosiPhos	(*R*)-(-)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine
$J_{XX'}$	bond coupling constant between atom X and atom X'
L	neutral 2-electron donor ligand
L_n	generic ligand set
m	multiplet
M	generic transition metal *or* mol/L *or* molecular ion
m/z	mass-to-charge ratio
Me	methyl
Me-DalPhos	2-(di-1-adamantylphosphino)-*N*,*N*-dimethylaniline

mol	mole(s)
Mor-DalPhos	N-[2-di(1-adamantylphosphino)phenyl]morpholine
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
NOESY	nuclear Overhauser effect spectroscopy
OAc	acetate
ORTEP	Oak Ridge thermal ellipsoid plot
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate (*p*-toluenesulfonate)
o	*ortho*
p	*para*
p-Mor-DalPhos	N-[4-di(1-adamantylphosphino)phenyl]morpholine
Ph	phenyl
*i*Pr	iso-propyl
ppm	parts per million
PTFE	poly(tetrafluoroethylene)
q	quartet
quint.	quintet
RuPhos	dicyclohexyl(2',6'-diisopropoxybiphenyl-2-yl)phosphine
s	singlet
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SIPr	1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine
SPhos	dicyclohexyl(2',6'-dimethoxybiphenyl-2-yl)phosphine

t	triplet
*t*Bu	tertiary-butyl
*t*Bu-XPhos	di-*tert*-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
X	generic anion *or* anionic ligand
XPhos	dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine

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As anyone who has experienced it knows, grad school can be a strange experience. One day you're on top of the world because a reaction worked, and the next day you want to crawl into bed and start looking at job ads because you had a rough lab day. You become friends with someone only to have them graduate and move on, and then meet a new friend from an incoming class. You start out thinking that the learning process is finally almost over, and then quickly realize that you’ve only really just started your education, both personally and professionally.

Above all, what I will remember most about this entire process, are the people I’ve met along the way, and the experiences I’ve been able to share with them. For better or worse, they’ve been a part of this strange journey, and have helped shape me into the person I am today. In many ways, this thesis is the sum total of that journey, both in and out of the lab, and hopefully it does justice to how great this ride has been.

Ben Tardiff,

April 2012

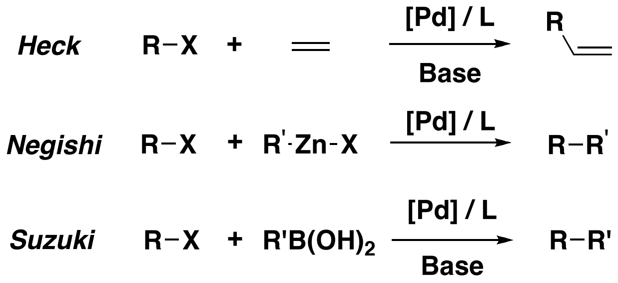
CHAPTER 1. INTRODUCTION TO PALLADIUM MEDIATED CATALYSIS

1.1. Introduction to Transition Metal Mediated Cross-Coupling Chemistry

The study of organometallic transition metal complexes has increased significantly over the past several decades, due in part to the unique reactivity that transition metal centres can impart upon organic fragments. In perhaps no area has this been as evident as in catalysis, where transition metal-mediated processes have risen in prominence. The ability to 'tune' the steric and electronic properties of ligands bound to transition metals in order to alter and control the properties of the resulting complex allows for potential reactivity enhancement or selectivity control at various steps within a catalytic cycle.[1] The syntheses of pharmaceuticals, fine chemicals, materials, polymers, and a number of other products have all been revolutionized by the exploration and expansion of the field of catalysis using transition metal complexes. In addition to these aforementioned products, the synthesis of small organic molecules (as well as larger organic frameworks) by transition metal catalysts has become standard protocol, and in many cases has replaced classical synthetic methods.[2, 3]

1.2. Selected Examples of Palladium Catalyzed Carbon-Carbon Bond Forming Reactions

Metal-catalyzed coupling reactions between aryl electrophiles and various nucleophilic substrates are among the most common, efficient, and effective methods of catalytically generating small organic molecules.[3, 4] A wide variety of such reactions are known, including transformations leading to carbon-carbon bond formation. Prominent reactions of this type include Suzuki-Miyaura, Heck, and Negishi cross-coupling reactions, all of which primarily utilize palladium-based catalyst systems, and for which the 2010 Nobel Prize in chemistry was awarded (Scheme 1.1).[3] Nonetheless, despite the versatile and useful products that can be synthesized via these palladium-mediated reactions, improvement of these reactions via ligand development remains an important goal. As such, ligand design remains a focal point of research within the field of organometallic chemistry.

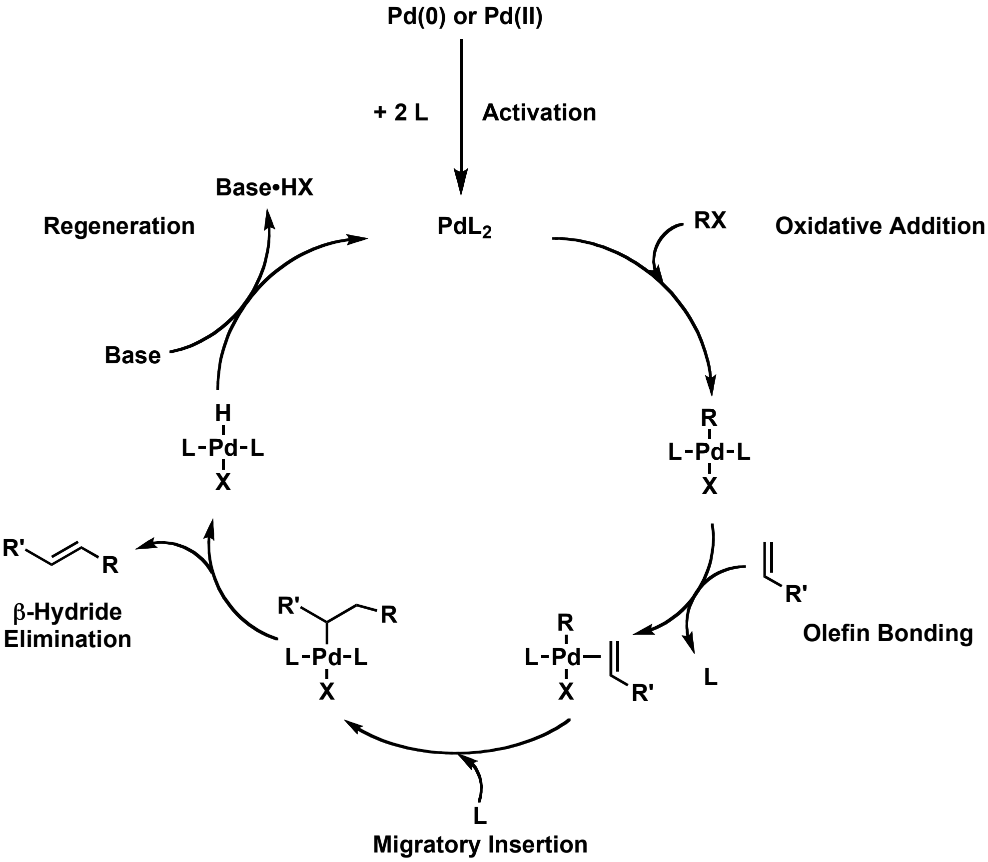


Scheme 1.1 Nobel Prize Winning Cross-Coupling Reactions

The cross-coupling of organic electrophiles and nucleophiles is a powerful method of constructing organic frameworks. Natural products, pharmaceuticals, pesticides, fine chemicals, and biologically-relevant molecules are only a small sampling of species that can and have been synthesized using some variation of palladium-catalyzed cross-coupling. Indeed, it has become increasingly rare to find examples of the preparation of these complex molecules that do not utilize a cross-coupling reaction in one or more key synthetic steps.[5]

One of the first great breakthroughs in metal-mediated cross-coupling chemistry was achieved the late 1960s, with the reported coupling of aryl or alkenyl halides with alkenes, in what would soon become known as the Heck reaction.[6] This reaction formally represents a direct functionalization reaction, where one vinyl C-H bond has been substituted.[7]

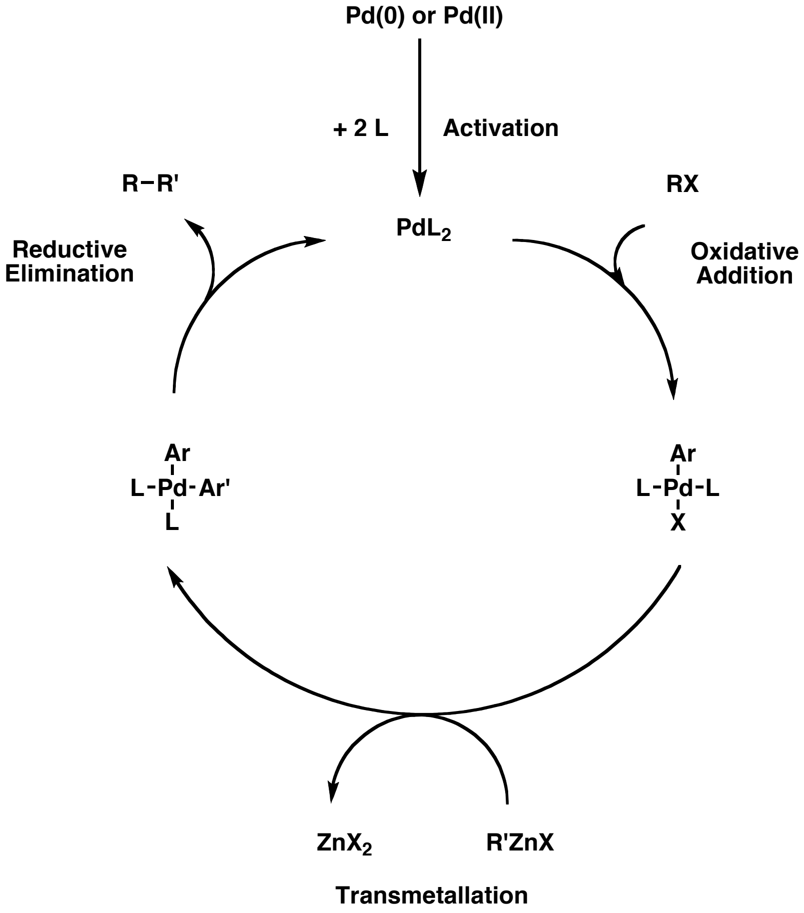
The Heck reaction is widely regarded as the 'father' of palladium-catalyzed cross-coupling processes, and its versatility in coupling olefins with a wide range of electrophiles represented a milestone in the practical synthesis of otherwise challenging molecules.[8] The major steps in the catalytic cycle for the Heck reaction using a representative PdL_2 catalyst are shown in Scheme 1.2.[9]



Scheme 1.2 Catalytic Cycle for the Heck Reaction

The catalytic cycle for the Heck reaction begins with activation of a palladium precatalyst via the introduction of appropriate ancillary ligands and/or reduction of the Pd(II) starting material to Pd(0). This is followed by oxidative addition of an aryl or vinyl halide, and olefin binding. After a migratory insertion step, β-hydride elimination results in ejection of the desired product, and dehydrohalogenation by base regenerates the active catalytic species. Study of this reaction mechanism has allowed for further expansion and optimization of the Heck reaction (and later, other palladium-mediated cross-coupling processes), and has spurred on ligand design and development as a crucial aspect of improving these types of processes.

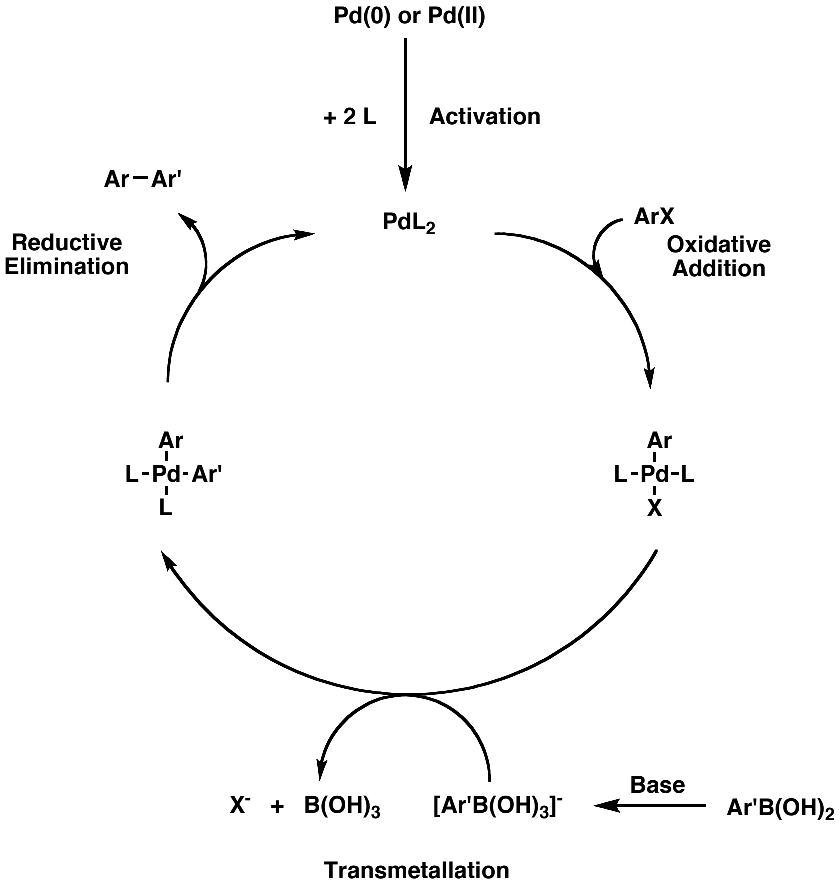
The coupling of an organozinc reagent with an aryl or alkyl halide was reported by Negishi[10] in 1977, and has since become generally referred to as Negishi coupling. The reaction mechanism (Scheme 1.3) is straightforward, beginning with oxidative addition of an aryl or alkyl halide to a Pd(0) centre. The resulting Pd(II) species then undergoes a transmetallation with an organozinc reagent, transferring an additional organic fragment to palladium. Reductive elimination then affords the product and regenerates the active catalyst. The Negishi reaction is a powerful bond forming reaction with the added benefit of being able to form new aryl-alkyl and alkyl-alkyl linkages. The downside of the reaction, however, is the requirement of an organozinc reagent, which creates an additional overall reaction step.[3]



Scheme 1.3 General Mechanism for Negishi Cross-Coupling

Perhaps the most widely employed carbon-carbon cross-couplings are Suzuki-Miyaura reactions, which involve the coupling of an aryl halide and a phenylboronic acid or ester.[11, 12] In general, Suzuki cross-coupling is considered to be one of the most efficient and environmentally benign methods of constructing carbon-carbon bonds. The nontoxic nature and commercial availability of substrates, relatively mild reaction conditions, and broad tolerance of functional groups make it very versatile. Additionally, the ease of handling and removal of nontoxic boron-containing byproducts make it an even more attractive synthetic tool, as does the ability to conduct the reaction using water as a solvent.[13,14]

The catalytic cycle for Suzuki cross-coupling is similar to those proposed for other palladium-mediated cross-coupling processes, and is nearly identical to that of Negishi coupling, with the exception of the transmetallation step (Scheme 1.4). The mechanism begins with activation of the palladium precatalyst, generating the active Pd(0) species. The aryl halide is then able to undergo oxidative addition, while the addition of base generates a four-coordinate boron species that can then undergo transmetallation with the aforementioned intermediate, with net exchange of the bound halide anion with the boron-bound organic fragment. That final intermediate can then undergo reductive elimination, ejecting the product, and regenerating the active catalytic species.



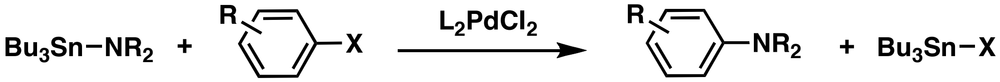
Scheme 1.4 Catalytic Cycle for Suzuki-Miyaura Cross-Coupling

1.3. Palladium-Catalyzed C-N Bond Formation

There can be no question that the coupling of aryl electrophiles and nucleophiles to form new carbon-carbon bonds is of great utility. However, although carbon-carbon bond formation processes dominated the beginnings of cross-coupling chemistry, in recent years the scope of metal-mediated cross-coupling has expanded immensely, with carbon-nitrogen cross-coupling emerging to the forefront as a versatile and useful method of preparing arylamines. Such nitrogen-containing fragments are ubiquitous in biologically-relevant molecules, pharmaceuticals, herbicides, as well as their smaller, organic precursors, making their efficient preparation of great interest.

Traditionally, these compounds were prepared via classical methods, such as nitration, reduction/reductive alkylation, copper-mediated chemistry at high temperatures, or direct nucleophilic substitution on electron-poor aromatic or heteroaromatic halides.[15] Several drawbacks are associated with these methods, including safety, cost, waste products, toxicity and synthetic efficiency. As such, a number of these methodologies have been abandoned in favor of catalytic methods, particularly as the scope and efficiency of catalytic C-N bond-forming methods has been expanded.

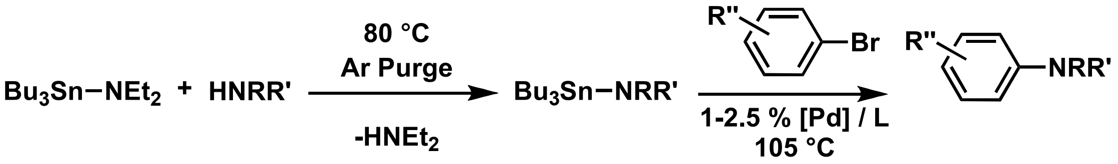
The demonstration of palladium-catalyzed cross-coupling chemistry to form amines was first reported by Migita[16] in 1983, and involved the coupling of tin amides with aryl halides in a reaction catalyzed by a palladium and P(o-tolyl)$_3$ catalyst system (Scheme 1.5).



Scheme 1.5 Palladium-Mediated Coupling of Aryl Halides With Tin Amides

Unfortunately, the lack of broad applicability of this method in the general synthesis of arylamines, due to the use of unstable and toxic amidostannane substrates, limited the utility of this protocol. However, the work did eventually prompt further research in this area, most notably by the groups of Hartwig and Buchwald.

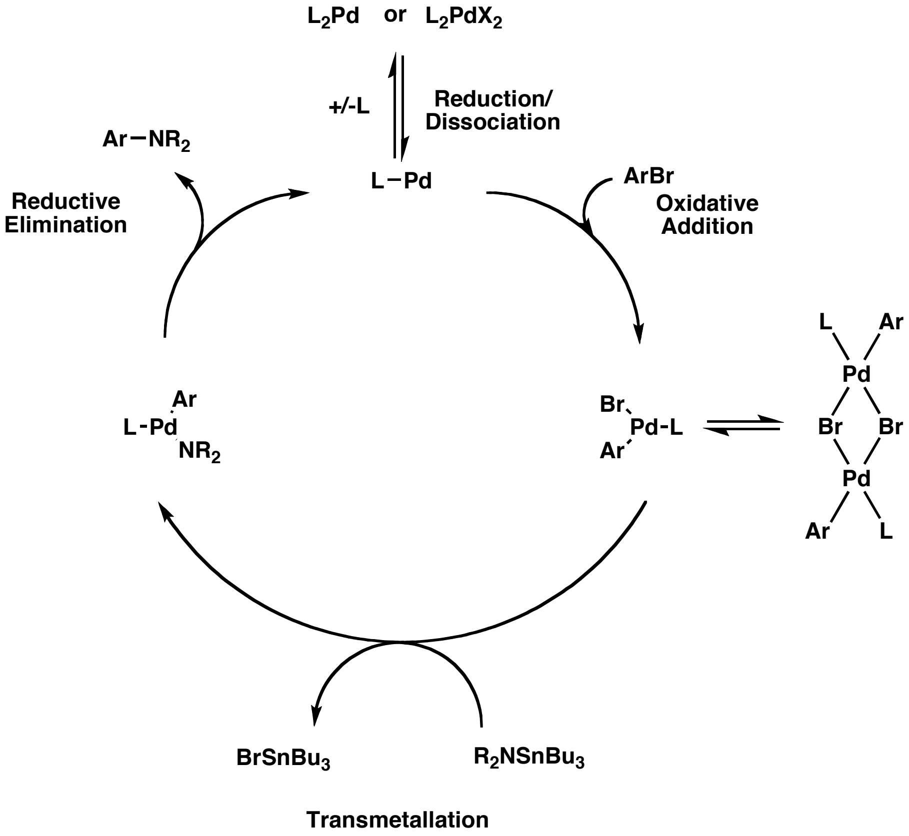
In 1994, Buchwald[17] reported a generalized palladium-mediated protocol that afforded a more attractive route to arylamines from tin amide precursors (Scheme 1.6), demonstrating that the initial reaction scope could be expanded upon by generating the desired amidostannane substrates *in situ* via a transmetallation reaction between the desired amine and an aminostannane derived from a volatile amine such as $Bu_3Sn\text{-}NEt_2$, with concomitant removal of $HNEt_2$.[18] This technique allowed for a reasonably general means of obtaining arylamines from a wide selection of *in situ* generated amidostannanes and aryl bromides.



Scheme 1.6 Generalized Procedure for Aryl Bromide-Tin Amide Coupling

Additionally, Buchwald demonstrated that the P(o-tolyl)$_3$ ligand was still desirable, noting that other $PdCl_2L_2$ catalysts (where L = PPh_3, 1,1'-bis(diphenylphosphino)ferrocene (DPPF) or $Ph_2P(CH_2)_3PPh_2$) were not effective, and only generated trace amounts of desired product.

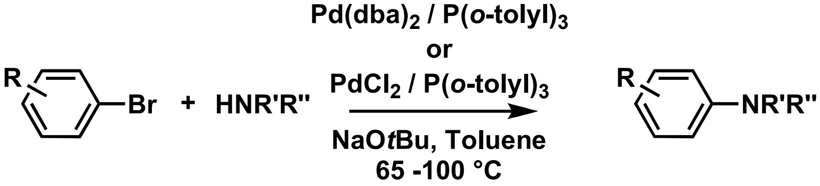
At the same time, Hartwig[19] reported several key intermediates in the proposed catalytic cycle for the cross-coupling of aryl halides and tin amides, as well as the expanded use of palladium compounds catalytically (Scheme 1.7). These contributions provided meaningful insight into the reaction mechanism (when a monodentate phosphine ligand is employed), and also paved the way for future expansion of palladium catalyzed carbon-nitrogen cross-coupling via ligand development.



Scheme 1.7 Catalytic Cycle for the Cross-Coupling of Aryl Bromides and Tin Amides

The use of palladium catalysts featuring phosphine ligands to mediate this reaction demonstrated the potential of this synthetic method to be as broadly applicable and useful as the aforementioned carbon-carbon bond formation reactions. Additionally, the isolation of key reaction intermediates provided a foundation upon which catalyst improvement via ligand development could be built. However, although a fairly general method of forming arylamines using this methodology was a breakthrough, the use of toxic and relatively unstable aminostannane reagents was less than ideal.

A breakthrough in palladium-mediated carbon-nitrogen bond formation occurred in 1995, when Hartwig[20] and Buchwald[21] concomitantly reported practical protocols for the catalytic generation of arylamines using the same catalyst system initially reported by Migita. This new cross-coupling reaction utilized aryl bromides and simple secondary amines, eliminating the need for aminostannane reagents, as well as ameliorating or eliminating many of the other drawbacks of those previous reactions, including the need to generate the reactive amine *in situ*, thereby eliminating the formation of tin byproducts altogether (Scheme 1.8).



Scheme 1.8 Initial Buchwald-Hartwig Amination

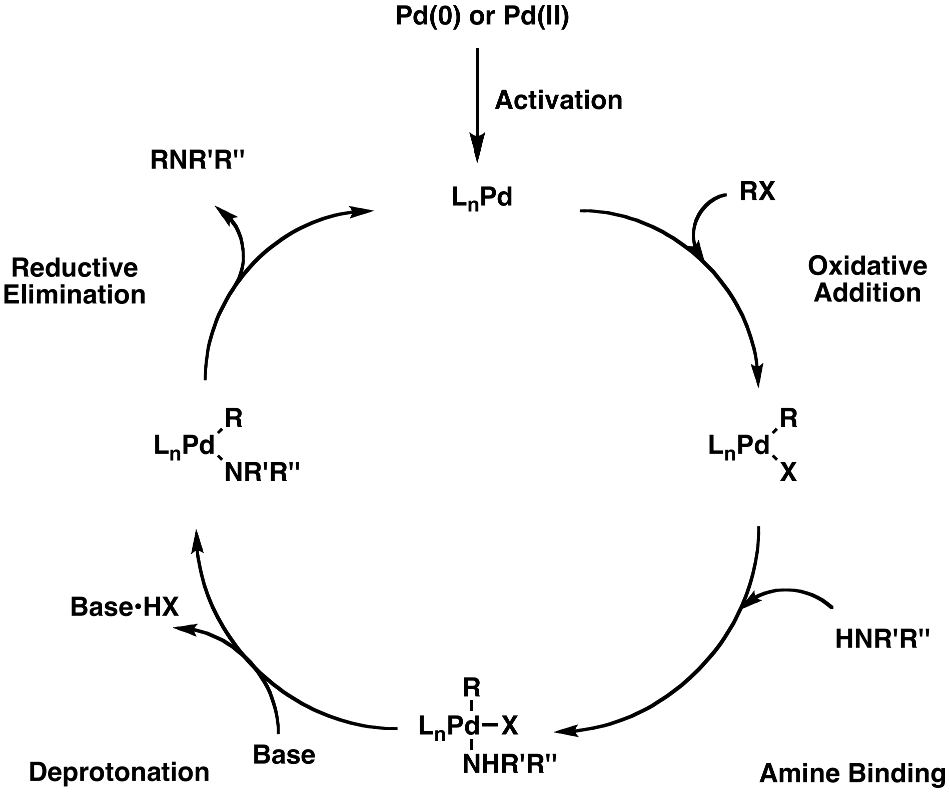
The reports by both Hartwig and Buchwald demonstrated the viability of both $Pd(dba)_2$ and $PdCl_2$ as palladium sources and $P(o\text{-tolyl})_3$ as a ligand, indicating that both Pd(0) and Pd(II) starting materials were viable catalyst precursors. In addition, both reports demonstrated that a reasonable range of electron-rich and electron-poor aryl bromides could be utilized, and that several varieties of secondary amines were suitable substrates.

However, this general method of cross-coupling simple amines and aryl bromides, though groundbreaking, did have several limitations, at least in this initial incarnation. Firstly, neither aryl chlorides nor iodides were usable substrates. As aryl chlorides are generally less expensive and are commercially available in greater variety than their bromide counterparts, their use as coupling partners with amines would be of substantial value.[22] Secondly, for the most part, only secondary amines were successfully cross-coupled in reasonable yields using the reported catalyst systems and reaction conditions, with only one example of a primary amine being coupled with an activated aryl bromide between the two reports.

As with carbon-carbon bond forming reactions, further ligand and catalyst development, coupled with mechanistic studies, would eventually assist in expanding this chemistry to a broader range of (hetero)aromatic (pseudo)halides, primary amines, and eventually challenging substrates such as ammonia and hydrazine. This has greatly broadened the range of arylamines that can be synthesized using this methodology, affording additional applicability and utility to the reaction.

1.4. Mechanism of Buchwald-Hartwig Amination

The generally accepted catalytic cycle for C-N cross-coupling featuring a palladium-based catalyst (widely referred to as Buchwald-Hartwig amination) is outlined in Scheme 1.9.[2] The cycle begins by activation of the precatalyst by base, and is followed by oxidative addition of the aryl halide to the activated $L_nPd(0)$ species, which is then followed by coordination of the amine to the resulting Pd(II) intermediate. The amine can then undergo deprotonation by the base, and reductive elimination of the resulting amido species yields the arylamine product, and regenerates the active catalyst.



Scheme 1.9 Catalytic Cycle for Buchwald-Hartwig Amination

Although rates of oxidative addition are certainly catalyst dependent (in that more electron-rich, sterically unhindered complexes promote oxidative addition more favourably), the steric and electronic characteristics of the substrates also influence reaction rates.[23, 24] For example, electron-rich aryl halide species can be more challenging to undergo oxidative addition with the palladium catalyst, and are often referred to as ‘deactivated’ substrates. Electron-poor aryl halides, on the other hand, typically undergo oxidative addition more easily, and are hence referred to as ‘activated’ substrates. In addition to the electronic properties of the aryl halide, steric properties can also play an important role, as more hindered substrates may also undergo oxidative addition more slowly than unhindered ones. The nature of the halide itself is also of great importance, both in terms of halide-carbon bond strength, and due to the fact that the mechanism of oxidative addition can vary depending on the halide in question.[25]

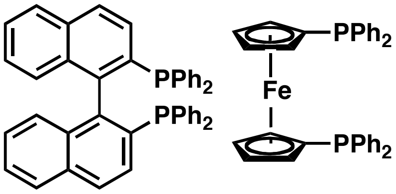
The amine-binding step is also dependent on both the catalyst and the substrate. More electron-rich (basic) amines typically bind more favourably with metal species, as do those that are not sterically hindered. Consequently, less basic or more sterically hindered amines often exhibit weaker coordination with the catalytic species, which can result in poorer reaction rates or yields. Deprotonation of the bound amine, on the other hand, depends primarily on the propensity of the amine to undergo deprotonation (e.g. 'acidity’). Binding to a transition metal centre greatly increases the relative acidity of the amine protons, but the fundamental acidity of the amine itself can still play an important role in determining conversion, and in the case of systems containing multiple amines, product formation.

The rate of reductive elimination of the arylamine product is primarily a function of the metal/ligand characteristics. Generally speaking, electron-poor complexes have a tendency to undergo reductive elimination more quickly, as do complexes that have bulky ancillary ligands, as reductive elimination reduces steric strain and renders a transition metal centre more electron-rich.[26] Within these general guidelines lie a number of factors that can also influence rates of reductive elimination in these systems, particularly the nature of the reacting ligands in question. For example, bulky groups on the metal-bound reactive ligands can also help to promote reductive elimination.[26] Additionally, in complexes containing bidentate phosphine ligands, it has been demonstrated that reductive elimination to form a new carbon-nitrogen bond proceeds more quickly when a more electron-rich amido reacting ligand is involved.[26,27] Similar studies with the same type of complexes have also shown that reductive elimination is also faster when a more electron-poor aryl group is bound to the palladium centre. [26,28]

1.5. Buchwald-Hartwig Amination Ligand Development

As mentioned previously, the first established catalyst system for palladium-mediated C-N cross-coupling employed both Pd(0) and Pd(II) starting material along with P(o-tolyl)$_3$ as a ligand.[20, 21] However, despite the seminal nature of this work, the catalyst system was fairly limited, as only aryl bromides and secondary amines were suitable substrates, with primary amines only able to be arylated with a limited class of electron-poor aryl bromides. In addition, the monodentate nature of the phosphine ligand was thought to be responsible for the presence of arene side-products resulting from β–hydride elimination of the amine. The expansion of this reaction to a broader range of aryl halides and amine substrates via further ligand development and mechanistic study was an obvious goal, and was the subject of intense focus by the groups of both Buchwald and Hartwig initially, which spurred on additional development as the chemistry become more broadly useful.

The ligand systems explored after the so called 'first-generation' P(o-tolyl)$_3$ ligand were aryl-substituted bisphosphines. Specifically, the Buchwald group focused on BINAP,[29] eventually moving towards the use of monodentate biarylphosphine ligands, while the Hartwig group turned its attention towards the use of DPPF (Figure 1.1).[30]



BINAP **DPPF**

Figure 1.1 'Second Generation' Ligands for Buchwald-Hartwig Aminations

The Buchwald group's interest in exploring BINAP (as well as other bidentate phosphines) as a ligand for C-N cross-coupling was, in part, based upon the fact that previous transition metal complexes featuring bidentate phosphine ligands had been shown to inhibit β–hydride elimination, as well as promote both the oxidative addition and reductive elimination steps of the catalytic cycle. During the course of their study it was determined that the combination of Pd_2dba_3 and BINAP constituted a catalyst system that successfully promoted the monoarylation of primary amines, as well as increased yields of products obtained using substrates that had previously performed poorly.[29] Buchwald also reported that other less-rigid bidentate phosphines were less effective in promoting the reaction, leading to the supposition that the efficacy of BINAP as a ligand could be related to its ability to inhibit β–hydride elimination, as well as its ability to inhibit the formation of catalytically inactive Pd(bis)amine aryl halide complexes.[31]

The Hartwig group's interest in using DPPF to expand the scope and utility of amine arylation was based in large part on their own previous studies of late transition metal amido complexes. Not only did this ligand enable the coupling of primary amines and aryl halides that were not possible with the $P(o\text{-tolyl})_3$ system, it demonstrated that sterically encumbered phosphines were not necessarily required for high yielding cross-couplings of aryl halides and primary amines, and that the favourable selectivity of reductive elimination over β-hydride elimination could be due to coordination geometry and bite angle.[30] In principle, this meant that employing other chelating ligands could lead to optimized reaction rates and yields, a conclusion that would have important implications for the selection and development of future cross-coupling ligands.

Additional examples of similar, chelating aryl bisphosphine ligands promoting C-N cross coupling were reported shortly thereafter.[32,33] However, even with these advancements, and with a wide range of effective bisphosphine ligands known, the cross-coupling process was ineffective for several substrate classes, such as acyclic secondary amines.[34] This limitation prompted further exploration of alternative ligand systems that would be effective for these substrates.

Buchwald began the search for an effective ligand system for these substrates by exploring Hayashi-type ferrocenyl ligands, primarily due to their straightforward synthesis and structural variability.[35] A survey of several ligand variants demonstrated the utility of PPFA and PPF-OMe in the cross coupling of deactivated aryl bromides and halo-pyridines with both hindered primary and secondary amines (Figure 1.2).

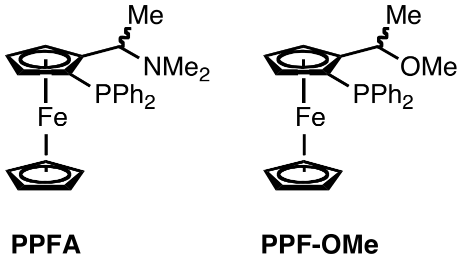
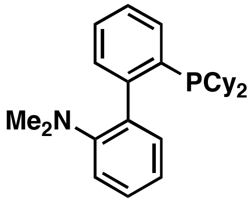


Figure 1.2 Structures of PPFA and PPF-OMe

The successful use of biarylphosphine ligands featuring appended amine donors in facilitating challenging transformations prompted the development of biaryl aminophosphine ligands, a class of ligand that helped expand the scope of this catalysis to unactivated aryl chlorides.

The first of these ligands, DavePhos,[36] enabled the coupling of a range of electronically and sterically diverse aryl halides, with both primary and secondary amines, employing low catalyst loadings and in some instances even promoting amination at room temperature (Figure 1.3).



DavePhos

Figure 1.3 Structure of DavePhos

Further work indicated that the substitution of the phosphine group could be varied, and that the presence of the amino group was not required for effective catalysis for some substrates. This allowed allowing further ligand modification to continue, with additional ligand variants soon reported.[37]

Later, coordination chemistry studies demonstrated that DavePhos did not bind to transition metals as a κ^2-P,N-bidentate ligand. Instead, this ligand (and other biaryl monopshosphines) have been shown to interact with palladium centres via the ipso-carbon of the lower arene ring, providing stabilization for catalytic intermediates, something lacking in previous non-biaryl monodentate ligand systems, and possibly explaining the unique reactivity imparted by biaryl monodentate phosphine ligands (Figure 1.4).[38]

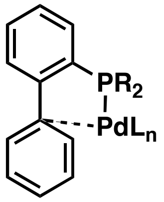


Figure 1.4 Stabilization of a Palladium Centre by a Biaryl Monodentate Phosphine Ligand

1.6. Notable Biaryl Monodentate Phosphines: 'Buchwald Ligands'

A number of 'Buchwald'-type biaryl monodentate phosphine ligands are now in widespread use, with multiple variants containing different groups on the phosphine donors and different functional groups on both arene rings. Many of these ligands are commercially available, although several variants in particular have proven especially useful, and have been employed in particularly noteworthy publications (Figure 1.5).

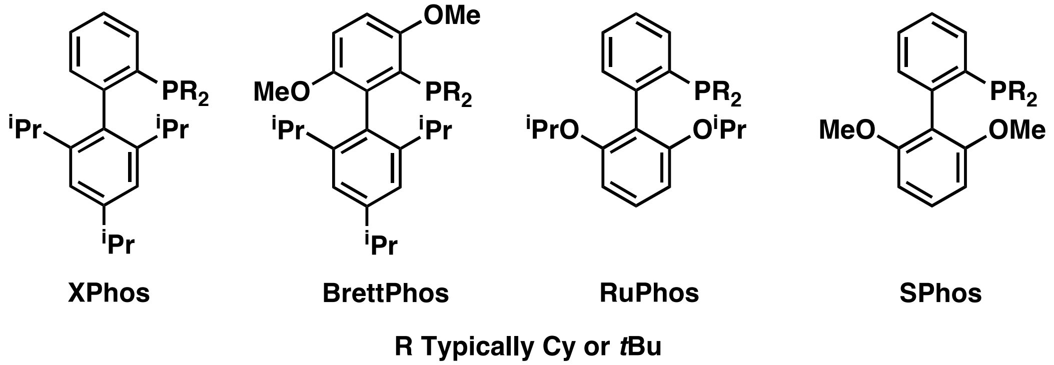


Figure 1.5 Notable Biaryl Monodentate Phosphine Ligand Types

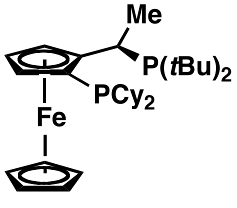
XPhos has found use in chemoselective aminations, where an aniline can undergo preferential arylation in the presence of another N-H containing group such as an amide, indole or an aliphatic amine.[39, 40] The 2003 report also contained several examples of Buchwald-Hartwig aminations conducted using water as a solvent, which though limited in scope, is still an excellent example of a 'green' amination reaction conducted in water without any additional additives or a modified ligand.[39] SPhos has proven to be useful in C-N cross-coupling ligand, and has been the subject of an excellent study on how electronic effects can determine chemoselectivity in Buchwald-Hartwig aminations,[41] with a specific focus on the roles that amine binding and acidity play in relation to product turnover. SPhos has also found additional utility as a superior ligand for promoting Suzuki-Miyaura cross-coupling reactions with challenging substrates at low loadings and at room temperature.[42] RuPhos has found use as an excellent ligand for the arylation of secondary amines using low catalyst loadings,[43,44] which can be challenging for other ligands, even structurally similar biaryl monodentate phosphines, due to their steric bulk. Additionally, RuPhos has also been used for promoting the palladium-catalyzed trifluoromethylation of aryl chlorides.[45] The differences in reactivity between RuPhos, XPhos and SPhos, all of which are structurally similar, are important to acknowledge, and illustrate the fact that subtle changes in ligand structure can ultimately have a large impact on reactivity.

BrettPhos has arguably had the greatest impact of all these biaryl monophosphine ligands in a relatively short amount of time. The first report of BrettPhos[46] demonstrated its ability to promote the amination of aryl mesylates, an area where XPhos, despite successfully promoting couplings of aryl sulfonates, fell short. Perhaps more importantly, the same report demonstrated the propensity of a BrettPhos-based catalyst system to promote the monoarylation of primary amines with aryl chlorides. This monoarylation work had two points of focus: the monoarylation of methylamine, which due to its size has a propensity to undergo diarylation and has traditionally been a challenging substrate, and the monoarylation of diamine substrates containing two reactive amine sites. BrettPhos proved effective at both, mediating the monoarylation of methylamine with high selectivity for the first reported time, and also promoting the selective arylation of primary amines over secondary amines in diamine substrates. Though BrettPhos has also been the focal point of groundbreaking work in palladium-mediated aryl fluorination[47] and trifluoromethylation,[45] it is still largely its utility as an exceptional ligand system for Buchwald-Hartwig monoarylations of primary amines that has helped it become such a broadly employed ligand in this field. In fact, The complementary nature of BrettPhos and RuPhos as ligands for the arylation of primary and secondary amines, respectively, led to the development of a multi-ligand catalyst system based upon both ligands[48] which not only encompasses the substrate scope of both, but also offers additional reactivity that neither can manifest on their own, demonstrating that even these well-established ligands can offer novel reactivity in some instances.

