Design and Application of P,N-Ligands for Platinum-Group Metal Catalyzed Reactions

by

Rylan J. Lundgren

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DALHOUSIE UNIVERSITY

DEPARTMENT OF CHEMISTRY

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ABSTRACT

Homogeneous organometallic species serve as useful catalysts for a vast number of chemical transformations. Ancillary ligands which bind to the metal center are employed to modulate the reactivity of the metal, and have been key to the discovery and improvement of most types of transition metal-mediated reactions. This thesis describes the design and application of P,N-ligands in platinum group-catalyzed reactions, specifically the Ru- and Ir-catalyzed ketone transfer hydrogenation (TH) and the Pd-catalyzed cross-coupling of aryl (pseudo)halides and N-H containing substrates. A zwitterionic Ru-species featuring a donor substituted P,N-indenide ligand was found to be an excellent catalyst for ketone TH, providing turnover frequencies (TOFs) as high as 300 000 h^{-1}, while related cationic Ru-complexes ligated by P,N-indene ligands were found to be rather poor catalysts. Ir-complexes supported by either indene or indenide P,N-ligands were also found to be active TH catalysts (TOFs ~30 000 h^{-1}), however phenylene P,N ligands, specifically (*o*-tBu_2P-C_6H_4)NMe_2, displayed optimal catalytic performance, allowing for rapid ketone reduction (TOFs of >100 000 h^{-1}), at low catalyst loadings (as low as 0.004 mol% Ir). Enantioselective TH was achieved by employing the suitably substituted, commercially available P,N-ligand, Cy-Mandyphos in combination with $[Ir(COD)Cl]_2$ and $NaPF_6$.

The use of P,N-ligands in Pd-catalyzed C-N cross coupling, specifically (*o*-R_2P-C_6H_4)NMe_2 (R = tBu or 1-Ad), allowed for the development of a highly versatile catalyst system for this reaction. In combination with $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$, the above described ligands enabled the cross-coupling of aryl and heteroaryl chlorides and bromides to a diverse range of amine and related substrates such as primary alkyl- and arylamines, cyclic and acyclic secondary amines, N-H imines, hydrazones, lithium amide, and ammonia. Reactions could be performed at low catalyst loadings (0.5-0.02 mol% Pd) with excellent functional group tolerance and chemoselectivity. The ligand N-[2-di(1-adamantylphosphino)phenyl]morpholine in combination with $[Pd(cinnamyl)Cl]_2$ was found to provide excellent reactivity for the cross-coupling of ammonia to aryl chlorides with catalyst loadings of 0.3-5 mol% Pd. Sterically unbiased substrates containing electron-donating groups were tolerated with minimal competing diarylation. Aryl tosylates could be coupled with ammonia at room temperature and chemoselective ammonia arylation in the presence of other amine functionality was well tolerated. Pd-catalyzed cross-coupling of hydrazine with aryl chlorides and tosylates was achieved employing N-[2-di(1-adamantylphosphino)phenyl]-morpholine as the ligand. Good yields of the desired, mono-functionalized aryl hydrazine product was observed for a range of substrates at 5 mol% Pd. Selective hydrazine coupling was observed in the presence of other NH-functionality and NH-indazoles could be prepared by the tandem cross-coupling/condensation of hydrazine with 2-chlorobenzaldehydes.

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
Anal. Calcd.	analysis calculated
app	apparent
BDE	bond dissociation energy
Bn	benzyl
br	broad
nBu	n-butyl
tBu	tert-butyl
COD	1,5-cyclooctadiene
conv	conversion
COSY	homonuclear shift correlation spectroscopy
Cp*	pentamethylcyclopentadienyl, η^5-C_5Me_5
Cy	cyclohexyl
Cy-MandyPhos	1,1′-bis(dicyclohexylphosphino)-2,2′-bis[(*S*)-α (dimethylamino)benzyl]ferrocene
Cy-Taniaphos	dicyclohexylphosphino-2-[(*R*)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl]ferrocene
d	doublet(s) *or* days(s)
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublets of doublets
dt	doublet of triplets
DiPPF	1,1’-bis(diisopropylphosphino)ferrocene
DMSO	dimethyl sulfoxide
ee	enantiomeric excess

ESI	electrospray ionization
Et	ethyl
GC	gas chromatography
h	hour(s)
Hex	hexane
HRMS	high-resolution mass spectrometry
Hz	Hertz
$^{n}J_{XX'}$	n bond coupling constant between atom X and atom X'
L	neutral 2-electron donor ligand
L_n	generic ligand set
m	multiplet or meta
M	generic transition metal *or* mol/L *or* molecular ion
m/*z*	mass-to-charge ratio
Me	methyl
min	minute(s)
mol	mole(s)
MPV	Meerwein-Ponndorf-Verley
nBu	neo-butyl
nd	not determined
NHC	N-heterocyclic carbene
NMR	nuclear magnetic resonance
nPent	neo-pentyl
OAc	acetate
ORTEP	Oak Ridge thermal ellipsoid plot
OTf	triflate (trifluoromethanesulfonate)
OTs	tosylate (*p*-toluenesulfonate)
o	ortho
p	para
Ph	phenyl
iPr	iso-propyl
ppm	parts per million

PTFE	poly(tetrafluoroethylene)
q	quartet
s	singlet
t	triplet
TBDMS	tert-butyl-dimethylsilyl
TH	transfer hydrogenation
THF	tetrahydrofuran
TLC	thin-layer chromatography
TOF	turnover frequency
TON	turnover number
TMS	trimethylsilyl
TsDPEN	*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine
X	generic anion *or* anionic ligand

ACKNOWLEDGEMENTS

Portions of the work in this thesis arose from a collaborative effort between myself and other members of the Stradiotto research group. Dr. Matthew A. Rankin synthesized the Ru-compounds studied for transfer hydrogenation in Section 2.2. Antonia Sappong assisted with the synthesis of the ligands discussed in Section 3.2 and Brendan D. Peters performed a number of optimization reactions as well as selected examples within the substrate scope in Section 3.3. Pamela G. Alsabeh prepared some of the Pd-complexes discussed in Section 3.3, and performed the stiochiometric reactions outlined in that Section, along with some of the room-temperature ammonia cross-coupling reactions.

I would like to thank Stradiotto group members, past and current, including Dom Wechsler, Steve Scully, Ben Tardiff, Pam Alsabeh, Chris Lavery, and Lauren Longobardi. Special gratitude is reserved for Antonia Sappong and Brendan Peters, who were two excellent undergraduate researchers that were able to assist significantly with some aspects of the Pd-cross-coupling chemistry presented in this thesis.

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we talked a lot of chemistry, and learned a lot of chemistry together, and am I glad to have got a chance to work with him everyday.

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CHAPTER 1. INTRODUCTION

1.1 General Introduction

With an estimated 80-90% of all chemical products being produced by catalytic processes,[1] the economic and environmental impact of catalysis is difficult to overstate. The successful implementation of catalytic methods allows for the conversion of abundant raw materials, such as CO, H_2, water, and petroleum, into higher-value products ranging from plastics and coatings to advanced pharmaceutical ingredients and designer electronic materials. Conversely, catalysts can be employed to convert waste products to more benign substances, or be used to recycle high-value products into forms that are again useful. The development and application of increasingly effective catalysts allow for both the economic and environmental costs associated with chemical synthesis to be reduced, promoting sustainable chemical practices.[2]

Homogeneous catalysis with transition metal complexes has led to the development of numerous new and/or more efficient methods for chemical synthesis. At the heart of the development of such catalysts is the design of ligands, which influence the steric and electronic properties of the metal and allow for catalyst tailoring. It is through ligand design that exquisite control over the reactivity and selectivity in transition metal catalysis has been achieved in a number of important transformations. Examples of indispensible processes catalyzed by transition metals in chemical production and synthesis include hydrogenations,[3] oxidations,[4] hydroformylations,[5] C-C cross-couplings,[6] and polymerizations.[7] In each case, highly evolved catalysts have arisen from an understanding of how catalyst performance can be optimized through altering ligand structure.

While research advancements in homogeneous catalysis to date are significant, there exist still many challenges related to the scope, efficiency, and applicability of most transition metal-catalyzed reactions. Studies aimed at the design and application of suitably engineered ligand sets will contribute to shedding light on what structural features engender desirable catalytic activity and should allow for the development of more effective and benign routes to the chemical products that pervade our daily lives.

1.2 Overview of the Thesis

The research encompassed within this thesis builds upon the Stradiotto research group's interest in the design and application of P,N-ligands in platinum group metal-mediated bond activation and catalysis. Previous work has documented the preparation, as well as preliminary surveys in a number of catalytic transformations of a series of transition metal complexes featuring P,N-indene and related ligand frameworks, examples of which are shown in Figure 1.1.[8]

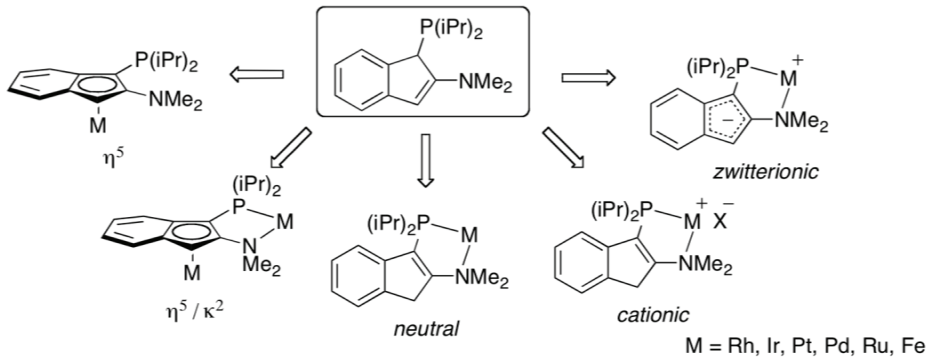


Figure 1.1 Previous research in the Stradiotto group involving P,N-substituted indene and indenide ligands with transition metals.

Chapter 2, Section 1 details the study of Ru complexes supported by P,N-substituted indene and indenide ligands for the transfer hydrogenation of ketones. Here, a remarkable divergence in reactivity between cationic and formally zwitterionic species was observed, indicating such strategies involving zwitterionic ligation may offer a complementary route to the generation of highly active ketone transfer hydrogenation catalysts. Chapter 2, Section 2 describes the development of related Ir transfer hydrogenation catalysts. It was found that simple, phenylene-based ligands provided optimal catalytic performance, allowing for rapid ketone reduction with low catalyst loadings and in short reaction times (Figure 1.2). Enantioselective transfer hydrogenation was also achieved by employing suitably substituted, commercially available P,N-ligands. A notable theme in both Sections 1 and 2 is the fact that both the Ru- and Ir-catalyst systems lack ancillary ligand NH-groups, a commonly employed design principle in the field, which is thought to be key in the generation of highly active transfer hydrogenation catalysts.[9]

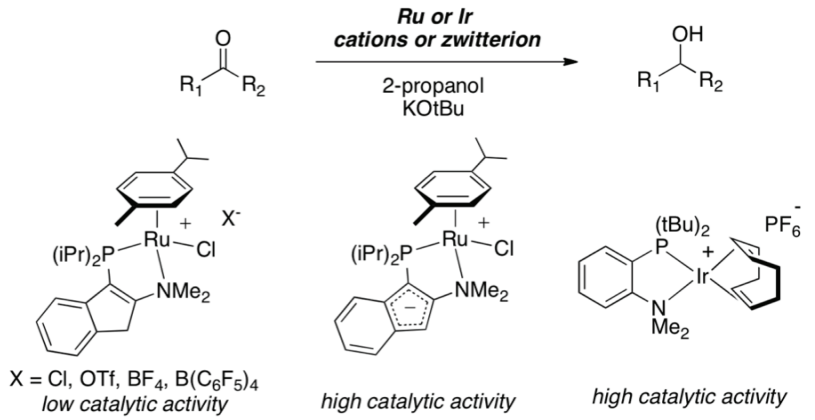


Figure 1.2 Ketone transfer hydrogenation by zwitterionic Ru complexes and cationic Ir complexes supported by P,N-ligands.

Chapter 3 describes the application of phenylene-based P,N-ligands in the Pd-catalyzed cross-coupling of aryl halides and N-H containing substrates. Chapter 3, Section 1 concerns the development of a highly versatile catalyst system for Buchwald-Hartwig amination. In combination with $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$, structurally simple and air-stable P,N ligands enabled the cross-coupling of aryl and heteroaryl chlorides including those featuring enolizable ketones, ethers, esters, carboxylic acids, phenols, alcohols, olefins, amides, and halogen functional groups, to a diverse range of amine and related substrates such as primary alkyl- and arylamines, cyclic and acyclic secondary amines, N-H imines, hydrazones, lithium amide, and ammonia. In many cases, the reactions could be performed at low catalyst loadings (0.5-0.02 mol% Pd) with excellent functional group tolerance and chemoselectivity (Figure 1.3).