1.7. Applications of JosiPhos in C-N Cross-Coupling

Although ligands such as these biaryl monodentate phosphines have clearly proven to be extremely useful for Buchwald-Hartwig aminations, bidentate phosphine ligands can be of great value as well, having benefits that mondentate ligands lack, due to their ability to stabilize a late transition metal such as palladium via two strongly donating phosphorus atoms. This bidentate coordination can be beneficial in Buchwald-Hartwig amination chemistry. For example, the increased steric bulk at the palladium centre disfavours the binding of bulky substrates. This can be beneficial when primary amine substrates are employed, which can undergo diarylation (via their resultant products undergoing additional arylation reactions) when some monodentate ligands are used, or require higher catalyst loadings in order for the reaction to proceed efficiently and with good selectivity for monoarylation. Additionally, a chelating ligand is less likely to be displaced by either nucleophilic amine substrates or heteroaromatic halides, which have traditionally proven to be very challenging substrates in this chemistry, and often require higher catalyst loadings. Displacement of ligands by these substrates can limit catalyst lifetime through the formation of catalytically inactive species, and has been shown to occur with pyridine,[49] and ammonia.[31]

These shortcomings prompted further ligand exploration, and led to the application of catalysts based upon bidentate, rigid, sterically hindered, and electron-rich 'JosiPhos' ligands, originally developed for use in asymmetric hydrogenation (Figure 1.6).[50,51]



JosiPhos

Figure 1.6 Structure of JosiPhos

The logic behind utilizing this ligand was two-fold. Firstly, the steric bulk provided by the ligand was hypothesized to improve its selectivity towards monoarylation over diarylation, by discouraging binding of the larger, secondary amines formed by primary amine arylation (and potentially even allowing for selective monoarylation of ammonia to form anilines). Secondly, the ligand backbone pre-disposes the ligand towards chelation with the metal, rendering the catalyst less susceptible to catalyst poisoning via displacement of the ancillary phosphine ligand by electron-rich amine substrates, or by heteroaromatic substrates. This would potentially allow for more efficient coupling of halopyridines, ammonia, and other challenging substrates, with the added benefit of reducing catalyst poisoning due to the formation of catalytically inactive adducts involving these species, thereby enabling the use of reduced catalyst loadings.

These attributes did, in fact, make JosiPhos a ligand useful for the selective monoarylation of primary amines as well as with halopyridines,[52] thereby addressing an area of reactivity lacking in previous ligands: the ability to facilitate C-N cross-coupling reactions at low catalyst loadings between primary amines and a variety of substituted aryl chlorides under mild conditions. Moreover, several varieties of chloropyridines, including *ortho*-substituted species, were shown to be effective coupling partners, resulting in high yields of the secondary amine products.[53]

Hartwig and coworkers[53] have indeed demonstrated that a JosiPhos-based catalyst system is particularly effective at promoting the amination of a range of heteroaromatic halides with primary amines, with monoarylation products selectively obtained in high yields. Furthermore, the catalyst loadings for these transformations are as low as 10 ppm Pd, still amongst the lowest reported, which is makes the catalyst both economical, and appealing from a pharmaceutical point of view, where palladium removal from the final product is required and can be challenging and costly.

Ammonia has long been a desired nitrogen source in synthetic chemistry due to its low cost and high abundance. However, it has traditionally been a challenging substrate for Buchwald-Hartwig aminations, due in part to its high basicity, and tendency to form stable adducts with transition metal centres.[31] In the case of Buchwald-Hartwig amination chemistry, the fact that ammonia has three potentially reactive N-H bonds is also problematic. In the same way that primary amines can be susceptible to diarylation, employing ammonia as a substrate can lead to di- and tri-arylation products forming as well. A 2007 report by Buchwald and co-workers[54] describes the use of biarylmonodentate phosphine-based catalysts for the coupling or aryl chlorides and ammonia, obtaining mixtures of anilines, as well as di- and triarylamines resulting from aniline products undergoing additional arylations. In contrast, Hartwig[55, 56] has demonstrated the ability of a Pd/JosiPhos catalyst system to promote the monoarylation of ammonia with aryl bromides, chlorides, iodides, and sulfonates, albeit with some limitations, such as coupling electron-rich, sterically unbiased substrates, diamine substrates, and with elevated catalyst loadings required for some substrates.

1.8. Employing DalPhos Ligands to Address Challenges in Buchwald-Hartwig Aminations

With the development of a vast array of different ligand sets capable of promoting Buchwald-Hartwig aminations with a broad variety of substrates, it is no surprise that C-N cross-coupling reactions have become commonplace synthetic techniques in many laboratories. Indeed, it is because of the extensive research into ligand design that practical structural and electronic tenets regarding ligand influences on metal-mediated reactivity exist. However, despite being the focus of intense research, significant challenges in this area remain. These challenges include the monoarylation of challenging substrates, such as ammonia and hydrazine, chemoselective transformations, and generality.

In this context, the Stradiotto group initiated a research program that employs phenylene-based P,N-ligands as useful alternatives to more commonly employed phosphine and bis(phosphine) ancillary ligands in metal-catalyzed C-N bond-forming reactions (Figure 1.7).

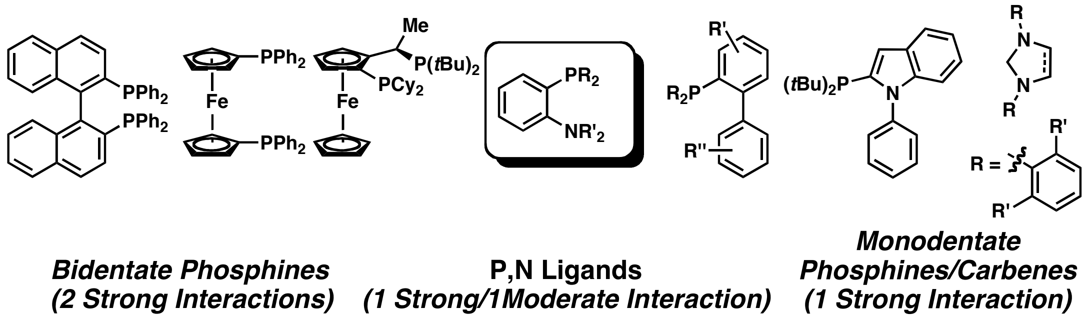
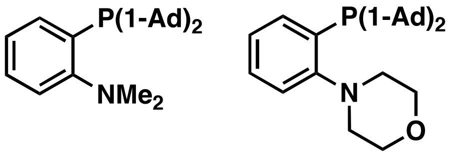


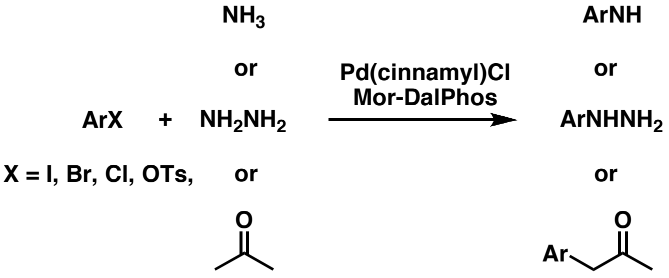
Figure 1.7 Buchwald-Hartwig Amination Ligands Featuring Different Metal-Ligand Binding Motifs

P,N-Ligands have the potential to engender different reactivity in transition metal complexes than monodentate or bidentate phosphine ligands, due to their ability to stabilize late transition metal centres such as palladium via a strong phosphine donor interaction, and a moderate nitrogen donor interaction. Building upon previous work in the Stradiotto group demonstrating that Me-DalPhos (Figure 1.8) is a broadly useful ligand for the Buchwald-Hartwig amination of aryl chlorides,[57] it has subsequently demonstrated that Mor-DalPhos (Figure 1.8) offers state-of-the-art performance in the Pd-catalyzed monoarylation of ammonia,[58] hydrazine,[59] and acetone[60] (Scheme 1.10).



Me-DalPhos **Mor-DalPhos**

Figure 1.8 Published DalPhos Ligand Variants

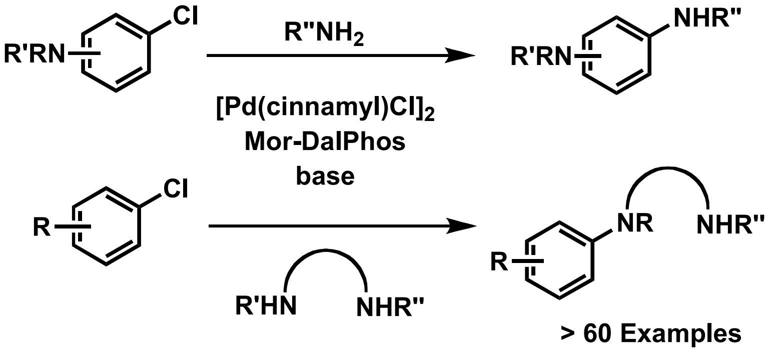


Scheme 1.10 Monoarylations Promoted by Pd/Mor-DalPhos Catalysts

Despite the utility of Mor-DalPhos in the monoarylation of these challenging substrates, the aforementioned challenges of chemoselectivity (where one amine undergoes selective arylation in the presence of another reactive amine) and catalyst generality (where a single catalyst system demonstrates utility with a broad range of substrates under mild conditions) remain.

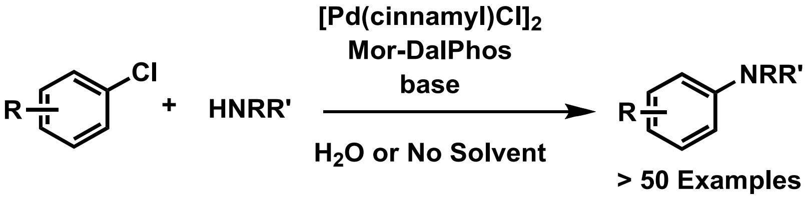
1.9. Thesis Overview

The research presented in this thesis outlines studies conducted with the ultimate goal of addressing the challenges of chemoselectivity and generality in Buchwald-Hartwig aminations. Chapter 2 describes the application of Mor-DalPhos and the new *p*-Mor-DalPhos ligand variant in the most extensive study of chemoselective Buchwald-Hartwig aminations yet reported in the literature. Section 2.2 provides an overview of previously reported chemoselective Buchwald-Hartwig aminations, while Section 2.3 begins with an outline of an extensive series of competition experiments employing both Mor-DalPhos and *p*-MorDalPhos, in which a single aryl halide was reacted with two discrete amines in order to determine which amine substrate underwent preferential arylation. On the basis of the chemoselective hierarchy established in these competitions, the remainder of Section 2.3 describes the synthesis of oligoamines via chemoselective aminations of aminoaryl halides, and the selective monoarylation of diamine substrates (Scheme 1.11). Additional binding studies of a diamine substrate and monoamine analogues are also discussed, so as to provide insight regarding the observed chemoselectivity.



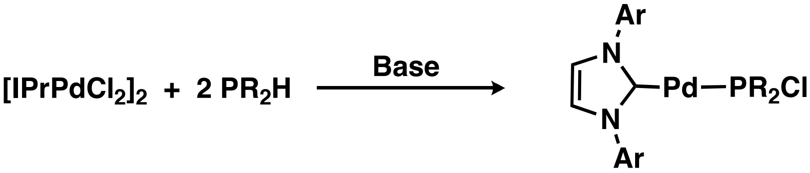
Scheme 1.11 Preparation of Oligoamines via Chemoselective Buchwald-Hartwig Aminations

Chapter 3 describes aqueous and solvent-free Buchwald-Hartwig aminations of primary and secondary amines, performed in an attempt to increase the generality of the Mor-DalPhos-based catalyst system. Section 3.1 outlines previously reported efforts directed at promoting aminations under aqueous conditions, including the limitations of current protocols. Section 3.2 describes the synthesis of products derived from the arylation of primary amines, secondary amines and diamine substrates under aqueous and solvent-free conditions, using the same $[Pd(cinnamyl)]_2$/Mor-DalPhos catalyst system employed in the aforementioned monoarylation of challenging substrates and in chemoselective aminations (Scheme 1.12). The results represent the largest array of Buchwald-Hartwig amination products obtained under either aqueous or solvent-free conditions to date, and also demonstrates that at least in some cases, rigorously air-sensitive conditions are not required for these aminations to proceed.



Scheme 1.12 Buchwald-Hartwig Aminations Conducted Under Aqueous and Solvent-Free Conditions

Chapter 4 outlines the preparation and isolation of a series of the first well-defined [(NHC)Pd(PR_2Cl)] complexes, via an unusual reductive-elimination of P-Cl from [(NHC)Pd$(Cl)_2$(PR_2H)] precursors. A discussion of the structural parameters of these complexes, including how they compare with previously reported [(NHC)Pd(PR_3)] analogues is also included (Scheme 1.13).



Scheme 1.13 Preparation of Mixed [(NHC)Pd(PR_2Cl)] Complexes

Finally, Chapter 5 concludes the thesis with a brief overview of the work presented herein, and a discussion of future directions of research that could be addressed on the basis of these results.

CHAPTER 2. CHEMOSELECTIVE PREPARATION OF OLIGOAMINES VIA BUCHWALD-HARTWIG AMINATION

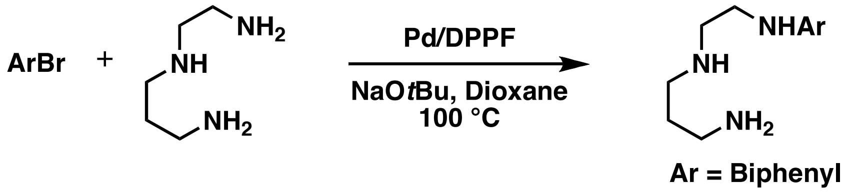
2.1. Introduction to Chemoselective Buchwald-Hartwig Aminations

As outlined in Chapter 1, the palladium-catalyzed cross-coupling of (hetero)aryl (pseudo)halides and N-H containing substrates (Buchwald-Hartwig amination) has emerged as an effective methodology for the construction of (hetero)arylamines that is broadly employed in both academic and industrial settings.[15,24,61-64] Following the establishment of such cross-coupling protocols independently by Buchwald[21] and Hartwig[20] in 1995, significant research effort has been directed toward evaluating how modifying various reaction parameters,[2] including the choice of solvent, base, palladium precursor, and most notably the ancillary co-ligand, influences the outcome of the cross-coupling reaction. Consequently, several highly effective classes of catalysts for Buchwald-Hartwig amination have emerged that offer broad substrate scope and excellent functional group tolerance at relatively low catalyst loadings, including for the cross-coupling of less expensive and more abundant (but less reactive), (hetero)aryl chloride substrates.[15, 22, 24, 61-64] Despite such progress, a number of significant challenges remain in Buchwald-Hartwig amination chemistry, including the establishment of catalysts for which predictably high yield and chemoselectivity has been achieved across a range of structurally diverse substrates featuring two or more competitive and chemically distinct N-H reactive functional groups.[65] The development of such chemoselective processes would further enhance the utility of Buchwald-Hartwig amination as a synthetic tool in the construction of structurally complex oligoamine targets, such as those commonly encountered in the synthesis of pharmaceuticals, natural products, and other nitrogenous materials, by offering more streamlined chemical pathways that circumvent the need for wasteful nitrogen protection/deprotection steps.

2.2. Previously Reported Chemoselective Buchwald-Hartwig Aminations

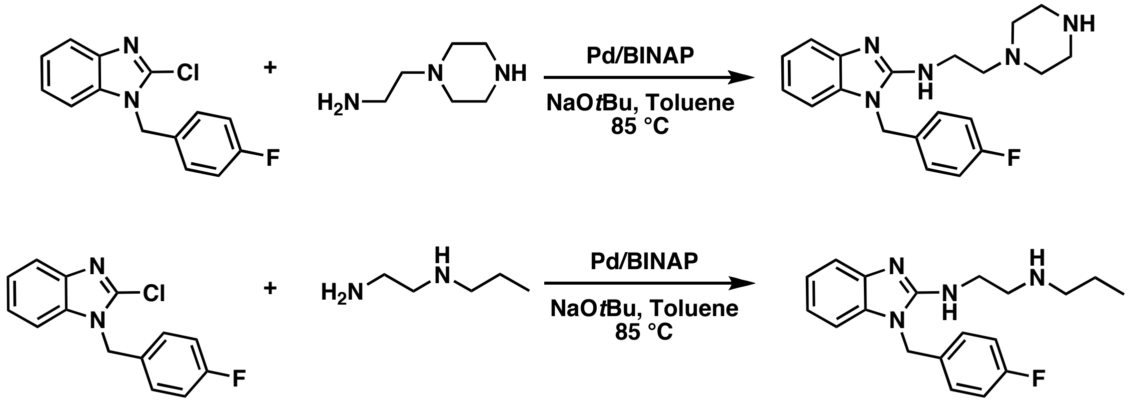
Despite the significant attention that has been given to the application of Buchwald-Hartwig amination protocols in organic synthesis, and the resulting proliferation of task-specific ligands for targeted substrate classes,[15, 64] reports documenting chemoselective Buchwald-Hartwig aminations involving the preferential arylation of one amine fragment in the presence of multiple chemically distinct competitor amine functionalities are relatively few. [39-41, 46, 66-77] Furthermore, among the reports of this type that have appeared, the demonstrated substrate scope is often very limited, with the chemoselective amination of inexpensive and abundant (hetero)aryl chlorides receiving relatively scant attention.

Beletskaya and co-workers[66-69] have demonstrated that the primary alkylamino groups in linear oligoamines such as 3,3′-diaminodipropylamine can be preferentially arylated by use of aryl bromides and (hetero)aryl iodides, as well as activated dichloroanthracenes, dichloroanthraquinones and dichloropyridines, when employing Pd/DPPF or Pd/BINAP catalysts (Scheme 2.1).



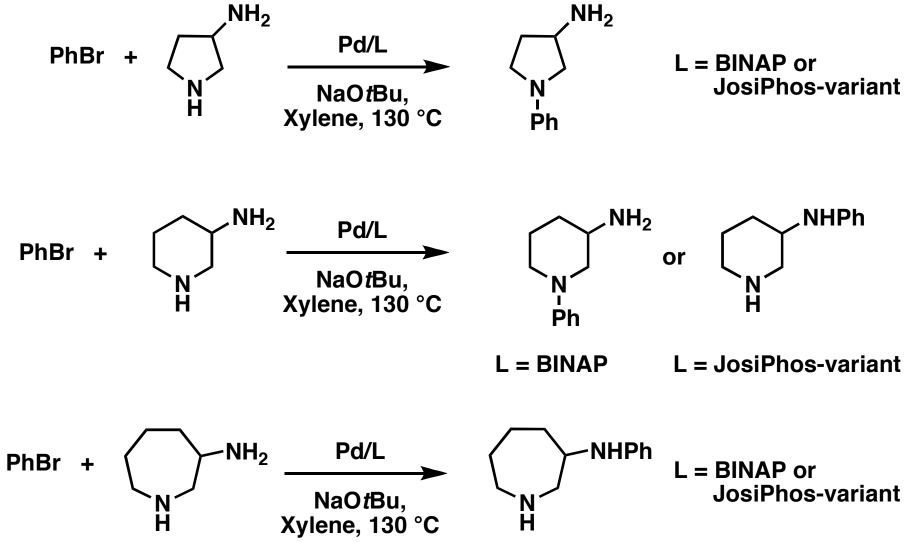
Scheme 2.1 Monoarylation of 3,3′-diaminodipropylamine. Reproduced from Beletskaya and Co-workers[68]

However, in most cases the statistical bias of primary-to-secondary amine functionalities in such substrates can be viewed as contributing to the observed product ratio. Senanayake and co-workers[71, 72] disclosed that a 2-chloro-1,3-azole derivative undergoes chemoselective amination in the presence of a Pd/BINAP pre-catalyst mixture at the primary amino functionality within di- and triamines containing primary alkylamino and linear/cyclic dialkylamino functionalities (Scheme 2.2).



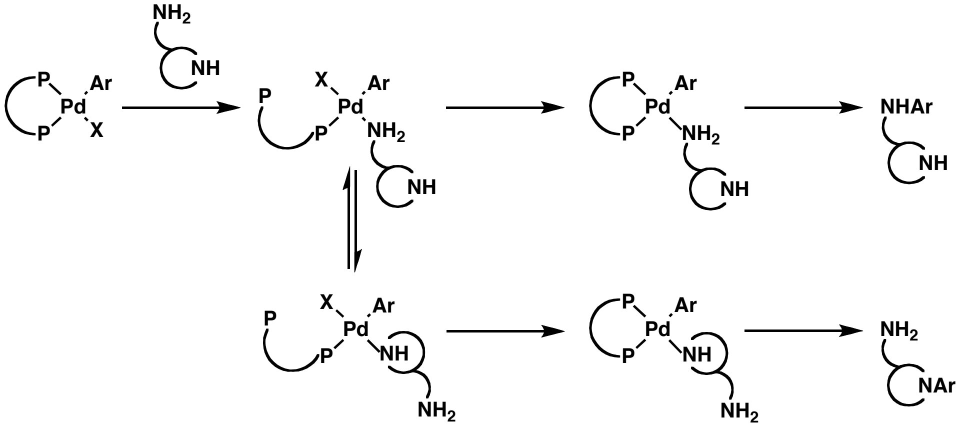
Scheme 2.2 Chemoselective Amination of an Activated Chloro-Azole Derivative. Reproduced From Senanayake and Co-workers[71]

In contrast, Rouden and co-workers[73, 74] have observed that the cyclic secondary dialkylamino group in 3-aminopyrrolidine is selectively arylated when employing bromobenzene in the presence of palladium/ligand mixtures, independent of the monodentate or bidentate ancillary phosphine ligand employed. In extending these studies to the arylation of 3-aminopiperidine, 4-aminopiperidine and 3-aminoazepinine, the substrate ring size as well as the ancillary ligand employed were found to influence the extent of arylation as well as primary versus secondary amine chemoselectivity (Scheme 2.3). For example, in the case of 3-aminopiperidine, the use of BINAP afforded preferential arylation at the secondary amine, whereas the use of a JosiPhos-type ligand enabled preferential arylation of the primary amino group. Additionally, whereas the use of chlorobenzene resulted in low-yielding arylation of 3-aminopiperidine when employing Pd/BINAP catalysts, the use of sterically biased *ortho*-substituted bromobenzenes led to an expected increase in arylation at the less-hindered primary amine locale. In the case of 3-aminoazepinine, primary amine arylation occurred preferentially when employing either BINAP or JosiPhos-type ligands.



Scheme 2.3 Chemoselective Aminations of 3-Aminopyrrolidine, 3-Aminopiperidine, and 3-Aminoazepinine. Reproduced From Rouden and Co-workers[73]

In exploring further the underpinnings of this demonstrated chemoselectivity phenomena when Pd/BINAP catalysts are employed, competition studies confirmed that 3-aminopyrrolidine or 3/4-aminopiperidine are preferentially arylated in the presence of pyrrolidine or piperidine, respectively, and that 3-aminopyrrolidine is preferrentially arylated in the presence of an equimolar amount of 3-aminopiperidine. On the basis of these data, and *in situ* room temperature NMR data obtained from mixtures of (BINAP)Pd(Ph)I and 3-aminopyrrolidine, the authors propose a reactivity model that involves initial coordination of the primary amino fragment to palladium accompanied by displacement of a phosphine donor group. Subsequent isomerization to afford a reactive palladium intermediate that features the diamine substrate bound exclusively via the secondary amino group (thereby leading to arylation at this site) is faciliated by the more rigid 3-aminopyrrolidine framework, relative to 3-aminopiperidine (Scheme 2.4).



Scheme 2.4 Reactivity Model for Chemoselective Arylation of Diamines Proposed by Rouden and Co-workers[73]

This work sheds light on some of the experimental parameters that influence chemoselectivity in the Buchwald-Hartwig amination of substrates containing multiple reactive amine sites, including the complex dependence of substrate structure on reactivity and the potential reactivity benefits of employing unsymmetrical bidentate ligands. However, the very limited substrate scope and the observation that in most instances the materials isolated during these investigations were obtained in less than 50 % yield as mixtures of monoarylation and diarylation products highlights the significant limitations of the synthetic protocols outlined in these reports.[73, 74]

To date, the most extensive investigations of chemoselective amine arylation have been published by the Buchwald group, using five variants of their biarylphosphine ligands (XPhos, *t*Bu-XPhos, SPhos, BrettPhos, and RuPhos).[39-41,46,75,76] In 2003, Buchwald and co-workers demonstrated that Pd/XPhos pre-catalyst mixtures and substituted aryl bromides could be employed for the chemoselective arylation of primary aniline fragments within diamines containing primary amide, indole, and primary alkylamino competitor functionalities, affording monoarylated products in synthetically useful yields (5 examples, 2 mol % Pd and 5 mol % XPhos, 74-96 %, 5:1-25:1 selectivity).[39] In a further demonstration of chemoselectivity, secondary amides derived from (pseudo)haloanilines (X = Cl, Br, OTs), halo(hetero)aryl primary amides, 3-bromoaniline, and halogenated heterocycles featuring competitor N-H functionalities were aminated by using nitrogen coupling partners that included anilines, primary alkyl amines, linear and cyclic secondary alkylamines, as well as amino-functionalized heterocyclic substrates (20 examples, 2-5 mol % Pd and 4-10 mol % XPhos or *t*Bu-XPhos depending on the substrate, 57-99 %; Figure 2.1).[39, 40]

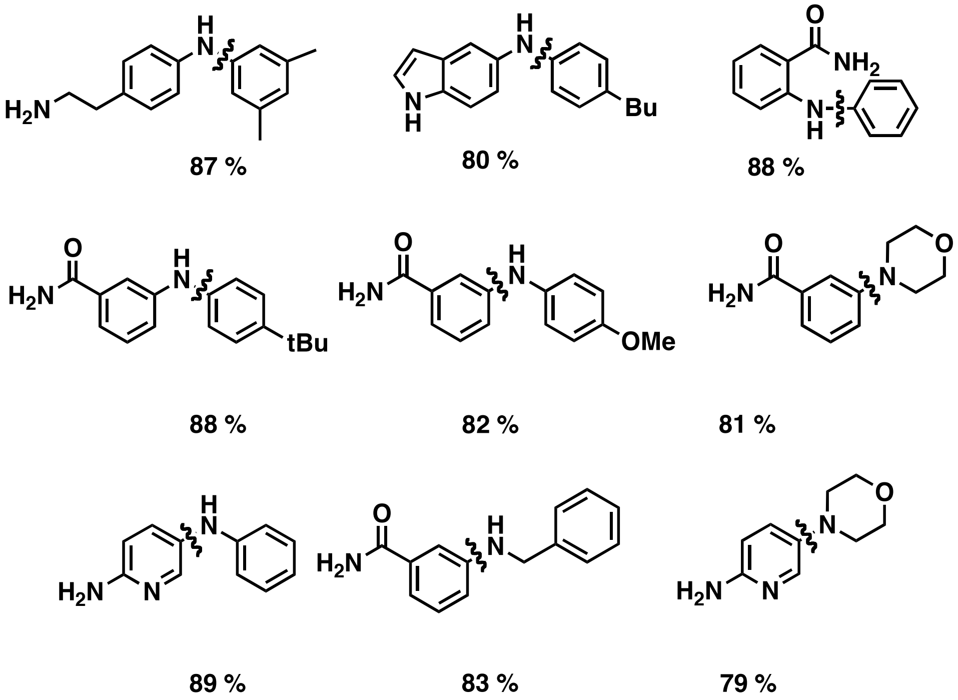
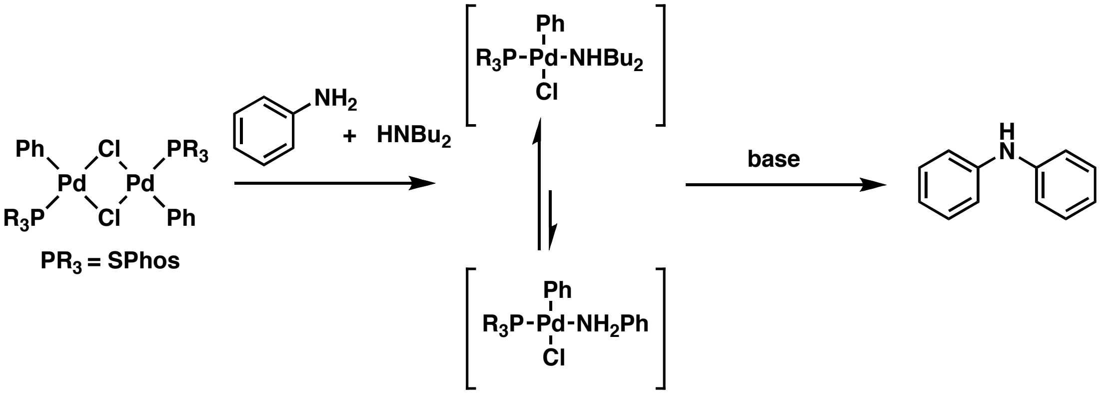


Figure 2.1 Selected Examples of Products Derived From Chemoselective Buchwald-Hartwig Aminations Employing XPhos[39, 40]

These results establish the following qualitative chemoselectivity hierarchy for Pd/XPhos-catalyzed amination: anilines >> primary and secondary (di)alkylamines > 2-aminoheteroaromatics > primary amides ≈ NH-heterocycles.[39, 40] In a subsequent report employing competition experiments between pairs of monoamine substrates, Buchwald and co-workers[41] examined the origins of chemoselectivity in Pd/SPhos-catalyzed amine arylations by evaluating the competitive role of amine binding and acidity in intermediates of the type [(SPhos)Pd(Ph)Cl(amine)]. Among isosteric aliphatic amines, amine acidity rather than the relative binding affinity was found to be the dominant factor in determining chemoselectivity; these observations suggest that such aminations occur under Curtin-Hammett control, whereby product formation arising from the more acidic, yet less favorably bound amine competitor substrate, is observed (Scheme 2.5).



Scheme 2.5 Chemoselective Buchwald-Hartwig Aminations Under Curtin-Hammett Control, Employing SPhos[41]

Conversely, binding affinity was found to be the primary determinant in the arylation of isosteric anilines, and such processes appear to not be under Curtin-Hammett control. These observations indicate that the origin of chemoselectivity in amine arylations employing Pd/SPhos-based catalysts cannot be rationalized on the basis of steric effects alone. Indeed, these competition studies establish the following heirarchical reactivity preference for the Pd/SPhos system for the amination of chlorobenzene: anilines >> cyclic secondary dialkylamines > small primary alkylamines > acyclic secondary dialkylamines > sterically demanding primary alkylamines. Unfortunately, the application of these competitive reactivity trends toward the rational, chemoselective arylation of oligoamines has yet to be reported.

In 2008, a report by Buchwald and co-workers[46] focusing on the application of Pd/BrettPhos pre-catalysts contained two examples in which amine arylation employing chlorobenzene occurred preferentially at the primary alkylamine fragment within diamine substrates featuring either a secondary arylalkylamine or cyclic secondary dialkylamine competitor fragment, and a third example whereby a primary aniline group was selectively arylated in the presence of a diarylamine functionality (3 examples, 1 mol % Pd and 2 mol % BrettPhos, 84-92 %; Figure 2.2). Most recently, Buchwald and co-workers[75, 76] demonstrated the utility of Pd/BrettPhos and Pd/RuPhos pre-catalysts in enabling the arylation of primary and secondary amine coupling partners, respectively, employing halogenated (X = Cl, Br) NH-heterocycles. The chemoselective arylation of primary and secondary amines with 3-bromo-2-aminopyridine by the use of Pd/BrettPhos or Pd/RuPhos pre-catalysts, respectively, has also been reported by Minatti.[77]

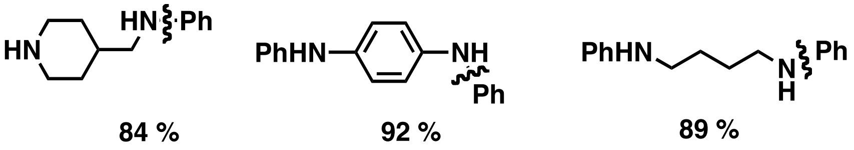


Figure 2.2 Selected Examples of Chemoselective Diamine Monoarylation Employing BrettPhos

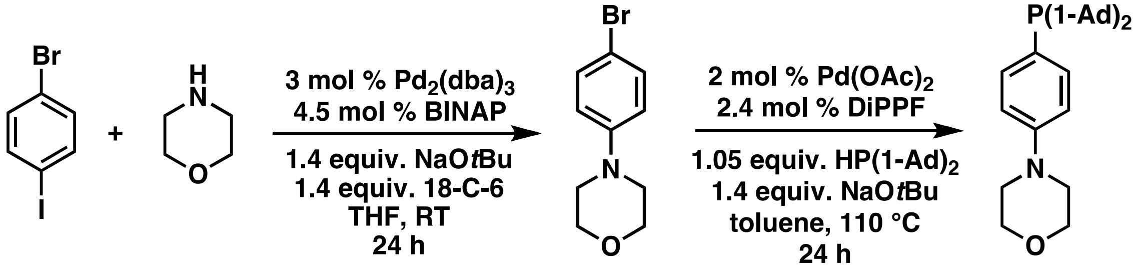
Notwithstanding the collective insights derived from the aforementioned isolated investigations employing a range of monodentate and bidentate ligands, the establishment of predictable and complementary chemoselective models, each based on a *single* high-performance Pd/L catalyst system, and the demonstrated application of such reactivity models with synthetically useful scope, remains an important goal in the quest to expand the utility and implementation of Buchwald-Hartwig amination chemistry. In the absence of such guiding chemoselectivity models, it is understandable that practitioners in the field may be less-motivated to undertake the rational synthesis of structurally complex oligoamine substrates by use of Buchwald-Hartwig amination chemistry, instead resorting to less atom-economical and often problematic nitrogen protecting-group chemistry to acheive a desired substitution pattern.

Given the remarkable preference exhibited by the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system for the selective monoarylation of ammonia and hydrazine when employing aryl chloride substrates bearing competitor primary amine (aryl and alkyl) or secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) functionalities,[57, 58] it was envisioned that the same catalyst system could be employed in the chemoselective synthesis of oligoamines employing Buchwald-Hartwig amination protocols. This could be accomplished via the development of a predictive chemoselectivity model for the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos catalyst system, and the broad application of this reactivity model in the chemoselective synthesis of a structurally diverse series of di-, tri- and tetraamine target compounds.

2.3. Results and Discussion

2.3.1 Competition Experiments Employing Mor-DalPhos and *p*-Mor-DalPhos

In an effort to establish a qualitative reactivity hierarchy for $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) catalyzed amine arylation under standard conditions that could be applied rationally to the chemoselective synthesis of oligoamines, competition experiments employing 4-chlorotoluene and various pairings of monoamine substrates were conducted. So as to place these results in context, and to gain an appreciation for the importance of *ortho*-disposed phosphorus and nitrogen donors in Mor-DalPhos (**L1**) on the observed chemoselectivity, parallel competition experiments were conducted with the isomeric ligand *p*-Mor-DalPhos (**L2**; Scheme 2.6). *p*-Mor-DalPhos was prepared in 63 % isolated yield via the Pd-catalyzed cross-coupling of di(1-adamantyl)phosphine with 4-(4-bromophenyl)morpholine, and was characterized by use of NMR, MS, and single-crystal X-ray diffraction techniques (Figure 2.3, Table 2.6).



Scheme 2.6 Synthesis of *p*-Mor-DalPhos (L2)

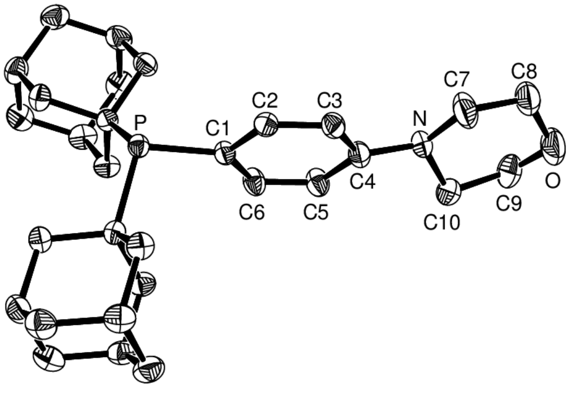
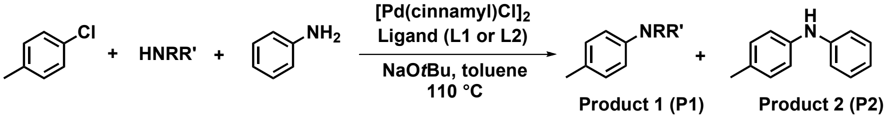
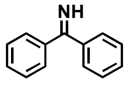
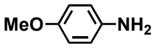
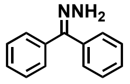
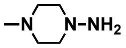
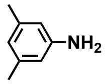
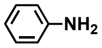
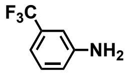
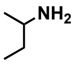
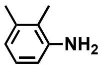
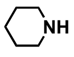
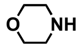
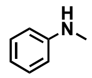
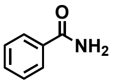


Figure 2.3 The synthesis and crystallographically determined structure of *p*-Mor-DalPhos (L2), shown with 50 % ellipsoids; hydrogen atoms have been omitted for clarity (P-C1 1.8368(15) Å, N-C4 1.416(6) Å).

The results of the competition experiments employing [Pd(cinnamyl)Cl]$_2$/L (L = **L1** or **L2**) pre-catalyst mixtures in combination with limiting 4-chlorotoluene, aniline (as the reference competitor), and a diverse series of competitor amine substrates spanning a wide range of steric and electronic characteristics (including *p*Ka) are collected in Table 2.1.

Table 2.1 Amine Arylation Competition Studies Employing Mor-DalPhos (L1) and *p*-Mor-DalPhos (L2)



Entry	HNRR'	P1 : P2 L1	P1 : P2 L2
1	octylamine	5.1:1	1:12
2		4.7:1	1:9.3
3[a]		2.1:1	1.6:1
4		2.0:1	1:1.1
5[b]		1.7:1	1:5.0
6		1.4:1	1.2:1
7	CyNH$_2$	1.4:1	1:20
8		-	-
9[b]		1:1.6	1.4:1
10		1:1.9	1:43
11		1:3.1	1:2.4
12		1:22	1:12
13		<1:50	1:8.0
14		<1:50	<1:50
15	*t*BuNH$_2$	<1:50	<1:50
16	(hex)$_2$NH	<1:50	<1:50
17	Ph$_2$NH	<1:50	<1:50
18[b,c]		<1:50	<1:50

Conditions: 0.25 mol % Pd, ArCl:Amine:Aniline:NaO*t*Bu = 1:1.2:1.2:1.4, Pd:L = 1:2, [ArCl] = 0.5 M, 12–48 h (reaction times not optimized). All reactions > 99 % conversion based on consumption of ArCl determined by use of GC analysis. Product ratios determined by use of GC analysis. Selected data (*entry*, *p*Ka(ammonium) in water): *1*, 10.65; *3*, 5.29; *6*, 4.74; *7*, 10.64; *8*, 4.58; *9*, 3.49; *10*, 10.56; *11*, 4.70; *12*, 11.22; *13*, 8.36; *15*, 10.55. [a]0.5 mol % Pd. [b]1 mol % Pd. [c]2.4 equiv. NaO*t*Bu used.

On the basis of these competition data, the following qualitative chemoselectivity hierarchy emerges for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system employing 4-chlorotoluene: linear primary alkylamines and imines > unhindered electron-rich primary anilines, primary hydrazones, *N*,*N*-dialkylhydrazines, and cyclic primary alkylamines >

unhindered electron-deficient primary anilines, α-branched acyclic primary alkylamines, hindered electron-rich primary anilines >> cyclic and acyclic secondary dialkylamines, secondary alkyl/aryl and diarylamines, α,α-branched primary alkylamines, and primary amides. This chemoselectivity trend, most notably the marked preference for linear primary alkylamines and the disfavoring of secondary dialkyl and alkyl/aryl amines that are preferred substrates for the majority of Buchwald-Hartwig amination catalysts, is divergent from that of the $[Pd(cinnamyl)Cl]_2$/**L2** catalyst system (i.e. primary anilines > linear primary alkylamines, imines, cyclic secondary dialkylamines, and *N*,*N*-dialkylhydrazines >> branched primary alkylamines, secondary acyclic dialkyl, alkyl/aryl and diarylamines, and primary amides), as well as previously reported catalysts employing XPhos or SPhos.[39-41] This trend establishes amine sterics as being the primary determining factor with regard to uptake by the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, with small nucleophilic amines being preferred substrates. These observations are entirely consistent with the demonstrated propensity of $[Pd(cinnamyl)Cl]_2$/**L1** to promote the monoarylation of both ammonia[58] and hydrazine,[59] and confirms the need for *ortho*-disposed pnictogen donors (as in Mor-DalPhos, **L1**) in order to achieve such selectivity.