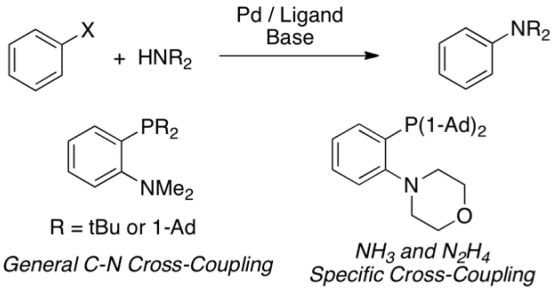


Figure 1.3 Pd-catalyzed cross-coupling of aryl halides and amines with P,N-phenylene ligands.

Chapter 3, Section 2 addresses limitations with respect to the arylation of ammonia in the "first generation" ligand system described in Section 1. From a series of prepared P,N-ligands, the ligand *N*-[2-di(1-adamantylphosphino)phenyl]morpholine combined with $[Pd(cinnamyl)Cl]_2$ was found to provide excellent reactivity for the cross-coupling of ammonia to aryl chlorides with catalyst loadings of 0.3-5 mol% Pd (Figure 1.3). Sterically unbiased substrates containing electron-donating groups were tolerated with minimal competing diarylation. Aryl tosylates could be coupled with ammonia at room temperature and chemoselective ammonia arylation in the presence of other amine functionality was well tolerated. Preparation of the oxidative addition product derived from Pd/ligand/aryl chloride mixtures allowed for the remarkably mild (room temperature) arylation of ammonia, employing aryl chlorides.

Chapter 3, Section 3 reports the first example of the Pd-catalyzed cross-coupling of aryl chlorides and tosylates with hydrazine. It was found that among the wide array of ligands screened for this transformation, *N*-[2-di(1-adamantylphosphino)phenyl]-morpholine provided good yields of the desired, mono-functionalized aryl hydrazine product. The reaction was found to proceed with reasonable substrate scope, and selective hydrazine coupling was observed in the presence of other NH-functionality. Additionally, NH-indazoles could be prepared via the tandem cross-coupling/condensation of hydrazine with 2-chlorobenzaldehydes.

Chapter 4 concludes the thesis with a brief summary of the work presented herein, in addition to a discussion of future avenues of research, building upon some of the successes and unanswered questions of this work.

CHAPTER 2. DEVELOPMENT AND APPLICATION OF P,N-LIGANDS FOR RU- AND IR-CATALYZED KETONE TRANSFER HYDROGENATION

2.1 INTRODUCTION

Transfer hydrogenation is an operationally simple, environmentally benign complement to direct hydrogenations employing dihydrogen gas and stoichiometric metal hydride reductions.[9a, 9c, 10] Key to this process is the use of non-toxic, readily available, inexpensive H_2 surrogates, such as 2-propanol or formic acid. The initial discovery that hydrogen may be transferred from a donor molecule such as an alcohol to an acceptor molecule such as a ketone was made in 1925, when it was found that aluminum isopropoxide could promote the transfer of hydrogen from 2-propanol to simple ketones in a reaction now referred to as the Meerwein-Ponndorf-Verley (MPV) reduction.[11] It was later revealed that this reaction can proceed in the reverse direction, resulting in oxidation of the substrate (Oppenauer oxidation), when the hydrogen acceptor (for example acetone) is supplied in excess.[12] Mechanistic studies suggested that the hydrogen transfer process occurs in a "direct" manner with both ketone and alcohol coordinated to the metal during hydrogen transfer rather than through Al-hydride complexes (Figure 2.1).[11a]

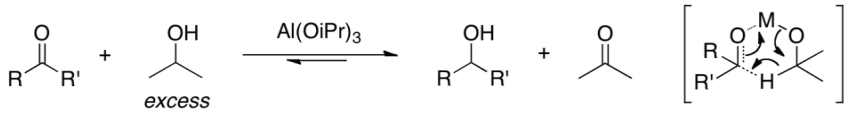


Figure 2.1 General scheme for the MPV reduction of ketones, with proposed concerted hydride transfer from a directly coordinated metal species (boxed).

The utility of early TH processes were limited by long reaction times and the necessity to use large amounts of the metal species, most commonly Ru, Rh, Ir, and lanthanides, to overcome the sluggish reactivity of these catalysts.[13] In 1991, Bäckvall and co-workers discovered that small amounts of base in the presence of $RuCl_2(PPh_3)_3$ led to the highly productive TH of ketones using catalyst loadings of 0.1 mol%.[14] In the absence of either Ru or base, minimal conversion was observed (Figure 2.2). Similar catalytic systems were then extended to the TH of imines[15] and the oxidation of secondary alcohols using acetone as the hydrogen acceptor and K_2CO_3 as the base.[16]

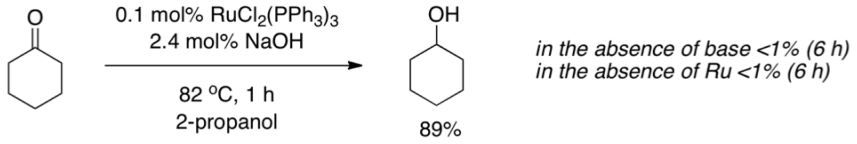


Figure 2.2 The dramatic effect of base on Ru-catalyzed TH of cyclohexanone in 2-propanol.

The role of base in TH using $RuCl_2(PPh_3)_3$ is to form catalytically active Ru-hydrides, more specifically $RuH_2(PPh_3)_3$, via a Ru-alkoxide species, generated by the loss of HCl, which can undergo β-elimination to yield Ru-H and acetone (Figure 2.3).[17] The Ru-H complex can then deliver hydride to the carbonyl moiety (typically via 1,2-insertion of C=O into the Ru-H) and release the product alcohol via protonation of the new Ru-alkoxide by the solvent, or alternatively undergo reductive elimination. Following a reductive elimination step, the transient Ru(0) intermediate would rapidly undergo O-H oxidative addition with a solvent molecule to reform a reactive Ru(H)(OR) intermediate.