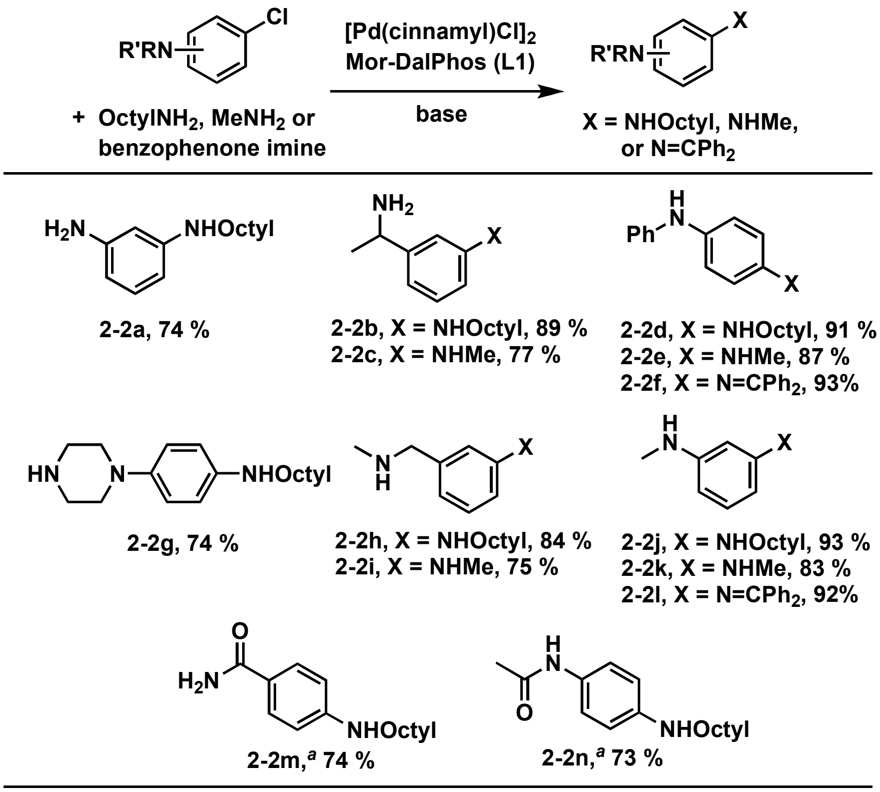
In considering the traditionally accepted Buchwald-Hartwig amination mechanism involving aryl halide oxidative addition, amine binding, deprotonation, and C-N reductive elimination, chemoselectivity can be envisioned to arise from the amine binding and/or deprotonation steps of the catalytic cycle (assuming the rate of amine exchange involving $[LPd(Ar)(NR_2)]$ and HNR'_2 to give $[LPd(Ar)(NR'_2)]$ and HNR_2 is slow relative to the rate of C−N reductive elimination).[78] The striking difference in competitiveness observed for unhindered and hindered primary amine substrates featuring closely matched *p*Ka(ammonium) values (Table 2.1, entries 1, 7, 10 and 15), and the observation that within a series of isostructural anilines (Table 2.1, entries 3, 6, 8, and 9) the substrate featuring the largest *p*Ka(ammonium) value proved to be the most competitive, suggest that the chemoselectivity exhibited by the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system can likely be attributed to the amine binding (rather than deprotonation) step of the catalytic cycle. This concept is further supported by the observation that while the conjugate acid of piperidine and morpholine differ in acidity by three orders of magnitude, both perform rather poorly when in competition with aniline, with the difference in chemoselectivity observed for piperidine (Table 2.1, entry 12) and morpholine (Table 2.1, entry 13) being relatively small in comparison to the other competition results. The unique chemoselectivity exhibited by [Pd(cinnamyl)Cl]$_2$/**L1** (versus XPhos, SPhos and **L2**) can likely be attributed to the chelating ability of the ligand.

2.3.2 Application of Chemoselectivity Model to the Synthesis of Di-, Tri- and Tetraamines

Having established a qualitative chemoselectivity model for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system, the observed reactivity trends were rationally applied toward the chemoselective synthesis of di-, tri- and tetraamines by use of two complementary synthetic strategies: the amination of aminoaryl chloride substrates (Tables 2.2-2.4) and the monoarylation of diamines (Table 2.5). Achieving high levels of chemoselectivity when employing the former synthetic strategy requires that the external amine coupling partner react preferentially relative to the competitor amine fragment that is bound to the aryl chloride substrate, while the latter requires the preferential arylation of one amine fragment in the presence of a chemically distinct competitor amine functionality. In both cases, diarylation represents an unwanted side-reaction that can be challenging to circumvent.[73, 74]

Having established linear primary alkylamines and imines as being substrates of choice when using the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, the chemoselective cross-coupling of octylamine, methylamine, or benzophenone imine with aminoaryl chlorides was examined (Table 2.2). The successful utilization of methylamine in this chemistry is noteworthy, given the challenges associated with the efficient monoarylation of this small nucleophilic amine in Buchwald-Hartwig amination chemistry.[46, 48, 57, 79, 80] In keeping with the reactivity heirarchy outlined in Table 2.1, octylamine, methylamine, and benzophenone imine could be employed in the amination of a diverse array of aryl chloride substrates bearing competitor α-branched primary alkylamine, primary arylamine, or secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) functionalities, providing the target di- or triamines in high isolated yield (74-93 %). Furthermore, the appropriate selection of base enabled the chemoselective amination of aryl chlorides featuring primary and secondary amides, thereby confirming the tolerance of the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system to such functional groups.

Table 2.2 Chemoselective Amination of Aminoaryl Chlorides Employing Octylamine, Methylamine, or Benzophenone Imine



2-2a, 74 %

2-2b, X = NHOctyl, 89 %
2-2c, X = NHMe, 77 %

2-2d, X = NHOctyl, 91 %
2-2e, X = NHMe, 87 %
2-2f, X = N=CPh$_2$, 93%

2-2g, 74 %

2-2h, X = NHOctyl, 84 %
2-2i, X = NHMe, 75 %

2-2j, X = NHOctyl, 93 %
2-2k, X = NHMe, 83 %
2-2l, X = N=CPh$_2$, 92%

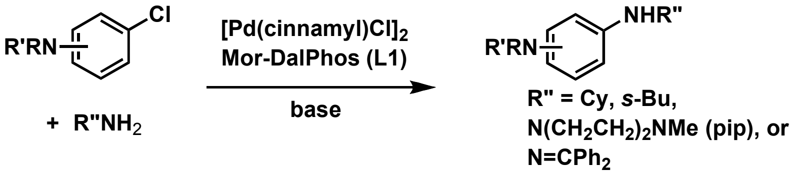
2-2m,[a] 74 %

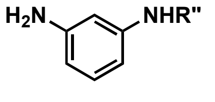
2-2n,[a] 73 %

Octylamine and benzophenone imine reactions: ArCl:Amine:NaO*t*Bu = 1:1.1:1.4, 1 mol % Pd, Pd:**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. Methylamine reactions: ArCl:Amine:NaO*t*Bu = 1:4:1.4, 2 mol % Pd, Pd:**L1** = 1:2, THF/toluene (1:1, resulting from use of commercial 2.0 M stock solutions of methylamine in THF), 85 °C, [ArCl] = 0.25 M. [a]ArCl:Amine:LiHMDS = 1:1.1:2.1, 8 mol % NaO*t*Bu, 2 mol % Pd, Pd:**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12-48 h (unoptimized); yields are of isolated material.

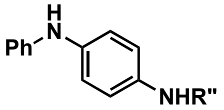
The relative success of 1-amino-4-methylpiperazine and benzophenone hydrazone, as well as the α-branched primary amines cyclohexylamine and *sec*-butylamine, in the preliminary competition experiments was reflected in the chemoselective amination of aminoaryl chloride substrates employing the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system (Table 2.3).

Table 2.3 Chemoselective Amination of Aminoaryl Chlorides Employing α-Branched Primary Alkylamines, 1-Amino-4-methylpiperazine or Benzophenone Hydrazone

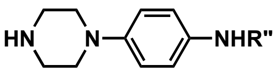




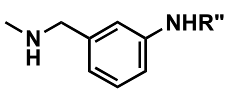
2-3a, R" = Cy, 55 %
2-3b, R" = pip, 50 %



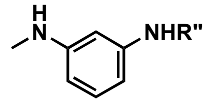
2-3c, R" = Cy, 94 %
2-3d, R" = *s*-Bu, 81 %
2-3e, R" = pip, 81 %



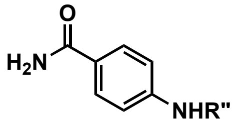
2-3f, R" = Cy, 74 %
2-3g, R" = *s*-Bu, 60 %



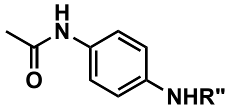
2-3h, R" = Cy, 92 %
2-3i, R" = *s*-Bu, 81 %
2-3j, R" = pip, 70 %



2-3k, R" = Cy, 89 %
2-3l, R" = *s*-Bu, 90 %
2-3m, R" = pip, 78 %
2-3n, R" = N=CPh$_2$,80 %



2-3o,[a] R" = Cy, 73 %
2-3p,[a] R" = *s*-Bu, 68 %



2-3q,[a] R" = Cy, 92 %
2-3r,[a] R" = *s*-Bu, 90 %

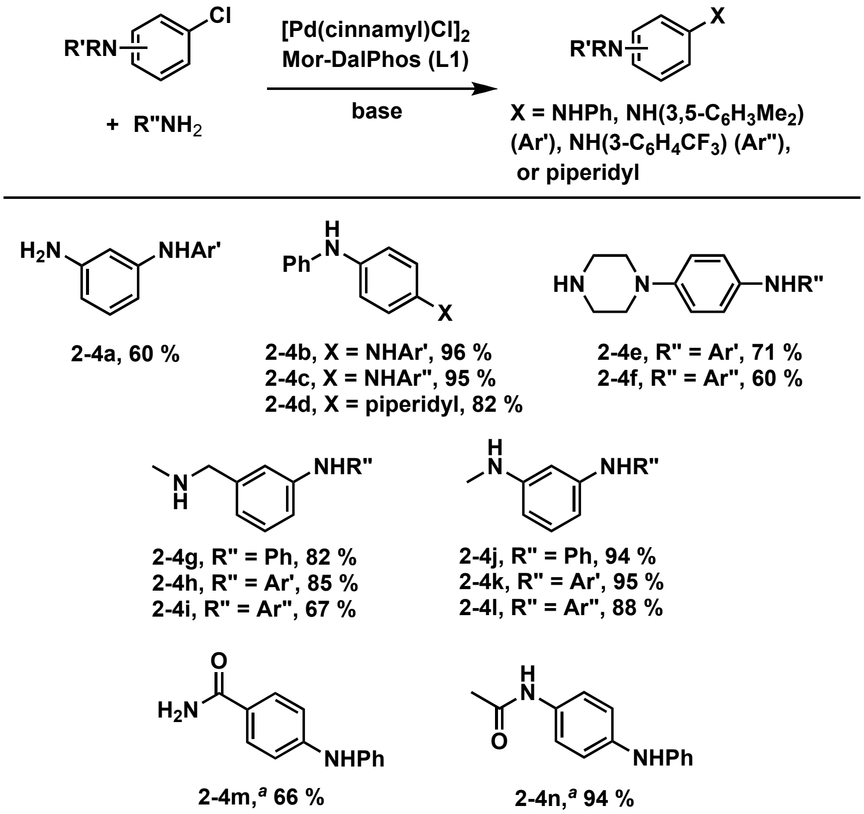
Conditions: ArCl:Amine:NaO*t*Bu = 1:1.1:1.4, 1 mol % Pd, Pd:**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [a]ArCl:Amine:LiHMDS = 1:1.1:2.1, 8 mol % NaO*t*Bu, 2 mol % Pd, Pd:**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12-48 h (unoptimized); yields are of isolated material.

Whereas cross-coupling reactions employing octylamine in combination with 3-chloroaniline afforded the desired octylamine-derived product (**2-2a**) in 74 % isolated yield, diminished levels of chemoselectivity were achieved when either cyclohexylamine or 1-amino-4-methylpiperazine was employed as a coupling partner under analogous conditions (**2-3a**, 55 %; **2-3b**, 50 %). These results are in keeping with the chemoselectivity ranking established for the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system (Table 2.1), whereby primary anilines proved to be competitive with 1-amino-4-

methylpiperazine and the aforementioned α-branched primary amines, but inferior to the linear primary alkylamine octylamine. Also consistent with the chemoselectivity trends noted for $[Pd(cinnamyl)Cl]_2$/**L1** is the observation that generally high isolated yields of the target di-, tri- and tetraamines (60-94 %) were achieved when 1-amino-4-methylpiperazine, benzophenone hydrazone, cyclohexylamine, or *sec*-butylamine was used in combination with aryl chloride substrates featuring various secondary amine (cyclic and acyclic dialkyl, alkyl/aryl, and diaryl) competitor moieties. Under appropriate conditions, cyclohexylamine and *sec*-butylamine each proved to be a suitable reaction partner for the chemoselective synthesis of phenylene-bridged diamines featuring an α-branched primary amine and either a primary or secondary amide (**2-3o-r**, 68-92 %).

To complete our investigation of the chemoselective amination of aminoaryl chloride substrates employing the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system, we turned our attention to the use of primary aniline substrates (Table 2.4). In keeping with the view that chemoselectivity exhibited by the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system is associated with the amine binding step of the catalytic cycle, 3,5-dimethylaniline proved to be a modestly more favorable amine coupling partner relative to the amino fragment in the relatively electron-poor 3-chloroaniline, resulting in 60 % isolated yield of the 3,5-dimethylaniline-derived species **2-4a**. In expanding this reactivity survey to include electron-rich, electron-neutral, and electron-poor anilines in combination with alternative aminoaryl chloride substrates featuring a diversity of appended secondary amine or primary/secondary amide functional groups, good-to-excellent isolated yields (60-96 %) of the corresponding primary aniline-derived cross-coupling products were obtained, as predicted for the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system on the basis of the reactivity trends delineated in the competition studies. Also in keeping with the reactivity hierarchy is the observation that whereas preferential uptake of piperidine leading to **2-4d** occurred in amination reactions employing *N*-(4-chlorophenyl)aniline, the use of *tert*-butylamine or dihexylamine under similar conditions failed to generate appreciable quantities of the desired cross-coupling product.

Table 2.4 Chemoselective Amination of Aminoaryl Chlorides Employing Anilines or Piperidine



2-4a, 60 %

2-4b, X = NHAr', 96 %
2-4c, X = NHAr", 95 %
2-4d, X = piperidyl, 82 %

2-4e, R" = Ar', 71 %
2-4f, R" = Ar", 60 %

2-4g, R" = Ph, 82 %
2-4h, R" = Ar', 85 %
2-4i, R" = Ar", 67 %

2-4j, R" = Ph, 94 %
2-4k, R" = Ar', 95 %
2-4l, R" = Ar", 88 %

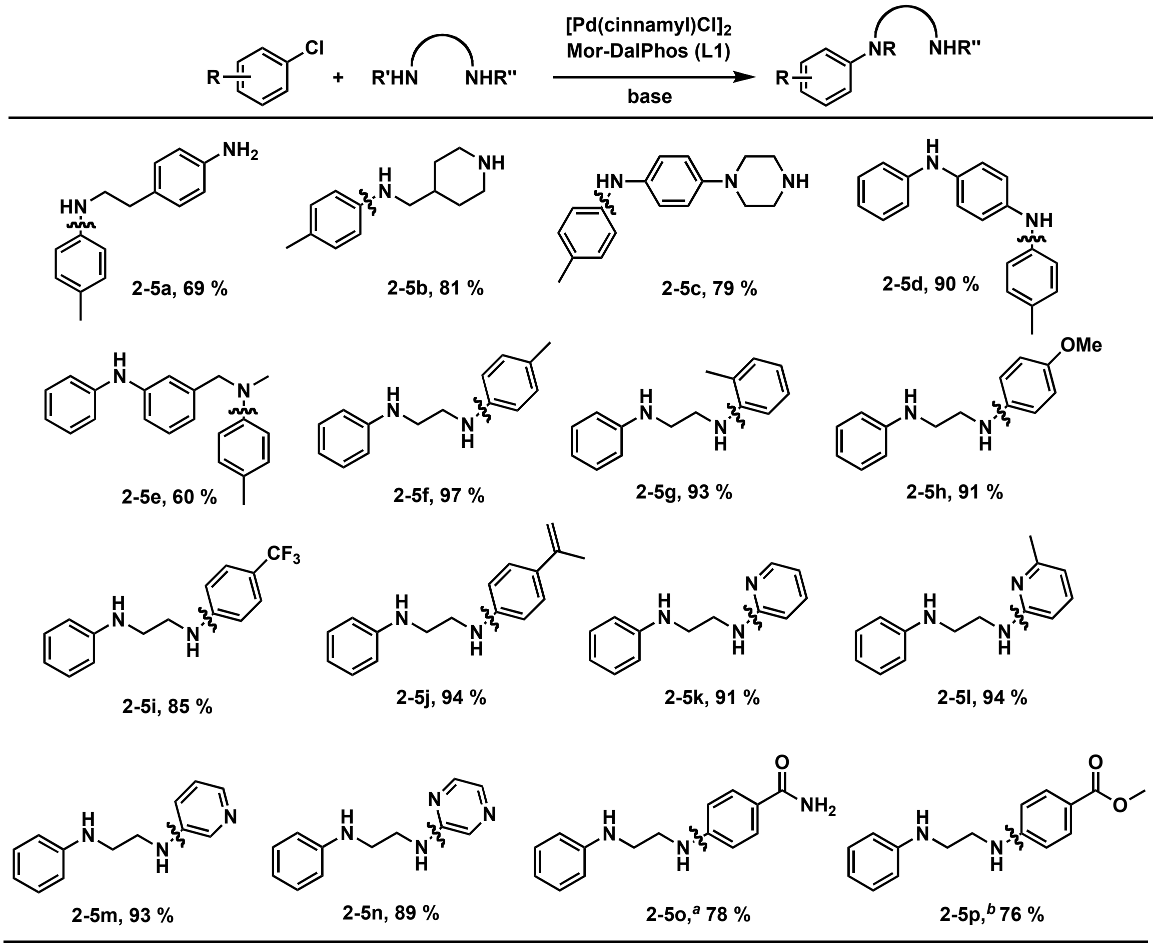
2-4m,[a] 66 %

2-4n,[a] 94 %

Conditions: ArCl:Amine:NaO*t*Bu = 1:1.1:1.4, 1 mol % Pd, Pd:**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [a]ArCl:Amine:LiHMDS = 1:1.1:2.1, 8 mol % NaO*t*Bu, 2 mol % Pd, Pd:**L1** = 1:2, 1,4-dioxane, 65 °C. All reactions on 0.5 mmol scale with reaction times of 12-48 h (unoptimized); yields are of isolated material.

As outlined previously, the high-yielding chemoselective arylation of substrates featuring two or more chemically distinct and potentially competitive N-H functional groups is not well-documented, and the substrate scope featured in such reports is often limited to a very small collection of diamine reactants, with the use of readily available (hetero)aryl chlorides receiving scant attention. Gratifyingly, [Pd(cinnamyl)Cl]$_2$/**L1** can be successfully applied in such Pd-catalyzed synthetic applications with good substrate scope (Table 2.5).

Table 2.5 Chemoselective Arylation of Diamines with (Hetero)aryl Chlorides



2-5a, 69 %; 2-5b, 81 %; 2-5c, 79 %; 2-5d, 90 %

2-5e, 60 %; 2-5f, 97 %; 2-5g, 93 %; 2-5h, 91 %

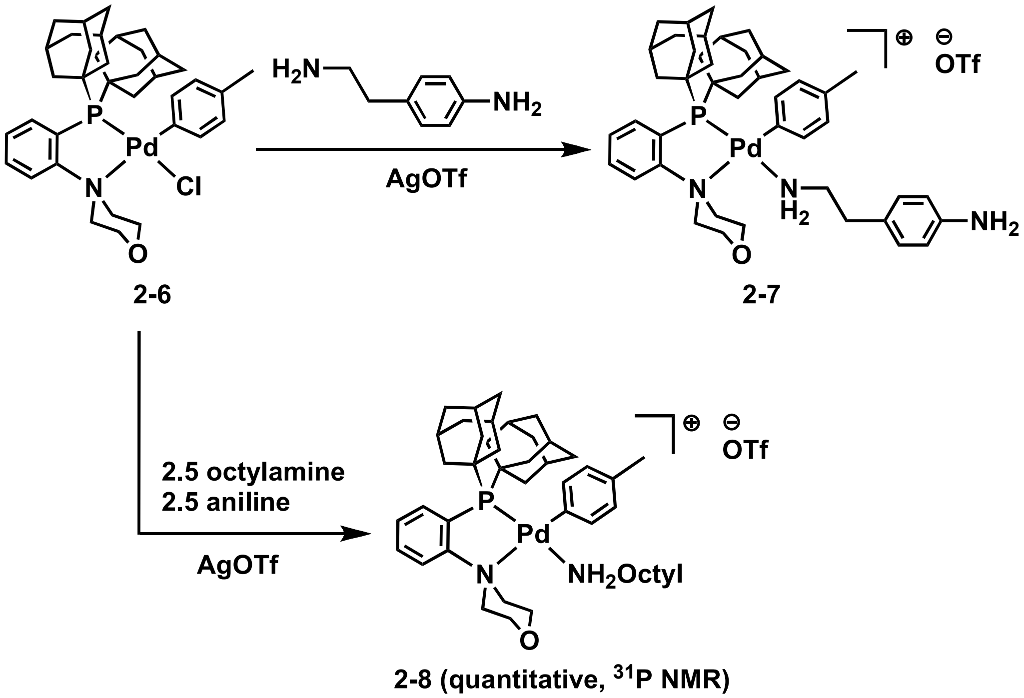
2-5i, 85 %; 2-5j, 94 %; 2-5k, 91 %; 2-5l, 94 %

2-5m, 93 %; 2-5n, 89 %; 2-5o,[a] 78 %; 2-5p,[b] 76 %

Conditions: ArCl:Amine:NaO*t*Bu = 1:1.1:1.4, 1 mol % Pd, Pd:**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. [a]ArCl:Amine:LiHMDS = 1:1.1:2.1, 8 mol % NaO*t*Bu (for use in catalyst activation), 5 mol % Pd, Pd:**L1** = 1:2, 65 °C, 1,4-dioxane, [ArCl] = 0.5 M. [b]ArCl:Amine:K_2CO_3 = 1:1.1:1.2, 8 mol % NaO*t*Bu (for use in catalyst activation), 2 mol % Pd, Pd:**L1** = 1:2, toluene, 110 °C, [ArCl] = 0.5 M. All reactions on 0.5 mmol scale with reaction times of 12-48 h (unoptimized); yields are of isolated material.

In keeping with the unusual preference of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system for the monoarylation of primary alkylamine fragments even when using unhindered aryl chloride substrates, the preferential amination of 4-chlorotoluene occurred at the primary alkylamine locale within substrates featuring potentially competitive primary aniline, cyclic dialkylamine, and acyclic secondary alkyl/arylamines, thereby affording **2-5a** (69 %), **2-5b** (81 %), and **2-5f** (97 %) respectively. Under analogous conditions, and consistent with the reactivity trends delineated in Table 2.1, primary aniline moieties were also selectively monoarylated in the presence of cyclic dialkylamine or diarylamine functional groups, giving **2-5c** (79 %) and **2-5d** (90 %), while the arylation of an acyclic dialkylamine moiety was achieved in the presence of a diarylamine competitor fragment (**2-5e**, 60 %). Scope in the (hetero)aryl chloride reaction partner also proved to be quite broad as evidenced by representative reactions employing *N*-phenylethylenediamine, whereby selective monoarylation at the primary amine locale occurred when using a range of hindered and unhindered (hetero)aryl chloride substrates, including those featuring electron-donating or electron-withdrawing substituents, unsaturated functionalities, and base-sensitive substituents (**2-5f-p**, 76-97 %).

The chemoselectivity preference displayed by the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system can be attributed to the amine binding step of the catalytic cycle, whereby small basic amines represent preferred substrates. This reactivity trend is manifested in the arylation experiments featured in Table 2.5 including the formation of **2-5a**, whereby preferential monoarylation is observed at the primary alkylamine locale despite the greater acidity of the competitor primary aniline fragment within the 2-(4-aminophenyl)ethylamine reactant. In an effort to establish the binding preference of 2-(4-aminophenyl)ethylamine to a (Mor-DalPhos)Pd(II) species, the 4-chlorotoluene C-Cl oxidative addition complex **2-6** was treated with silver triflate in the presence of this diamine (Scheme 2.7).



Scheme 2.7 Competitive Binding of Primary Alkylamines to the $[(L1)Pd(p\text{-tolyl})]^+$ Fragment Affording 2-7 and 2-8.

Monitoring of the reaction by use of ^{31}P NMR methods confirmed the consumption of **2-6** along with the clean formation of a single phosphorus-containing product (**2-7**), which was subsequently isolated in 72 % yield as an analytically pure solid and structurally characterized (Figure 2.4).

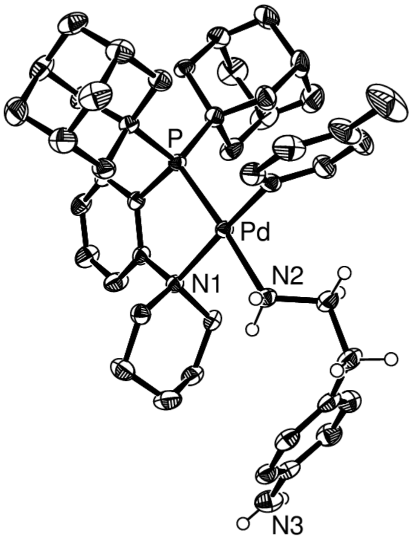
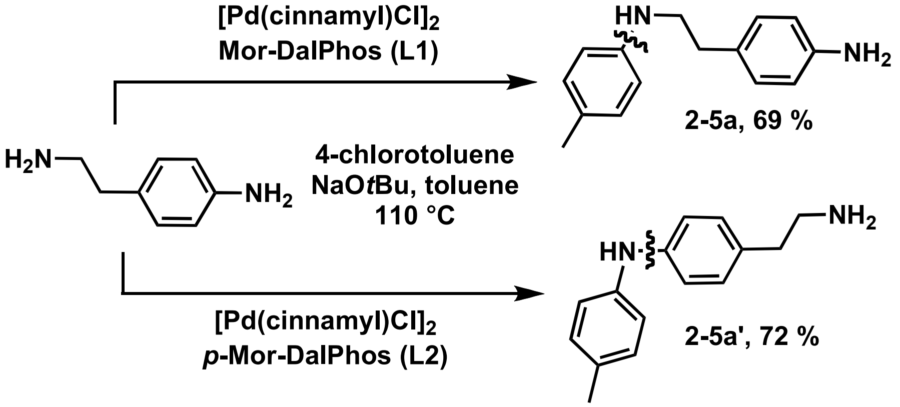


Figure 2.4 The crystallographically determined structure of 2-7•CH_2Cl_2 shown with 50 % ellipsoids; selected hydrogen atoms, the dichloromethane solvate, and the triflate counter-anion have been omitted for clarity. Selected interatomic distances (Å): Pd-P 2.2625(5), Pd-N1 2.2265(15), Pd-C_{aryl} 2.0068(19), Pd-N2 2.1629(15).

The crystallographic characterization of **2-7** (Figure 2.4, Table 2.6) confirms the formation of a square planar, cationic (κ^2-*P*,*N*-**L1**)Pd(II) species in which the alkylamino substituent of the diamine is coordinated to palladium. The preferential binding in solution of a primary alkylamine in the presence of a potentially competitive primary arylamine was further confirmed through a competition study in which a mixture of **2-6** and 2.5 equivalents each of octylamine and aniline was treated with silver triflate ($CDCl_3$, room temperature, 1 h); whereas independent syntheses confirmed the viability of both potential [(**L1**)Pd(*p*-tolyl)$NH_2R]^+OTf^-$ products of this reaction (**2-8**, R = octyl; **2-9**, R = phenyl), only **2-8** was observed (^{31}P NMR) in this competition scenario (Scheme 2.7). The lack of reactivity observed between **2-6** and either 2-(4-aminophenyl)ethylamine, octylamine, or aniline (^{1}H and ^{31}P NMR) in the absence of base suggests that cationic species analogous to **2-7**, **2-8**, and **2-9** arising from chloride displacement by the amine are unlikely to represent important catalytic intermediates in Buchwald-Hartwig amination chemistry when employing **L1**. Nonetheless, the preferential binding of the diamine alkylamino fragment in **2-7**, and the observation that the use of the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system results in chemoselective monoarylation at the alkylamino locale to afford **2-5a**, provide indirect support for the view that this process is not operating under Curtin-Hammett control. While efforts to compare the coordination chemistry of **L2** with that of **L1** did not yield informative results, orthogonal chemoselectivity giving rise to **2-5a′** (72 %) was observed when employing the $[Pd(cinnamyl)Cl]_2$/**L2** catalyst system in the monoarylation of 2-(4-aminophenyl)ethylamine) with 4-chlorotoluene (Scheme 2.8).



Scheme 2.8 Divergent Chemoselectivity for the Arylation of 2-(4-aminophenyl)ethylamine Employing Mor-DalPhos (L1) and *p*-Mor-DalPhos (L2)

2.4. Summary

The results presented in this chapter establish $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) as being a highly effective catalyst system for the chemoselective synthesis of a structurally diverse set of di-, tri- and tetraamine compounds in synthetically useful yields by use of Buchwald-Hartwig amination protocols. Indeed, this study represents the most extensive compilation of such reactivity to be reported thus far in the literature. Despite the distinct preference of [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**) for unhindered nucleophilic amine reaction partners, this catalyst system has proven useful in the chemoselective arylation of a series of alternative amine functionalities (e.g. linear and α-branched primary alkylamines, imines, primary hydrazones, *N*,*N*-dialkylhydrazines, substituted anilines, and piperidine), while tolerating the presence of a range of potential competitor amine fragments as well as varied substitution within the (hetero)aryl chloride reactant partner. Comparative reactivity studies involving the new isomeric ligand *p*-Mor-DalPhos (**L2**) confirmed that the *ortho*-disposition of phosphorus and nitrogen donors is the key to achieving the distinct chemoselectivity behavior that is observed when employing Mor-DalPhos (**L1**). Furthermore, the reactivity profile exhibited by [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**) suggests that the chemoselectivity enabled by use of this catalyst system is attained in the amine binding step of the catalytic cycle, whereby amine sterics represent the key parameter in determining preferential substrate uptake. These results represent a proven reactivity model for chemoselective Buchwald-Hartwig amination reactions employing the Mor-DalPhos (**L1**) ligand, and are an important contribution toward addressing the challenge of enabling the more widespread application of Buchwald-Hartwig amination protocols in the chemoselective synthesis of high-value oligoamine target molecules, thereby circumventing problematic nitrogen protecting-group chemistry.

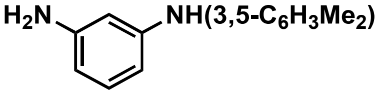
2.5. Experimental

2.5.1 General Considerations

All reactions were set up inside a dinitrogen-filled, inert atmosphere glovebox, while the organic products of the catalytic reactions were isolated following workup by using standard benchtop conditions. Toluene, dichloromethane and diethyl ether used in the glovebox were deoxygenated by sparging with dinitrogen followed by passage through a double column solvent purification system equipped either with one alumina-packed column and one column packed with copper-Q5 reactant (toluene), or two alumina-packed columns (dichloromethane and diethyl ether). 1,4-Dioxane was dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Deuterated solvents used for the characterization of organic reaction products were used as received, while the $CDCl_3$ used in the characterization of **L2** and **2-7**, **2-8**, and **2-9** was degassed by using three repeated freeze-pump-thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use within the glovebox. Mor-DalPhos (**L1**),[58] (Mor-DalPhos)Pd(*p*-tolyl)Cl,[58] $[Pd(cinnamyl)Cl]_2$,[81] di(1-adamantyl)phosphine,[82] 4-(4-bromophenyl)morpholine,[83] 1-(4-chlorophenyl)piperazine,[84] and 4-chloro-*N*-phenylaniline[85] were prepared according to literature procedures. All methylamine cross-coupling reactions were conducted by using purchased 2.0 M $MeNH_2$ solutions in THF. Prepared and purchased solid reagents were evacuated under reduced pressure for 24 h prior to use and were stored in an inert atmosphere glovebox. All other reagents, solvents (including those used on the benchtop), and materials were used as received from commercial sources. Flash column chromatography was performed on silica gel

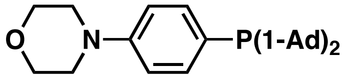
(SiliaFlash P60, Silicycle). GC data were obtained on an instrument equipped with a SGE BP-5 30 m, 0.25 mm I.D. column. In the case of the competition experiments (Table 2.1), conversions are given on the basis of the consumption of the aryl chloride as determined by use of GC methods; otherwise, stated yields correspond to isolated products. Unless otherwise stated, ^{1}H, ^{13}C, and ^{31}P NMR characterization data were collected at 300K on an 11.7 T spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) with chemical shifts reported in parts per million downfield of $SiMe_4$ (for ^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Where required, structural elucidation was enabled through analysis of ^{1}H-^{1}H COSY, and ^{1}H-^{1}H NOESY data. In some cases, quaternary carbons could not be observed despite prolonged acquisition times.

General Procedure: Representative Catalytic Preparation of of 2-4a



In an inert atmosphere glovebox, $[Pd(cinnamyl)Cl]_2$ (1 mol % Pd, from a toluene stock solution) and Mor-DalPhos (**L1**, 2 mol %) were combined, along with sufficient toluene so as to create a 0.5 M solution of the aryl chloride in the final reaction solution. This mixture was added to a vial containing a stir bar and NaO*t*Bu (67 mg, 0.70 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. 3-Chloroaniline (53 μL, 0.50 mmol) and (3,5-dimethylphenyl)amine (69 μL, 0.55 mmol) were added via microlitre syringe. The reaction was heated at 110 °C for 16 h and the consumption of the aryl chloride was confirmed by use of GC methods. The reaction mixture was then cooled, opened to air, filtered through a layer of neutral alumina and the alumina was then washed with dichloromethane (15 mL). Following removal of solvent from the combined eluent, the crude product was purified via column chromatography on silica (4:1 hex:EtOAc), affording N^1-(3,5-dimethylphenyl)benzene-1,3-diamine (**4a**) as a brown oil in 60 % isolated yield (64 mg, 0.30 mmol). ^{1}H NMR ($CDCl_3$): δ 7.06 (t, 1H, *J* = 8 Hz, ArH), 6.72 (s, 2H, ArH), 6.60 (s, 1H, ArH), 6.48 (m, 1H, ArH), 6.41 (t, 1H, *J* = 2 Hz), 6.27 (m, 1H, ArH), 5.55 (br s, 1H, NH), 3.62 (br s, 2H, NH_2), 2.29 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.8, 144.8, 143.3, 139.3, 130.4, 123.2, 116.4, 108.7, 108.2, 104.4, 21.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{17}N_2$: 213.1386. Found: 213.1378.

2.5.2 Preparation of *N*-(4-(di(1-adamantyl)phosphino)phenyl)morpholine (*p*-Mor-DalPhos) (L2)

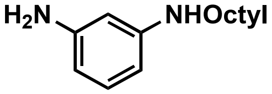


Using a method analogous to that described for the synthesis of Mor-DalPhos,[58] within a glovebox $Pd(OAc)_2$ (3 mol %) and DiPPF (1,1'-bis(diisopropylphosphino)ferrocene; Pd:L ~ 1:1.2) were combined in a vial containing a magnetic stir bar and 3 mL of toluene, and stirred magnetically for 10 minutes. This solution was then added to a vial containing di(1-adamantyl)phosphine (124 mg, 0.41 mmol) and NaO*t*Bu (48 mg, 0.50 mmol), followed by the addition of *N*-(4-bromophenyl)morpholine (104 mg, 0.43 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. The mixture was heated at 110 °C under the influence of magnetic stirring and the consumption of the phosphine was monitored periodically by use of ^{31}P NMR techniques. After 18 h, the reaction mixture was then cooled and filtered through a plug of alumina, which was then washed with dichloromethane. The combined eluant was collected and the solvent was removed in vacuo, followed by washing of the solid with Et_2O to afford

L2 as an off-white solid in 63 % yield (122 mg, 0.26 mmol). ^{1}H NMR ($CDCl_3$): δ 7.53 (br m, 2H, ArH), 6.85 (d, 2H, J = 6.5 Hz, ArH), 3.86 (app. t, 4H, J = 4.5 Hz, CH_2), 3.21 (app. t, 4H, J = 4.5 Hz, CH_2), 1.96 – 1.86 (m, 18H, Ad), 1.66 (s, 12H, Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.5 (ArC), 123.8 (d, J_{PC} = 16.4 Hz, ArC), 114.2 (ArC), 67.2 (CH_2), 48.7 (CH_2), 41.9 (d, J_{PC} = 11.3 Hz, Ad), 37.3 – 36.6 (m, Ad), 29.1 (d, J_{PC} = 14.2 Hz, Ad). ^{31}P NMR ($CDCl_3$): δ 38.8. HRMS (ESI/[M+H]$^+$) calcd. for $C_{30}H_{43}N_1O_1P_1$: 464.3077. Found: 464.3090. Crystals suitable for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated solution of **L2** in dichloromethane at -30 °C. Broadening of the aryl ^{1}H NMR resonances arising due to apparent restricted rotation about aryl-P bond is observed at 300 K (500 MHz); such dynamic processes also likely account for the observation of fewer than expected aryl resonances in the accompanying $^{13}C\{^1H\}$ NMR spectrum. Such dynamic behavior is not manifested in the ^{1}H and ^{13}C resonances of the morpholino group, possibly due to rapid rotation about the aryl-N linkage with concomitant inversion at nitrogen. Support for restricted rotation about the aryl-P linkage was obtained from variable-temperature ^{1}H NMR data (250 MHz, 223 – 328 K), whereby initially broad aryl resonances (223 K) were observed to sharpen to an apparent triplet (7.54 ppm) and doublet (6.84 ppm) upon warming to 328 K ($\Delta G^{\ddagger}_{288}$ = 14.1 kcal/mol). ^{1}H NMR ($CDCl_3$, 250 MHz, 328 K): δ 7.54 (app. t, 2H, J = 7.7 Hz, ArH), 6.85 (d, 2H, J = 8.5 Hz, ArH), 3.85 (app. t, 4H, J = 5 Hz, CH_2), 3.22 (app. t, 4H, J = 4 Hz, CH_2), 1.96 – 1.84 (m, 18H, Ad), 1.68 (s, 12H, Ad).

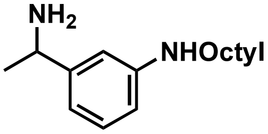
2.5.3 Preparation of Compounds From Table 2.2

Preparation of *N*^{1}-octylbenzene-1,3-diamine (2-2a)



The general procedure was followed, with 3-chloroaniline (53 μL, 0.50 mmol) and H_2NOctyl (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (4:1 hex:EtOAc), and isolated as a brown oil in 74 % yield (82 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 6.95 (t, 1H, *J* = 8 Hz, ArH), 6.06 (m 2H, ArH), 5.96 (s, 1H, ArH), 3.53 (br s, 3H, NH), 3.06 (t, 2H, *J* = 7.5 Hz, NCH_2), 1.58 (m, 2H, CH_2), 1.41 – 1.29 (m, 10 H, octyl), 1.29 (t, 3H, *J* = 6.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.1, 147.8, 130.4, 104.9, 104.3, 99.6, 44.3, 32.2, 29.9, 29.8, 29.6, 27.5, 22.9, 14.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{25}N_2$: 221.2012. Found: 221.1995.

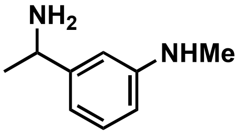
Preparation of 3-(1-aminoethyl)-*N*-octylaniline (2-2b)



The general procedure was followed, with 4-chloro-α-methylbenzylamine (70 μL, 0.50 mmol) and H_2NOctyl (90 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (DCM - 100:10:1 DCM:MeOH:NH_4OH), and isolated as dark yellow oil in 89 %

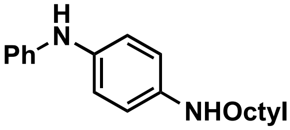
yield (112 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.15 (d, 2H, *J* = 8.5 Hz, ArH), 6.58 (m, 2H, ArH), 4.02 (quart., 1H, *J* = 7 Hz, CH), 3.08 (t, 2H, *J* = 7 Hz, CH_2), 2.39 (br s, 2H, NH), 1.63 – 1.57 (m, 2H, CH_2N), 1.39 – 1.28 (m, 13 H, octyl), 0.90 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.9, 135.8, 127.0, 112.9, 51.1, 44.4, 32.1, 29.9, 29.7, 29.6, 27.5, 25.4, 23.0, 14.4. HRMS (ESI/[M+H]$^+$) calcd. for $C_{16}H_{29}N_2$: 249.2325. Found: 249.2322.

Preparation of 3-(1-aminoethyl)-*N*-methylaniline (2-2c)



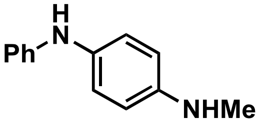
The general procedure was followed, with 4-chloro-α-methylbenzylamine (70 μL, 0.50 mmol) and methylamine (2 mmol from a 2M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 48 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM:MeOH:NH_4OH), and isolated as yellow oil in 77 % yield (58 mg, 0.39 mmol). ^{1}H NMR ($CDCl_3$): δ 7.19 – 7.16 (m, 2H, ArH), 6.61 – 6.58 (m, 2H, ArH), 4.03 (quart., 1H, *J* = 6.5 Hz, CH), 2.83 (s, 3H, CH_3), 1.81 (br s, 2H, NH), 1.36 (d, 3H, *J* = 6.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.6, 136.7, 126.9, 112.8, 51.1, 31.2, 25.8. HRMS (ESI/[M+Na]$^+$) calcd. for $C_9H_{14}N_2Na$: 173.1049. Found: 173.1053.