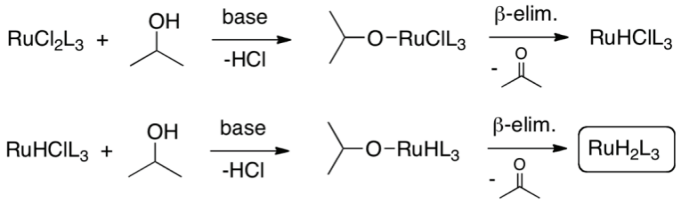


Figure 2.3 Proposed mechanism for the formation of $RuH_2(PPh_3)_3$, the active species in TH employing $RuCl_2(PPh_3)_3$ as a pre-catalyst.

The field of transition metal catalyzed TH was revolutionized in the mid-90's when Noyori and co-workers published a series of papers exploring the use of chiral N-sulfonated 1,2-diamines and amino alcohols as ligands for asymmetric reductions of aryl ketones and imines in combination with $[RuCl_2(arene)]_2$ precursors (Figure 2.4).[9c, 18] Up until this time, while some catalytic systems were observed to show good activity in TH, asymmetric versions of the transformation typically afforded only modest enantioselectivities, and reaction conditions were typically harsh (2-propanol at refluxing temperatures).[13] Furthermore, high chemoselectivity for carbonyl and imine unsaturation in the presence of olefins and alkynes remained unresolved issues. The use of mixtures of

Ru-arene precursor complexes and chiral diamine or amino alcohol ligands in the presence of base were found to reduce a wide variety of aryl ketones with good to excellent enantioselectivities (80-99% *ee*; commonly >95% *ee*) at room temperature with impressive rates (typically >95% conversion in 1-20 h at catalyst loadings between 0.5-0.1 mol% Ru at room temperature).[9c, 18a-c] From these studies, a number of key design principles for highly productive, selective, asymmetric TH catalysts were uncovered; 1) NH-functionality in the ligand is essential to high activity, as evidenced by the fact that dimethylamino ligand analogues were found to be totally ineffective; 2) an anti-1,2 *(trans*) relationship between the donor atoms is required in order to achieve high enantioselectivities; and 3) when using 2-propanol, reactions are best carried out under dilute conditions (0.1 M) to prevent back reaction (substrate dehydrogenation) and racemization. The origin of high enantioselectivity as been postulated to involve C-H/arene interactions between a Ru-arene C-H bond and the aromatic ring of the substrate.[19]

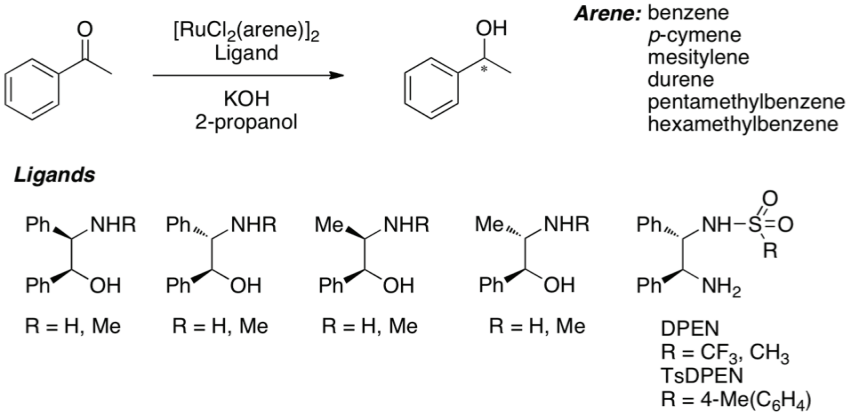


Figure 2.4 Initial metal and chiral ligand sets employed by Noyori for the highly selective TH of aryl ketones.

Systems comprising of RuCl(arene)(TsDPEN) emerged not only as excellent catalysts for the asymmetric TH of aryl ketones, but also for imine substrates,[18c] as well as unsaturated ketones, with remarkable selectivity for carbonyl reduction.[20] To prevent racemization of the chiral alcohol product at high conversion as a result of the back reaction with acetone, mixtures of formic acid and triethylamine were used as the hydrogen source, as the delivery of H_2 from formic acid to the catalyst resulted in the

irreversible loss of CO_2. The HCO_2H/NEt_3 solvent system provided the ability to conduct TH reactions under considerably higher concentrations than could be employed when using 2-propanol (up to 10 M vs. 0.1 M), an attractive protocol for large scale syntheses (Figure 2.5).[21]

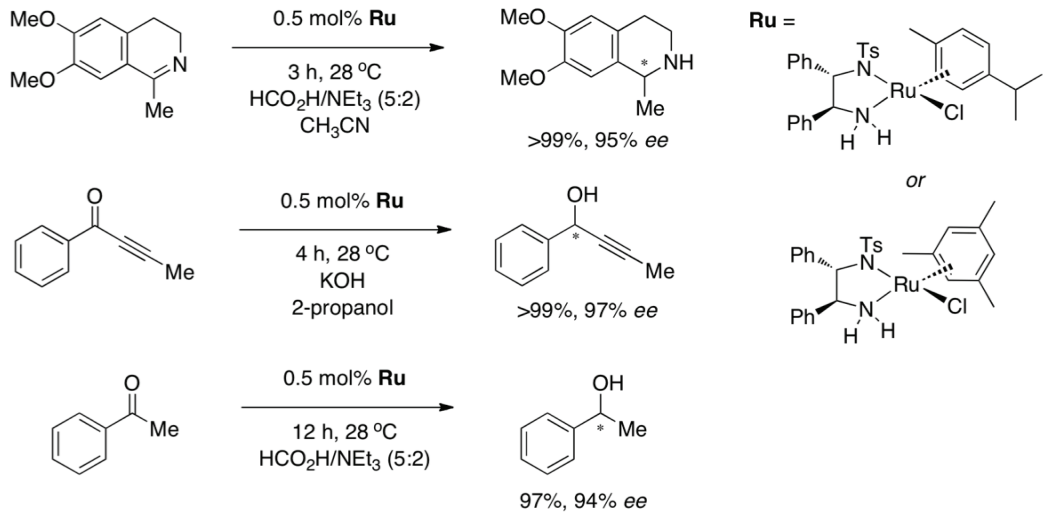


Figure 2.5 Extensions of Noyori's RuCl(arene)TsDPEN asymmetric TH catalyst to imines, acetylenic ketones, and high substrate concentrations with formic acid/triethylamine.