Preparation of *N*^{1}-octyl-*N*^{4}-phenylbenzene-1,4-diamine (2-2d)



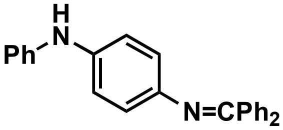
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox, $H_2NOctyl$ (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a white solid in 91 % yield (134 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.19 (t, 2H, *J* = 8 Hz, ArH), 7.05 – 7.01 (m, 2H, ArH), 6.83 – 6.78 (m, 3H, ArH), 6.78 (m, 1H, ArH), 6.64 – 6.56 (m, 2H, ArH), 5.37 (br s, 1H, NH), 3.09 (br s, 1H, NH), 1.63 (quint, 2H, *J* = 7.5 Hz, NCH_2), 1.44 – 1.27 (m, 12H, CH_2), 0.90 (t, 3H, 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.1, 132.8, 129.5, 124.3, 119.0, 115.0, 114.8, 114.0, 44.9, 32.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{29}N_2$: 297.2325. Found: 297.2351.

Preparation of *N*^{1}-methyl-*N*^{4}-phenylbenzene-1,4-diamine (2-2e)



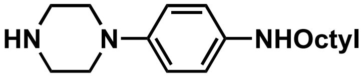
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and methylamine (2 mmol from a 2M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 48 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an orange-brown solid in 87 % yield (86 mg, 0.44 mmol). ^{1}H NMR (MeOD): δ 7.13 (t, 2H, *J* = 8.5 Hz, ArH), 7.00 (d, 2H, *J* = 8.5 Hz, ArH), 6.87 (d, 2H, *J* = 8 Hz, ArH), 6.72 – 6.66 (m, 3H, ArH), 4.91 (s, 3H, CH_3), 2.78 (br s, 2H, NH). $^{13}C\{^1H\}$ NMR (MeOD): δ 147.6, 136.1, 130.8, 124.5, 120.1, 116.7, 115.9, 32.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{15}N_2$: 199.1230. Found: 199.1224.

Preparation of *N*^{1}-(diphenylmethylene)-*N*^{4}-phenylbenzene-1,4-diamine (2-2f)



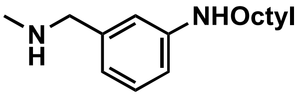
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) and benzopheneone imine (100 mg, 0.55 mmol) weighed out in the glovebox. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH: NH_4OH), and isolated as an orange oil in 93 % yield (162 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.77 – 7.75 (m, 2H, ArH), 7.47 (tt, 1H, *J* = 7 Hz, *J* = 1.5 Hz, ArH), 7.43 – 7.39 (m, 2H, ArH), 7.35 – 7.29 (m, 3H, ArH), 7.25 – 7.2 (m, 2H, ArH), 7.19 – 7.15 (m, 2H, ArH), 6.97 – 6.94 (m, 2H, ArH), 6.91 – 6.89 (m, 3H, ArH), 6.71 – 6.68 (m, 2H, ArH), 5.57 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.0, 145.5, 144.1, 140.3, 138.9, 137.0, 130.9, 129.9, 129.6, 129.5, 128.8, 128.5, 128.4, 123.0, 120.6, 119.2, 117.6. HRMS (ESI/$[M+H]^+$) calcd. for $C_{25}H_{21}N_2$: 349.1699. Found: 349.1706.

Preparation of *N*-octyl-4-(piperazin-1-yl)aniline (2-2g)



The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed in the glovebox and $H_2NOctyl$ (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 74 % yield (107 mg, 0.37 mmol). ^{1}H NMR ($CDCl_3$): δ 6.86 – 6.83 (m, 2H, ArH), 6.60 – 6.57 (m, 2H, ArH), 3.07 – 2.99 (m, 10 H, CH_2), 2.67 (br s, 2H, NH), 1.60 (m, 2H, CH_2), 1.41 – 1.25 (m, 10H, CH_2), 0.88 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.3, 143.5, 119.3, 114.1, 52.7, 46.6, 45.1, 32.2, 30.0, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{18}H_{32}N_3$: 290.2591. Found: 290.2584.

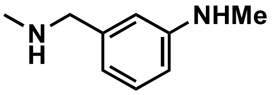
Preparation of 3-((methylamino)methyl)-*N*-octylaniline (2-2h)



The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and $H_2NOctyl$ (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 20 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (80:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow oil in 84 % yield (104 mg, 0.42

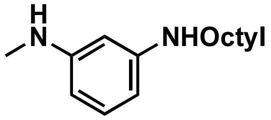
mmol). ^{1}H NMR (CDCl$_3$): δ 7.12 (t, 1H, *J* = 8 Hz, ArH), 6.62 (d, 1H, *J* = 7.5 Hz, ArH), 6.58 (t, 1H, *J* = 1.5 Hz, ArH), 6.49 (m, 1H, ArH), 3.68 (s, 2H, NCH$_2$), 3.10 (t, *J* = 7 Hz, CH$_2$), 2.45 (s, 1H, CH$_3$), 1.59 (m, 2H, CH$_2$), 1.40 – 1.26 (m, 10H, CH$_2$), 0.89 (t, 3H, *J* = 7 Hz). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 149.1, 141.3, 129.6, 117.3, 112.8, 111.7, 56.6, 44.3, 36.3, 32.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/[M+H]$^+$) calcd. for $C_{16}H_{29}N_2$: 249.2325. Found: 249.2329.

Preparation of *N*-methyl-3-((methylamino)methyl)aniline (2-2i)



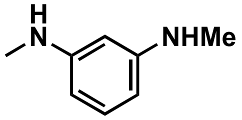
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and methylamine (2 mmol from a 2M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 24 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM:MeOH:NH$_4$OH), and isolated as an orange oil in 75 % yield (56 mg, 0.38 mmol). ^{1}H NMR (CDCl$_3$): δ 7.14 (t, 1H, *J* = 7.5 Hz, ArH), 6.65 (d, 1H, *J* = 7.5 Hz, ArH), 6.60 (s, 1H, ArH), 6.51 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz, ArH), 3.69 (s, 2H, CH$_2$), 2.82 (s, 3H, CH$_3$), 2.48 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 149.9, 129.6, 117.6, 112.6, 111.6, 56.4, 36.1, 31.1. HRMS (ESI/[M+H]$^+$) calcd. for $C_9H_{15}N_2$: 151.1230. Found: 151.1236.

Preparation of *N*^{1}-methyl-*N*^{3}-octylbenzene-1,3-diamine (2-2j)



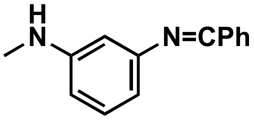
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and H_2NOctyl (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 93 % yield (109 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 6.99 (t, 1H, *J* = 8 Hz, ArH), 6.05 – 6.02 (m, 2H, ArH), 5.89 (t, 1H, *J* = 2 Hz, ArH), 3.66 (br s, 2H, NH), 3.09 (t, 2H, *J* = 7 Hz, CH_2), 2.81 (s, 3H, CH_3), 1.60 (m, 2H, CH_2), 1.40 – 1.26 (m, 10H, CH_2), 0.89 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 149.9, 130.3, 103.3, 102.9, 97.2, 44.5, 32.2, 31.2, 29.9, 29.8, 29.6, 27.5, 23.0, 14.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{27}N_2$: 235.2169. Found: 235.2169.

Preparation of *N*^{1},*N*^{3}-dimethylbenzene-1,3-diamine (2-2k)



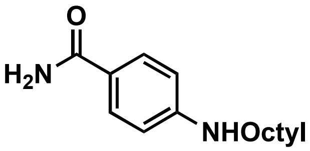
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and methylamine (2 mmol from a 2M stock solution in THF) added via a microlitre syringe. The reaction was allowed to proceed for 21 h at 85 °C, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a dark orange oil in 83 % yield (57 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 7.01 (t, 1H, *J* = 8 Hz, ArH), 6.05 (dd, 2H, *J* = 8 Hz, *J* = 2 Hz, ArH), 5.91 (t, 1H, *J* = 2 Hz, ArH), 2.82 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 130.2, 102.9, 96.8, 31.2. HRMS (ESI/[M+H]$^+$) calcd. for $C_8H_{13}N_2$: 137.1073. Found: 137.1079.

Preparation of *N*^{1}-(diphenylmethylene)-*N*^{3}-methylbenzene-1,3-diamine (2-2l)



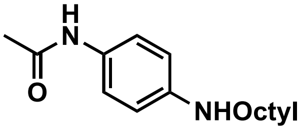
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) added by a microlitre syringe and benzopheneone imine (100 mg, 0.55 mmol) weighed in the glovebox. The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow oil in 92 % yield (132 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.76 – 7.74 (m, 2H, ArH), 7.45 (m, 1H, ArH), 7.42 – 7.39 (m, 2H, ArH), 7.28 – 7.26 (m, 3H, ArH), 7.18 – 7.16 (m, 2H, ArH), 6.93 (t, 1H, *J* = 8 Hz, ArH), 6.21 (ddd, 1H, *J* = 8 Hz, *J* = 2Hz, *J* = 1Hz, ArH), 6.09 (t, 1H, *J* = 2 Hz, ArH), 6.05 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 1Hz, ArH), 3.60 (br s, 1H, NH), 2.71 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.0, 152.6, 150.0, 140.2, 136.8, 130.9, 129.8, 129.6, 129.4, 128.8, 128.5, 128.1, 110.4, 108.4, 105.4, 31.0. HRMS (ESI/[M+H]$^+$) calcd. for $C_{20}H_{19}N_2$ 287.1543. Found: 287.1552.

Preparation of 4-(octylamino)benzamide (2-2m)



The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and $H_2NOctyl$ (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as a white solid in 74 % yield (92 mg, 0.37 mmol). ^1H NMR (MeOD): δ 7.71-7.68 (m, 2H, ArH), 6.63-6.59 (m, 2H, ArH), 4.91 (br s, NH), 3.15 (t, 2H, *J* = 7.5 Hz, CH_2), 1.65 (m, 2H, CH_2), 1.46-1.35 (m, 10H, CH_2), 0.93 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.8, 154.8, 131.4, 121.7, 113.0, 44.9, 33.9, 31.5, 31.3, 31.1, 29.1, 24.6, 15.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{25}N_2O$: 249.1961. Found: 249.1966.

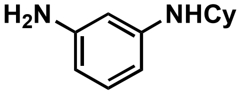
Preparation of *N*-(4-(octylamino)phenyl)acetamide (2-2n)



The general procedure was followed, *N*-(4-chlorophenyl)acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and $H_2NOctyl$ (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 73 % yield (96 mg, 0.37 mmol). ^{1}H NMR (MeOD): δ 7.26 (d, 2H, *J* = 9 Hz, ArH), 6.62 (d, 2H, *J* = 8.5 Hz, ArH), 4.91 (br s, 3H, NH), 3.06 (t, 2H, *J* = 7 Hz, CH_2), 2.09 (s, 3H, CH_3), 1.62 (m, 2H, CH_2), 1.44 – 1.33 (m, 10H, CH_2), 0.93 (t, 3H, J = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 172.1, 148.5, 130.3, 124.2, 114.9, 46.2, 33.9, 31.5, 31.3, 31.2, 29.2, 24.6, 24.3, 15.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{27}N_2O$: 263.2118. Found: 263.2115. Agrees with: Shen, Q.; Ogata, T.; Hartwig, J.F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

2.5.4 Preparation of Compounds From Table 2.3

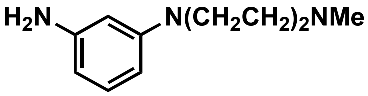
Preparation of *N*^{1}-cyclohexylbenzene-1,3-diamine (2-3a)



The general procedure was followed, with 3-chloroaniline (53 μL, 0.50 mmol) and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 14 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (8:1 Hex:EtOAc – 5:1 Hex:EtOAc), and isolated as a dark brown solid in 55 % yield (52 mg, 0.28 mmol). ^{1}H NMR ($CDCl_3$): δ 6.94 (t, 1H, *J* = 8 Hz, ArH), 6.07 – 6.04 (m, 2H, ArH), 5.97 (t, 1H, *J* = 2 Hz, ArH), 3.5 (br s, 2H, NH), 3.20 (m, 1H, CH), 2.28 – 2.03 (m, 2H, Cy), 1.78 – 1.73 (m, 2H, Cy), 1.65 (m, 1H, Cy), 1.39 – 1.09 (m, 5H, Cy). $^{13}C\{^1H\}$ NMR

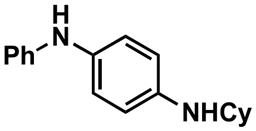
($CDCl_3$): δ 148.8, 147.8, 130.4, 104.8, 100.1, 52.0, 33.9, 26.3, 25.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{19}N_2$: 191.1543. Found: 191.1543.

Preparation of *N*^{1}-(4-methylpiperazin-1-yl)benzene-1,3-diamine (2-3b)



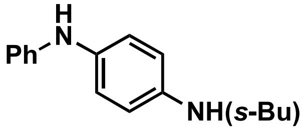
The general procedure was followed, with 3-chloroaniline (53 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (200:10:1 – 70:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow solid in 50 % yield (52 mg, 0.25 mmol). ^{1}H NMR ($CDCl_3$): δ 6.96 (t, 1H, *J* = 7.5 Hz, ArH) 6.34 (t, 1H, *J* = 2 Hz, ArH), 6.25 (m, 1H, ArH), 6.14 (m, 1H, ArH), 4.29 (br s, 1H, NH), 3.59 (br s, 1H, NH), 2.88 – 2.40 (br m, 8 H, CH_2), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.9, 147.9, 130.3, 107.1, 104.8, 100.6, 56.0, 55.4, 46.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{19}N_4$: 207.1604. Found: 207.1603.

Preparation of *N*^{1}-cyclohexyl-*N*^{4}-phenylbenzene-1,4-diamine (2-3c)



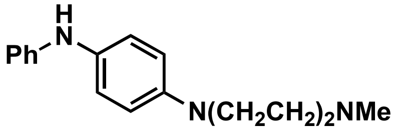
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as a dark yellow solid in 94 % yield (125 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.19 – 7.16 (m, 2H, ArH), 6.99 (d, 2H, *J* = 8.5 Hz, ArH), 6.82 (d, 2H, *J* = 8 Hz, ArH), 6.77 (t, 1H, *J* = 7 Hz, ArH), 6.58 (d, 2H, *J* = 8.5 Hz, ArH), 5.37 (br s, 1H, NH), 3.41 (br s, 1H, NH), 3.22 (m, 1H, Cy), 2.09 – 2.06 (m, 2H, Cy), 1.80 – 1.75 (m, 2H, Cy), 1.66 (m, 1H, Cy), 1.42 – 1.34 (m, 2H, Cy), 1.33 – 1.45 (m, 3H, Cy). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.7, 144.1, 132.4, 129.5, 124.4, 118.9, 115.0, 114.5, 52.6, 33.9, 26.3, 25.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{18}H_{23}N_2$: 267.1856. Found: 267.1849.

Preparation of *N*^{1}-*sec*-butyl-*N*^{4}-phenylbenzene-1,4-diamine (2-3d)



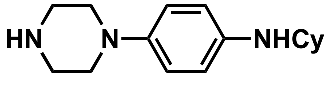
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and *s*BuNH_2 (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH) and isolated as a brown oil in 81 % yield (97 mg, 0.41 mmol). ^{1}H NMR (MeOD): δ 7.13 (t, 2H, *J* = 8 Hz, ArH), 6.97 (d, 2H, *J* = 8 Hz, ArH), 6.87 (d, 2H, *J* = 8 Hz, ArH), 6.72 – 6.68 (m, 3H, ArH), 4.91 (s, 2H, NH), 1.65 (m, 1H, CH), 1.45 (m, 1H, CH), 1.17 (d, 3H, *J* = 6 Hz, CH_3), 0.99 (t, 3H, *J* = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR (MeOD): δ 135.8, 130.8, 124.5, 120.1, 117.2, 116.7, 52.9, 31.2, 20.9, 11.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{16}H_{21}N_2$: 241.1699. Found: 241.1701.

Preparation of N^1-(4-methylpiperazin-1-yl)-N^4-phenylbenzene-1,4-diamine (2-3e)



The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow solid in 81 % yield (115 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.21 – 7.18 (m, 2H, ArH), 7.02 – 7.01 (m, 2H, ArH), 6.89 – 6.87 (m, 4H, ArH), 6.79 (m, 1H, ArH), 5.47 (br s, 1H, NH), 4.28 (br s, 1H, NH), 2.78 – 2.47 (m, 8H, CH_2), 2.34 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.0, 143.4, 135.0, 129.6, 123.1, 119.3, 115.5, 115.2, 56.0, 55.4, 46.1. HRMS (ESI/[M-H]$^+$) calcd. for $C_{17}H_{21}N_4$: 281.1761. Found: 281.1772.

Preparation of *N*-cyclohexyl-4-(piperazin-1-yl)aniline (2-3f)

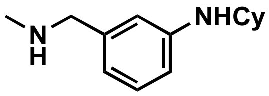


The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow solid in 74 % yield (96 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 6.84 – 6.81 (m, 2H, ArH), 6.58 – 6.55 (m, 2H, ArH), 3.17 (m, 1H, CH), 3.05 – 2.99 (m, 8H, NCH_2), 2.50 – 2.26 (br s, 2H, NH), 2.05 – 2.02 (m, 2H, Cy), 1.76 – 1.72 (m, 2H, Cy), 1.63 (m, 1H, Cy), 1.39 – 1.35 (m, 2H, Cy), 1.25 – 1.07 (m, 3H, Cy). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9, 142.4, 119.4, 114.7, 52.8, 52.4, 46.4, 34.0, 26.3, 25.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{26}N_3$: 260.2121. Found: 260.2112.

Preparation of *N*-*sec*-butyl-4-(piperazin-1-yl)aniline (2-3g)

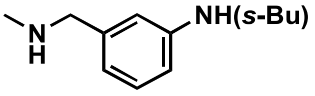
The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and *s*BuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow solid in 60 % yield (70 mg, 0.30 mmol). ^1H NMR ($CDCl_3$): δ 6.84 (d, 2H, $J = 8.5$ Hz, ArH), 6.55 (d, 2H, $J = 8.5$ Hz, ArH), 3.31 (m, 1H, CH), 3.09 – 3.02 (m, 8H, CH_2), 2.87 (br s, 2H, NH), 1.57 (m, 1H, CH), 1.46 (m, 1H, CH), 1.25 (m, 1H, CH), 1.15 (d, 3H, $J = 6.5$ Hz, CH_3), 0.94 (t, 3H, $J = 7.5$ Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9, 142.7, 119.4, 114.6, 52.4, 50.8, 46.4, 30.0, 20.7, 10.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{24}N_3$: 234.1965. Found: 234.1966.

Preparation of *N*-cyclohexyl-3-((methylamino)methyl)aniline (2-3h)



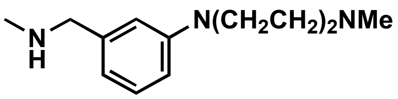
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (80:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow oil in 92 % yield (100 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.10 (t, 1H, *J* = 8 Hz, ArH), 6.59 (d, 1H, *J* = 7.5 Hz, ArH), 6.56 (br s, 1H, ArH), 6.49 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz, ArH), 3.66 (s, 2H, NCH_2), 3.27 (m, 1H, CH), 2.45 (s, 3H, CH_3), 2.06 – 2.03 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 1.64 (m, 1H, CH), 1.38 – 1.13 (m, 5H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.9, 141.2, 129.6, 117.1, 113.2, 112.1, 56.5, 51.2, 36.2, 33.8, 26.2, 25.3. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{23}N_2$: 219.1856. Found: 219.1853.

Preparation of *N*-*sec*-butyl-3-((methylamino)methyl)aniline (2-3i)



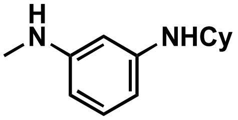
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and *s*BuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (40:10:1 DCM:MeOH:NH$_4$OH), and isolated as a yellow oil in 81 % yield (78 mg, 0.41 mmol). ^{1}H NMR (CDCl$_3$): δ 7.11 (t, 1H, *J* = 7.5 Hz, ArH), 6.59 (d, 1H, *J* = 7.5 Hz, ArH), 6.56 (s, 1H, ArH), 6.47 (dd, 1H, *J* = 7.5 Hz, *J* = 2 Hz, ArH), 3.67 (s, 2H, CH$_2$), 3.41 (m, 1H, CH), 2.45 (s, 3H, CH$_3$), 4.37 (br s, 1H, NH), 1.57 (m, 1H, CH), 1.47 (m, 1H, CH), 1.15 (d, *J* = 6 Hz, 3H, CH$_3$), 0.94 (t, 3H, *J* = 7.5 Hz, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 148.2, 141.3, 129.6, 117.0, 113.3, 112.0, 56.5, 50.0 36.2, 30.0, 20.6, 10.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{12}H_{21}N_2$: 193.1699. Found: 193.1701.

Preparation of 4-methyl-*N*-(3-((methylamino)methyl)phenyl)piperazin-1-amine (2-3j)



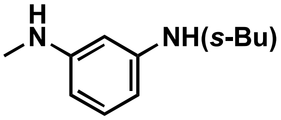
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of the solvent, the product was purified using column chromatography on silica (30:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow oil in 70 % yield (83 mg, 0.35 mmol). ^{1}H NMR ($CDCl_3$): δ 7.14 (t, 1H, *J* = 7.5 Hz, ArH), 6.84 (s, 1H, ArH), 6.79 (d, 1H, *J* = 8 Hz, ArH), 6.72 (d, 1H, *J* = 7.5 Hz, ArH), 4.37 (br s, 1H, NH), 3.67 (s, 2H, CH_2), 2.97 – 2.54 (m, 8H, CH_2), 2.46 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.05 (br s, 1H, NH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.9, 141.2, 129.5, 119.7, 113.6, 112.7, 56.4, 56.0, 55.4, 46.1, 36.2. HRMS (ESI/[M+H]$^+$) calcd. for $C_{13}H_{23}N_4$: 235.1917. Found: 235.1908.

Preparation of *N*^{1}-cyclohexyl-*N*^{3}-methylbenzene-1,3-diamine (2-3k)



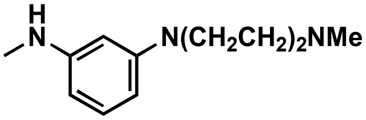
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as an orange oil in 89 % yield (91 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.01 (t, 1H, *J* = 8 Hz, ArH), 6.05 – 6.01 (m, 2H, ArH), 5.89 (t, 1H, *J* = 2 Hz, ArH), 3.55 (br s, 2H, NH), 3.27 (m, 1H, CH), 2.29 (s, 3H, CH_3), 2.10 -2.08 (m, 2H, CH_2), 1.81 – 1.76 (m, 2H, CH_2), 1.67 (m, 1H, CH), 1.41 – 1.35 (m, 2H, CH_2), 1.29 – 1.16 (m, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 150.9, 148.9, 130.3, 103.4, 102.5, 97.5, 52.0, 39.9, 31.1, 26.3, 25.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{21}N_2$: 205.1699. Found: 205.1702.

Preparation of *N*^{1}-*sec*-butyl-*N*^{3}-methylbenzene-1,3-diamine (2-3l)



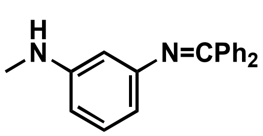
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and *s*$BuNH_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a brown oil in 90 % yield (80 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 6.99 (t, 1H, *J* = 8 Hz, ArH), 6.00 (dt, 2H, *J* = 8 Hz, *J* = 2.5 Hz, ArH), 5.87 (t, 1H, *J* = 2.5 Hz, ArH), 3.49 (br s, 2H, NH), 3.39 (m, 1H, CH), 2.82 (s, 3H, CH_3), 1.60 (m, 1H, CH), 1.47 (m, 1H, CH), 1.17 (d, 3H, *J* = 6.5 Hz, CH_3), 0.96 (t, 3H, *J* = 7.5 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.9, 149.2, 130.2, 103.4, 102.4, 97.4, 50.1, 31.1, 30.1, 20.7, 10.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{19}N_2$: 179.1543. Found: 179.1540.

Preparation of *N*^{1}-methyl-*N*^{3}-(4-methylpiperazin-1-yl)benzene-1,3-diamine (2-3m)



The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and 1-amino-4-methylpiperazine (66 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (100:10:1 – 50:10:1 DCM:MeOH:NH_4OH) and isolated as a dark red oil in 78 % yield (86 mg, 0.39 mmol). ^1H NMR ($CDCl_3$): δ 7.02 – 6.98 (m, 1H, ArH), 6.25 – 6.23 (m, 2H, ArH), 6.10 – 6.08 (m, 1H, ArH), 4.30 (br s, 1H, NH), 2.80 (s, 3H, CH_3), 2.74 – 2.36 (m, 8H, CH_2), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 148.8, 130.1, 104.6, 103.6, 97.9, 55.9, 55.4, 46.1, 31.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{21}N_4$: 221.1761. Found: 221.1752.

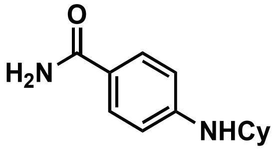
Preparation of 3-(2-(diphenylmethylene)hydrazinyl)-*N*-methylaniline (2-3n)



The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) added by a microlitre syringe and benzophenone hydrazone (108 mg, 0.55 mmol) weighed out in the glovebox. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a dark red oil in 80 % yield (121 mg, 0.40 mmol). ^1H NMR ($CDCl_3$): δ 7.63 – 7.59 (m, 4H, ArH), 7.55 (m, 1H, ArH), 7.59 (br s, 1H, ArH), 7.38 – 7.29 (m, 4H, ArH), 7.08 (t, 1H, *J* = 8 Hz, ArH), 6.5 (t, 1H, *J* = 2 Hz, ArH), 6.39 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 1 Hz, ArH), 6.18 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 1 Hz, ArH), 2.86 (s, 3H, CH_3).

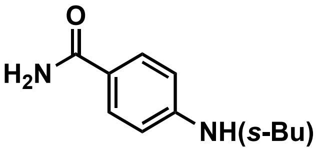
$^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 145.9, 143.9, 138.8, 133.2, 130.2, 129.9, 129.5, 129.5, 128.5, 128.2, 126.7, 105.3, 102.8, 97.0, 31.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{20}N_3$: 302.1652. Found: 302.1642.

Preparation of 4-(cyclohexylamino)benzamide (2-3o)



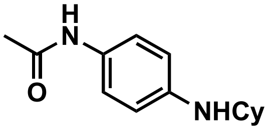
The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 73 % yield (80 mg, 0.37 mmol). ^1H NMR (MeOD): δ 7.65 (m, 2H, ArH), 6.59 (m, 2H, ArH), 3.33 (m, 1H, CH), 2.09 – 2.07 (m, 2H, Cy), 1.82 – 1.79 (m, 2H, Cy), 1.69 (m, 1H, Cy), 1.47 – 1.19 (m, 5 H, Cy). $^{13}C\{^1H\}$ NMR (MeOD): δ 169.3, 151.1, 129.7, 121.1, 112.2, 51.8, 33.6, 26.3, 25.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{19}N_2O$: 219.1492. Found: 219.1497. Agrees with: Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109.

Preparation of 4-(*sec*-butylamino)benzamide (2-3p)



The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and *s*BuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH$_4$OH), and isolated as a yellow solid in 68 % yield (65 mg, 0.34 mmol). ^{1}H NMR (MeOD): δ 7.68 (m, 2H, ArH), 6.61 (m, 2H, ArH), 4.91 (br s, 3H, NH), 3.48 (m, 1H, CH), 1.64 (m, 1H, CH), 1.55 (m, 1H, CH), 1.20 (d, 3H, *J* = 6 Hz, CH$_3$), 0.99 (t, 3H, *J* = 7.5 Hz, CH$_3$). ^{13}C{^{1}H} NMR (MeOD): δ 173.8, 154.2, 131.4, 121.4, 113.3, 51.3, 31.3, 21.1, 11.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{11}H_{17}N_2O$:193.1335. Found: 193.1340.

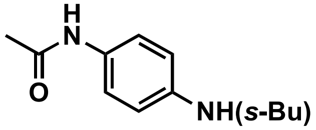
Preparation of *N*-(4-(cyclohexylamino)phenyl)acetamide (2-3q)



The general procedure was followed, *N*-(4-chlorophenyl)acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol

(15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as a brown solid in 92% yield (106 mg, 0.46 mmol). ^{1}H NMR (MeOD): δ 7.25 (m, 2H, ArH), 6.64 (m, 2H, ArH), 4.91 (br s, 3H, NH), 3.21 (m, 1H, CH), 2.09 (s, 3H, CH_3), 2.05 – 1.93 (m, 2H, Cy), 1.82 – 1.78 (m, 2H, Cy), 1.69 (m, 1H, Cy), 1.43 – 1.17 (m, 5H, Cy). ^{13}C{^{1}H} NMR (MeOD): δ 172.1, 147.2, 130.4, 124.2, 115.9, 54.4, 35.1, 27.9, 27.1, 24.3. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{21}N_2O$: 233.1648. Found: 233.1644.

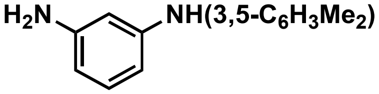
Preparation of *N*-(4-(*sec*-butylamino)phenyl)acetamide (2-3r)



The general procedure was followed, with *N*-(4-chlorophenyl)acetamide (84 mg, 0.50 mmol) weighed out in the glovebox and *s*BuNH$_2$ (56 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow oil in 90 % yield (93 mg, 0.45 mmol). ^{1}H NMR (MeOD): δ 7.24 (m, 2H, ArH), 6.61 (m, 2H, ArH), 4.91 (br s, 2H, NH), 3.37 (m, 1H, CH), 2.09 (s, 3H, CH_3), 1.62 (m, 1H, CH), 1.47 (m, 1H, CH), 1.16 (d, 3H, J = 6 Hz, CH_3), 0.97 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C{^{1}H} NMR (MeOD): δ 172.1, 147.8, 130.0, 124.3, 115.5, 52.2, 31.2, 24.3, 21.1, 11.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{12}H_{19}N_2O$: 207.1492. Found: 207.1497.

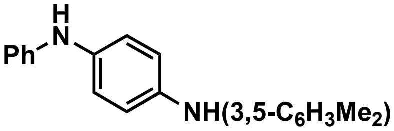
2.5.5 Preparation of Compounds From Table 2.4

Preparation of *N*¹-(3,5-dimethylphenyl)benzene-1,3-diamine (2-4a)



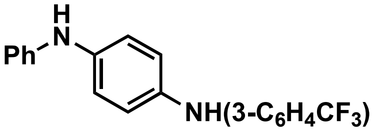
See General Procedure.

Preparation of N^1-(3,5-dimethylphenyl)-N^4-phenylbenzene-1,4-diamine (2-4b)



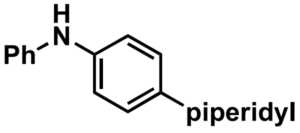
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 3,5-dimethylaniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 16 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH: NH_4OH), and isolated as a yellow solid in 96 % yield (138 mg, 0.48 mmol). ^{1}H NMR (MeOD): δ 7.19 – 7.17 (m, 2H, ArH), 7.06 – 7.03 (m, 4H, ArH), 6.99 (dd, 2H, *J* = 8.5 Hz, *J* = 1 Hz, ArH), 6.77 (t, 1H, *J* = 7.5 Hz, ArH), 6.63 (s, 2H, ArH), 6.46 (s, 1H, ArH), 4.91 (s, 2H, NH), 2.23 (s, 6H, ArH). $^{13}C\{^1H\}$ NMR (MeOD): δ 147.7, 147.4, 140.5, 139.9, 139.3, 130.9, 122.8, 122.4, 122.3, 120.9, 117.6, 115.8, 22.5. HRMS (ESI/[M+H]$^+$) calcd. for $C_{20}H_{21}N_2$: 289.1699. Found: 289.1685.

Preparation of *N*¹-phenyl-*N*⁴-(3-(trifluoromethyl)phenyl)benzene-1,4-diamine (2-4c)



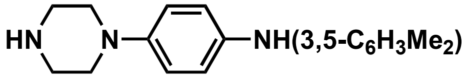
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and 3-CF_3-aniline (68 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH: NH_4OH), and isolated as a yellow solid in 95 % yield (156 mg, 0.48 mmol). ^1H NMR (MeOD): δ 7.30 (t, 1H, *J* = 8 Hz, ArH), 7.22 – 7.19 (m, 2H, ArH), 7.16 – 7.13 (m, 2H, ArH), 7.12 – 7.07 (m, 4H, ArH), 7.05 – 7.03 (m, 2H, ArH), 6.96 (d, 1H, *J* = 7.5 Hz, ArH), 6.80 (tt, 1 H, *J* = 7.5 Hz, *J* = 1 Hz, ArH), 4.92 (br s, 2H, NH). $^{13}C\{^1H\}$ NMR (MeOD): δ 148.9, 146.9, 141.1, 137.4, 133.3 (q, J_{CF} = 31.5 Hz), 131.7, 130.9, 123.9, 121.5, 121.3, 119.7 (q, J_{CF} = 171.2 Hz), 119.6, 118.2, 116.1 (m), 112.6 (m). HRMS (ESI/[M+H]$^+$) calcd. for $C_{19}H_{16}F_3N_2$: 329.1260. Found: 329.1265.

Preparation of *N*-phenyl-4-(piperidin-1-yl)aniline (2-4d)



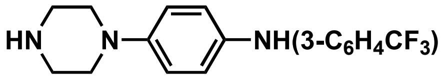
The general procedure was followed, with 4-chloro-*N*-phenylaniline (102 mg, 0.50 mmol) weighed out in the glovebox and piperidine (54 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 46 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as a brown solid in 82 % yield (104 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.22 – 7.19 (m, 2H, ArH), 7.05 (d, 2H, *J* = 9 Hz, ArH), 6.92 (d, 4H, *J* = 8 Hz, ArH), 6.82 (t, 1H, *J* = 7 Hz, ArH), 5.48 (br s, 1H, NH), 3.10 (s, 4H, CH_2), 1.76 – 1.71 (m, 4H, CH_2), 1.59 – 1.55 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.5, 145.6, 135.2, 129.6, 122.1, 119.7, 118.4, 115.9, 51.9, 26.4, 24.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{17}H_{21}N_2$: 253.1699. Found: 253.1705.

Preparation of 3,5-dimethyl-*N*-(4-(piperazin-1-yl)phenyl)aniline (2-4e)



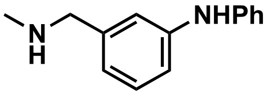
The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and 3,5-Me-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:15:1.5 DCM:MeOH:NH_4OH), and isolated as an orange oil in 71 % yield (100 mg, 0.36 mmol). ^1H NMR ($CDCl_3$): δ 7.05 (m, 2H, ArH), 6.90 (m, 2H, ArH), 6.57 (s, 2H, ArH), 6.50 (s, 1H, ArH), 5.45 (br s, 1H, NH), 3.11 – 3.03 (m, 8H, CH_2), 2.25 (s, 6H, CH_3), 1.82 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.6, 145.3, 139.2, 135.9, 121.9, 121.7, 117.8, 113.9, 51.6, 46.5, 21.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{18}H_{24}N_3$: 282.1965. Found: 282.1962.

Preparation of *N*-(4-(piperazin-1-yl)phenyl)-3-(trifluoromethyl)aniline (2-4f)



The general procedure was followed, with 1-(4-chlorophenyl)piperazine (98 mg, 0.50 mmol) weighed out in the glovebox and 3-trifluoromethylaniline (68 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (100:15:1.5 DCM:MeOH:NH_4OH), and isolated as a yellow solid in 60 % yield (96 mg, 0.30 mmol. ^1H NMR ($CDCl_3$): δ 7.27 (t, 1H, *J* = 8 Hz, ArH), 7.10 – 7.06 (m, 3H, ArH), 7.03 – 6.99 (m, 2H, ArH), 6.94 – 6.91 (m, 2H, ArH), 5.68 (br s, 1H, NH), 3.13 – 3.04 (m, 8 H, CH_2), 1.95 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): 148.7, 146.3, 134.0, 131.9 (q, J_{CF} = 31 Hz), 130.0, 124.5 (q, J_{CF} = 273 Hz), 123.2, 118.2, 117.8, 115.7 (m), 111.5 (m), 51.2, 46.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{17}H_{19}F_3N_3$: 322.1526. Found: 322.1528.

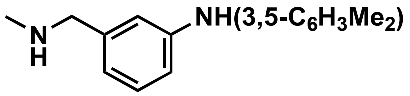
Preparation of 3-((methylamino)methyl)-*N*-phenylaniline (2-4g)



The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica

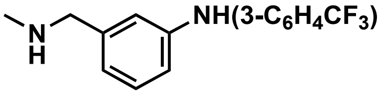
(80:10:1 DCM:MeOH:NH_4OH), and isolated as a white solid in 82 % yield (86 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.29 - 7.25 (m, 2H, ArH), 7.22 (t, 1H, *J* = 8 Hz, ArH), 7.09 - 7.07 (m, 2H, ArH), 7.02 (m, 1H, ArH), 6.99 (ddd, 1H, *J* = 8 Hz, *J* = 2.5 Hz, *J* = 1 Hz, ArH), 6.93 (t of t, 1H, *J* = 7.5 Hz, *J* = 1Hz, ArH), 6.88 (m, 1H, ArH), 5.77 (br s, 1H, NH), 3.71 (s, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.69 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.6, 143.4, 141.7, 129.7, 121.3, 121.1, 118.2, 117.8, 116.5, 56.3, 36.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{17}N_2$: 213.1386 Found: 213.1381.

Preparation of 3,5-dimethyl-*N*-(3-((methylamino)methyl)phenyl)aniline (2-4h)



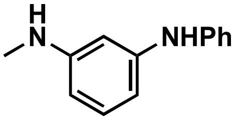
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and 3,5-Me-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 85 % yield (102 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.23 (t, 1H, *J* = 7.5 Hz, ArH), 7.02 – 6.99 (m, 2H, ArH), 6.87 (d, 1H, *J* = 7.5 Hz, ArH), 6.72 (s, 2H, ArH), 6.62 (s, 1H, ArH), 5.74 (br s, 1H, NH), 3.72 (s, 2H, CH_2), 2.47 (s, 3H, CH_3), 2.29 (s, 6H, CH_3), 2.07 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.8, 143.3, 141.4, 139.3, 129.6, 123.2, 120.8, 117.9, 116.5, 116.1, 56.1, 36.1, 21.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{21}N_2$: 241.1699 Found: 241.1700.

Preparation of 3-((methylamino)methyl)-*N*-(3-(trifluoromethyl)phenyl)aniline (2-4i)



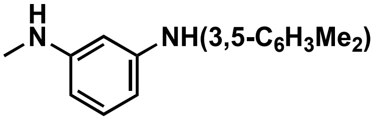
The general procedure was followed, with 3-chloro-*N*-methylbenzylamine (73 μL, 0.50 mmol) and 3-CF_3-aniline (68 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (50:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 67 % yield (94 mg, 0.34 mmol). ^1H NMR ($CDCl_3$): δ 7.34 (t, 1H, *J* = 8 Hz, ArH), 7.28 (t, 2H, *J* = 8 Hz, ArH), 7.19 (m, 1H, ArH), 7.13 (d, 1H, *J* = 8 Hz, ArH), 7.07 (s, 1H, ArH), 7.04 (dd, 1H, *J* = 8 Hz, *J* = 1.5 Hz, ArH), 6.97 (d, 1H, *J* = 8 Hz, ArH), 5.95 (br s, 1H, NH), 3.74 (s, 2H, CH_2), 2.48 (s, 3H, CH_3), 2.02 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.3, 142.4, 141.8, 132.0 (q, J_{CF} = 32.7 Hz), 130.2, 129.9, 124.4 (q, J_{CF} = 276.8 Hz), 122.4, 120.2, 119.1, 117.7, 117.2 (m), 113.6 (m), 56.1, 36.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{16}F_3N_2$: 281.1260. Found: 281.1258.

Preparation of *N*^{1}-methyl-*N*^{3}-phenylbenzene-1,3-diamine (2-4j)



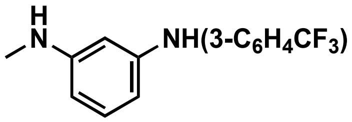
The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an orange oil in 94 % yield (93 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.32 – 7.29 (m, 2H, ArH), 7.15 – 7.12 (m, 3H, ArH), 6.96 (t, 1H, *J* = 7 Hz, ArH), 6.50 (m, 1H, ArH), 6.39 (t, 1H, *J* = 2.5 Hz), 6.28 (m, 1H, ArH), 5.70 (br s, 1H, NH), 3.61 (br s, 1H, NH), 2.86 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 144.5, 143.6, 130.3, 129.6, 121.0, 118.3, 107.6, 106.1, 101.9, 31.1. HRMS (ESI/[M+H]$^+$) calcd. for $C_{13}H_{15}N_2$: 199.1230. Found: 199.1225.