Detailed studies with RuCl(arene)TsDPEN catalysts concerning the isolation of catalytically relevant intermediates revealed the excellent activity of these catalysts to be attributed to a metal/NH acid-base synergy. Noyori has termed this combination of Lewis acid and Lewis base functionality *bifunctional catalysis*. A similar effect was observed in the case of the landmark RuX_2(diphosphine)(diamine) H_2 hydrogenation catalysts.[3i, 9b] The loss of HCl from (arene)RuCl(amidoamine) complexes in the presence of base results in the formation of the related 16-electron diamido complex which readily dehydrogenates 2-propanol (or formic acid) to produce an (arene)Ru(H)(amidoamine) complex as a single diastereomer. The structures of both of these species have been determined unequivocally by use of X-ray crystallography. Kinetic studies, isotope labeling and computational analysis have all confirmed that hydrogen transfer in these systems occurs via a unique bifunctional pathway where both hydride and proton are transferred via a six-membered transition state (Figure 2.6).[18d, 19, 22] Concerted proton-

hydride transfer has also been invoked in rationalizing the high catalytic activity for TH processes employing Shvo's catalyst (actually developed prior to Noyori's TH-system).[23] In this case, a dimeric complex is postulated to be in equilibrium with monomeric species, one of which is a Ru-hydride possessing an acidic OH-proton. The presence of both acidic and hydridic moieties within the catalyst structure results in rates of TH reactions that are significantly higher than traditional Ru-H species (Figure 2.7).

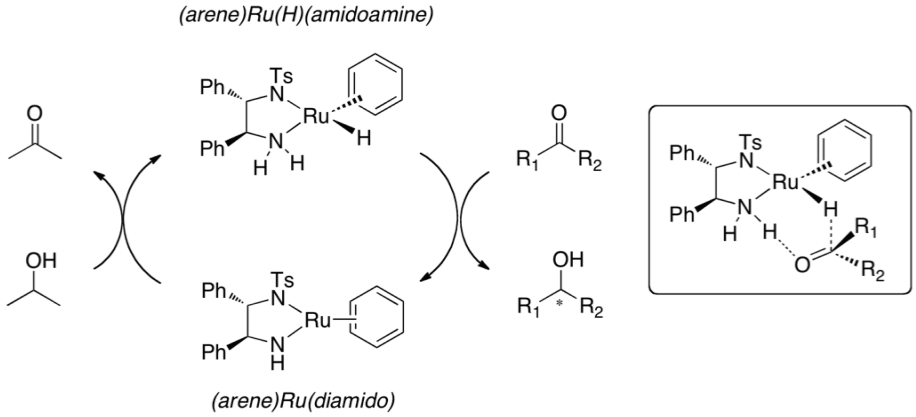


Figure 2.6 Bifunctional catalysis in the TH of ketones via the interconversion of Ru-amido and Ru-amine hydrido complexes through a possible six-membered transition state.

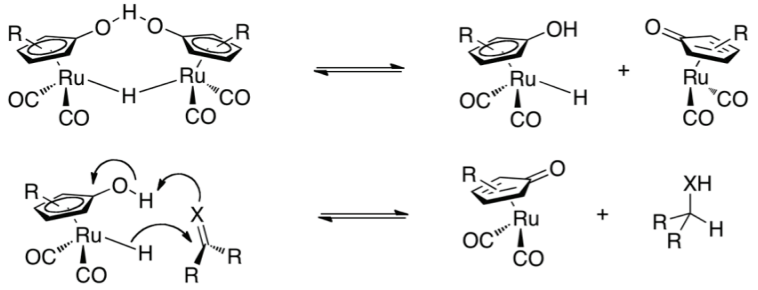


Figure 2.7 Shvo's catalyst in equilibrium with the derived 16- and 18-electron monomers and concerted proton/hydride transfer mechanism for the hydrogenation of polar bonds.

Given the remarkable success of Noyori's Ru(diamine) and Ru(aminoalcohol) TH catalysts, many other research groups have subsequently adopted this design principle to prepare other active, selective ligands for asymmetric TH. Bidentate, tridentate, and tetradentate ligand motifs have been employed with success, including NNN, NNO, ONNO, PNNP, and (NN)(PP) type donor ligands (Figure 2.8).[9a, 10a] Although initial

studies suggested Ir and Rh based catalysts supported by NH-ligands were inferior to Ru complexes,[24] many systems featuring these metals have emerged (see Section 3 for a more detailed discussion of Ir-based catalysts).