Preparation of *N*^{1}-(3,5-dimethylphenyl)-*N*^{3}-methylbenzene-1,3-diamine (2-4k)



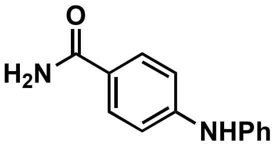
The general procedure was followed, with 3-chloro-N-methylaniline (61 μL, 0.50 mmol) and 3,5-Me-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 12 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH), and isolated as an orange oil in 95 % yield (107 mg, 0.48 mmol). ^{1}H NMR ($CDCl_3$): δ 7.11 (t, 1H, *J* = 8 Hz, ArH), 6.75 (s, 2H, ArH), 6.61 (s, 1H, ArH), 6.47 (m, 1H, ArH), 6.36 (t, 1H, *J* = 2 Hz, ArH), 6.25 (m, 1H, ArH), 2.83 (s, 3H, CH_3), 2.30 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.6, 144.6, 143.5, 139.2, 130.3, 122.9, 116.1, 107.7, 105.9, 102.1, 31.1, 21.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{19}N_2$: 227.1543. Found: 227.1541.

Preparation of *N*^{1}-methyl-*N*^{3}-(3-(trifluoromethyl)phenyl)benzene-1,3-diamine (2-4l)



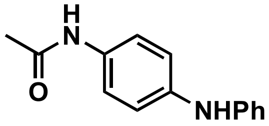
The general procedure was followed, with 3-chloro-N-methylaniline (61 μL, 0.50 mmol) and 3-CF_3-aniline (68 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (DCM - 1000:10:1 DCM:MeOH:NH_4OH), and isolated as a dark orange oil in 88 % yield (118 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 7.33 (t, 1H, *J* = 8 Hz, ArH), 7.29 (s, 1H, ArH), 7.29 (dd, 1H, *J* = 8 Hz, *J* = 2 Hz, ArH), 7.14 – 7.10 (m, 2H, ArH), 6.47 (ddd, 1H, *J* = 8 Hz, *J* = 2 Hz, *J* = 1 Hz, ArH), 6.37 (t, 1H, *J* = 2 Hz, ArH), 6.31 (ddd, 1H, *J* = 8 Hz, *J* = 2Hz, *J* = 1Hz, ArH), 5.78 (br s, 1H, NH), 2.83 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 144.5, 143.2, 131.9 (q, J_{CF} = 32.7 Hz), 130.6, 130.1, 124.5 (q, J_{CF} = 272.9 Hz), 120.3, 116.9 (m), 113.7 (m), 108.6, 107.5, 103.0, 31.1. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{14}F_3N_2$: 267.1104. Found: 267.1120.

Preparation of 4-(phenylamino)benzamide (2-4m)



The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) weighed out in the glovebox and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 66 % yield (70 mg, 0.33 mmol). ^{1}H NMR (MeOD): δ 7.79 – 7.76 (m, 2H, ArH), 7.33 - 7.29 (m, 2H, ArH), 7.21 – 7.18 (m, 2H, ArH), 7.09 – 7.06 (m, 2H, ArH), 6.99 (t of t, 1H, *J* = 8 Hz, *J* = 1Hz, ArH), 4.92 (br s, 3H, NH). ^{13}C{^{1}H} NMR (MeOD): δ 173.2, 150.4, 144.1, 131.3, 131.1, 125.2, 123.9, 121.5, 116.3. HRMS (ESI/[M+Na]$^+$) calcd. for $C_{13}H_{12}N_2NaO$: 235.0842. Found: 235.0843.

Preparation of *N*-(4-(phenylamino)phenyl)acetamide (2-4n)

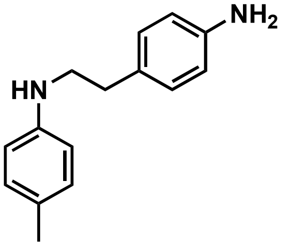


The general procedure was followed, with *N*-(4-chlorophenyl)acetamide (84 mg, 0.50 mmol) weighed in the glovebox and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Following removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 94 % yield (106 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.39 - 7.37 (m, 2H, ArH), 7.25 - 7.23 (m, 2H, ArH), 7.05 – 7.00 (m, 4H, ArH), 6.90 (t, 1H, *J* = 7.5 Hz, ArH), 5.67 (br s, 1H, NH), 2.16 (s, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 168.5, 143.8, 139.9, 131.9, 129.7, 122.0, 121.0, 119.3, 117.5, 24.8. HRMS (ESI/[M+Na]$^+$) calcd. for $C_{14}H_{14}N_2NaO$:

249.0998. Found: 249.1001. Agrees with: Struijk, M. P.; Janssen, R. A. *J. Synth. Met.* **1999**, *103*, 2287.

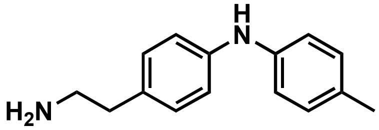
2.5.6 Preparation of Compounds from Table 2.5

Preparation of *N*-(4-aminophenethyl)-4-methylaniline (2-5a)



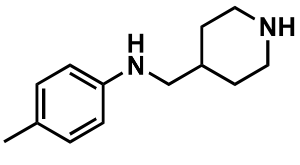
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and 2-(4-aminophenyl)ethylamine (79 μL, 0.60 mmol) added via a microlitre syringe The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (4:3 hex: EtOAc), and isolated as a sticky, orange solid in 69 % yield (78 mg, 0.35 mmol). ^{1}H NMR ($CDCl_3$): δ 7.05 – 7.00 (m, 4H, ArH), 6.68 – 6.65 (m, 2H, ArH), 6.58 – 6.55 (m, 2H, ArH), 3.56 (br s, 3H, NH), 3.34 (t, 2H, J = 7 Hz, CH_2), 2.82 (t, 2H, J = 7 Hz, CH_2), 2.27 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.2, 145.1, 130.0, 129.9, 129.5, 126.9, 115.7, 113.6, 45.9, 34.9, 20.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{19}N_2$: 227.1543. Found: 227.1525.

Preparation of 4-(2-aminoethyl)-*N*-*p*-tolylaniline (2-5a')



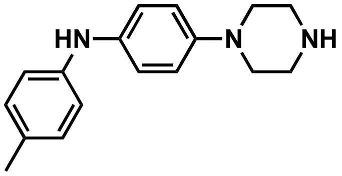
The general procedure was followed, with *p*-Mor-DalPhos (**L2**) employed as the ligand (2 mol % Pd, 4 mol % **L2**), with 4-chlorotoluene (58 μL, 0.50 mmol) and 2-(4-aminophenyl)ethylamine (79 μL, 0.60 mmol) added via a microlitre syringe The reaction was allowed to proceed for 48 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (500:10:1 DCM:MeOH:NH_4OH), and isolated as an orange solid in 72 % yield (81 mg, 0.36 mmol). ^{1}H NMR ($CDCl_3$): δ 7.08 (m, 4H, ArH), 6.98 (m, 4H, ArH), 5.69 (br s, 1H, NH) 2.94 (t, 2H, *J* = 7 Hz, CH_2), 2.69 (t, 2H, *J* = 7 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.45 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.3, 141.0, 132.0, 130.7, 130.1, 129.9, 118.6, 117.7, 44.0, 39.5, 20.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{19}N_2$ 227.1543. Found: 227.1545.

Preparation of 4-methyl-*N*-(piperidin-4-ylmethyl)aniline (2-5b)



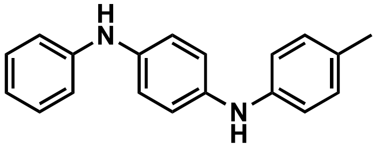
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and 4-(aminomethyl)-piperidine (72 μL, 0.60 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the solid was washed with pentane (3 x 5 mL) and dried in vacuo to obtain the pure product as an off-white solid in 81 % yield (83 mg, 0.41 mmol). ^{1}H NMR (CDCl$_3$): δ 6.99 – 6.97 (m, 2H, ArH), 6.53 – 6.51 (m, 2H, ArH), 3.59 (br s, 1H, NH), 3.09 (dt, 2H, *J* = 12 Hz, *J* = 3Hz, CH$_2$), 2.98 (d, 2H, *J* = 6.5 Hz, CH$_2$), 2.59 (dt, 2H, *J* = 2 Hz, *J* = 2.5 Hz, CH$_2$), 2.23 (s, 3H, CH$_3$), 1.80 – 1.75 (m, 2H, CH$_2$), 1.70 (m, 1H, CH), 1.52 (br s, 1H, NH), 1.18 (m, 2H, CH$_2$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 146.5, 130.0, 126.6, 113.1, 51.0, 46.8, 36.5, 32.0, 20.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{13}H_{21}N_2$: 205.1699. Found: 205.1703.

Preparation of 4-methyl-*N*-(4-(piperazin-1-yl)phenyl)aniline (2-5c)



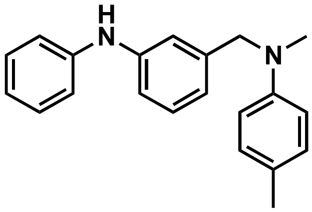
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) added via a microlitre syringe and *N*-(4-aminophenyl)-piperazine (106 mg, 0.60 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (9:1 DCM:MeOH), and isolated as an orange solid in 79 % yield (105 mg, 0.40 mmol). ^{1}H NMR (CDCl$_3$): δ 7.05 – 6.99 (m, 4 H, ArH), 6.90 – 6.86 (m, 4H, ArH), 5.47 (br s, 1H, NH), 3.09 – 3.03 (m, 8H, CH$_2$), 2.28 (s, 3H, CH$_3$), 1.92 (br s, 1H, NH). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 147.2, 142.5, 136.7, 130.0, 129.5, 120.7, 118.0, 116.9, 57.7, 46.5, 20.9. HRMS (ESI/[M+H]$^+$) calcd. for $C_{17}H_{22}N_3$: 268.1808. Found: 268.1793.

Preparation of *N*^{1}-phenyl-*N*^{4}-*p*-tolylbenzene-1,4-diamine (2-5d)



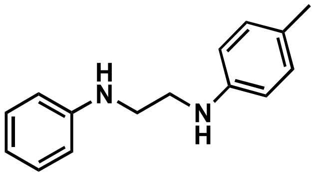
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) added via a microlitre syringe and *N*-phenyl-1,4-phenylene-diamine (111 mg, 0.60 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (4:1 hex:EtOAc), and isolated as a pale orange solid in 90 % yield (122 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.25 (t, 2H, *J* = 7.5 Hz, ArH), 7.09-6.94 (m, 10 H, ArH), 6.87 (t, 1 H, *J* = 7 Hz, ArH), 5.54 (br s, H, NH), 5.49 (br s, 1H, NH), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.1, 141.9, 138.6, 136.7, 130.2, 129.6, 121.7, 120.0, 117.7, 116.3, 20.9. HRMS (ESI/[M]$^+$) calcd. for $C_{19}H_{18}N_2$: 274. 1465. Found: 274.1454.

Preparation of *N*,4-dimethyl-*N*-(3-(phenylamino)benzyl)aniline (2-5e)



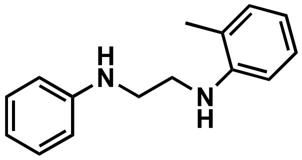
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.5 mmol) added via a microlitre syringe and 3-((methylamino)methyl)-*N*-phenylaniline (111 mg, 0.53 mmol) weighed out in the glovebox for convenience. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (DCM) and isolated as a yellow solid in 60 % yield (91 mg, 0.30 mmol). ^{1}H NMR (CDCl$_3$): δ 7.28 – 7.21 (m, 3 H, ArH), 7.08 – 7.03 (m, 4H, ArH), 6.99 (dd, 1H, *J* = 8 Hz, *J* = 1.5 Hz, ArH), 6.96 – 6.93 (m, 2H, ArH), 6.83 (d, 1H, *J* = 8Hz, ArH), 6.72 – 6.71 (m, 2H, ArH), 5.71 (br s, 1H, NH), 4.48 (s, 2H, CH$_2$), 3.01 (s, 3H, CH$_3$), 2.29 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 148.0, 143.6, 143.3, 141.0, 130.0, 129.8, 129.6, 126.1, 121.2, 119.7, 118.0, 116.3, 116.1, 113.1, 57.3, 39.1, 20.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{21}H_{23}N_2$: 303.1856. Found: 303.1849.

Preparation of N^1-phenyl-N^2-p-tolylethane-1,2-diamine (2-5f)



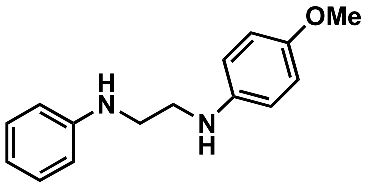
The general procedure was followed, with 4-chlorotoluene (58 μL, 0.5 mmol) and *N*-phenylethylenediamine (72 μL, 0.60 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Following removal of solvent, the resulting solid was washed with pentane (3 x 5 mL) and dried in vacuo to obtain the pure product as an off-white solid in 97 % yield (110 mg, 0.49 mmol). ^{1}H NMR ($CDCl_3$): δ 7.22 - 7.18 (m, 2 H, ArH), 7.03 – 7.00 (m, 2 H, ArH), 6.73 (tt, 1H, *J* = 7 Hz, *J* = 1 Hz, ArH), 6.67 – 6.65 (m, 2H, ArH), 6.61 – 6.58 (m, 2H, ArH), 3.39 (s, 4H, CH_2), 2.26 (s, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.3, 146.1, 130.2, 129.7, 127.4, 118.1, 113.6, 113.4, 44.0, 43.7, 20.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{19}N_2$: 227.1543. Found: 227.1535.

Preparation of *N*^{1}-phenyl-*N*^{2}-*o*-tolylethane-1,2-diamine (2-5g)



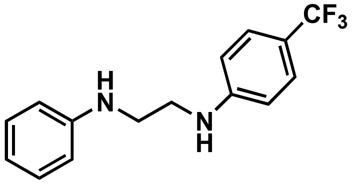
The general procedure was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a brown solid in 93 % yield (105 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.23 – 7.19 (m, 2H, ArH), 7.15 (m, 1H, ArH), 7.08 (d, 1H, *J* = 7 Hz, ArH), 6.76 (m, 1H, ArH), 6.72 – 6.68 (m, 4H, ArH), 3.98 (br s, 2H, NH), 3.46 (s, 4H, CH_2), 2.13 (s, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.2, 146.1, 130.6, 129.7, 127.5, 122.9, 118.4, 117.4, 113.5, 110.4, 43.7, 43.6, 17.9. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{19}N_2$: 227.1543. Found: 227.1539.

Preparation of ***N*^{1}-(4-methoxyphenyl)-*N*^{2}-phenylethane-1,2-diamine (2-5h)**



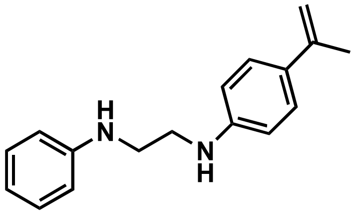
The general procedure was followed, with 4-chloroanisole (61 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (DCM) and isolated as a brown solid in 91 % yield (110 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.24 – 7.20 (m, 2H, ArH), 6.84 – 6.81 (m, 2H, ArH), 6.76 (t, 1H, *J* = 7.5 Hz, ArH), 6.68 – 6.63 (m, 4H, ArH), 3.78 (s, 3H, CH_3), 3.40 – 3.34 (m, 4 H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.7, 148.4, 142.5, 129.6, 118.0, 115.2, 114.7, 113.3, 56.1, 44.6, 43.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{19}N_2O$: 243.1492. Found: 243.1482.

Preparation of *N*^{1}-phenyl-*N*^{2}-(4-(trifluoromethyl)phenyl)ethane-1,2-diamine (2-5i).



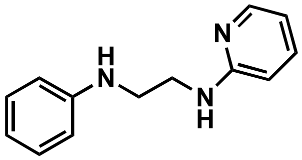
The general procedure was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of silica and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a yellow oil in 85 % yield (119 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 7.43 (d, 2H, *J* = 8.5 Hz, ArH), 7.24 – 7.21 (m, 2H, ArH), 6.78 (t, 1H, *J* = 7 Hz, ArH), 6.69 – 6.64 (m, 4H, ArH), 4.25 (br s, 1H, NH), 3.79 (br s, 1H, NH), 3.43 (s, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 148.1, 129.8, 127.0, 125.2 (q, $J_{C\text{-}F}$ = 270.5 Hz), 119.2 (q, $J_{C\text{-}F}$ = 32.7 Hz), 118.4, 113.4, 112.4, 43.4, 43.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{16}F_3N_2$: 281.1260. Found: 281.1266.

Preparation of *N*^{1}-phenyl-*N*^{2}-(4-(prop-1-en-2-yl)phenyl)ethane-1,2-diamine (2-5j)



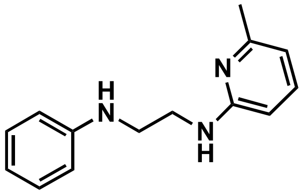
The general procedure was followed, with 4-chloro-α-methylstyrene (60 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of silica and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a brown solid in 94 % yield (119 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.42 (d, 2H, *J* = 8.5 Hz, ArH), 7.27 (t, 2H, *J* = 8 Hz, ArH), 6.82 (t, 1H, *J* = 7 Hz, ArH), 6.69 (m, 4H, ArH), 5.35 (s, 1H, CH), 5.01 (s, 1H, CH), 3.95 – 3.88 (m, NH), 3.42 (s, 4H, CH_2), 2.19 (s, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.2, 147.7, 142.9, 130.9, 129.6, 126.8, 118.1, 113.3, 112.9, 109.4, 43.5, 43.3, 22.1. HRMS (ESI/[M+H]$^+$) calcd. for $C_{17}H_{21}N_2$: 253.1699. Found: 253.1688.

Preparation of *N*^{1}-phenyl-*N*^{2}-(pyridin-2-yl)ethane-1,2-diamine (2-5k)



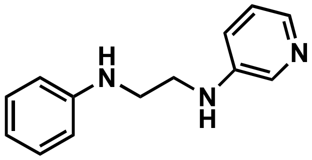
The general procedure was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a yellow oil in 91% yield (97 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 8.11 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.21 – 7.16 (m, 2H, ArH), 6.72 (m, 1H, ArH), 6.63 (m, 2H, ArH), 6.59 (m, 1H, ArH), 6.40 (m, 1H, ArH), 4.76 (br s, 1H, NH), 4.17 (br s, 1H, NH), 3.59 (t, 2 H, *J* = 6 Hz, CH_2), 3.38 (t, 2H, *J* = 6 Hz, CH_2). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.0, 148.4, 148.3, 137.7, 129.6, 117.8, 113.5, 113.2, 107.9, 44.2, 41.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{13}H_{16}N_3$: 214.1339. Found: 214.1342.

Preparation of *N*^{1}-(6-methylpyridin-2-yl)-*N*^{2}-phenylethane-1,2-diamine (2-5l)



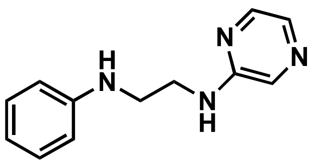
The general procedure was followed, with 2-chloro-6-methylpyridine (56 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 18 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). Removal of the solvent afforded the product as a dark yellow oil in 94 % yield (106 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 7.33 (t, 1H, *J* = 7 Hz, ArH), 7.22-7.18 (m, 2H, ArH), 6.73 (m, 1H, ArH), 6.65 – 6.63 (m, 2H, ArH), 6.49 (d, 1H, *J* = 7.5 Hz), 6.22 (d, 1H, *J* = 8 Hz, ArH), 4.77 (br s, 1H, NH), 4.38 (br s, 1H, NH), 3.55 (m, 2H, CH_2), 3.36 (m, 2H, CH_2), 2.43 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 158.7, 157.1, 148.4, 138.1, 129.5, 117.6, 113.1, 112.7, 104.0, 44.4, 41.7, 24.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{18}N_3$: 228.1495. Found: 228.1487. Agrees with: Revlee, I.; Sivakumar, R.; Muruganantham, N.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Chem. Pharm. Bull.* **2003**, *51*, 162.

Preparation of *N*^{1}-phenyl-*N*^{2}-(pyridin-3-yl)ethane-1,2-diamine (2-5m)



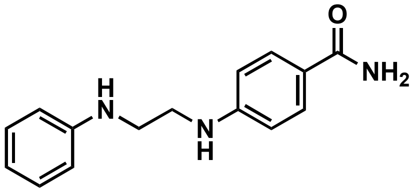
The general procedure was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a dark yellow oil in 93 % yield (99 mg, 0.47 mmol). ^{1}H NMR ($CDCl_3$): δ 8.04 (d, 1H, *J* = 8 Hz, ArH), 7.97 (dd, 1H, *J* = 4.5 Hz, *J* = 1 Hz, ArH), 7.22 – 7.18 (m, 2H, ArH), 7.08 (ddd, 1H, *J* = 8 Hz, *J* = 4.5 Hz, *J* = 0.5 Hz, ArH), 6.90 (ddd, 1H, *J* = 8.5 Hz, *J* = 3 Hz, *J* =1.5 Hz, ArH), 6.75 (m, 1H, ArH), 6.67 – 6.64 (m, 2H, ArH), 4.09 (br s, 1H, NH), 3.42 – 3.38 (m, 4 H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.1, 144.4, 139.3, 136.4, 129.7, 124.1, 119.1, 118.3, 113.3, 43.4, 43.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{16}N_3$: 214.1339. Found: 214.1338.

Preparation of *N*^{1}-phenyl-*N*^{2}-(pyrazin-2-yl)ethane-1,2-diamine (2-5n)



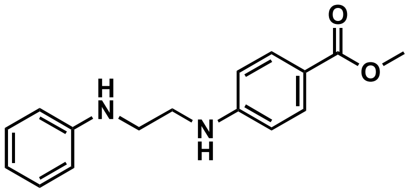
The general procedure was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow oil in 89 % yield (96 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.98 (s, 1H, ArH), 7.85 (s, 1H, ArH), 7.79 (d, 1H, *J* = 2.5 Hz, ArH), 7.18 (t, 2H, *J* = 2.5 Hz, ArH), 6.72 (t, 1H, *J* = 8.5 Hz, ArH), 6.62 (d, 2H, *J* = 7.5 Hz, ArH), 5.09 (br s, 1H, NH), 4.07 (br s, 1H, NH), 3.60 (m, 2H, CH_2), 3.38 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.9, 148.2, 142.0, 133.0, 129.6, 117.9, 113.1, 43.8, 40.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{15}N_4$: 215.1291. Found: 215.1294.

Preparation of 4-(2-(phenylamino)ethylamino)benzamide (2-5o)



The general procedure was followed, with 4-chlorobenzamide (77 mg, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 40 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with methanol (15 mL). Removal of the solvent afforded the product as a white solid in 78 % yield (100 mg, 0.39 mmol). ^1H NMR (MeOD): δ 7.72 – 7.70 (m, 2H, ArH), 7.16 – 7.12 (m, 2H, ArH), 6.71 – 6.66 (m, 5H, ArH), 4.92 (br s, NH), 3.41 – 3.35 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.7, 154.5, 150.8, 131.4, 130.9, 122.3, 119.1, 114.9, 113.2, 44.8, 44.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{18}N_3O$: 256.1444. Found: 256.1440.

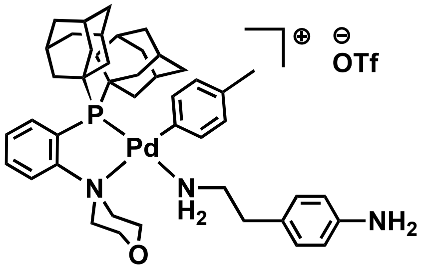
Preparation of methyl 4-(2-(phenylamino)ethylamino)benzoate (2-5p)



The general procedure was followed, methyl 4-chlorobenzoate (85 mg, 0.50 mmol) weighed out in the glovebox and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and the reaction mixture was then cooled and filtered through a layer of neutral alumina and washed with dichloromethane (15 mL). After concentrating the mixture, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a brown oil in 76 % yield (103 mg, 0.38 mmol). ^{1}H NMR ($CDCl_3$): δ 7.87 (d, 2H, *J* = 9 Hz, ArH), 7.22 – 7.16 (m, 2H, ArH), 6.76 (t, 1H, *J* = 7 Hz, ArH), 6.65 (d, 2H, *J* = 8 Hz), 6.58 (d, 2H, *J* = 8.5 Hz), 3.85 (s, 3H, CH_3), 3.45 – 3.42 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 167.6, 152.1, 148.1, 131.9, 129.7, 119.1, 118.4, 113.4, 112.0, 51.9, 43.4, 43.0. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{19}N_2O_2$: 271.1441. Found: 271.1451.

2.5.7 Preparation of 2-7, 2-8, and 2-9

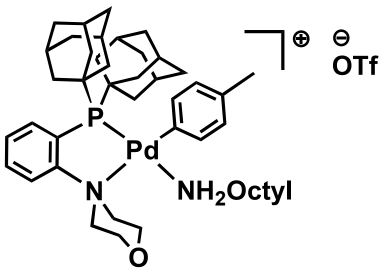
Preparation of 2-7



To a vial containing a magnetic stir bar and (Mor-DalPhos)Pd(*p*-tolyl)Cl (174 mg, 0.25 mmol) in $CDCl_3$ (2 mL) was added 4-(2-aminoethyl)aniline (66 μL, 0.50 mmol) and AgOTf (192 mg, 0.275 mmol). The reaction mixture was stirred magnetically for 2 h at room temperature, over which time a white precipitate formed. ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of starting material to a single phosphorus-containing product. The reaction mixture was filtered through Celite, and the solvent removed under reduced pressure to afford **2-7** as an analytically pure brown solid

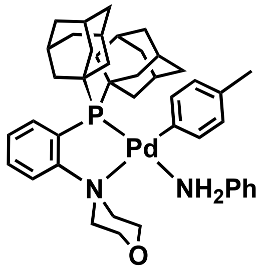
(0.171 g, 0.181 mmol, 72 %). Anal. Calcd. for $C_{46}H_{61}F_3N_3O_4P_1S_1Pd_1$: C 58.36; H 6.50; N 4.44. Found: C 58.17; H 6.34; N 4.29. Crystals suitable for X-ray diffraction were grown by vapor diffusion of diethyl ether into a concentrated solution of **2-7** in CH_2Cl_2 at -30 °C. ^1H NMR ($CDCl_3$): δ 8.07 (dd, 1H, *J* = 8 Hz, *J* = 3 Hz, ArH), 7.81 (t, 1H, *J* = 6.5 Hz, ArH), 7.67 (t, 1H, *J* = 8 Hz, ArH), 7.45 – 7.41 (m, 3H, ArH), 6.89 (d, 2H, *J* = 7.5 Hz, ArH), 6.85 (d, 2H, *J* = 7.5 Hz, ArH), 6.59 (d, 2H, *J* = 8 Hz, ArH), 4.07 – 3.96 (m, 4H, CH_2), 3.82 – 3.79 (m, 2H, CH_2), 3.66 (br s, 2H, CH_2 or NH_2), 3.18 – 3.15 (m, 2H, CH_2), 3.05 (br s, 2H, CH_2 or NH_2), 2.54 (br s, 4H, CH_2 and/or NH_2), 2.27 (s, 3H, CH_3), 2.21 (m, 6H, Ad), 1.92 (m, 12H, Ad), 1.67 (s, 12H, Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.2 (m, ArC), 145.4 (ArC), 139.7 (ArC), 137.5 (ArC), 136.3 (ArC), 133.8 (ArC), 130.0 (ArC), 128.9 (ArC), 127.3 (d, J_{PC} = 7.5 Hz, ArC), 126.9 (ArC), 126.2 (ArC), 126.0 (ArC), 119.9 (ArC), 115.9 (ArC), 62.0 (morpholino), 55.6 (morpholino), 44.6 (CH_2), 43.4 (d, J_{PC} = 15 Hz, Ad), 41.0 (Ad), 37.4 (CH_2), 36.4 (Ad), 28.7 (d, J_{PC} = 10 Hz, Ad), 21.0 (CH_3). ^{31}P NMR ($CDCl_3$): δ 62.3.

Preparation of 2-8



A protocol similar to that used for the synthesis of **2-7** was employed, using (Mor-DalPhos)Pd(*p*-tolyl)Cl (100 mg, 0.14 mmol), $CDCl_3$ (3 mL), octylamine (48 μL, 0.29 mmol) and AgOTf (41 mg, 0.16 mmol). ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of **2-6** to **2-8**. The reaction mixture was filtered through Celite and the solvent removed under reduced pressure, followed by trituration of the resulting solid with pentane (3 x 2 mL) and diethyl ether (3 x 2 mL). The remaining material was dried in vacuo to afford **2-8** as an analytically pure brown solid (0.089 g, 0.095 mmol, 66 %). Anal. Calcd. for $C_{46}H_{68}F_3N_2O_4P_1S_1Pd_1$: C 58.81; H 7.30; N 2.98. Found: C 59.06; H 7.22; N 2.95. ^1H NMR ($CDCl_3$): δ 8.12 (dd, 1H, *J* = 8 Hz, *J* = 3 Hz, ArH), 7.83 (t, 1H, *J* = 6.5 Hz, ArH), 7.70 (t, 1H, *J* = 8 Hz, ArH), 7.47 – 7.42 (m, 3H, ArH), 6.90 (d, 2H, *J* = 7.5 Hz, ArH), 4.27 – 4.24 (m, 2H, CH_2), 4.13 – 4.07 (m, 4H, CH_2), 3.24 (m, 2H, CH_2), 3.06 (br s, 2H, octylamine), 2.34 (br s, 2H, octylamine), 2.25 – 2.22 (m, 9H, CH_3 and Ad), 1.99 – 1.94 (m, 12H, Ad), 1.68 (m, 12 H, Ad), 1.38 – 1.03 (m, 15H, octylamine). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 162.2 (ArC), 140.0 (ArC), 137.5 (ArC), 136.4 (ArC), 133.8 (d, J_{PC} = 7.5 Hz, ArC), 129.4 (d, J_{PC} = 13.8 Hz, ArC), 129.0 (ArC), 127.1 (m, ArC), 126.2 (d, J_{PC} = 28.9 Hz, ArC), 62.5 (morpholino), 55.9 (morpholino), 43.5 (d, J_{PC} = 15.1 Hz, Ad), 43.2 (CH_2), 41.0 (Ad), 36.4 (Ad), 32.4 (CH_2), 32.1 (CH_2), 29.4 – 29.3 (m, CH_2), 28.8 (d, J_{PC} = 10.1 Hz, Ad), 26.6 (CH_2), 22.9 (CH_2), 21.0 (CH_3), 14.4 (CH_3). ^{31}P NMR ($CDCl_3$): δ 62.2.

Preparation of 2-9



A protocol directly analogous to that used for the synthesis of **2-8** was employed, using aniline (26 μL, 0.29 mmol) in place of octylamine. ^{31}P NMR analysis of the crude reaction mixture indicated complete conversion of **2-6** to **2-9**, and **2-9** was obtained as an analytically pure brown solid (0.083 g, 0.092 mmol, 64 %). Anal. Calcd. for $C_{44}H_{56}F_3N_2O_4P_1S_1Pd_1$: C 58.50; H 6.20; N 3.10. Found: C 58.54; H 6.17; N 3.02. ^{1}H NMR ($CDCl_3$): δ 8.20 (m, 1H, ArH), 7.83 (t, 1H, *J* = 7 Hz, ArH), 7.64 (t, 1H, *J* = 7.5 Hz), 7.44 – 7.39 (m, 4H, ArH), 7.15 (t, 1H, *J* = 8 Hz, ArH), 6.82 (d, 2H, *J* = 8 Hz, ArH), 6.77 (t, 1H, *J* = 7 Hz, ArH), 6.70 (d, 2H, *J* = 15 Hz, ArH), 5.01 (br s, 2H, NH_2), 4.06 – 3.99 (m, 4H, morpholino), 3.74 (br s, 2H, morpholino), 2.98 (br s, 2H, morpholino), 2.29 – 2.28 (m, 6 H, Ad), 2.22 (s, 3H, CH_3), 1.99 – 1.69 (m, 24 H, Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 138.6 (ArC), 136.4 (ArC), 132.9 (ArC), 129.6 (ArC), 128.7 (ArC), 128.0 (ArC), 126.3 (ArC), 119.1 (ArC), 115.8 (ArC), 62.1 (morpholino), 55.2 (morpholino), 43.6 (d, J_{PC} = 16.4 Hz, Ad), 40.9 (Ad), 36.5 (Ad), 28.9 (d, J_{PC} = 10.1 Hz, Ad), 21.1 (CH_3). ^{31}P NMR ($CDCl_3$): δ 59.8.

Crystallographic Solution and Refinement Details for *p*-MorDalPhos (L2) and 2-7•CH_2Cl_2

Crystallographic data were obtained at 173(±2) K on a diffractometer using a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer. Gaussian integration (face-indexed) was employed as the absorption correction method. The structure of p-MorDalPhos (**L2**) was solved by use of direct methods, while the structure of **2-7**•CH_2Cl_2 was solved by use of a Patterson search/structure expansion. The structures were refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. Anisotropic displacement parameters were employed for all the non-hydrogen atoms. Disorder involving the two *C*H_2-O carbon atoms as well as the nitrogen atom in **L2** was identified during the solution process; these atoms were each refined anisotropically over two positions employing an occupancy factor of 0.5. During the structure solution process for **2-7**•CH_2Cl_2, one equivalent of dichloromethane was located in the asymmetric unit and refined anisotropically. Furthermore, disorder involving one of the adamantyl substituents was identified during the solution process for **2-7**•CH_2Cl_2; these atoms were each refined anisotropically over two positions employing an occupancy factor ratio of 0.4:0.6. During the refinement, the P–C21A and P–C21B distances were constrained to be equal (within 0.03 Å), and the C21A–C22A, C21A–C26A, C21A–C27A, C21B–C22B, C21B–C26B, and C21B–C27B distances were constrained to be equal (within 0.03 Å) to a common refined value. For simplicity, only the major disorder components of **L2** and **2-7**•CH_2Cl_2 are depicted and discussed in the text. All hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom. Additional crystallographic information is provided in Table 2.6.

Table 2.6 Crystallographic Data for L2 and 2-7• CH_2Cl_2

	L2	**2-7• CH_2Cl_2**
Empirical formula	$C_{30}H_{42}NOP$	$C_{47}H_{63}Cl_2F_3N_3O_4PPdS$
Formula weight	463.62	1031.33
Crystal dimensions	0.36 x 0.35 x 0.19	0.41 × 0.31 × 0.26
Crystal system	triclinic	triclinic
Space group	$P1$	$P1$
a (Å)	10.2665 (6)	10.6924 (7)
b (Å)	11.0209 (6)	12.4945 (8)
c (Å)	12.1446 (7)	18.4352 (12)
α (deg)	67.6814 (7)	102.5936 (7)
β (deg)	81.4590 (7)	96.5551 (8)
γ (deg)	79.9256 (7)	96.1075 (7)
V (Å^3)	4304.0 (7)	2365.9 (3)
Z	2	2
ρ_{calcd} (g cm^{-3})	1.235	1.448
μ (mm^{-1})	0.134	0.641
Range of transmission	0.9745–0.9538	0.8531–0.7782
2θ limit (deg)	55.24	54.98
	$-13 \leq h \leq 13$	$-13 \leq h \leq 13$
	$-14 \leq k \leq 14$	$-16 \leq k \leq 16$
	$-15 \leq l \leq 15$	$-23 \leq l \leq 23$
Total data collected	11062	21291
Independent reflections	5699	10798
R_{int}	0.0179	0.0103
Observed reflections	4727	10218
Data/restraints/parameters	5699 / 0 / 325	10798/ 7 / 645
Goodness-of-fit	1.042	1.066
$R1$ $[F_o^2 \geq 2\sigma(F_o^2)]$	0.0437	0.0308
$wR2$ $[F_o^2 \geq -3\sigma(F_o^2)]$	0.1232	0.0888
Largest peak, hole (eÅ^{-3})	0.610, –0.355	0.876, –1.307

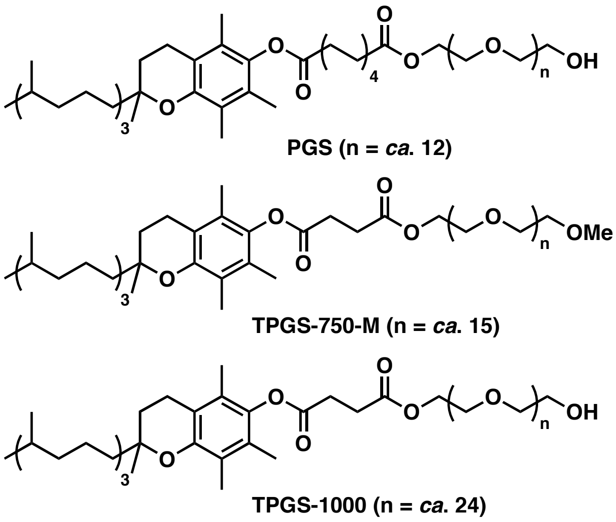
CHAPTER 3. BUCHWALD-HARTWIG AMINATIONS CONDUCTED UNDER AQUEOUS AND SOLVENT-FREE CONDITIONS

3.1. Introduction

The establishment of Buchwald-Hartwig amination chemistry as a means of constructing arylamines on both benchtop and industrial scales has led to significant attention being directed toward evaluating how the choice of base, palladium precursor, and ancillary co-ligand influences the outcome of these reactions. [15, 22, 61-64]As a result, a number of extremely effective classes of catalysts for Buchwald-Hartwig amination have been identified that offer broad substrate scope and excellent functional group tolerance at relatively low catalyst loadings, including for the cross-coupling of more abundant, but less reactive, (hetero)aryl chloride substrates.

In recent years, increased emphasis has been placed on performing synthetic chemistry under 'green' conditions.[86] Although the use of transition metal catalysts is in itself green (as opposed to employing stoichiometric reagents), performing reactions with minimal waste (whether due to protection steps, workup, or byproduct formation) and using environmentally benign solvents such as water are increasingly desirable goals. Given the established reactivity benefits that can be derived from conducting other metal-catalyzed coupling reactions in or on water,[87-91] and in light of the emphasis that has been placed on performing synthetic chemistry in more environmentally benign media,[86, 92, 93] it is surprising that little attention has been given to the study of Buchwald-Hartwig aminations conducted under strictly aqueous conditions.

A breakthrough in this area was disclosed by Buchwald and co-workers in 2003,[39] who reported the use of Pd/XPhos pre-catalyst mixtures for the cross-coupling of (hetero)aryl (pseudo)halides, albeit with a limited substrate scope (9 examples, 1 mol % Pd and 1-2.5 mol % XPhos, 84-96 %). Additionally, the advancement of aqueous Buchwald-Hartwig amination protocols has benefitted from the use of supported catalysts, [94-96] as well as the application of additives including co-solvents,[97, 98] and surfactants[99, 100] (Figure 3.1), the latter of which aggregate in water to form hydrophobic 'pockets' within which organic molecules and catalysts are able to interact, thus circumventing the limitation of many organic molecules in water. However, the demonstrated substrate scope exhibited by both supported catalyst systems and those employing surfactants is often limited in terms of the diversity of amine substrates employed, as well as the dearth of examples involving (hetero)aryl chlorides.



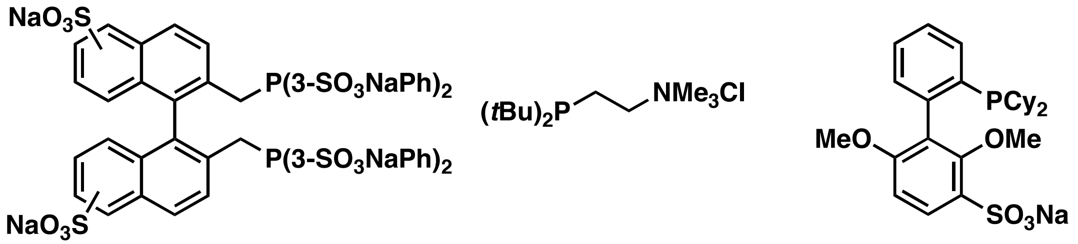
PGS (n = *ca*. 12)

TPGS-750-M (n = *ca*. 15)

TPGS-1000 (n = *ca*. 24)

Figure 3.1 Selected Examples of Surfactants Employed in Pd-Mediated Catalysis

It is worth noting that the modification of established ancillary ligands with hydrophilic substituents that render the resultant metal catalyst soluble in water has been employed successfully in the pursuit of increasingly effective catalysts for use in aqueous media (Figure 3.2).[89, 90]



BINAS-6 ***t*Bu-Amphos** **Sulfonated-SPhos**

Figure 3.2 Selected Examples of Ligands Employed in Cross-Coupling Conducted in Aqueous Media

Although the application of such hydrophilic ligands in Buchwald-Hartwig amination chemistry has received scant attention, one could envision the potential benefits of employing such ligands in terms of enabling catalyst recovery and recycling under biphasic conditions. However, this approach is not without drawbacks, in that the appending of hydrophilic addenda onto a ligand whose structure has been optimized so as to offer desirable catalytic performance can alter the behavior of the resulting catalyst, often in ways that cannot easily be predicted *a priori*.[87, 89, 90] Moreover, the preparation of tailor-made ligands for use in water can represent a practical impediment to the broader implementation of more environmentally friendly aqueous protocols, including in Buchwald-Hartwig amination chemistry.

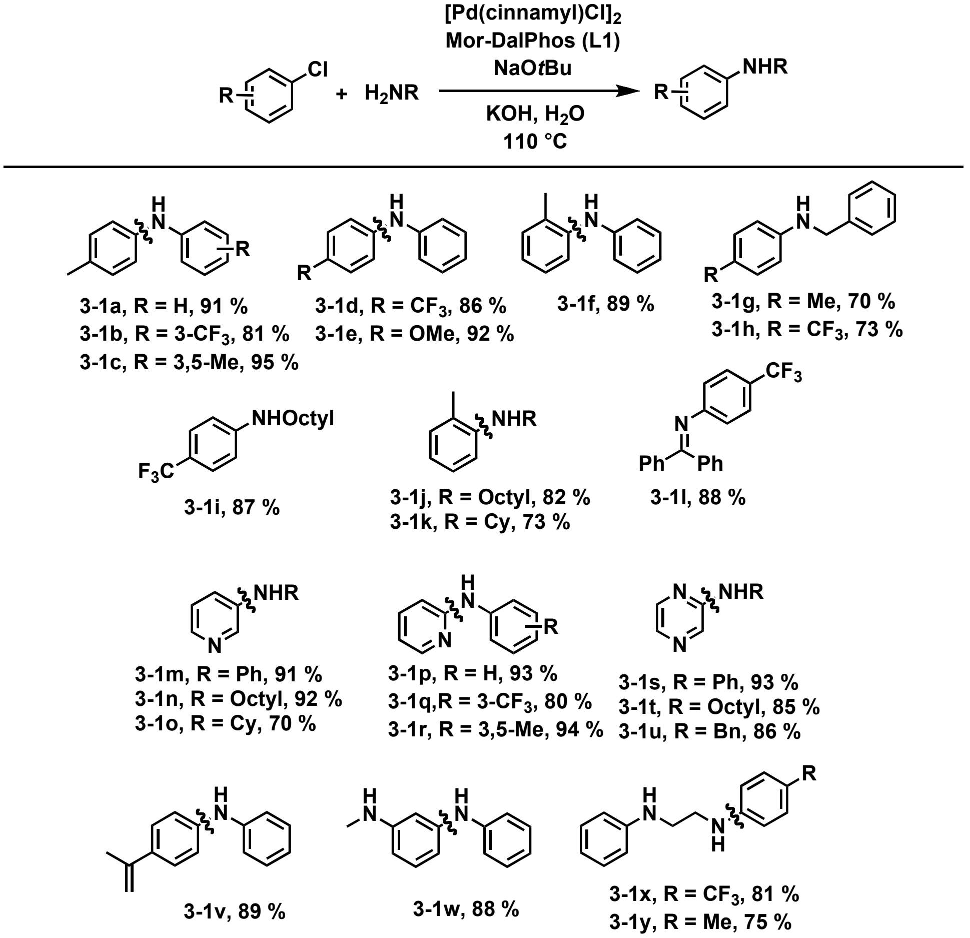
In this regard, the investigation of Buchwald-Hartwig aminations conducted under strictly aqueous conditions without the use of additives, and employing unmodified, commercially available catalyst systems that have an established track-record of desirable catalytic performance under non-aqueous conditions, represents an important avenue of inquiry in the quest to advance green chemistry concepts. Such a catalyst system would represent an easily implemented and cost-effective green alternative to conducting reactions in organic solvents. Moreover, from a practical point of view, a single ligand that can be employed in both organic and aqueous Buchwald-Hartwig aminations (with a broad substrate scope) is significantly more desirable than purchasing or synthesizing an array of ligands to accommodate varying conditions and substrates.

As illustrated in Chapters 1 and 2, the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst has proven useful for the monoarylation of ammonia[58] and hydrazine,[59] as well for chemoselective Buchwald-Hartwig aminations conducted in organic media. In the context of the considerations outlined above, and having demonstrated that this catalyst system offers excellent performance in Buchwald-Hartwig amination chemistry employing a broad array of amine and (hetero)aryl chloride coupling partners, a study exploring the behavior of this commercially available catalyst system under strictly aqueous conditions, as well as under solvent-free (neat) conditions, was initiated. The results of these studies are reported herein, and include the observation that the desirable catalytic performance exhibited by the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system for the cross-coupling of primary or secondary amines with (hetero)aryl chlorides is retained in aqueous media, and also under solvent-free conditions. It is also established that reactions of this type can be conducted without the rigorous exclusion of air, and in the case of solvent-free reactions, that appropriately selected liquid and solid reagents can be employed successfully.

3.2. Results and Discussion

Initial efforts to survey the utility of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system in Buchwald-Hartwig amination chemistry conducted under strictly aqueous conditions (i.e. in the absence of additives such as co-solvents or surfactants) focused on the arylation of aniline using the unhindered and modestly deactivated substrate 4-chlorotoluene. Gratifyingly, under reasonable catalyst loadings (3 mol % Pd, unoptimized) the desired cross-coupling product **3-1a** (Table 3.1) was obtained in 91 % isolated yield. While for convenience the catalytic reaction mixtures for the studies reported herein are typically prepared within a dinitrogen-filled glovebox, followed by the addition of non-degassed distilled water to the sealed (dinitrogen-filled) reaction vessel, it was found that the preparation of **3-1a** could alternatively be conducted under air with negligible impact on catalytic performance. No conversion to **3-1a** was achieved in control experiments in which either [Pd(cinnamyl)Cl]$_2$ or **L1** was excluded from the reaction mixture.

Table 3.1 Arylation of Primary Amines Under Aqueous Conditions



3-1a, R = H, 91 %
3-1b, R = 3-CF$_3$, 81 %
3-1c, R = 3,5-Me, 95 %
3-1d, R = CF$_3$, 86 %
3-1e, R = OMe, 92 %
3-1f, 89 %
3-1g, R = Me, 70 %
3-1h, R = CF$_3$, 73 %
3-1i, 87 %
3-1j, R = Octyl, 82 %
3-1k, R = Cy, 73 %
3-1l, 88 %
3-1m, R = Ph, 91 %
3-1n, R = Octyl, 92 %
3-1o, R = Cy, 70 %
3-1p, R = H, 93 %
3-1q,R = 3-CF$_3$, 80 %
3-1r, R = 3,5-Me, 94 %
3-1s, R = Ph, 93 %
3-1t, R = Octyl, 85 %
3-1u, R = Bn, 86 %
3-1v, 89 %
3-1w, 88 %
3-1x, R = CF$_3$, 81 %
3-1y, R = Me, 75 %

Reagents and conditions: ArCl:Amine:KOH = 1:1.1:1.2, 8 mol % NaO*t*Bu (for use in catalyst activation), 3 mol % Pd, Pd:**L1** = 1:2, H$_2$O, 110 °C, nominal [ArCl] = 2.0 M. All reactions on 0.5 mmol scale with reaction times of 12-36 h (unoptimized); yields are of isolated material.

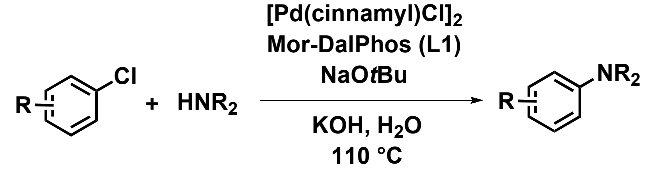
With this promising result in hand, we sought to explore the scope of this chemistry with both primary (Table 3.1) and secondary (Table 3.2) amines.

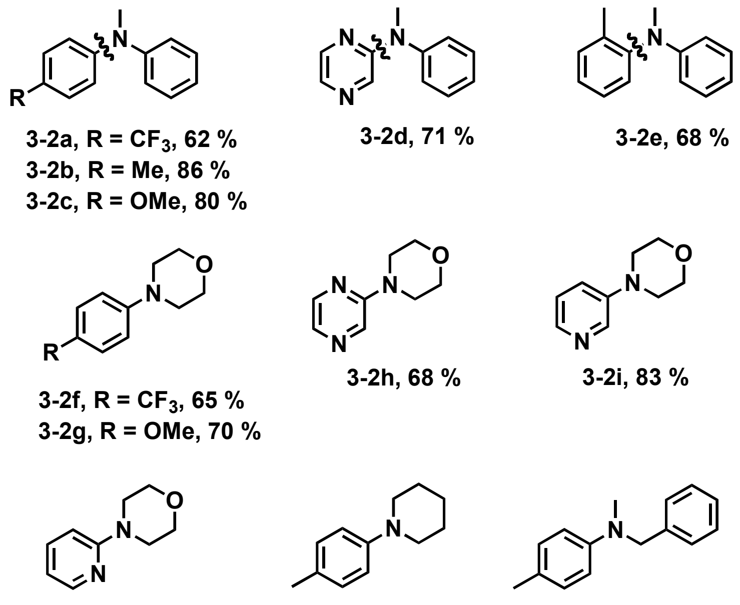
Electronically activated and deactivated unhindered aryl chlorides proved to be suitable coupling partners when paired with anilines (**3-1a-e**, 81–95 %); this trend also held for benzylamine (**3-1g**, 70 %; **3-1h** 73 %). *Ortho*-substituted aryl chlorides were also found to be suitable reaction partners, including in combination with aniline (**1f**, 89 %), octylamine (**3-1j**, 82 %) and cyclohexylamine (**3-1k**, 73 %). Using the same protocol, benzophenone imine was found to be a good amine coupling partner (**1l**, 88 %), and 2-chloropyridine, 3-chloropyridine and 2-chloropyrazine were cross-coupled successfully with anilines (**3-1m**, **3-1p-s**), octylamine (**3-1n**, **3-1t**), cyclohexylamine (**3-1o**) and benzylamine (**3-1u**) in good to excellent yields (70-93 %). The presence of an alkene functional group was also tolerated under these reaction conditions, enabling the isolation of **3-1v** in high yield (89 %).

The study presented in Chapter 2 has established the utility of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system in chemoselective Buchwald-Hartwig aminations conducted under non-aqueous conditions, whereby primary amines are preferentially arylated in the presence of competitor secondary amine fragments. While this trend holds under the aqueous conditions surveyed herein (3 mol % Pd, water, KOH), allowing for the isolation of the primary amine monoarylation products **3-1w** (88 %), **3-1x** (81 %), and **3-1y** (75 %), the use of aqueous reaction conditions results in a lower yield of the target complex, despite the use of higher catalyst loading.

Despite the preference of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system for primary amine subtrates, secondary amines can also undergo arylation under aqueous conditons (Table 3.2).

Table 3.2 Arylation of Secondary Amines Under Aqueous Conditions





3-2a, R = CF$_3$, 62 %
3-2b, R = Me, 86 %
3-2c, R = OMe, 80 %

3-2d, 71 %

3-2e, 68 %

3-2f, R = CF$_3$, 65 %
3-2g, R = OMe, 70 %

3-2h, 68 %

3-2i, 83 %

3-2j,76 %

3-2k, 70 %

3-2l, 71 %

Reagents and conditions: ArCl:Amine:KOH = 1:1.1:1.2, 8 mol % NaO*t*Bu (for use in catalyst activation), 3 mol % Pd, Pd:**L1** = 1:2, H_2O, 110 °C, nominal [ArCl] = 2.0 M. All reactions on 0.5 mmol scale with reaction times of 12-36 h (unoptimized); yields are of isolated material.

N-methylaniline was found to be a suitable cross-coupling substrate under aqueous conditions when paired with electronically activated or deactivated unhindered aryl chlorides (**3-2a-c**, 62-86 %), 2-chloropyrazine (**3-2d**, 71 %), or 2-chlorotoluene (**3-2e**, 68 %). Morpholine, piperidine, and *N*-methyl benzylamine also proved to be suitable cross-coupling substrates in combination with electronically activated and deactivated unhindered aryl chlorides, as well as heteroaryl chlorides (**3-2f-l**, 65-83 %). The capacity of the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system to accomodate both primary and secondary amines under aqueous conditions is attractive from a practical perspective, given current interest in the establishment of Buchwald-Hartwig amination catalyst systems that can operate across both amine substrate classes. Furthermore, the viability of conducting such catalytic transformations under benchtop conditions was established in the aforementioned preparation of the representative substrates **3-1h**, **3-1j**, **3-1x**, **3-1y**, and **3-2k**, where the reactions were conducted under air, rather than an atmosphere of dry dinitrogen. Unfortunately, organic solvents are required in order to isolate and purify the arylamine products described herein, which is a drawback in terms of the chemistry being truly 'green'. However, this could be circumvented on an industrial scale by using supercritical CO_2 to extract the products, essentially eliminating the need for organic solvents altogether.

It is not possible to comment definitively regarding the nature of the aqueous reaction chemistry described herein (e.g. homogeneous versus heterogeneous; in versus on water). However, a preliminary assessment of the solubility of **L1**, whereby 50 mg of the ligand was stirred in 1 mL of distilled water for 48 h at ambient temperature followed by filtration and removal of the water in vacuo, revealed negligible quantities of dissolved ligand.

Despite the considerable interest in carrying out synthetic organic transformations in the absence of added solvent,[101,102] little attention has been paid to the development of synthetically useful solvent-free Buchwald-Hartwig amination protocols. Such protocols are attractive, not only in terms of advancing green chemistry concepts, but also in terms of allowing for the possible application of a more wide range of bases in such catalytic chemistry, relative to reactions conducted under aqueous conditions. Noteworthy reports in this area include the work of Yoshifuji and co-workers,[103] who describe the application of a Pd pre-catalyst featuring a diphosphinidenecyclobutene ancillary ligand (DPCB,

Figure 3.3) for use in the solvent-free amination of aryl bromides at room temperature, although with a limited substrate scope. Additionally, Beccalli and co-workers,[104] have reported the use of solvent-free Buchwald-Hartwig amination methods employing IAPU as a ligand (Figure 3.3) with microwave heating for the preparation of a series of substituted *N*-aryl indolines employing aryl bromides, chlorides, and iodides, though these transformations are limited to indole substrates (Figure 3.3).

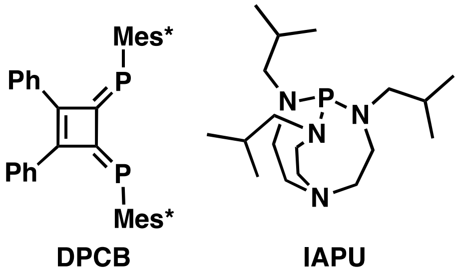
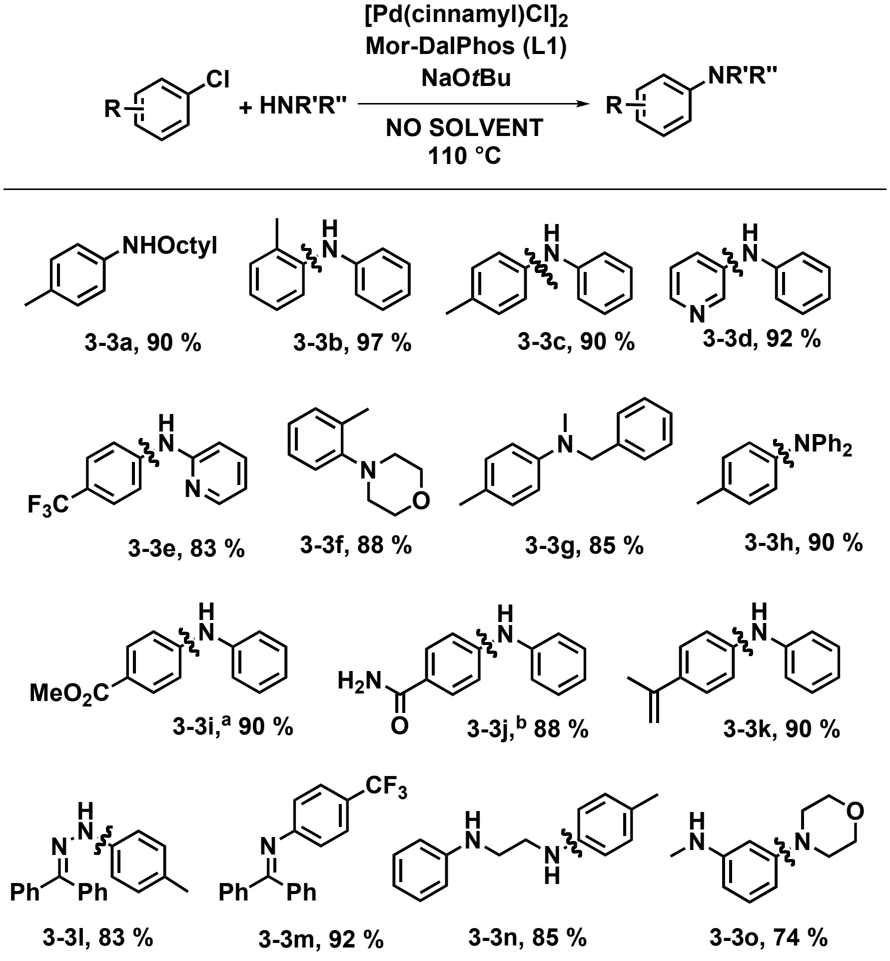


Figure 3.3 Ligands Previously Employed in Solvent-Free Buchwald-Hartwig Aminations

The results of the experimentation directed toward utilizing the [Pd(cinnamyl)Cl]$_2$/**L1** catalyst system for Buchwald-Hartwig amination reactions conducted under solvent-free conditions are collected in Table 3.3. Notably, a range of amine and aryl chloride coupling partners can be employed, including examples featured in the aqueous reactivity survey (**3-3b**, **3-3c**, **3-3d**, **3-3g**, **3-3k**, **3-3m**, **3-3n**), as well as substrate pairings that were found to be incompatible with the aqueous conditions (**3-3h**, **3-3l**). Primary amines were coupled with hindered and unhindered tolyl chlorides in excellent yield (**3-3a-c**, 90-97 %). In addition, 3-chloropyridine proved to be a suitable reaction partner with aniline (**3-3d**, 92 %), affording the resultant product in high yield that is comparable to that obtained under the aqueous protocol (Table 3.1). The successful cross-coupling of 2-aminopyridine and 4-trifluoromethyl-chlorobenzene to give **3-3e** in

83 % isolated yield demonstrates that room temperature solids can successfully be employed as substrates under this solvent-free protocol.

Table 3.3 Arylation of Primary and Secondary Amines Under Solvent-Free Conditions



Reagents and conditions: Unless stated otherwise, ArCl:Amine:NaO*t*Bu = 1:1.1:1.4, 3 mol % Pd, Pd:**L1** = 1:2, 110 °C. [a]ArCl:Amine:K_2CO_3 = 1:1.1:1.2, 8 mol % NaO*t*Bu (for use in catalyst activation), 3 mol % Pd, Pd:**L1** = 1:2, 110 °C. [b]ArCl:Amine:LiHMDS = 1:1.1:2.1, 8 mol % NaO*t*Bu (for use in catalyst activation), 3 mol % Pd, Pd:**L1** = 1:2, 110 °C. All reactions on 0.5 mmol scale with reaction times of 12-36 h (unoptimized); yields are of isolated material.

Secondary amines are also viable substrates in this chemistry, as demonstrated in the case of morpholine (**3-3f**, 88 %), *N*-methyl benzylamine (**3-3g**, 85 %), and diphenylamine (**3-3h**, 90 %). The ability to employ alternative bases such as K_2CO_3 or

LiHMDS under these solvent-free conditions allowed for aryl chloride substrates containing base sensitive functional groups (esters, amides) to be employed, as demonstrated by the high-yielding formation of **3-3i** (90 %) and **3-3j** (88 %). In keeping with reactions conducted in organic and aqueous media, the presence of an alkene functional group within the aryl chloride was tolerated under solvent-free conditions, affording **3-3k** (90 %). Benzophenone hydrazone was unsuccessfully employed as a substrate under aqueous conditions, with negligible product formation observed by use of GC methods. However, under solvent-free conditions this proved to be a viable substrate in combination with 4-chlorotoluene, giving **3-3l** (83 %), thereby further demonstrating the utility of this solvent-free procedure. Benzophenone imine was also successfully arylated under solvent-free conditions with 4-chlorobenzotrifluoride, affording the target product in high yield (**3-3m**, 92 %). The propensity of the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system to promote chemoselective Buchwald-Hartwig aminations at primary amine sites within diamine substrates in organic and aqueous media is maintained under these solvent free conditions (**3-3n**, 85 %). Moreover, 3-chloro-*N*-methylaniline was successfully aminated in a chemoselective fashion by use of morpholine (**3-3o**, 74 %), in keeping with the tendency of the $[Pd(cinnamyl)Cl]_2$/**L1** catalyst system for uptake of the more electron-rich amine substrate that binds more efficiently when two sterically comparable secondary amine species are in competition. As was noted for reactions conducted under aqueous conditions, the viability of utilizing benchtop reaction protocols was confirmed in the aforementioned preparation of the representative substrates **3-3d** and **3-3f**, where the reactions were conducted under air.

3.3. Summary

The results presented herein establish that the commercially available [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**) catalyst system is effective for the cross-coupling of (hetero)aryl chlorides and primary or secondary amines under aqueous conditions without the use of additives (e.g. co-solvents or surfactants), or structural modifications, and also under solvent-free (neat) conditions. This study represents the most extensive compilation of such reactivity to be reported thus far in the literature. An array of activated and deactivated (hetero)aryl chlorides can be employed as substrates in combination with aryl and aliphatic amines (both primary and secondary), employing reasonable catalyst loadings and without the rigorous exclusion of air. Included in the substrate scope are examples of functionalized and base-sensitive substrates, as well as chemoselective transformations leading to arylated diamine products, whereby the observed chemoselectivity parallels that achieved in organic media. Althought the use of organic solvents to isolate the products obtained under aqueous conditions is less than ideal, the fundamental issue of conducting the catalysis under aqueous conditions has been addressed, and on larger scales, other methods (such as the aforementioned use of supercritical CO_2) of isolating the organic products can be employed.

As shown in Chapters 1 and 2, the [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**) catalyst system offers broad reactivity for both the monoarylation of challenging substrates like ammonia and hydrazine, as well as good selectivity for a broad range of chemoselective Buchwald-Hartwig aminations. With the results presented in Chapter 3, the scope of utility of this catalyst system has been further expanded to Buchwald-Hartwig aminations conducted under aqueous and solvent-free conditions, with the chemistry (at least in some instances) not requiring the rigorous exclusion of air, thereby addressing the issue of catalyst generality in these reactions. The fact that a single, unmodified, and commercially available ligand such as Mor-DalPhos (**L1**) is able to promote all of these transformations is especially noteworthy, and has not yet been reported in the literature, further adding to the utility and generality of the catalyst system.

3.4. Experimental

3.4.1 General Considerations

Unless noted, all reactions were set up inside a dinitrogen-filled, inert atmosphere glovebox, while the organic products of the catalytic reactions were isolated following workup by using standard benchtop conditions. Deuterated solvents (Cambridge Isotopes) were used as received. Mor-DalPhos (**L1**),[58] and [Pd(cinnamyl)Cl]$_2$,[81] were prepared according to literature procedures. All other reagents, solvents (including those used on the benchtop), and materials were used as received from commercial sources. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle). GC data were obtained on a Shimadzu GC-2014 equipped with a SGE BP-5 30 m, 0.25 mm I.D. column. Stated yields correspond to isolated products. ^{1}H and ^{13}C NMR characterization data were collected at 300K on a Bruker AV-500 spectrometer operating at 500.1 Hz and 125.8 Hz (respectively) with chemical shifts reported in parts per million downfield of SiMe$_4$.

General Procedure A: Aqueous Catalytic Reactions

Within an inert atmosphere glovebox, [Pd(cinnamyl)Cl]$_2$ (3 mol % Pd) and Mor-DalPhos (6 mol %) were combined in a vial, along with a stir bar, KOH (34 mg, 0.60 mmol) and

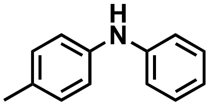
NaO*t*Bu (8 mol %). While selected control experiments confirmed that the reactions can be conducted successfully without added NaO*t*Bu, a catalytic amount of NaO*t*Bu (despite the short lifetime associated with the butoxide anion in water) was added to the reaction in the event that this might assist in catalyst activation very early in the reaction for given substrate pairings. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox; reagents were added in the glovebox for convenience, or on the bench top (for **1h**, **1j**, **1x**, **1y**, and **2k**) via a microlitre syringe (as needed), as was distilled water (0.25 mL). Reaction mixtures were heated at 110 °C for 12-36 h (times not optimized) and the consumption of the aryl chloride was confirmed by use of GC methods. The reaction mixture was then cooled, opened to air, and Et_2O (5 mL) was added to the vial. The reaction mixture was then filtered through a layer of neutral alumina, which was then washed with DCM (5 mL) and MeOH (5 mL). Following removal of solvent, the crude product was purified via column chromatography on silica, and characterized by using ^1H NMR and ^{13}C NMR methods, as well as HRMS (for new compounds).

General Procedure B: Solvent Free Catalytic Reactions

Within an inert atmosphere glovebox, $[Pd(cinnamyl)Cl]_2$ (3 mol % Pd) and Mor-DalPhos (6 mol %) were combined in a vial, along with a stir bar and NaO*t*Bu (67 mg, 0.7 mmol). The vial was sealed with a cap containing a PTFE septum and removed from the glovebox; reagents were added in the glovebox for convenience, or on the bench top (for **3d** and **3f**) via a microlitre syringe (as needed). Reaction mixtures were heated at 110 °C for 12-36 h (times not optimized) and the consumption of the aryl chloride was confirmed by use of GC methods. The reaction mixture was then cooled, opened to air, and DCM (5 mL) was added to the vial. The reaction mixture was then filtered through a layer of neutral alumina, which was then washed with DCM (5 mL) and MeOH (5 mL). Following removal of solvent, the crude product was purified via column chromatography on silica, and characterized by using ^{1}H NMR and ^{13}C NMR methods, as well as HRMS (for new compounds).

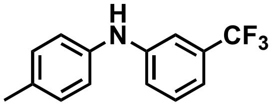
3.4.2 Preparation of Compounds From Table 3.1

Preparation of 4-methyl-*N*-phenylaniline (3-1a)



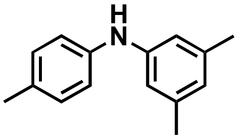
General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an off-white solid in 91 % yield (84 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 7.33 – 7.29 (m, 2H, ArH), 7.16 (d, 2H, J = 8.5 Hz, ArH), 7.09 – 7.06 (m, 4H, ArH), 6.98 – 6.94 (m, 1H, ArH), 5.64 (br s, 1H, NH), 2.38 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.2, 140.6, 131.2, 130.2, 129.6, 120.6, 119.2, 117.1, 21.0. Agrees with: Liu, X.; Zhang, S. *Synlett* **2011**, 1137.

Preparation of *N*-*p*-tolyl-3-(trifluoromethyl)aniline (3-1b)



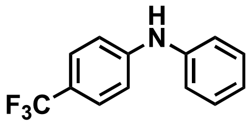
General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and 3-CF_3-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an off-white solid in 81 % yield (102 mg, 0.41 mmol). ^{1}H NMR (CDCl$_3$): δ 7.33 (t, 1H, *J* = 8 Hz, ArH), 7.22 (s, 1H, ArH), 7.17 (d, 2H, *J* = 8.5 Hz, ArH), 7.15 – 7.11 (m, 2H, ArH), 7.07 – 7.05 (m, 2H, ArH), 5.73 (br s, 1H, NH), 2.37 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 145.2, 139.3, 132.7, 132.0 (q, J_{CF} = 32.7 Hz), 130.4, 130.1, 124.5 (q, J_{CF} = 271.7 Hz), 120.5, 119.2, 116.5 (q, J_{CF} = 3.8 Hz), 112.6 (q, J_{CF} = 3.8 Hz), 21.1. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{13}F_3N$: 252.0995. Found: 252.1000

Preparation of 3,5-dimethyl-*N*-*p*-tolylaniline (3-1c)



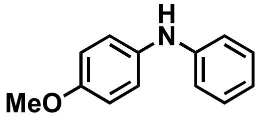
General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and 3,5-Me-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an orange solid in 95 % yield (100 mg, 0.48 mmol). ^{1}H NMR (CDCl$_3$): δ 7.16 – 7.14 (m, 2H, ArH), 7.06 – 7.05 (m, 2H, ArH), 6.71 (s, 2H, ArH), 6.62 (s, 1H, ArH), 5.57 (br s, NH), 2.38 (s, 3H, CH$_3$), 2.33 (s, 6H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 144.2, 140.8, 139.3, 130.9, 130.1,122.5, 119.3,114.9, 21.7, 21.0. Agrees with: Liu, X.; Zhang, S. *Synlett* **2011**, 1137.

Preparation of *N*-phenyl-4-(trifluoromethyl)aniline (3-1d)



General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as an off-white solid in 86 % yield (100 mg, 0.43 mmol). ^{1}H NMR (CDCl$_3$): δ 7.49 (d, 2H, *J* = 8.5 Hz, ArH), 7.38 – 7.33 (m, 2H, ArH), 7.18 – 7.15 (m, 2H, ArH), 7.10 – 7.05 (m, 3H, ArH), 5.91 (br s, 1H, NH). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 147.2, 141.5, 129.9, 127.0 (q, J_{CF} = 2.5 Hz), 125.0 (q, J_{CF} = 270.5 Hz), 123.3, 121.9 (q, J_{CF} = 32.7 Hz), 120.4, 115.7. Agrees with: Xie, X.; Ni, G.; Ma, F.; Ding, L.; Xu, S.; Zhang, Z. *Synlett* **2011**, 955.

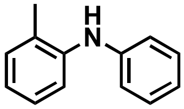
Preparation of 4-methoxy-*N*-phenylaniline (3-1e)



General procedure A was followed, with 4-chloroanisole (61 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as an off-white solid in 92 % yield (92 mg, 0.46 mmol). ^{1}H NMR (CDCl$_3$): δ 7.31 – 7.27 (m, 2H, ArH), 7.16 – 7.13 (m, 2H, ArH), 6.99 – 6.89 (m, 5H, ArH), 5.56 (br s, 1H, NH), 3.87 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR

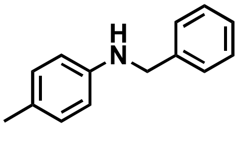
($CDCl_3$): δ 155.5, 145.4, 136.0, 129.6, 122.5, 119.8, 115.9, 114.9, 55.8. Agrees with: Louie, J.; Driver, M. S; Hamann, B.C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

Preparation of 2-methyl-*N*-phenylaniline (3-1f)



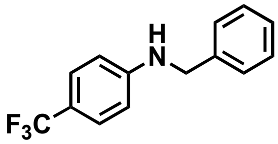
General procedure A was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an off-white solid in 89 % yield (81 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.36 – 7.32 (m, 3H, ArH), 7.29 (d, 1H, J = 7.5 Hz, ArH), 7.23 (m, 1H, ArH), 7.05 – 6.98 (m, 4H, ArH), 5.44 (br s, 1H, NH), 2.34 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.3, 141.5, 131.2, 129.6, 128.6, 127.1, 122.3, 120.7, 119.1, 117.7, 18.2. Agrees with: Louie, J.; Driver, M. S; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

Preparation of *N*-benzyl-4-methylaniline (3-1g)



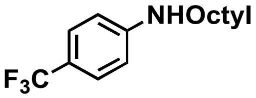
General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and benzylamine (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (20:1 hex:EtOAc), and isolated as a yellow oil in 70 % yield (69 mg, 0.35 mmol). ^{1}H NMR (CDCl$_3$): δ 7.44 – 7.38 (m, 4H, ArH), 7.33 (m, 1H, ArH), 7.06 – 7.01 (m, 2H, ArH), 6.64 – 6.61 (m, 2H, ArH), 4.36 (s, 2H, CH$_2$), 3.95 (br s, 1H, NH), 2.31 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 146.2, 139.9, 130.1, 128.9, 127.8, 127.4, 127.0, 113.3, 48.9, 20.7. Agrees with: Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

Preparation of *N*-benzyl-4-(trifluoromethyl)aniline (3-1h)



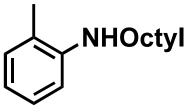
General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and benzylamine (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as a yellow solid in 73 % yield (92 mg, 0.37 mmol). ^{1}H NMR (CDCl$_3$): δ 7.42 – 7.40 (m, 2H, ArH), 7.39 – 7.36 (m, 4H, ArH), 7.32 (m, 1H, ArH), 6.64 (d, 2H, J = 8.5 Hz, ArH), 4.39 (s, 3H, CH$_2$, NH). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 150.8, 138.8, 129.1, 127.9, 127.7, 126.9 (q, J_{CF} = 3.8 Hz), 125.3 (q, J_{CF} = 270.5 Hz) 119.3 (q, J_{CF} = 32.7 Hz), 112.3, 48.1. Agrees with: Fuwa, H; Kobayashi, T; Tokitoh, T; Torii, Y.; Natsugari, H. *Tetrahedron* **2005**, *61*, 4297.

Preparation of *N*-octyl-4-(trifluoromethyl)aniline (3-1i)



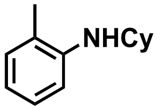
General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and octylamine (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow oil in 87 % yield (119 mg, 0.44 mmol). ^1H NMR ($CDCl_3$): δ 7.42 (d, 2H, *J* = 8.5 Hz, ArH), 6.60 (d, 2H, *J* = 8.5 Hz, ArH), 3.97 (br s, 1H, NH), 3.15 (t, 2H, *J* = 7 Hz, CH_2), 1.67 – 1.62 (m, 2H, CH_2), 1.48 – 1.31 (m, 10H, CH_2), 0.94 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.2, 126.8 (app. d, J_{CF} = 3.8 Hz), 125.5 (q, J_{CF} = 270.5 Hz), 118.6 (q, J_{CF} = 32.7 Hz), 111.9, 43.8, 32.2, 29.7, 29.6, 29.5, 27.4, 23.0, 14.4. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{23}F_3N$: 274.1777. Found: 274.1771.

Preparation of 2-methyl-*N*-octylaniline (3-1j)



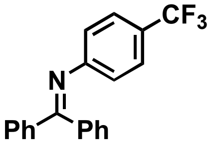
General procedure A was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and octylamine (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 20 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as a yellow oil in 82 % yield (89 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.16 (m, 1H, ArH), 7.08 (d, 1H, *J* = 7 Hz, ArH), 6.69 – 6.64 (m, 2H, ArH), 3.48 (br s, 1H, NH), 3.17 (t, 2H, *J* = 7 Hz, CH_2), 2.16 (s, 3H, CH_3), 1.73 – 1.67 (m, 2H, CH_2), 1.47 – 1.29 (10 H, CH_2), 0.93 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.7, 130.3, 127.5, 121.9, 116.9, 109.9, 44.3, 32.2, 29.9, 29.8, 29.6, 27.6, 23.0, 17.8, 14.5. Agrees with: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371.

Preparation of *N*-cyclohexyl-2-methylaniline (3-1k)



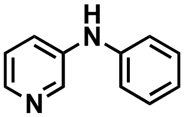
General procedure A was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 25 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH_4OH), and isolated as a yellow oil in 73 % yield (69 mg, 0.37 mmol). ^1H NMR ($CDCl_3$): δ 7.16 (m, 1H, ArH), 7.10 (dd, 1H, *J* = 7.5 Hz, *J* = 0.5 Hz, ArH), 6.69 – 6.65 (m, 2H, ArH), 3.43 (br s, 1H, NH), 3.37 (m, 1H, CH), 2.17 (s, 3H, CH_3), 2.16 – 2.13 (m, 2H, CH_2), 1.85 – 1.81 (m, 2H, CH_2), 1.71 (m, 1H, CH), 1.49 – 1.41 (m, 2H, CH_2), 1.35 – 1.22 (m, 3H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.6, 130.6, 127.4, 121.9, 116.5, 110.4, 51.8, 33.9, 26.3, 25.4, 17.9. Agrees with: Lee, D.-H.; Taher, A.; Hossain, S.; Jin, M.-J. *Org. Lett.* **2011**, *20*, 5540.

Preparation of *N*-(diphenylmethylene)-4-(trifluoromethyl)aniline (3-1l)



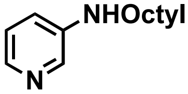
General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and benzophenone imine (92 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow oil in 88 % yield (143 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 7.78 – 7.76 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.45 – 7.39 (m, 4H, ArH), 7.31 – 7.25 (m, 3H, ArH), 7.13 – 7.11 (m, 2H, ArH), 6.81 – 6.79 (m, 2H, ArH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 169.6, 154.7, 139.4, 135.9, 131.5, 130.4 – 128.5, 126.1 (q, J_{CF} = 3.8 Hz), 125.3 (q, J_{CF} = 32.7 Hz), 124.7 (q, J_{CF} = 270.5 Hz), 121.2. HRMS (ESI/[M+H]$^+$) calcd. for $C_{20}H_{15}F_3N$: 326.1151. Found: 326.1138.

Preparation of *N*-phenylpyridin-3-amine (3-1m)



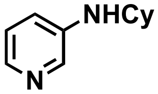
General procedure A was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 91 % yield (77 mg, 0.46 mmol). ^{1}H NMR ($CDCl_3$): δ 8.39 (d, 1H, J = 2 Hz, ArH), 8.15 (d, 1H, J = 4.5 Hz, ArH), 7.41 (ddd, 1H, J = 8.5 Hz. J = 2.5 Hz, J = 1 Hz, ArH), 7.31 – 7.28 (m, 2 H, ArH), 7.17 – 7.15 (m, 1H, ArH), 7.08 (dd, 2H, *J* = 8.5 Hz, *J* = 1 Hz, ArH), 6.99 (t, 1H, *J* = 7.5 Hz. ArH), 6.19 (br s, 1H, NH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.3, 141.9, 140.3, 129.8, 124.0, 123.6, 122.2, 118.5.

Preparation of *N*-octylpyridin-3-amine (3-1n)



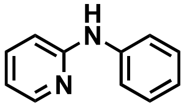
General procedure A was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and octylamine (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 92 % yield (95 mg, 0.46 mmol). ^1H NMR ($CDCl_3$): δ 8.01 (d, 1H, *J* = 3 Hz, ArH), 7.93 (dd, 1H, *J* = 4.5 Hz, *J* = 1.5 Hz, ArH), 7.06 (m, 1H, ArH), 6.85 (ddd, 1H, *J* = 8 Hz, *J* = 2.5 Hz, *J* = 1 Hz, ArH), 3.66 (br s, 1H, NH), 3.10 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 1.43 – 1.25 (m, 10 H, CH_2), 0.90 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 144.7, 138.8, 136.3, 124.0, 118.6, 43.9, 32.1, 29.8, 29.7, 29.6, 27.4, 23.0, 14.4. Agrees with: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371.

Preparation of *N*-cyclohexylpyridin-3-amine (3-1o)



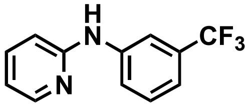
General procedure A was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and cyclohexylamine (63 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (100:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 70 % yield (62 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 7.98 (dd, 1H, *J* = 3 Hz, *J* = 1.5 Hz, ArH), 7.89 (dd, 1H, *J* = 5 Hz, *J* = 1.5 Hz, ArH), 7.05 (ddd, 1H, *J* = 8.5 Hz, *J* = 5 Hz, *J* = 1 Hz, ArH), 6.84 (ddd, 1H, *J* = 8 Hz, *J* = 2.5 Hz, *J* = 1 Hz, ArH), 3.56 (br s, 1H, NH), 3.24 (m, 1H, CH), 2.06 – 2.02 (m, 2H, CH), 1.78 – 1.64 (m, 3 H, CH), 1.41 – 1.19 (m, 5 H, CH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.7, 138.6, 136.7, 124.0, 119.0, 51.8, 33.6, 26.1, 25.2. Agrees with: Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371.

Preparation of *N*-phenylpyridin-2-amine (3-1p)



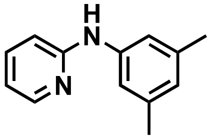
General procedure A was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an off-white solid in 93 % yield (79 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 8.22 (ddd, 1H, *J* = 5 Hz, *J* = 2 Hz, *J* = 0.5 Hz, ArH), 7.48 (m, 1H, ArH), 7.38 (br s, 1H, NH), 7.37 – 7.33 (m, 4H, ArH), 7.06 (m, 1H, ArH), 6.91 (dt, 1H, *J* = 8 Hz, *J* = 1 Hz, ArH), 6.73 (m, 1H, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.5, 148.7, 140.9, 138.0, 129.6, 123.1, 120.7, 115.2, 108.4. Agrees with: Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

Preparation of *N*-(3-(trifluoromethyl)phenyl)pyridin-2-amine (3-1q)



General procedure A was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and 3-CF$_3$-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM - 200:10:1 DCM:MeOH:NH$_4$OH), and isolated as an off-white solid in 80 % yield (95 mg, 0.40 mmol). ^{1}H NMR (CDCl$_3$): δ 8.25 (dd, 1H, *J* = 5 Hz, *J* = 1 Hz, ArH), 7.67 (s, 1H, ArH), 7.57 – 7.52 (m, 2H, ArH), 7.41 (t, 1H, *J* = 8 Hz), 7.24 (s, 1H, ArH), 6.86 (d, 1H, *J* = 8.5 Hz), 6.80 (m, 1H, ArH). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 155.6, 148.6, 141.6, 138.3, 131.9 (q, J_{CF} = 31.5 Hz), 130.0, 124.4 (q, J_{CF} = 272.9 Hz), 122.8, 119.0, 116.2 (q, J_{CF} = 3.8 Hz), 116.2, 109.5. HRMS (ESI/[M+H]$^+$) calcd. for $C_{12}H_{10}F_3N_2$: 239.0791. Found: 239.0795.