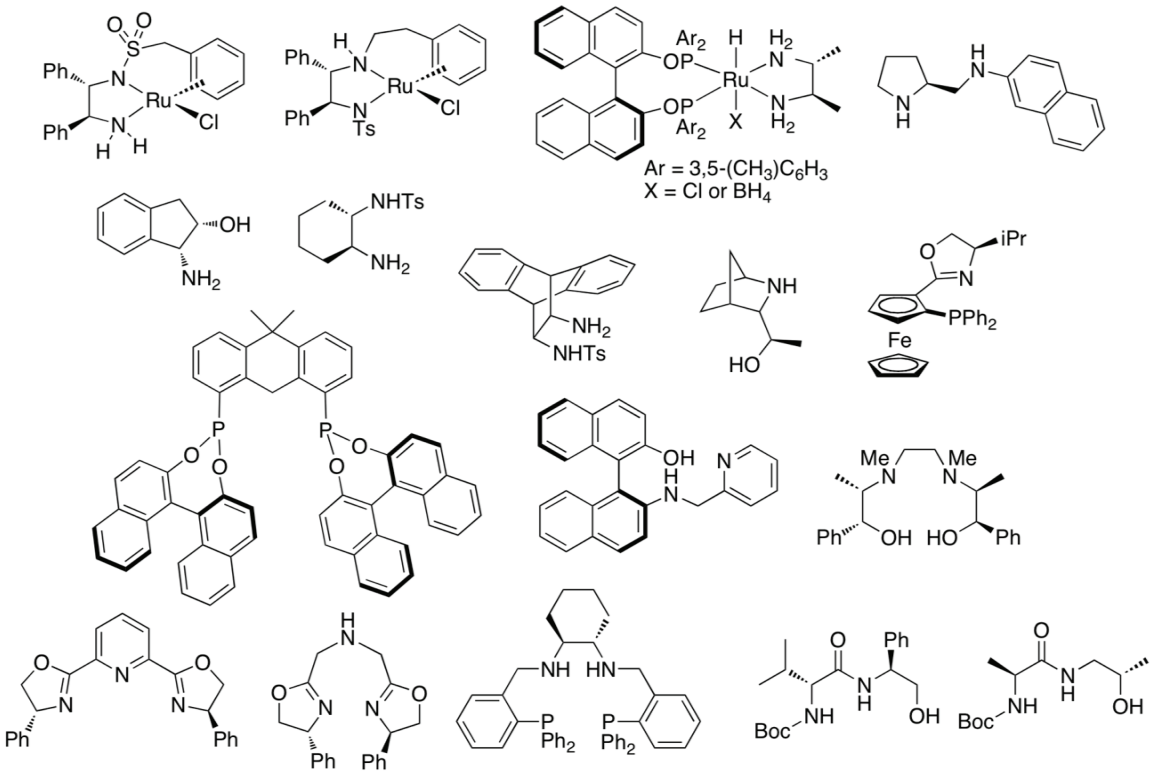


Figure 2.8 A selection of active and selective ligands and complexes for the asymmetric TH of aryl ketones.

Despite the remarkable success of Noyori's TH system, the relatively high catalyst loadings employed (typically 1-0.5 mol%) represent a disadvantage in comparison to direct H_2 hydrogenations employing Ru, where generally, 0.1 mol% metal (or less) can be used. This is especially true in large-scale hydrogenation operations. Recently, Baratta's research group has attempted to address this issue, developing a series of complexes contain Ru-NH linkages that can operate at high temperatures (60-82 ºC) leading to extraordinarily high turnover numbers and turnover frequencies for the TH of ketones[25] and aldehydes.[26] Using complexes possessing 2-(aminomethyl)pyridine derivatives as ligands, Baratta's family of complexes can be employed as catalysts at loadings ranging from 0.05 to 0.0005 mol% Ru, offering TOFs consistently in the 10^5-10^6 h^{-1} range for a diverse range of ketone substrates (TOFs for typical "active" TH catalysts range 10^2-10^3).

Catalysts consisting of chiral 2-(aminomethyl)pyridine ligands and chiral diphosphine co-ligands have been employed in asymmetric TH, leading to good to excellent enantioselectivity with high TOFs (Figure 2.9). Osmium-based catalyst systems using similar ligand sets have also provided good activity and in some cases, excellent enantioselectivity.[27]

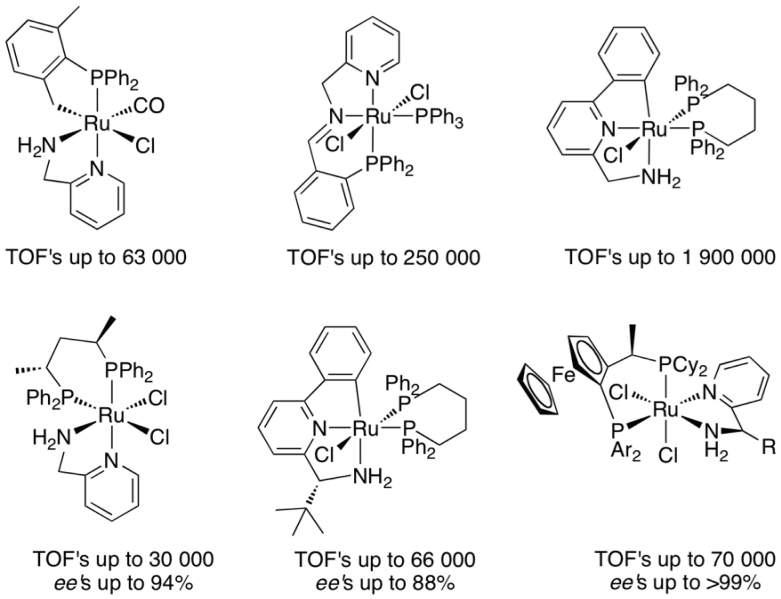


Figure 2.9 Baratta's family of Ru-[2-(aminomethyl)pyridine] catalysts for extremely rapid ketone TH. Maximum TOF's and enantioselectivities are indicated below the applicable complex.

Similar to Noyori's system, replacement of the NH-linkages in the 2-(aminomethyl)pyridine ligand with methylated versions dramatically lowered the activity of the complexes, thereby providing persuasive evidence of a bifunctional mechanism. However, unlike the Noyori system, Ru-alkoxides have been isolated as intermediates in such catalytic reactions, rather than Ru-amido complexes.[25c, 25h, 25j]

Due to the experimental simplicity and environmentally friendly nature of transition metal-catalyzed transfer hydrogenations, such reactions have found widespread application in polar bond reductions in organic synthesis. Current challenges in the field include the pursuit of more active catalysts, as well as the identification of catalysts for the selective reduction of ketones in sterically demanding molecules and those possessing multiple functional groups. Notably, hydrogen transfer reactions are not limited to the

simple oxidation or reduction of polar bonds, but can also be utilized to access reactive intermediates via "borrowing hydrogen" methodologies.[28]

Notwithstanding the advancements in transition metal-mediated TH that have been enabled through the development of ancillary ligands featuring N-H donors, such a structural prerequisite limits the future design of alternative classes of Ru-based TH catalysts for use in mediating new and increasingly challenging substrate transformations. In this context, the identification of novel ligation strategies that do not rely on the N-H effect and which give rise to highly active and selective Ru-based TH catalysts represents an important goal in hydrogenation catalysis research. Sections 2.2 and 2.3 are concerned with the application of new classes of highly active Ru- and Ir-based complexes for ketone TH.

2.2 Application of Zwitterionic Ru Complexes Possessing P,N-Substituted Indenide Ligands in Ketone Transfer Hydrogenation

Encouraged by the catalytic abilities of Noyori's (arene)Ru(diamido) complexes, and in light of the observation that the pairing of P- and N-donor ligands is a common feature in several highly effective Ru-based TH catalysts,[10b, 25g, 25j, 25k, 29] complexes **2-2**-**2-5** and **2-6** were identified as intriguing target compounds for application in ketone TH (Figure 2.10). The synthesis and characterization of the complexes featured in Figure 2-10 were carried out in collaboration with another member of the Stradiotto research group (Matthew A. Rankin), by employing the known ligand precursor **2-1**.[8b]

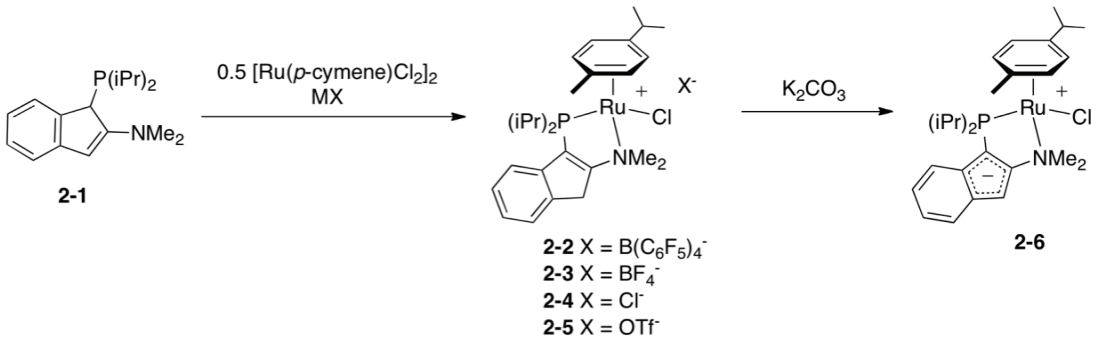
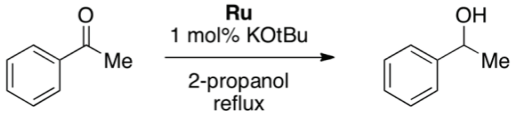


Figure 2.10 Cationic (**2-2**-**2-5**) and zwitterionic (**2-6**) (*p*-cymene)Ru complexes supported by P,N-substituted indene and indenide ligands employed in ketone TH.

The reduction of acetophenone in 2-propanol heated to reflux temperature in the presence of 1 mol% KOtBu was selected to assess the catalytic ability of cations **2-2**-**2-5** and **2-6**. At a catalyst loading of 0.05 mol%, the cationic species exhibited modest activity, with conversions of acetophenone to 1-phenylethanol ranging between 4-23% after 15 minutes (Table 2.1). In contrast, the zwitterion **2-6** proved to be an extremely active catalyst providing 99% conversion into 1-phenylethanol after only 5 minutes, and with a high TOF value at ~50% conversion (180 000 h^{-1}). Excellent catalytic performance for the TH of acetophenone was also observed when employing 0.025 mol% **2-6** or by use of 0.2 mol% **2-6** at 45 ºC (97%, 15 h). The nature of other ancillary ligands supporting Ru proved important as both neutral and zwitterionic Cp*Ru complexes derived from **2-1** proved to be inactive in the TH of acetophenone.[8f,8g] *In situ* formed catalyst mixtures generated via the addition of ligand **2-1** to Ru(II) starting materials including Ru(*p*-cymene)Cl_2, $RuCl_2(PPh_3)_3$, and Ru(methallyl)$_2$COD afforded poor conversions of acetophenone to 1-phenylethanol when compared to the pre-formed complex **2-6**. Catalysts bearing a diphenyl-substituted phosphorus donor were also considerably less active than the parent isopropyl version. An examination of various other bases showed catalytic systems employing **2-6** are amenable to a variety of strong bases such as NaOtBu or Cs_2CO_3, however NEt_3 proved to be ineffective under the standard conditions displayed in Table 2.2.

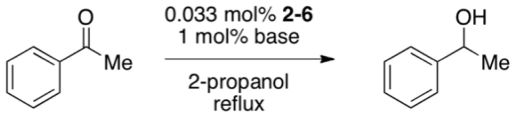
Table 2.1 Ru-catalyzed TH of acetophenone in 2-propanol with KOtBu.



entry	Ru	mol% catalyst	t (min)	conv. (%)[a]	TOF (h^{-1})[b]
1	**2-2**	0.05	15	4	1 000
2	**2-3**	0.05	15	7	13 000
3	**2-4**	0.05	15	9	5 400
4	**2-5**	0.05	15	23	11 000
5	**2-6**	0.05	5	99	180 000
6	**2-6**	0.033	10	97	240 000
7	**2-6**	0.025	15	95	300 000

Conditions: 0.8 mmol scale (acetophenone 0.1 M), in 2-propanol at reflux temperature. [a] Conversion to 1-phenylethanol determined on the basis of GC data at time stated t. [b] TOF measured at 20 seconds.

Table 2.2 Effect of base (1 mol%) on TH of acetophenone (0.1 M) employing Ru-zwitterion **2-6** at 0.033 mol%.



entry	base	t (min)	conv. (%)[a]	TOF (h^{-1})[b]
1	NaOtBu	10	98	310 000
2	KOtBu	10	97	240 000
3	NaOH	10	92	220 000
4	Cs_2CO_3	10	99	110 000
5	K_2CO_3	10	72	> 5 000
6	NEt_3	10	0	0

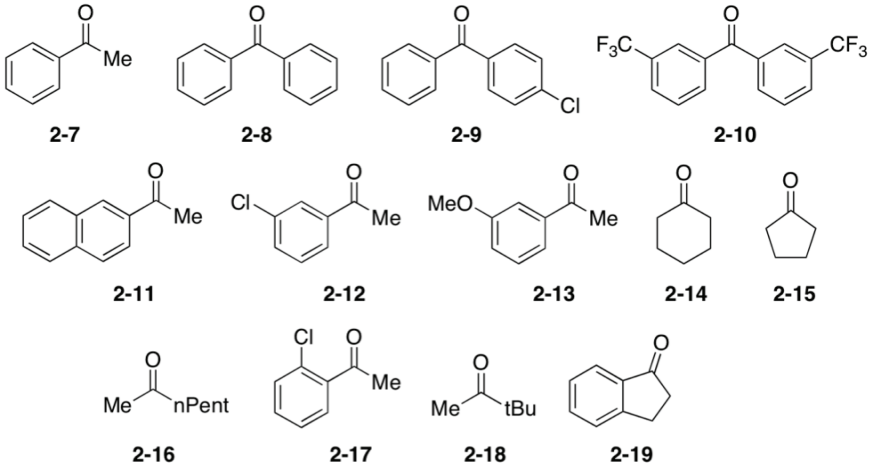
Conditions: 0.8 mmol scale (acetophenone 0.1 M), in 2-propanol at reflux temperature. [a] Conversion to 1-phenylethanol determined on the basis of GC data at time stated t. [b] TOF measured at 20 seconds.