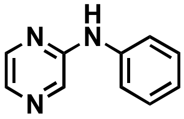
Preparation of *N*-(3,5-dimethylphenyl)pyridin-2-amine (3-1r)



General procedure A was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and 3,5-Me-aniline (69 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 19 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH$_4$OH), and isolated as an orange solid in 94 % yield (93 mg, 0.47 mmol). ^{1}H NMR (CDCl$_3$): δ 8.20 (ddd, 1H, *J* = 5 Hz, *J* = 2Hz, *J* =1 Hz, ArH), 7.49 (m, 1H, ArH), 7.04 (br s, 1H, NH), 6.95

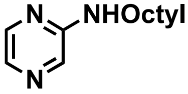
(s, 2H, ArH), 6.91 (d, 1H, *J* = 8.5 Hz. ArH), 6.72 – 6.69 (m, 2H, ArH), 2.32 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.6, 148.7, 140.7, 139.3, 137.9, 125.0, 118.6, 114.9, 108.4, 21.7. Agrees with: Lundgren, R. J.; Sappong-Kumankumah, A.; Stradiotto, M. *Chem. Eur. J.* **2010**, *16*, 1983.

Preparation of *N*-phenylpyrazin-2-amine (3-1s)



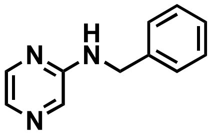
General procedure A was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as a brown solid in 93 % yield (80 mg, 0.47 mmol). ^1H NMR ($CDCl_3$): δ 8.24 (d, 1H, *J* = 1 Hz, ArH), 8.10 (m, 1H, ArH), 7.96 (d, 1H, *J* = 2.5 Hz, ArH), 7.46 – 7.44 (m, 2H, ArH), 7.37 – 7.33 (m, 2H, ArH), 7.09 (t, 1H, *J* = 7 Hz, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.6, 142.2, 139.5, 135.0, 133.3, 129.7, 123.8, 120.4. Agrees with: Kim, B. R.; Cho, S.-D.; Kim, E. J.; Lee., I.-H.; Sung, G.H.; Kim, J.-J.; Lee, S.-G.; Yoon, Y.-J. *Tetrahedron* **2012**, *68*, 287.

Preparation of *N*-octylpyrazin-2-amine (3-1t)



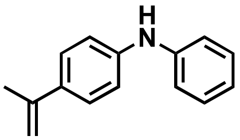
General procedure A was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and octylamine (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a brown oil in 85 % yield (88 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.96 (dd, 1H, *J* = 3 Hz, *J* = 1.5 Hz, ArH), 7.86 (d, 1H, *J* = 1.5 Hz, ArH), 7.77 (d, 1H, *J* = 3 Hz, ArH), 4.59 (br s, 1H, NH), 3.34 – 3.29 (m, 2H, CH_2), 1.60 (m, 2H, CH_2), 1.40 – 1.26 (m, 10H, CH_2), 0.87 (t, 3H, *J* = 7 Hz, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 155.1, 142.4, 133.0, 132.1, 42.0, 32.1, 29.9, 29.7, 29.6, 27.3, 22.9, 14.4. Agrees with: Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

Preparation of *N*-benzylpyrazin-2-amine (3-1u)



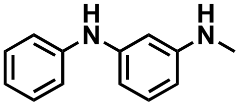
General procedure A was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and benzylamine (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as an orange oil in 86 % yield (80 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.99 (m, 1H, ArH), 7.88 (d, 1H, *J* = 1.5 Hz, ArH), 7.81 (d, 1H, *J* = 3 Hz, ArH), 7.35 -7.34 (m, 4H, ArH), 7.29 (m, 1H, ArH), 5.04 (br s, 1H NH), 4.56 (d, 2H, *J* = 5.5 Hz, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.8, 142.3, 138.8, 133.4, 132.4 129.1, 127.9, 45.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{12}N_3$:186.1026. Found: 186.1032.

Preparation of *N*-phenyl-4-(prop-1-en-2-yl)aniline (3-1v)



General procedure A was followed, with 4-chloro-α-methylstyrene (71 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH_4OH), and isolated as a yellow solid in 89 % yield (94 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 7.41 – 7.39 (m, 2H, ArH), 7.29 – 7.26 (m, 2H ArH), 7.09 – 7.08 (m, 2H, ArH), 7.05 – 7.03 (m, 2H, ArH), 6.94 (tt, 1H, *J* = 7 Hz, *J* = 1 Hz, ArH), 5.74 (br s, 1H, NH), 5.31 (d, 1H, *J* = 1 Hz, CH), 4.99 (d, 1H, *J* = 1Hz, CH), 2.14 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.2, 142.9, 142.8, 134.1, 129.7, 126.8, 121.5, 118.3, 117.6, 110.7, 22.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{15}N$: 210.1277. Found: 210.1272.

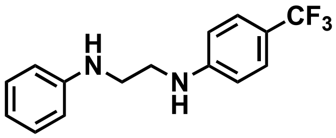
Preparation of *N*^{1}-methyl-*N*^{3}-phenylbenzene-1,3-diamine (3-1w)



The general procedure was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM - 1000:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow oil in 88 % yield (87 mg, 0.44 mmol). ^1H NMR ($CDCl_3$): δ 7.34 – 7.30 (m, 2H, ArH), 7.17 – 7.12 (m, 3H, ArH), 6.96 (t, 1H, *J* = 7

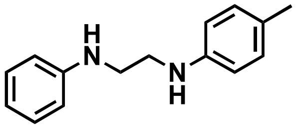
Hz, ArH), 6.50 (m, 1H, ArH), 6.39 (t, 1H, *J* = 2.5 Hz), 6.28 (m, 1H, ArH), 5.69 (br s, 1H, NH), 3.57 (br s, 1H, NH), 2.84 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.7, 144.4, 143.6, 130.3, 129.5, 121.0, 118.2, 107.5, 106.1, 101.9, 31.1. Agrees with characterization data provided in Chapter 2.

Preparation of *N*^{1}-phenyl-*N*^{2}-(4-(trifluoromethyl)phenyl)ethane-1,2-diamine (3-1x)



General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) to and isolated as a yellow oil in 81 % yield (113 mg, 0.41 mmol). ^1H NMR ($CDCl_3$): δ 7.43 (d, 2H, *J* = 8.5 Hz, ArH), 7.24 – 7.21 (m, 2H, ArH), 6.78 (t, 1H, *J* = 7 Hz, ArH), 6.69 – 6.64 (m, 4H, ArH), 4.25 (br s, 1H, NH), 3.79 (br s, 1H, NH), 3.43 (s, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.8, 148.1, 129.8, 127.0, 125.2 (q, $J_{C\text{-}F}$ = 270.5 Hz), 119.2 (q, $J_{C\text{-}F}$ = 32.7 Hz), 118.4, 113.4, 112.4, 43.4, 43.1. Agrees with characterization data provided in Chapter 2.

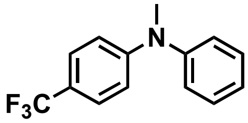
Preparation of *N*^{1}-phenyl-*N*^{2}-p-tolylethane-1,2-diamine (3-1y)



General procedure A was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and *N*-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM – 1000:10:1 DCM: MeOH: NH_4OH) and isolated as a yellow oil in 75 % yield (84 mg, 0.38 mmol). ^{1}H NMR ($CDCl_3$): δ 7.25 – 7.20 (m, 2 H, ArH), 7.06 – 7.03 (m, 2 H, ArH), 6.77 (m, 1H, ArH), 6.69 – 6.67 (m, 2H, ArH), 6.63 – 6.60 (m, 2H, ArH), 3.88 (br s, 2H, NH), 3.39 (s, 4H, CH_2), 2.29 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.3, 146.1, 130.2, 129.7, 127.4, 118.1, 113.6, 113.4, 44.0, 43.7, 20.7. Agrees with characterization data provided in Chapter 2.

3.4.3 Preparation of Compounds From Table 3.2

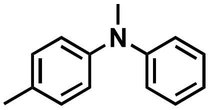
Preparation of *N*-methyl-*N*-phenyl-4-(trifluoromethyl)aniline (3-2a)



General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and *N*-Me-aniline (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as a brown oil in 62 % yield (77 mg, 0.31 mmol). ^{1}H NMR ($CDCl_3$): δ 7.46 –

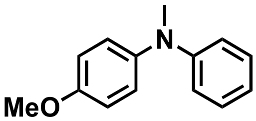
7.39 (m, 4H, ArH), 7.23 – 7.20 (m, 3H, ArH), 6.87 (d, 2H, *J* = 8.5 Hz, ArH), 3.37 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.8, 148.1, 130.1, 126.5 (q, J_{CF} = 3.8 Hz), 125.6, 125.3, 125.2 (q, J_{CF} = 271.7 Hz), 120.2 (q, J_{CF} = 31.5 Hz), 115.1, 40.5. Agrees with: Manolikakes, G.; Gavryushin, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 1429.

Preparation of *N*,4-dimethyl-*N*-phenylaniline (3-2b)



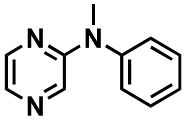
General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and *N*-Me-aniline (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as a brown oil in 86 % yield (85 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.31 – 7.27 (m, 2H, ArH), 7.17 (d, 2H, *J* = 8.5 Hz, ArH), 7.07 – 7.05 (m, 2H, ArH), 6.98 (d, 2H, *J* = 9 Hz, ArH), 6.92 (m, 1H, ArH), 3.44 (s, 3H, CH_3), 2.38 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.7, 146.9, 132.4, 130.2, 129.3, 122.9, 120.1, 118.5, 40.7, 21.1. Agrees with: Wolfe, J. P.; Buchwald. S. L. *J. Org. Chem.* **1996**, *61*, 1133.

Preparation of 4-methoxy-*N*-methyl-*N*-phenylaniline (3-2c)



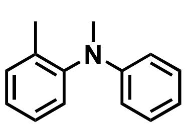
General procedure A was followed, with 4-chloroanisole (61 μL, 0.50 mmol) and *N*-Me-aniline (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH), and isolated as an orange oil in 80 % yield (86 mg, 0.40 mmol). ^{1}H NMR ($CDCl_3$): δ 7.29 – 7.26 (m, 2H, ArH), 7.18 – 7.16 (m, 2H, ArH), 6.98 – 6.96 (m, 2H, ArH), 6.88 – 6.87 (m, 3H, ArH), 3.89 (s, 3H, CH_3), 3.34 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.6, 150.0, 142.5, 129.3, 126.5, 118.6, 116.0, 115.1, 55.8, 40.8. Agrees with: Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

Preparation of *N*-methyl-*N*-phenylpyrazin-2-amine (3-2d)



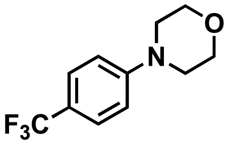
General procedure A was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and N-Me-aniline (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as an orange oil in 71 % yield (65 mg, 0.36 mmol). ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 1H, ArH), 7.94 (d, 1H, *J* = 1.5 Hz, ArH), 7.82 (d, 1H, *J* = 2.5 Hz, ArH), 7.46 – 7.43 (m, 2H, ArH), 7.29 – 7.27 (m, 3 H, ArH), 3.46 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 155.1, 145.5, 141.8, 133.3, 132.9, 130.4, 126.9, 126.7, 38.6. Agrees with: Maes, B. U. W.; Loones, K. T. J.; Lemiere, G. L. F.; Dommisse, R. A. *Synlett* **2003**, 1822.

Preparation of *N*,2-dimethyl-*N*-phenylaniline (3-2e)



General procedure A was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and N-Me-aniline (60 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as a yellow oil in 68 % yield (67 mg, 0.34 mmol). ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 1H, ArH), 7.31 (m, 1H, ArH), 7.29 – 7.20 (m, 4H, ArH), 6.68 (m, 1H, ArH), 6.62 – 6.60 (m, 2H, ArH), 3.29 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.4, 147.1, 137.1, 131.7, 129.3, 128.7, 127.8, 126.7, 117.1, 113.1, 39.4, 18.2. Kataoka, K.; Shelby, Q; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.

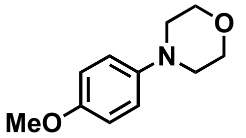
Preparation of 4-(4-(trifluoromethyl)phenyl)morpholine (3-2f)



General procedure A was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as an off-white solid in 65 % yield (75 mg, 0.33 mmol). ^{1}H NMR ($CDCl_3$): δ 7.50 (d, 2H, *J* = 9 Hz, ArH), 6.92 (d, 2H, *J* = 9 Hz, ArH), 3.86 (app. t, 4H, *J* = 5 Hz, CH_2), 3.24 (app. t, 4H, *J* = 5 Hz. CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.7, 127.1 (q, J_{CF} =

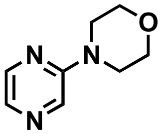
271.7 Hz), 126.8 (q, J_{CF} = 3.8 Hz), 121.3 (q, J_{CF} = 32.7 Hz), 114.6, 67.0, 48.5. Agrees with: Ackermann L.; Born, R. *Angew. Chem. Int. Ed.* **2005**, *44*, 2444.

Preparation of 4-(4-methoxyphenyl)morpholine (3-2g)



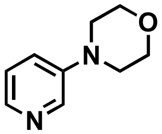
General procedure A was followed, with 4-chloroanisole (61 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH), and isolated as an orange solid in 70 % yield (67 mg, 0.35 mmol). ^{1}H NMR ($CDCl_3$): δ 6.90 – 6.84 (m, 4H, ArH), 3.87 – 3.85 (m, 4H, CH_2), 3.77 (s, 3H, CH_3), 3.07 – 3.05 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 154.3, 145.9, 118.1, 114.8, 67.4, 55.9, 51.1. Agrees with: Ackermann L.; Born, R. *Angew. Chem. Int. Ed.* **2005**, *44*, 2444.

Preparation of 4-(pyrazin-2-yl)morpholine (3-2h)



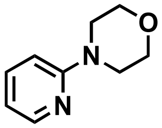
General procedure A was followed, with 2-chloropyrazine (45 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as an orange solid in 68 % yield (56 mg, 0.34 mmol). ^{1}H NMR ($CDCl_3$): δ 8.00 (s, 1H, ArH), 7.95 (s, 1H, ArH), 7.76 (s, 1H, ArH), 3.71 – 3.69 (m, 4H, CH_2), 3.43 – 3.41 (m, 4H, CH_2). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 155.4, 142.0, 133.9, 131.2, 66.8, 45.0. Agrees with: Organ, M. G.; Abdel-Hadi. M.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Sayah, M.; Valente, C. *Chem. Eur J.* **2008**, *14*. 2443

Preparation of 4-(pyridin-3-yl)morpholine (3-2i)



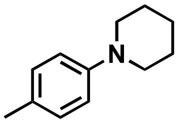
General procedure A was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an orange oil in 83 % yield (68 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 8.28 (s, 1H, ArH), 8.10 (s, 1H, ArH), 7.15 (d, 2H, J = 2 Hz, ArH), 3.84 (app. t, 4H, J = 4.5 Hz, CH_2), 3.15 (app. t, 4H, J = 4.5 Hz, CH_2). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.2, 141.4, 138.5, 123.8, 122.4, 66.9, 48.8. Agrees with: Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

Preparation of 4-(pyridin-2-yl)morpholine (3-2j)



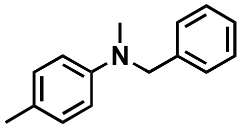
General procedure A was followed, with 2-chloropyridine (47 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as an orange oil in 76 % yield (62 mg, 0.38 mmol). ^1H NMR ($CDCl_3$): δ 8.20 (d, 1H, *J* = 5 Hz, ArH), 7.50 (m, 1H, ArH), 6.67 – 6.63 (m, 2H, ArH), 3.83 (app. t, 4H, *J* = 5 Hz, CH_2), 3.49 (app. t, 4H, *J* = 5 Hz, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.6, 148.3, 137.9, 114.2, 107.3, 67.1, 45.9. Agrees with: Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240

Preparation of 1-*p*-tolylpiperidine (2k)



General procedure A was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and piperidine (54 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (20:1 hex:EtOAc) and isolated as an orange oil in 70 % yield (61 mg, 0.35 mmol). ^1H NMR ($CDCl_3$): δ 7.11 – 7.08 (m, 2H. ArH), 6.92 – 6.89 (m, 2H, ArH), 3.13 (t, 4H, *J* = 5.5 Hz, CH_2), 2.31 (s, 3H, CH_3), 1.77 – 1.73 (m, 4H, CH_2), 1.62 – 1.57 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 150.6, 129.8, 129.1, 117.3, 51.6, 26.3, 24.6, 20.7. Agrees with: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

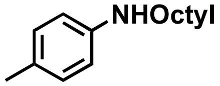
Preparation of *N*-benzyl-*N*,4-dimethylaniline (3-2l)



General procedure A was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and *N*-Me-benzylamine (71 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH), and isolated as a yellow solid in 71 % yield (76 mg, 0.36 mmol). ^1H NMR ($CDCl_3$): δ 7.36 – 7.33 (m, 2H, ArH), 7.28 – 7.27 (m, 3H, ArH), 7.08 – 7.06 (m, 2H, ArH), 6.73 – 6.72 (m, 2H, ArH), 4.53 (s, 2H, CH_2), 3.01 (s, 3H, CH_3), 2.29 (s, 3H. CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.1, 139.6, 130.0, 128.8, 127.2, 127.1, 126.1, 113.0, 57.3, 38.9, 20.6.
Agrees with: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

3.4.4 Preparation of Compounds From Table 3.3

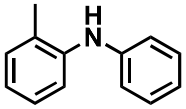
Preparation of 4-methyl-*N*-octylaniline (3-3a)



General procedure B was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and octylamine (91 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as a yellow solid in 90 % yield (98 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 7.03 - 7.01 (m, 2H, ArH), 6.59 – 6.56 (m, 2H, ArH), 3.45 (br s, 1H, NH), 3.11 (t, 2H, J = 7 Hz, CH_2), 2.28 (s, 3H, CH_3), 1.63 (m, 2H, CH_2), 1.44 – 1.32 (m, 10H, CH_2), 0.93 (t, 3H, J = 7 Hz, CH_3).$^{13}C\{^1H\}$ NMR

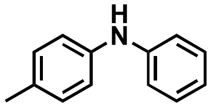
(CDCl$_3$): δ 146.6, 130.0, 126.6, 113.2, 44.7, 32.2, 29.9, 29.8, 29.6, 27.5, 23.0, 20.7, 14.4. Agrees with: Shen, Q.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 4109.

Preparation of 2-methyl-*N*-phenylaniline (3-3b)



General procedure B was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH$_4$OH), and isolated as an off-white solid in 97 % yield (89 mg, 0.49 mmol). ^{1}H NMR (CDCl$_3$): δ 7.36 – 7.32 (m, 3H, ArH), 7.29 (d, 1H, J = 7.5 Hz, ArH), 7.23 (m, 1H, ArH), 7.05 – 6.98 (m, 4H, ArH), 5.44 (br s, 1H, NH), 2.34 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 144.3, 141.5, 131.2, 129.6, 128.6, 127.1, 122.3, 120.7, 119.1, 117.7, 18.2. Agrees with: Louie, J.; Driver, M. S; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.

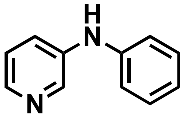
Preparation of 4-methyl-*N*-phenylaniline (3-3c)



General procedure B was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as an off-white solid in 90 % yield

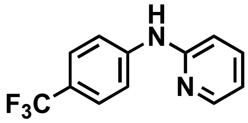
(82 mg, 0.45 mmol). ^{1}H NMR (CDCl$_3$): δ 7.33 – 7.29 (m, 2H, ArH), 7.16 (d, 2H, *J* = 8.5 Hz, ArH), 7.09 – 7.06 (m, 4H, ArH), 6.98 – 6.94 (m, 1H, ArH), 5.64 (br s, 1H, NH), 2.38 (s, 3H, CH$_3$). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 144.2, 140.6, 131.2, 130.2, 129.6, 120.6, 119.2, 117.1, 21.0. Agrees with: Liu, X.; Zhang, S. *Synlett* **2011**, 1137.

Preparation of *N*-phenylpyridin-3-amine (3-3d)



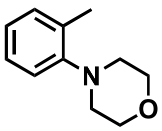
General procedure B was followed, with 3-chloropyridine (47 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH$_4$OH), and isolated as an off-white solid in 92 % yield (77 mg, 0.46 mmol). ^{1}H NMR (CDCl$_3$): δ 8.39 (d, 1H, *J* = 2 Hz, ArH), 8.15 (d, 1H, *J* = 4.5 Hz, ArH), 7.41 (ddd, 1H, *J* = 8.5 Hz. *J* = 2.5 Hz, *J* = 1 Hz, ArH), 7.31 – 7.28 (m, 2 H, ArH), 7.17 – 7.15 (m, 1H, ArH), 7.08 (dd, 2H, *J* = 8.5 Hz, *J* = 1 Hz, ArH), 6.99 (t, 1H, *J* = 7.5 Hz. ArH), 6.19 (br s, 1H, NH). ^{13}C{^{1}H} NMR (CDCl$_3$): δ 142.3, 142.2, 140.5, 140.2, 129.9, 124.0, 123.7, 122.3, 118.6. Agrees with: Liu, X.; Zhang, S. *Synlett* **2011**, 1137.

Preparation of *N*-(4-(trifluoromethyl)phenyl)pyridin-2-amine (3-3e)



General procedure B was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) added via a microlitre syringe and 2-aminopyridine (52 mg, 0.55 mmol) weighed out. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow solid in 83 % yield (99 mg, 0.42 mmol). ^{1}H NMR ($CDCl_3$): δ 8.27 (ddd, 1H, *J* = 5 Hz, *J* = 2 Hz, *J* = 1 Hz, ArH), 7.58 – 7.54 (m, 3H, ArH), 7.46 (d, 2H, *J* = 8.5 Hz, ArH), 7.36 (br s, 1H, NH), 6.93 (dt, 1H, *J* = 8.5 Hz, *J* = 1 Hz, ArH), 6.83 (m, 1H, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 155.2, 148.6, 144.3, 138.2, 126.8 (q, J_{CF} = 2.5 Hz), 124.8 (q, J_{CF} = 270.5 Hz), 123.9 (q, J_{CF} = 31.5 Hz), 118.6, 116.5, 110.1. Agrees with: Masters, K.-M.; Rauws, T. R. M.; Yadav, A. K.; Herrebout, W. A.; Van der Veken, B.; Maes, B. U. W. *Chem. Eur. J.* **2011**, *17*, 6315.

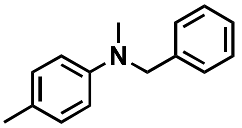
Preparation of 4-*o*-tolylmorpholine (3-3f)



General procedure B was followed, with 2-chlorotoluene (58 μL, 0.50 mmol) and morpholine (48 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH_4OH), and isolated as a brown oil in 88 % yield (76 mg, 0.44 mmol). ^{1}H NMR ($CDCl_3$): δ 7.21 –

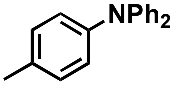
7.18 (m, 2H, ArH), 7.04 – 6.99 (m, 2H, ArH), 3.86 (app. t, 4 H, *J* = 4.5 Hz, CH_2), 2.92 (app. t, 4H, *J* = 4.5 Hz, CH_2), 2.33 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.6, 132.9, 131.5, 127.0, 123.7, 119.3, 67.8, 52.6, 18.2. Agrees with: Hartwig, J.F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

Preparation of *N*-benzyl-*N*,4-dimethylaniline (3-3g)



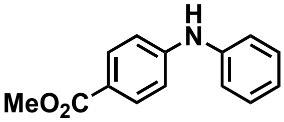
General procedure B was followed, with 4-chlorotoluene (59 μL, 0.50 mmol) and *N*-Me-benzylamine (71 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM), and isolated as a yellow solid in 85 % yield (91 mg, 0.43 mmol). ^1H NMR ($CDCl_3$): δ 7.36 – 7.33 (m, 2H, ArH), 7.28 – 7.27 (m, 3H, ArH), 7.08 – 7.06 (m, 2H, ArH), 6.73 – 6.72 (m, 2H, ArH), 4.57 (s, 2H, CH_2), 3.06 (s, 3H, CH_3), 2.34 (s, 3H. CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.1, 139.6, 130.0, 128.8, 127.2, 127.1, 126.1, 113.0, 57.3, 38.9, 20.6. Agrees with: Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 1133.

Preparation of 4-methyl-*N*,*N*-diphenylaniline (3-3h)



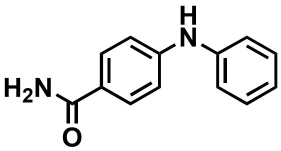
General procedure B was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) added via a microlitre syringe and diphenylamine (92 mg, 0.55 mmol) weighed out. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM) and isolated as a white solid in 90 % yield (117 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.28 – 7.25 (m, 4H, ArH), 7.12 – 7.10 (m, 6 H, ArH), 7.06 - 7.05 (m, 2H, ArH), 7.01 (t, 2 H, *J* = 7.5 Hz, ArH), 2.36 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.4, 145.6, 133.1, 130.3, 129.4, 125.3, 123.9, 122.6, 21.2. Agrees with: Dai, Q.; Gao, W.; Liu, D.; Kapes, L. M.; Zhang, X. *J. Org. Chem.* **2006**, *71*, 3928.

Preparation of methyl 4-(phenylamino)benzoate (3-3i)



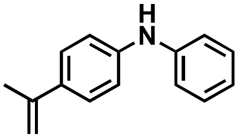
General procedure B was followed, with methyl 4-chlorobenzoate (85 mg, 0.50 mmol) weighed out and aniline (50 μL, 0.55 mmol) added via a microlitre syringe, K_2CO_3 (83 mg, 0.6 mmol) used as base, and NaO*t*Bu (8 mol %) added for catalyst activation. The reaction was allowed to proceed for 20 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as a white solid in 90 % yield (121 mg, 0.45 mmol). ^{1}H NMR ($CDCl_3$): δ 7.93 – 7.90 (m, 2H, ArH), 7.35 – 7.32 (m, 2H, ArH), 7.17 (d, 2H, *J* = 7.5 Hz, ArH), 7.07 (t, 1H, *J* = 7.5 Hz, ArH), 6.99 – 6.97 (m, 2H, ArH), 6.06 (br s, 1H, NH), 3.87 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 167.3, 148.5, 141.3, 131.8, 129.9, 123.5, 121.6, 120.9, 115.0, 52.0. Agrees with: Anderson, K. W.; Mendex-Perez, M.; Priego, J.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 9563.

Preparation of 4-(phenylamino)benzamide (3-3j)



General procedure B was followed, with methyl 4-chlorobenzamide (78 mg, 0.50 mmol) weighed out and aniline (50 μL, 0.55 mmol) added via a microlitre syringe, LiHMDS (180 mg, 1.1 mmol) used as base, and NaO*t*Bu (8 mol %) added for catalyst activation. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM:MeOH:NH_4OH) and isolated as an off-white solid in 88 % yield (94 mg, 0.44 mmol). ^1H NMR (MeOD): δ 7.79 – 7.76 (m, 2H, ArH), 7.32 – 7.29 (m, 2H, ArH), 7.20 – 7.18 (m, 2H, ArH), 7.09 – 7.06 (m, 2H, ArH), 6.99 (m, 1H, ArH), 4.92 (br s, 3H, NH). $^{13}C\{^1H\}$ NMR (MeOD): δ 173.3, 150.4, 144.1, 131.3, 131.1, 125.2, 123.9, 121.4, 116.3. Agrees with characterization data provided in Chapter 2.

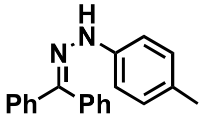
Preparation of *N*-phenyl-4-(prop-1-en-2-yl)aniline (3-3k)



General procedure B was followed, with 4-chloro-α-methylstyrene (71 μL, 0.50 mmol) and aniline (50 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 24 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH_4OH), and isolated as a yellow solid in 90 % yield (95 mg, 0.45 mmol). ^1H NMR ($CDCl_3$): δ 7.41 –

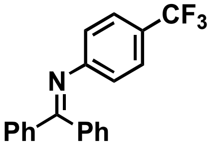
7.39 (m, 2H, ArH), 7.29 – 7.26 (m, 2H ArH), 7.09 – 7.08 (m, 2H, ArH), 7.05 – 7.03 (m, 2H, ArH), 6.94 (tt, 1H, *J* = 7 Hz, *J* = 1 Hz, ArH), 5.74 (br s, 1H, NH), 5.31 (d, 1H, *J* = 1 Hz, CH), 4.99 (d, 1H, *J* = 1Hz, CH), 2.14 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.2, 142.9, 142.8, 134.1, 129.7, 126.8, 121.5, 118.3, 117.6, 110.7, 22.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{15}N$: 210.1277. Found: 210.1272.

Preparation of 1-(diphenylmethylene)-2-*p*-tolylhydrazine (3-3l)



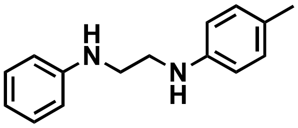
General procedure B was followed, with 4-chlorotoluene (58 μL, 0.50 mmol) and benzophenone hydrazone (98 mg, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 23 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM: MeOH: NH_4OH) and isolated as an off-white solid in 83 % yield (119 mg, 0.42 mmol). ^1H NMR ($CDCl_3$): δ 7.63 – 7.59 (m, 4 H, ArH), 7.56 – 7.54 (m, 1H, ArH), 7.47 (br s, 1H, NH), 7.37 – 7.30 (m, 5H, ArH), 7.09 - 7.08 (m, 2H, ArH), 7.03 – 7.01 (m, 2H, ArH), 2.30 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 143.9, 142.7, 138.8, 133.2, 130.0, 129.9, 129.6, 129.5, 129.4, 128.5, 128.2, 126.7, 113.2, 20.9. Agrees with: Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.

Preparation of *N*-(diphenylmethylene)-4-(trifluoromethyl)aniline (3-3m)



General procedure B was followed, with 4-chlorobenzotrifluoride (62 μL, 0.50 mmol) and benzophenone imine (92 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 36 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (1000:10:1 DCM:MeOH:NH_4OH) and isolated as a yellow oil in 92 % yield (150 mg, 0.46 mmol). ^1H NMR ($CDCl_3$): δ 7.78 – 7.76 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.45 – 7.39 (m, 4H, ArH), 7.31 – 7.25 (m, 3H, ArH), 7.13 – 7.11 (m, 2H, ArH), 6.81 – 6.79 (m, 2H, ArH). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 169.6, 154.7, 139.4, 135.9, 131.5, 130.4 – 128.5, 126.1 (q, J_{CF} = 3.8 Hz), 125.3 (q, J_{CF} = 32.7 Hz), 124.7 (q, J_{CF} = 270.5 Hz), 121.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{15}F_3N$: 326.1151. Found: 326.1138.

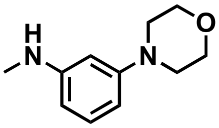
Preparation of N^1-phenyl-N^2-p-tolylethane-1,2-diamine (3-3n)



General procedure B was followed, with 4-chlorotoluene (58 μL, 0.5 mmol) and N-phenylethylenediamine (72 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 21 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (DCM – 1000:10:1 DCM: MeOH: NH_4OH) and isolated as a yellow oil in 85 % yield (96 mg, 0.43 mmol). ^1H NMR

($CDCl_3$): δ 7.25 – 7.20 (m, 2H, ArH), 7.06 – 7.03 (m, 2H, ArH), 6.77 (t of t, 1H, *J* = 7 Hz, *J* = 1 Hz, ArH), 6.69 – 6.67 (m, 2H, ArH), 6.63 – 6.60 (m, 2H, ArH), 3.88 (br s, 2H, NH), 3.39 (s, 4H, CH_2), 2.29 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.3, 146.1, 130.2, 129.7, 127.4, 118.1, 113.6, 113.4, 44.0, 43.7, 20.7. Agrees with characterization data provided in Chapter 2.

Preparation of *N*-methyl-3-morpholinoaniline (3-3o)



General procedure B was followed, with 3-chloro-*N*-methylaniline (61 μL, 0.50 mmol) and morpholine (49 μL, 0.55 mmol) added via a microlitre syringe. The reaction was allowed to proceed for 22 h, and following workup and removal of solvent, the product was purified using column chromatography on silica (200:10:1 DCM: MeOH: NH_4OH), and isolated as a red oil in 88 % yield (84 mg, 0.44 mmol). ^1H NMR ($CDCl_3$): 7.10 (t, 1H, *J* = 8 Hz, ArH), 6.32 (ddd, 1H, *J* = 8 Hz, *J* = 2.5 Hz, *J* = 1 Hz, ArH), 6.20 (ddd, 1H, *J* = 8 Hz, *J* = 2.5 Hz, *J* = 1Hz, ArH), 6.16 (t, 1H, *J* = 2.5 Hz, ArH), 3.87 – 3.85 (m, 4H, CH_2), 3.69 (br s, 1H, NH), 3.16 – 3.14 (m, 4H, CH_2), 2.83 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.9, 150.7, 130.1, 105.7, 105.2, 100.3, 67.3, 49.9, 31.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{17}N_2O$: 193.1335. Found: 193.1338.

CHAPTER 4. GENERATION OF MIXED NHC-PALLADIUM-CHLOROPHOSPHINE COMPLEXES

4.1. N-Heterocyclic Carbenes In Palladium-Mediated Catalysis

Since the first report of their isolation by Arduengo and co-workers,[105] *N*-heterocyclic carbenes (NHCs) have emerged as an extremely useful class of ancillary ligands that are complementary to phosphines in a range of transition metal-catalyzed reactions, owing to their strong σ-donating ability and their steric 'shielding' ability, which can both help stabilize a transition metal centre and enhance catalytic activity.[106-115] This is certainly true in palladium-mediated cross-coupling processes, where NHCs have proven particularly useful, both for carbon-carbon and carbon-nitrogen bond forming reactions.[110,116-118] As with other ligand classes (such as biaryl monodentate phosphines), several NHC variants have proven especially noteworthy. Among these, SIPr (1,3-Bis(2,6-diisopropylphenyl)-4,5-dihydroimidazol-2-ylidine)[119] and IPr (1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene)[120] have proven especially useful in Buchwald-Hartwig amination chemistry (Figure 4.1).

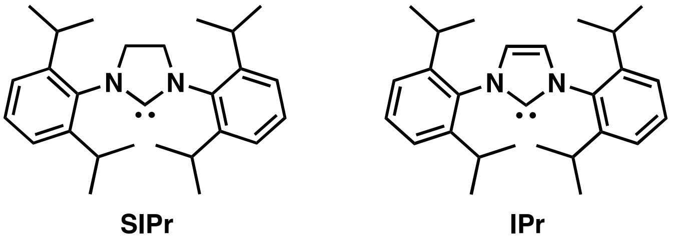


Figure 4.1 Structures of SIPr and IPr

The first report of an NHC being used as a ligand in C-N cross-coupling was published by Nolan and co-workers in 1999,[120] where the authors employed the imidazolium-chloride precursor of IPr to couple aryl chlorides, bromides and iodides with both acyclic primary and secondary alkylamines, the first methodology to do so at the time. Shortly thereafter, Hartwig[121] reported a similar array of aryl halide aminations using the saturated SIPr analogue, but with lower reaction temperatures. With the utility of NHCs in this chemistry now proven, it did not take long for well-defined NHC-palladium complexes to be employed as catalysts for Buchwald-Hartwig aminations. In this vein, complexes of the type $[(\mathrm{NHC})\mathrm{PdCl}_2]_2$[122] and [(NHC)Pd(cinnamyl)Cl][123] are now employed in this chemistry. Nolan's use of $[(\mathrm{NHC})\mathrm{PdCl}_2]_2$ as a catalyst precursor for Buchwald-Hartwig chemistry is particularly noteworthy, as not only does this catalyst show high activity for a reasonably broad substrate scope at low catalyst loadings, but the amination reactions it catalyzes can be conducted under aerobic conditions, and the complex itself is stable to air and moisture, allowing it to be stored on a benchtop.

Although NHCs are now widely used as ligands in transition-metal mediated catalysis in their own right, they have also been employed in so-called 'mixed-ligand' complexes containing both NHC and phosphine ligands. In exploring the interplay between phosphine and NHC ligands in tuning the reactivity properties of associated transition metal centers, the pairing of such ligands has in some cases been shown to offer inroads to reactivity manifolds that cannot be accessed by metal species supported by either of these ligands in isolation. Grubbs' second-generation olefin metathesis catalyst[119, 124] represents an excellent example of this reactivity enhancement, with the substitution of a PCy_3 ligand for IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) enhancing the activity of the mixed-ligand species (Figure 4.2).

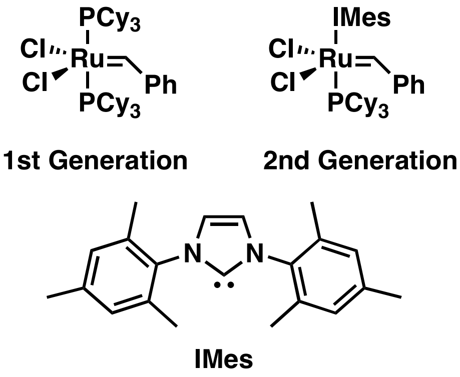
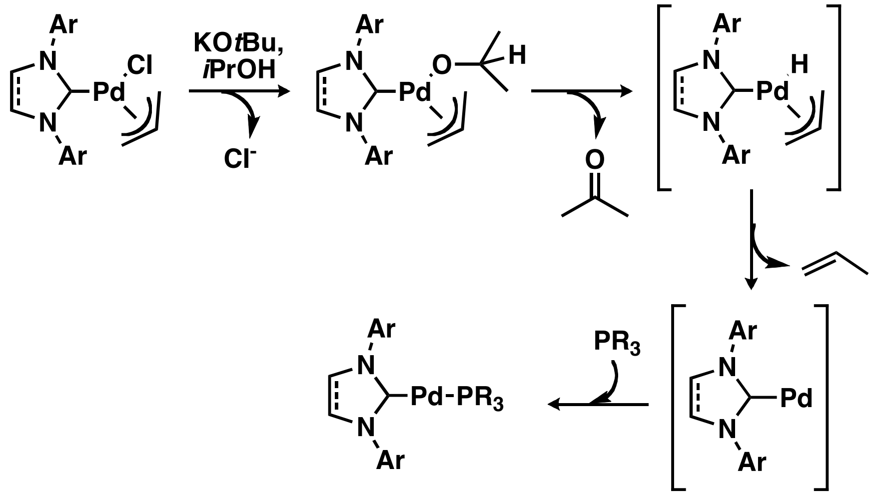


Figure 4.2 Grubbs' 1st and 2nd Generation Olefin Metathesis Catalysts

Mixed NHC-phosphine complexes of the type [(NHC)Pd(PR_3)] have proven useful as pre-catalysts in transformations ranging from cross-coupling to the hydrogenation of C-C multiple bonds.[125-129] Employing a pre-formed Pd(0) pre-catalyst rather than attempting to generate such species via *in situ* reduction of a Pd(II) precursor can be helpful in avoiding the formation of catalytically inactive Pd(0) precipitate (palladium black). Additionally, the pairing of the strongly donating NHC ligand with the comparatively weaker σ-donating phosphine ligand affords stabilization of the low-coordinate pre-catalyst, while presumably allowing for facile release of the phosphine ligand to generate monoligated [(NHC)Pd(0)] species that have been implicated as key catalytic intermediates.[130] The reduction of [(NHC)Pd(allyl)Cl] in basic alcohol represents one of the most convenient routes to [(NHC)Pd(PR_3)] complexes,[131] a process which is believed to proceed via formation of [(NHC)Pd(allyl)H], followed by C-H reductive elimination of propene (Scheme 4.1). [(NHC)Pd(P(*o*-tolyl)$_3$)] complexes have also been synthesized from [Pd(P(*o*-tolyl)$_3$)$_2$] precursors, although their preparation is sensitive to the reaction stoichiometry and to the structural attributes of the NHC.[132, 133]



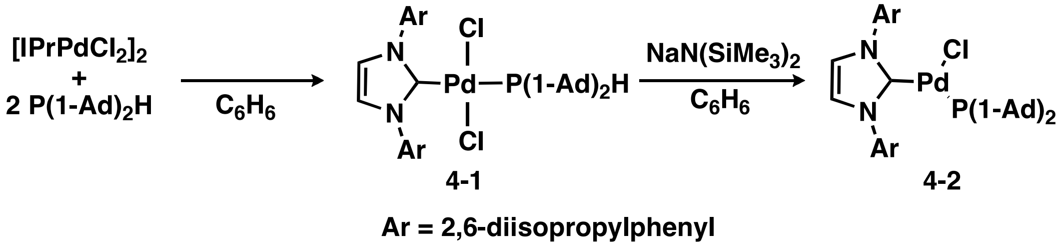
Scheme 4.1 Synthesis of [(NHC)Pd(PR$_3$)] via Reduction of [(NHC)Pd(allyl)Cl]

An alternative method for synthesizing [(NHC)Pd(PR$_3$)] complexes has been reported by Lee and co-workers,[134] and proceeds via the generation of [(PR$_3$)$_2$Pd(η^2-alkene)] species from [(PR$_3$)$_2$PdEt$_2$] precursors, followed by phosphine and alkene displacement upon treatment with the NHC ligand.

Given the aforementioned utility of these [(NHC)Pd(PR$_3$)] complexes in catalysis, alternative methods of synthesizing similar mixed-ligand species could be of great value. The work reported herein outlines an unusual alternative method of forming related [(IPr)Pd(PR$_2$Cl)] complexes (R = Cy, *t*Bu, or 1-Ad), by a net dehydrohalogenation/P-Cl reductive elimination sequence that occurs upon treatment of [(IPr)Pd(Cl)$_2$(PR$_2$H)] with NaN(SiMe$_3$)$_2$.

4.2. Results and Discussion

As part of an ongoing interest in organometallic reactivity, particularly within the context of catalysis,[135-137] the preparation of new low-coordinate NHC-ligated Pd species became a point of interest in the Stradiotto group. In this vein, it was envisioned that the reaction of $[(IPr)PdCl_2]_2$ with a secondary phosphine such as $P(1\text{-}Ad)_2H$ would generate the corresponding $[(IPr)Pd(Cl)_2(P(1\text{-}Ad)_2H)]$, which upon exposure to base might afford a low-coordinate phosphido complex of the type $[(IPr)Pd(Cl)(P(1\text{-}Ad)_2)]$ resulting from net dehydrohalogenation (Scheme 4.2).



Scheme 4.2 Proposed Synthesis of $[(IPr)Pd(Cl)(P(1\text{-}Ad)_2)]$

In monitoring the reaction of $[(IPr)PdCl_2]_2$ with two equivalents of $P(1\text{-}Ad)_2H$ at room temperature over the course of an hour by use of ^{31}P NMR techniques, the consumption of the secondary phosphine was observed with concomitant formation of a single new phosphorus-containing product (56.3 ppm), **4-1**, which in turn was obtained in 94 % isolated yield as an analytically pure solid. The identification of **4-1** as the target $[(IPr)Pd(Cl)_2(P(1\text{-}Ad)_2H)]$ complex was confirmed on the basis of NMR spectroscopic and single-crystal X-ray diffraction data (Figure 4.3).

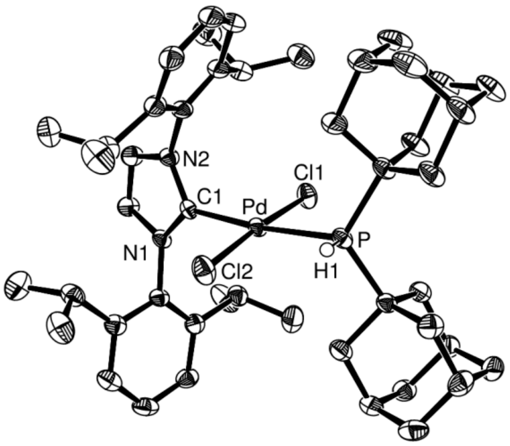
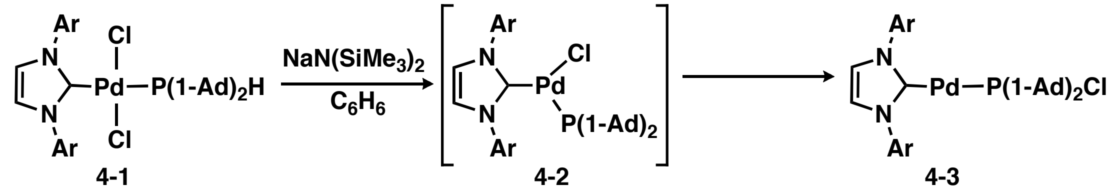


Figure 4.3 ORTEP diagram for 4-1 shown with 50 % ellipsoids. Selected hydrogen atoms have been omitted for clarity. Selected interatomic distances (Å) and angles (°): Pd-Cl1, 2.3024(7); Pd-Cl2, 2.3070(7); Pd-P, 2.3268(7); Pd-C1, 2.045(2); P-Pd-C1, 173.99(7); Cl1-Pd-Cl2, 174.53(3).

The *trans*-geometry featured in **4-1**, as well as the observed metal-ligand metrical parameters, mirror those found in other crystallographically characterized [(IPr)Pd(X)$_2$(PR$_3$)] complexes (X = halide, PR$_3$ = phosphine or phosphite).[126, 128]

Subsequent treatment of **4-1** with NaN(SiMe$_3$)$_2$ resulted in complete consumption of the starting material within three hours at room temperature as confirmed by use of ^{31}P NMR techniques, and concomitant formation of a single new phosphorus-containing species at 159.6 ppm. This new compound was isolated as an analytically pure solid in 75 % yield and was structurally characterized. However, whereas analysis of the ^{1}H and ^{31}P NMR data confirmed the absence of a P-H unit in this new complex, in keeping with the anticipated Pd(II) [(IPr)Pd(Cl)(PR$_2$)] complex, crystallographic data established its identity as being the two-coordinate chlorophosphine Pd(0) adduct [(IPr)Pd(P(1-Ad)$_2$Cl)] (**4-3**), which can be viewed as arising via net P-Cl reductive elimination within the putative phosphido intermediate (Scheme 4.3, Figure 4.4).



Scheme 4.3 Synthesis of 4-3

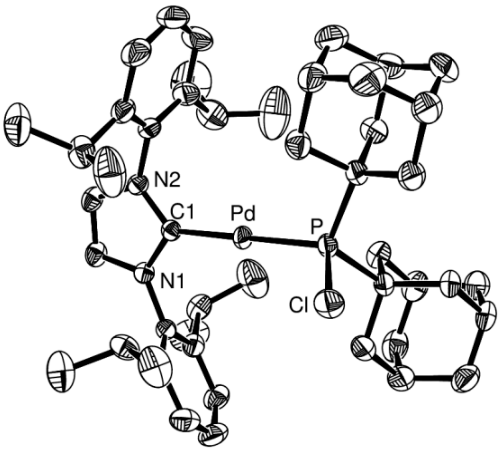
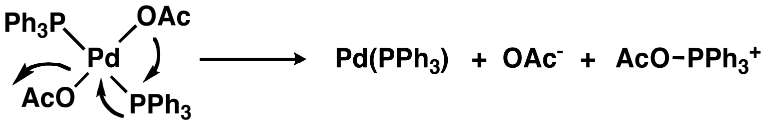


Figure 4.4 ORTEP diagram for 4-3 shown with 50 % ellipsoids. Selected hydrogen atoms have been omitted for clarity. Selected interatomic distances (Å) and angles (°): Pd-P, 2.1893(7); Pd-C1, 2.027(3); P-Pd-C1, 176.58(8).

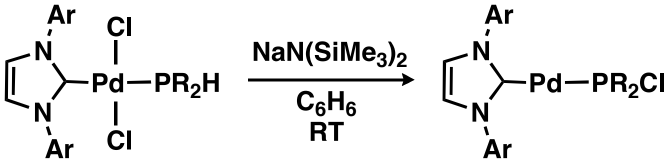
The Pd-P bond distance in the **4-1** (2.3268(7) Å) is significantly longer than the related distance in the **4-3** (2.1893(7) Å), owing in part to the lower coordination number of **4-3** as well as to the potentially greater π-accepting ability of the P(1-Ad)$_2$Cl ligand in **4-3** versus P(1-Ad)$_2$H in **4-1**. The Pd-C1 and Pd-P distances within **4-3** are in general comparable to those of the crystallographically characterized [(IPr)Pd(PR$_3$)] compounds reported by Fantasia and Nolan[131] (R = Ph: Pd-C1, 2.0547(8) Å and Pd-P, 2.2100(2) Å; R = Cy: Pd-C1, 2.0292(9) Å and Pd-P, 2.2212(3) Å), with the Pd-P distance in **4-1** being modestly shorter relative to both of these compounds, and the Pd-C1 distance in **4-3** being shorter than the related distance in [(IPr)Pd(PPh$_3$)] but statistically indistinguishable from that found in [(IPr)Pd(PCy$_3$)]. Furthermore, the P-Pd-C1 angle in **4-3** (176.58(8)°) more closely approaches linearity in comparison to the related bond angles found in the aforementioned [(IPr)Pd(PR$_3$)] compounds (R = Ph: P-Pd-C1, 169.49(2)°; R = Cy: 170.88(2)°).[131]

While the use of chlorophosphines as ancillary ligands in nickel- and palladium-catalyzed C-C and C-N bond-forming reactions has been reported,[138, 139] well-documented P-Cl reductive elimination processes (as featured in the net conversion of **4-1** to **4-3**) leading to the formation of isolable, two-coordinate Pd(0) complexes has not previously been documented in the literature prior to this work. However, carbene-halide reductive elimination from [(NHC)CuX] complexes has recently been reported,[140] as has chloride migration from a platinum centre to a phosphenium fragment that does not involve reduction at the metal.[141] The unusual manner in which the Pd(II) precursor **4-1** is reduced to the Pd(0) species **4-3** via the net reductive elimination of two relatively electronegative elements is also conceptually related to the formation of zerovalent (PR$_3$)$_n$Pd complexes from pre-catalyst mixtures featuring Pd(OAc)$_2$ and an excess of phosphine, which has been shown to proceed via P-O reductive elimination, affording [(OAc)PR$_3$]$^+$ as a byproduct (Scheme 4.4).[142-144]



Scheme 4.4 P-O Reductive Elimination to Form 'AcO-PPh$_3^+$'

Considering the limited number of two-coordinate [(NHC)Pd(PR$_3$)] complexes reported to date, and the unusual (and unexpected) formation of **4-3** via a net reductive elimination of P-Cl from **4-1**, the expansion of this chemistry to additional secondary phosphines was explored. Gratifyingly, treatment of [(IPr)PdCl$_2$]$_2$ with either P(*t*Bu)$_2$H or PCy$_2$H (thereby affording the presumptive intermediates **4-4** and **4-5**, respectively) followed by the addition of NaN(SiMe$_3$)$_2$ generated, over the course of one to three hours at room temperature, the anticipated two-coordinate chlorophosphine Pd(0) adducts [(IPr)Pd(PR$_2$Cl)] (R = *t*Bu, **4-6**, 68 %; R = Cy, **4-7**, 74 %) (Scheme 4.5), which were isolated and structurally characterized. Efforts to extend this chemistry to PPh$_2$H were unsuccessful, possibly owing to the relatively poor Lewis basicity of the anticipated PPh$_2$Cl co-ligand, affording an intractable mixture of phosphorus-containing species under similar reaction conditions (^{31}P NMR).

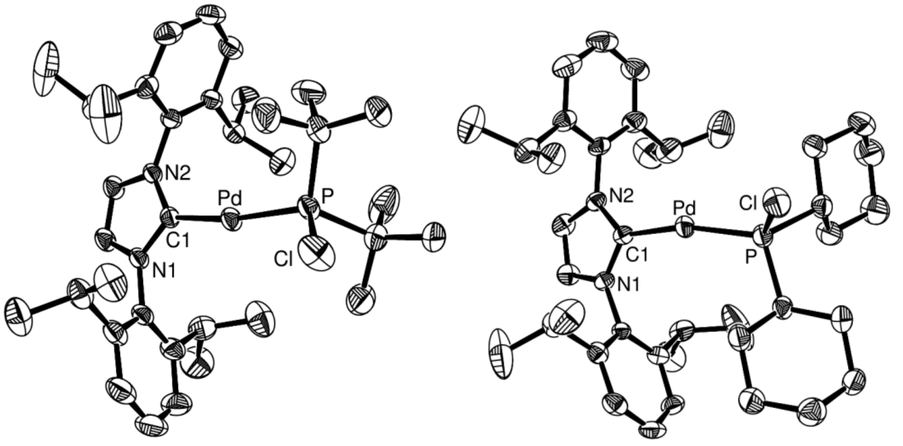


4-4 (R = *t*Bu)
4-5 (R = Cy)

4-6 (R = *t*Bu)
4-7 (R = Cy)

Scheme 4.5 Synthesis of 4-6 and 4-7

The crystallographically determined structures of **4-6** and **4-7** are presented in Figure 4.5. Whereas the Pd-P and Pd-C1 distances in **4-6** and **4-7** are comparable to those observed in **4-3**, a somewhat more significant variation in the P-Pd-C1 angle is observed across this series, with the PCy$_2$Cl adduct **4-7** deviating most significantly from linearity (164.03(9)°).



4-6 **4-7**

Figure 4.5 ORTEP diagrams for 4-6 and 4-7 shown with 50 % ellipsoids. Selected hydrogen atoms have been omitted for clarity. Selected interatomic distances (Å) and angles (°): For 4-6: Pd-P, 2.1947(6); Pd-C1, 2.061(2); P-Pd-C1, 169.00(6). For 4-7: Pd-P, 2.1763(10); Pd-C1, 2.043(3); P-Pd-C1, 164.03(9).

4.3. Summary

In conclusion, the preparation and isolation of the first well-defined [(NHC)Pd(PR_2Cl)] complexes has been achieved. These complexes are formed by way of an unusual P-Cl bond reductive elimination process upon treatment of readily available [(NHC)Pd$(Cl)_2$(PR_2H)] precursors with $NaN(SiMe_3)_2$. Given the significant interest in identifying pre-catalysts that afford access to monoligated [(NHC)Pd(0)] species under mild reaction conditions,[106-115,130,145] the facile protocol outlined herein is attractive in providing access to pre-formed [(NHC)Pd(PR_2Cl)] complexes bearing dialkylchlorophosphine ligands that are likely to be displaced more readily under catalytic conditions relative to their more electron-rich trialkylphosphine analogues. These complexes represent a potentially new class of pre-catalysts for Buchwald-Hartwig aminations and other palladium-mediated processes.

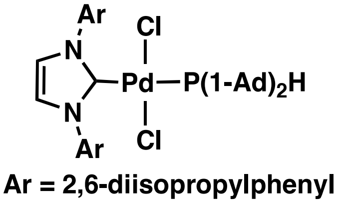
4.4. Experimental

4.4.1 General Considerations

All manipulations were conducted at ambient temperature in the absence of oxygen and water under an atmosphere of dinitrogen, either by use of standard Schlenk methods or within an mBraun glovebox apparatus, utilizing glassware that was oven-dried (130 ºC) and evacuated while hot prior to use. Celite (Aldrich) was oven-dried for 5 d and then evacuated for 24 h prior to use. Pentane and benzene were deoxygenated and dried by sparging with dinitrogen gas, followed by passage through a double-column solvent purification system purchased from mBraun Inc (one alumina-packed column and one column packed with copper-Q5 reactant). Diethyl ether was dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. Benzene-*d*$_6$ (Cambridge Isotopes) was degassed by using at least three repeated freeze-pump-thaw cycles and stored over 4 Å molecular sieves for 24 h prior to use. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. $[(\text{IPr})\text{PdCl}_2]_2$[122] and P(1-Ad)$_2$H[82] were prepared according to literature procedures, while $\text{NaN(SiMe}_3)_2$ (Aldrich), PCy_2H (Cytec), and P(*t*Bu)$_2$H (Strem) were purchased. Prepared and purchased solid reagents were evacuated under reduced pressure for 24 h prior to use and were stored in an inert atmosphere glovebox; otherwise chemicals were used as received. ^{1}H, ^{13}C, and ^{31}P NMR characterization data were collected at 300K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) with chemical shifts reported in parts per million downfield of SiMe_4 (for ^{1}H and ^{13}C) and 85% H_3PO_4 in D_2O (for ^{31}P). Elemental analyses were performed by Canadian Microanalytical Service Ltd., Delta, BC (Canada) and Midwest Microlab, LLC, Indianapolis, IN (USA).

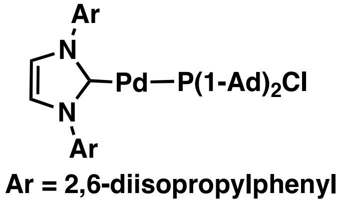
4.4.2 Preparation of Mixed NHC-Pd-Chlorophosphine Complexes

Preparation of 4-1



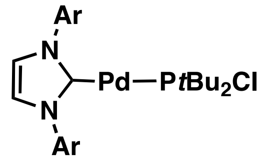
To a magnetically stirred suspension of [(IPr)PdCl$_2$]$_2$ (143 mg, 0.126 mmol) in THF (2 mL) was added P(1-Ad)$_2$H (77 mg, 0.252 mmol) at room temperature. After one hour, ^{31}P NMR analysis of the crude reaction mixture indicated consumption of P(1-Ad)$_2$H and the formation of a new phosphorus-containing species (**4-1**). The solvent was removed under reduced pressure followed by trituration of the resulting crude solid with pentane (3 x 2 mL). The remaining solid was dried in vacuo to afford **4-1** as an analytically pure off-white solid in 94 % yield (206 mg, 0.237 mmol). Anal Calcd for $C_{47}H_{67}N_2Cl_2P_1Pd_1$: C 65.01; H 7.78; N 3.23. Found: C 64.82; H 7.56; N 3.31. ^{1}H NMR (C_6D_6): δ 7.39-7.23 (m, 6H, ArH), 6.66 (d, J = 1.2 Hz, 2H, NCH=CHN), 3.52 (d, $^1J_{PH}$ = 350.3 Hz, 1H, PH), 3.48 (m, 4H, C*H*Me$_2$), 2.20-2.09 (m, 6H, Ad), 1.98-1.89 (m, 6H, Ad), 1.81-1.73 (m, 6H, Ad), 1.64 (d, $^3J_{HH}$ = 6.8 Hz, 12H, CH*Me*$_2$), 1.56-1.53 (m, 12H, Ad), 1.08 (d, $^3J_{HH}$ = 7.0 Hz, CH*Me*$_2$); ^{13}C{^{1}H} NMR (C_6D_6): δ 174.8 (d, $^2J_{PC}$ = 189.2 Hz, NCN), 146.4 (ArC), 135.2 (ArC), 129.1 (ArC), 123.1 (d, J_{PC} = 5.2 Hz, NCH=CHN), 122.8 (ArC), 41.2 (Ad), 37.4 (d, J_{PC} = 13.9 Hz, Ad), 35.7 (Ad), 28.0 (*C*HMe$_2$), 27.9 (d, J_{PC} = 8.8 Hz, Ad), 25.7 (CH*Me*$_2$), 22.1 (CH*Me*$_2$); ^{31}P NMR (C_6D_6): δ 56.3. Crystals suitable for X-ray crystallographic analysis were grown by vapor diffusion of pentane into a concentrated solution of **4-1** in benzene.

Preparation of 4-3



To a magnetically stirring solution of **4-1** (0.107 g, 0.123 mmol) in benzene (2 mL) was added $NaN(SiMe_3)_2$ (24 mg, 0.129 mmol). After three hours of stirring at room temperature, ^{31}P NMR analysis of the crude reaction mixture indicated complete consumption of **4-1**, and formation of a single phosphorus-containing product (**4-3**). The reaction mixture was diluted with pentane (4 mL) and filtered through Celite. The eluent was collected and the solvent was removed under reduced pressure. The crude solid was then triturated with pentane (3 x 2 mL) and diethyl ether (3 x 2 mL), and dried in vacuo to give **4-3** as an analytically pure dark yellow solid in 75 % yield (77 mg, 0.092 mmol). Anal Calcd for $C_{47}H_{66}N_2Cl_1P_1Pd_1$: C 67.84; H 8.00; N 3.37. Found: C 67.52; H 7.72; N 3.41. ^1H NMR (C_6D_6): δ 7.31-7.26 (m, 2H, ArH), 7.17-7.14 (m, 4H, ArH), 6.46 (s, 2H, NCH=CHN), 2.83 (m, 4H, C*H*Me$_2$), 2.10-1.98 (m, 12H, Ad), 1.91-1.84 (m, 6H, Ad), 1.68 (d, $^3J_{HH}$ = 7.0 Hz, 12H, CH*Me*$_2$), 1.66-1.59 (m, 12H, Ad), 1.20 (d, $^3J_{HH}$ = 7.9 Hz, 12H, CH*Me*$_2$); $^{13}C\{^1H\}$ NMR (C_6D_6): δ 197.2 (d, $^2J_{PC}$ = 224.2 Hz, NCN), 145.4 (ArC), 136.4 (ArC), 128.3 (ArC), 122.5 (ArC), 120.1 (NCH=CHN), 42.4 (d, J_{PC} = 8.8 Hz, Ad), 39.2 (d, J_{PC} = 9.8 Hz, Ad), 36.3 (Ad), 28.2 (d, J_{PC} = 9.8 Hz, Ad), 28.1 (*C*HMe$_2$), 24.5 (CH*Me*$_2$), 22.9 (CH*Me*$_2$); ^{31}P NMR (C_6D_6): δ 159.6. Crystals suitable for X-ray crystallographic analysis were grown by vapor diffusion of pentane into a concentrated solution of **4-3** in benzene.

Preparation of 4-6

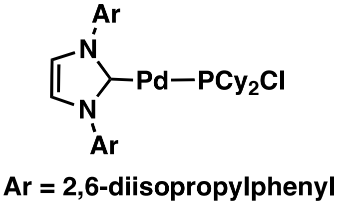


Ar = 2,6-diisopropylphenyl

To a magnetically stirring solution of $[(IPr)PdCl_2]_2$ (80 mg, 0.071 mmol) in benzene (1.5 mL) was added $P(tBu)_2H$ (25 µL, 0.138 mmol). After one hour, ^{31}P NMR analysis of the crude reaction mixture indicated consumption of $P(tBu)_2H$ and the formation of a new phosphorus-containing species (58.5 ppm, the presumptive intermediate **4-4**). The reaction mixture was diluted with pentane (4 mL), and filtered through Celite. The eluent was collected and the solvent was removed under reduced pressure to afford a yellow solid. This solid was dissolved in benzene (1.5 mL) and magnetic stirring was initiated. To this solution was added $NaN(SiMe_3)_2$ (25 mg, 0.138 mmol). After three hours of stirring at room temperature, ^{31}P NMR analysis of the crude reaction mixture indicated clean conversion to a single phosphorus-containing product (**4-6**). The reaction mixture was diluted with pentane (4 mL) and filtered through Celite. The eluent was collected and the solvent was removed under reduced pressure. The crude solid was then triturated with pentane (3 x 2 mL) and diethyl ether (3 x 2 mL), and dried in vacuo to give **4-6** as an analytically pure orange-brown solid in 68 % yield (64 mg, 0.094 mmol). Anal Calcd for $C_{35}H_{54}N_2Cl_1P_1Pd_1$: C 62.22; H 8.06; N 4.15. Found C 61.97; H 8.12; N 3.89. ^1H NMR (C_6D_6): δ 7.27 (m, 2H, ArH), 7.16-7.15 (m, 4H, ArH), 6.45 (s, 2H, NCH=CHN), 2.85 (m, 4H, C*H*Me$_2$), 1.66 (d, $^3J_{HH}$ = 6.5 Hz, 12H, CH*Me*$_2$), 1.19-1.15 (m, 30H, CH*Me*$_2$ and C*Me*$_3$); $^{13}C\{^1H\}$ NMR (C_6D_6): δ 146.9 (ArC), 137.9 (ArC), 130.0 (ArC), 124.2 (NCH=CHN or ArC), 121.9 (ArC or NCH=CHN), 39.8 (d, $^1J_{PC}$ = 7.5 Hz, *C*Me$_3$), 29.6-

29.5 (m, *C*HMe$_2$ and C*Me*$_3$), 26.0 (CH*Me*$_2$), 24.5 (CH*Me*$_2$), the carbene NCN resonance could not be identified unambiguously; ^{31}P NMR (C_6D_6): δ 163.7. Crystals suitable for X-ray diffraction were grown from a concentrated solution of **4-6** in pentane that was stored at -30 °C.

Preparation of 4-7



To a magnetically stirring solution of [(IPr)PdCl$_2$]$_2$ (70 mg, 0.062 mmol) in benzene (1.5 mL) was added PCy$_2$H (25 μL, 0.121 mmol). After one hour, ^{31}P NMR analysis of the crude reaction mixture indicated consumption of PCy$_2$H and the formation of a new phosphorus-containing species (25.9 ppm, the presumptive intermediate **4-5**). The reaction mixture was diluted with pentane (4 mL), and filtered through Celite. The eluent was collected and the solvent was removed under reduced pressure to afford a yellow solid. This solid was dissolved in benzene (1.5 mL) and magnetic stirring was initiated. To this solution was added NaN(SiMe$_3$)$_2$ (22 mg, 0.121 mmol). After one hour of stirring at room temperature, ^{31}P NMR analysis of the crude reaction mixture indicated clean conversion to a single phosphorus-containing product (**4-7**). The reaction mixture was diluted with pentane (4 mL) and filtered through Celite. The eluent was collected and the solvent was removed under reduced pressure. The crude solid was then triturated with pentane (3 x 2 mL) and diethyl ether (3 x 2 mL), and dried in vacuo to give **4-7** as an orange-brown solid in 74 % yield (65 mg, 0.089 mmol). ^{1}H NMR (C_6D_6): δ 7.05 (m, 2H, ArH), 6.95-6.93 (m, 4H, ArH), 6.21 (s, 2H, NCH=CHN), 2.62 (m, 4H, C*H*Me$_2$), 1.70-0.95 (m, 46H, Cy and CH*Me*$_2$; distinct CH*Me*$_2$ resonances observed at 1.44 (d, $^3J_{\mathrm{HH}}$ = 6.5 Hz) and 0.97 (d, $^3J_{\mathrm{HH}}$ = 7.0 Hz)); ^{13}C{^{1}H} (C$_6$D$_6$): δ 146.3 (ArC), 137.3 (ArC), 129.5 (ArC), 123.6 (NCH=CHN or ArC), 121.5 (ArC or NCH=CHN), 42.3 (Cy), 29.1-28.8 (m, Cy and *C*HMe$_2$), 28.0-26.9 (m, Cy), 26.7 (Cy), 25.6 (CH*Me*$_2$), 23.9 (CH*Me*$_2$), the carbene NCN resonance could not be identified unambiguously; ^{31}P NMR (C$_6$D$_6$): δ 138.4. Crystals suitable for X-ray diffraction were grown from a concentrated solution of **4-7** in pentane that was stored at -30 °C.

4.4.3 Crystallographic Solution and Refinement Details

Crystallographic data were obtained at 173(±2) K on either a Bruker D8/APEX II CCD or a Bruker PLATFORM/APEX II CCD diffractometer using a graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation, employing samples that were mounted in inert oil and transferred to a cold gas stream on the diffractometer. Programs for diffractometer operation, data collection, and data reduction (including SAINT) were supplied by Bruker. Gaussian integration (face-indexed) was employed as the absorption correction method and the structures were each solved by use of direct methods (*SHELXS-97* for **4-1**, **4-3·0.5C$_5$H$_{12}$**, and **4-7**; *SIR-97* for **4-6**). The structures were refined by use of full-matrix least-squares procedures (on F^2; *SHELXL-97*) with R_1 based on $F_o^2 \geq 2\sigma(F_o^2)$ and wR_2 based on $F_o^2 \geq -3\sigma(F_o^2)$. Anisotropic displacement parameters were employed for all the non-hydrogen atoms; during the structure solution process for **4-3**, half of an equivalent of pentane was located in the asymmetric unit and was refined anisotropically. All hydrogen atoms were added at calculated positions and refined by use of a riding model employing isotropic displacement parameters based on the isotropic displacement parameter of the attached atom. Additional crystallographic information is provided in Table 4.1 and Table 4.2.

Table 4.1 Crystallographic Data for 4-1 and 4-3• $0.5C_5H_{12}$

	4-1	**4-3• $0.5C_5H_{12}$**
Empirical formula	$C_{47}H_{67}Cl_2N_2PPd$	$C_{49.50}H_{72}ClN_2PPd$
Formula weight	868.30	867.91
Crystal dimensions	0.23 x 0.19 x 0.15	0.50 × 0.31 × 0.27
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$C2/c$
a (Å)	16.2112 (16)	21.4934 (7)
b (Å)	12.1097 (12)	13.5722 (5)
c (Å)	22.836 (2)	31.6794 (11)
α (deg)	90	90
β (deg)	106.2460 (10)	95.8069 (4)
γ (deg)	90	90
V (Å^3)	4304.0 (7)	9193.9 (6)
Z	4	8
ρ_{calcd} (g cm^{-3})	1.340	1.254
μ (mm^{-1})	0.627	0.531
Range of transmission	0.9102–0.8671	0.8691–0.7768
2θ limit (deg)	55.04	50.98
	$-20 \le h \le 21$	$-26 \le h \le 26$
	$-15 \le k \le 15$	$-16 \le k \le 16$
	$-29 \le l \le 29$	$-38 \le l \le 38$
Total data collected	37222	33027
Independent reflections	9881	8574
R_{int}	0.0667	0.0156
Observed reflections	8010	8131
Data/restraints/parameters	9881 / 0 / 478	8574 / 0 / 492
Goodness-of-fit	1.019	1.033
$R1$ [$F_o^2 \ge 2\sigma(F_o^2)$]	0.0420	0.0467
$wR2$ [$F_o^2 \ge -3\sigma(F_o^2)$]	0.1139	0.1267
Largest peak, hole (eÅ^{-3})	1.551, –1.537	3.996, –0.642

Table 4.2 Crystallographic Data for 4-6 and 4-7

	4-6	**4-7**
Empirical formula	$C_{39}H_{58}ClN_2PPd$	$C_{35}H_{54}ClN_2PPd$
Formula weight	727.69	675.62
Crystal dimensions	0.42 × 0.08 × 0.04	0.35 × 0.14 × 0.10
Crystal system	monoclinic	monoclinic
Space group	$P2_1/n$	$C2/c$
a (Å)	12.3612 (6)	18.2945 (11)
b (Å)	21.7925 (10)	18.0530 (10)
c (Å)	14.5546 (7)	22.0271 (13)
α (deg)	90	90
β (deg)	96.2170 (10)	96.3508 (7)
γ (deg)	90	90
V (Å^3)	3897.7 (3)	7230.3 (7)
Z	4	8
ρ_{calcd} (g cm^{-3})	1.240	1.241
μ (mm^{-1})	0.613	0.655
Range of transmission	0.9747–0.7816	0.9350–0.8031
2θ limit (deg)	53.02	52.84
	$-15 \leq h \leq 15$	$-22 \leq h \leq 22$
	$-27 \leq k \leq 27$	$-22 \leq k \leq 22$
	$-18 \leq l \leq 18$	$-27 \leq l \leq 27$
Total data collected	31101	28604
Independent reflections	8058	7417
R_{int}	0.0784	0.0366
Observed reflections	5491	6018
Data/restraints/parameters	8058 / 0 / 397	7417 / 0 / 361
Goodness-of-fit	1.007	1.029
R_1 [$F_o^2 \geq 2\sigma(F_o^2)$]	0.0426	0.0298
wR_2 [$F_o^2 \geq -3\sigma(F_o^2)$]	0.1023	0.0745
Largest peak, hole (eÅ^{-3})	1.009, –0.704	0.533, –0.434

CHAPTER 5. CONCLUSIONS AND FUTURE WORK

5.1. Chapter 2 Conclusions and Future Work

The studies presented in Chapter 2 help to address the challenge of achieving chemoselectivity in Buchwald-Hartwig amination chemistry. By conducting a series of competition experiments in which two competing amines were reacted with 4-chlorotoluene in order to determine which substrate undergoes preferential arylation when a $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) catalyst system is employed, a chemoselectivity hierarchy was determined. This hierarchy allowed for the predictable amination of aminoaryl halides containing reactive amine moieties (Tables 2.2-2.4; 46 examples, 50-96 %) and the monoarylation of diamine substrates (Table 2.5; 16 examples, 60-97 %).

Alongside of this work, a complementary ligand, *p*-Mor-DalPhos (**L2**) was synthesized and employed in a similar series of competition experiments, in some instances engendering orthogonal chemoselectivity. The complementary selectivity exhibited by these ligands was demonstrated in the synthesis of **5a** and **5a'**, whereby arylation occurs at different sites within a diamine substrate depending on which ligand is employed. Finally, complexes **2-7**, **2-8** and **2-9** were synthesized, which when viewed alongside of the chemoselectivity hierarchy, suggests that the chemoselectivity exhibited in these reactions are dependent on the amine binding step of the catalytic cycle.

The totality of this work represents the most extensive study yet presented on the topic of chemoselective aminations. In particular, the synthetic focus of this study (63 total examples of structurally diverse di-, tri-, and tetraamines synthesized via chemoselective Buchwald-Hartwig aminations) differentiates it from previous reports, and demonstrates the potential of this methodology in the construction of oligoamine targets. Given that Mor-DalPhos (**L1**) has proven extremely useful in the monoarylation of both ammonia and hydrazine, it is perhaps no surprise that it is also useful in these chemoselective aminations. Given the commercial availability of this ligand, this study could represent a breakthrough in the synthesis of high-value oligoamines.

The first-generation DalPhos ligand, Me-DalPhos (Figure 1.8), offers good generality in terms of the ability to promote the palladium-catalyzed arylation of primary and secondary amines with both activated and deactivated (hetero)aromatic halides.[57] However, its ability to promote the monoarylation of ammonia with a wide-range of aryl halides is significantly poorer than that of Mor-DalPhos **(L1)**, despite the fact that both ligands contain a di(1-adamantyl)phosphine donor, and a dialkylamine donor (with the difference being that the amine donor in Me-DalPhos is a dimethylamino group, and the donor in Mor-DalPhos (**L1)** is in the form of a morpholino group). The fact that such a drastic change in reactivity is induced from a relatively small structural modification illustrates the fact that slight variations in the electronics and sterics of ancillary ligands can greatly impact catalyst activity.

Amphos (di-*tert*-butylphosphino)-*N*,*N*-dimethylaniline, Figure 5.1) has been successfully employed as a ligand in Buchwald-Hartwig aminations,[146] Suzuki cross-couplings,[147] and Negishi couplings.[148,149] As Amphos is a phenylene-based ligand with a bulky, electron-rich phosphine donor, and a dialkylamine functional group, it is easy to see the structural similarities between Amphos and *p*-Mor-DalPhos (**L2**).

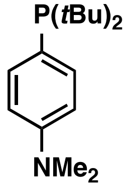


Figure 5.1 Structure of Amphos

However, to date, *p*-MorDalPhos (**L2**) has only been employed as a ligand in a somewhat limited series of Buchwald-Hartwig amination reactions, in the form of competition experiments (Table 2.1) and in the synthesis of **5a'**. Given the utility of Amphos in the aforementioned reactions, and considering the improved reactivity exhibited by modifying the dimethylamino group on Me-DalPhos to the morpholino-group on Mor-DalPhos (**L1**), examining the reactivity of *p*-Mor-DalPhos (**L2**) in an extended array of Buchwald-Hartwig amination reactions, and in additional palladium-mediated processes would be worthwhile, and could potentially expand the utility of DalPhos ligands beyond their current scope.

5.2. Chapter 3 Conclusions and Future Work

The results reported in Chapter 3 outline successful efforts made to conduct Buchwald-Hartwig aminations under aqueous and solvent-free conditions, an area to which surprisingly little attention has been paid in the literature. By employing the same, unmodified [Pd(cinnamyl)Cl]$_2$/Mor-DalPhos (**L1**) catalyst system that has proven useful in ammonia arylation,[58] hydrazine arylation,[59] and in the chemoselective aminations presented in Chapter 2, both primary and secondary amines (Tables 3.1 and 3.2, 37 examples, 62-95 % yield) can be monoarylated in synthetically useful yields without the need to add a co-solvent or surfactant to the reactions. The same catalyst system was again employed in Buchwald-Hartwig aminations conducted under solvent-free (neat) conditions (Table 3.2, 15 examples, 74-97 %), with the resultant products obtained in good to excellent yields. This solvent-free protocol also has the benefit of expanding the reaction scope to substrates not adaptable to the aqueous protocol, further increasing the utility of $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) as a catalyst system for Buchwald-Hartwig aminations conducted under these green conditions.

That both of these methodologies can be conducted using an unmodified ligand that has already proven to be extremely useful in Buchwald-Hartwig aminations, without requiring additional additives such as surfactants or co-solvents, makes the $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) catalyst system valuable as a practical green catalyst. Considering the broad substrate scope of these methodologies, and the fact that these aminations can in some cases be conducted without the rigorous exclusion of air, this study has indeed helped to address the challenge of catalyst generality in Buchwald-Hartwig aminations.

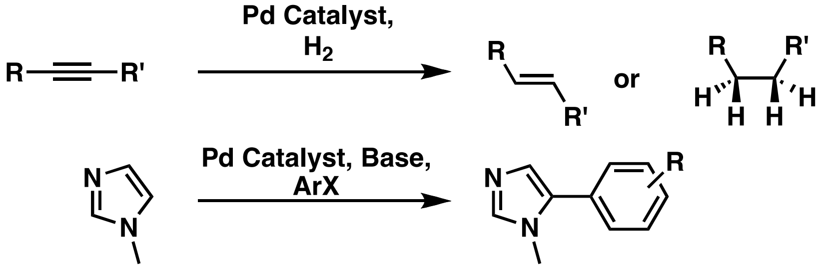
Considering the surprising activity of unmodified Mor-DalPhos (**L1**) in the aqueous and solvent-free chemistry described in Chapter 3, expansion of these methodologies to other palladium-mediated processes could also be explored. Acetone monoarylation chemistry has previously been reported by the Stradiotto group,[60] and is promoted by $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) with acetone used as both a solvent and a reagent. Given the miscibility of acetone and water, conducting this chemistry using only a stoichiometric amount of acetone (via a prepared stock solution of acetone in water) could greatly reduce the amount of acetone required for the reactions to proceed, thereby increasing the 'greenness' of the chemistry. Additionally, as Mor-DalPhos (**L1**) has not yet been employed in Suzuki cross-couplings, where aqueous reaction conditions are well known, employing the same $[Pd(cinnamyl)Cl]_2$/Mor-DalPhos (**L1**) catalyst in this chemistry could also prove interesting, and further expand the utility of Mor-DalPhos (**L1**) in palladium-mediated catalysis.

5.3. Chapter 4 Conclusions and Future Work

Chapter 4 outlines the preparation and characterization of a series of the first reported $[(NHC)Pd(PR_2Cl)]$ complexes (where NHC = IPr, and R = 1-Ad, Cy and *t*Bu) via an unusual net reductive elimination of P-Cl. The formation of these complexes occurs under mild reaction conditions via the addition of NaHMDS to $[(NHC)Pd(Cl)_2(PR_2H)]$ precursors at room temperature, potentially giving this methodology broader variability than what has been described in this work, via variation at both the NHC and chlorophosphine ligands.

Given the success that transition metal complexes featuring both NHC and phosphine ligands have had in catalysis, and the fact that $[(NHC)Pd(PR_3)]$ species have proven useful as pre-catalysts for several palladium-mediated processes (likely due to the ability of the phosphine donor to be released *in situ* to generate the catalytically active [(NHC)Pd(0)] species), these chlorophosphine complexes could represent the first of a new class of well-defined Pd(0) pre-catalysts for palladium-mediated catalytic processes. However, the utility of these complexes in catalysis has not yet been studied.

Due to the inferior electron-donating ability of a dialkylchlorophosphine ligand compared to its trialkylphosphine analogue, the release of the chlorophosphine ligands *in situ* to generate a monoligated [(NHC)Pd(0)] species could potentially occur more readily with these complexes. With this in mind, **4-3**, **4-6** and **4-7** are good candidates to be screened for their potential ability to act as pre-catalysts for palladium-mediated processes. Besides their potential to effectively mediate Buchwald-Hartwig amination reactions, this set of complexes could be screened for their ability to promote the hydrogenation of unsaturated substrates, a reaction class for which NHC-palladium catalysts,[150] including [(NHC)Pd(PCy$_3$)] complexes, have proven useful (Scheme 5.1).[125] Additionally, given that the pre-formed mixed palladium complex [(NHC)Pd(PCy$_3$)(OAc)$_2$] has been shown to be an effective pre-catalyst for the palladium-mediated C5-arylation of imidazoles at moderate catalyst loadings (2.5 % Pd),[129] the potential use of **4-3**, **4-6** and **4-7** as pre-catalysts for this reaction should also not be overlooked (Scheme 5.1).



Scheme 5.1 Test Catalytic Reactions for [(NHC)Pd(PR$_2$Cl)] Complexes

Although the air-sensitive nature of these complexes is less than ideal, the straightforward method of generating these species from simple secondary phosphines under mild conditions is appealing, as is the low cost of the secondary phosphine ligand precursor. Finally, the potential to modify both the NHC and dialkylchlorophosphine ligands in these complexes, coupled with their potential for demonstrating enhanced catalytic activity relative to the currently employed library of palladium complexes featuring both NHC and phosphine ligands, could be very beneficial in the aforementioned palladium-mediated catalytic reactions.

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