Complex **2-6** also proved to be an effective precatalyst for the TH of other diaryl (Table 2.3 entries 2 to 4), aryl alkyl (Table 2.3 entries 5 to 7), and dialkyl (Table 2.3 entries 8 and 10) ketones. Notably, the ability of **2-6** to mediate the rapid (5-15 min) reduction of such structurally diverse ketones with high TOF values (54 000-220 000 h^{-1}) is remarkable for a precatalyst not featuring a Ru-NH linkage. The practical utility of **2-6** was demonstrated through the 0.91 g scale reduction of benzophenone to afford

benzhydrol in 82% isolated yield (91% conversion by GC) using only 0.01 mol% (~0.25 mg) catalyst. Other substrates examined including 2'-chloroacetophenone (74%), pinacalone (71%), and indanone (85%) were reduced with slightly lower conversions at 15 minutes at 0.05 mol% **2-6**, perhaps due to steric reasons. Preliminary attempts to reduce aldehydes and unsaturated ketones proved unsuccessful under standard conditions.

Table 2.3 TH of ketones (0.1 M) with **2-6** (0.05 mol%) and KOtBu (1 mol%) in 2-propanol at reflux temperature.

entry	substrate	t (min)	conv. (%)[a]	TOF (h^{-1})[b]
1	**2-7**	5	99	180 000
2	**2-8**	5	98[c]	220 000
3	**2-9**	15	94	180 000
4	**2-10**	5	97	180 000
5	**2-11**	15	95	180 000
6	**2-12**	15	99	57 000
7	**2-13**	5	97	120 000
8	**2-14**	5	99	54 000
9	**2-15**	5	99	91 000
10	**2-16**	15	99	150 000
11	**2-17**	15	74	*nd*
12	**2-18**	15	71	*nd*
13	**2-19**	15	85	*nd*



Conditions: 0.8 mmol scale in 2-propanol at reflux temperature. [a] Conversion to alcohol determined on the basis of GC data at time stated t. [b] TOF measured at 20 seconds. [c] When conducted on a 2.0 mmol scale, benzhydrol was isolated in 96% yield.

Perhaps the most interesting aspect of the comparative study between the catalytic activity of cations **2-2**-**2-5** and **2-6** is the remarkable divergence in efficiency, given the close structural relationship between these two species. Under strongly basic conditions the cations **2-2**-**2-5** would presumably be rapidly deprotonated by KOtBu to potentially generate zwitterions similar to **2-6** via loss of KX (X = Cl, OTf, BF_4, or $B(C_6F_5)_4$) and HOtBu. Catalytic studies conducted with a vast excess of KCl (ca. 150 equiv.) only diminished slightly the catalytic ability of **2-6**, indicating that the difference in activity between cationic and zwitterionic species cannot be rationalized simply in terms of (the rather unlikely) inhibition by KCl. Subjecting both **2-4** and **2-6** to catalytic conditions (10 equiv. KOtBu in 2-propanol) results in the rapid and quantitative formation of a new zwitterionic Ru-hydride species **2-20** (Figure 2-11). The formation of Ru-H complexes from Ru-Cl precursors under basic conditions is well established (see Section 2.1);[17, 30] furthermore these hydrido species are typically the active catalysts formed *in situ* from Ru-Cl precatalysts during the course of ketone TH reactions conducted in basic 2-propanol.[9a, 10b, 10c, 11a] In this regard, the observation that **2-20** is completely inactive for ketone TH (0.05 or 0.2 mol%) in the presence or absence of additional KOtBu was surprising.

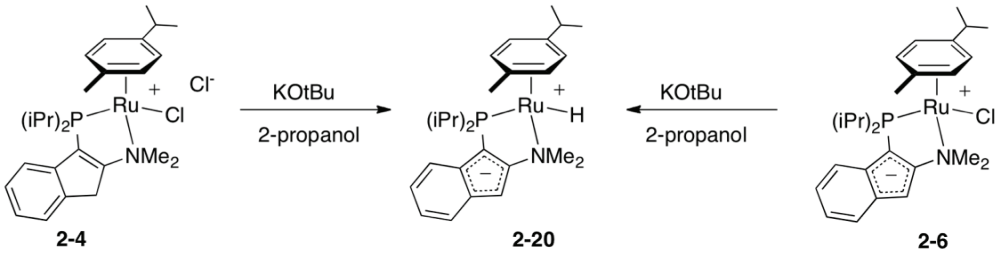
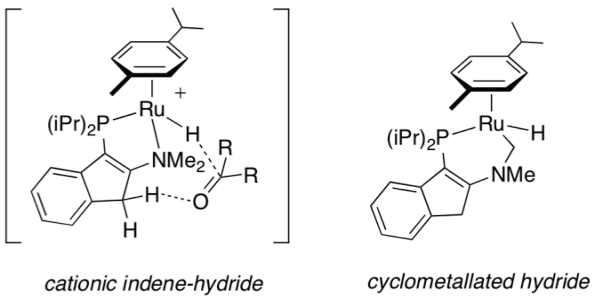


Figure 2.11 Subjecting both cationic **2-4** and zwitterionic **2-6** to KOtBu in 2-propanol leads to the formation of the zwitterionic hydride **2-20**, a species not active in ketone TH.

Evidently, the formation of **2-20** represents a catalyst deactivation pathway in ketone TH when employing both cationic Ru-complexes such as **2-4** or the zwitterion **2-6**. This fact is supported by the observation that re-addition of substrate to catalytic mixtures containing **2-2** and KOtBu results in incomplete conversion to product, indicating that over the period of the reaction (5-15 min) catalyst decomposition (presumably to **2-20**)

becomes significant. Preliminary attempts to regenerate catalytically active species by addition of HCl to **2-20** under catalytic conditions (no KOtBu) were not successful. However, the preparation of cationic, ligand-protonated (indene-hydride) relatives of the Ru-H **2-20** (ie. the conjugate acid of **2-20**) by treatment with acid is a subject of ongoing investigation (Figure 2.12). These observations do not rule out the involvement of alternative hydrido species as catalysts in reactions involving precatalysts **2-4** or **2-6**, including species that might arise from intramolecular C-H activation involving a ligand NMe fragment,[8f, 8g] or perhaps (but more unlikely) N-Me dealkylation under catalytic conditions to generate a NH containing ligand.[31] An intriguing mechanistic postulate would be that involving a concerted proton/hydride transfer from a cationic Ru-hydride species (Figure 2.12), which is akin to concerted H_2 transfers reported by Milstein and co-workers involving pincer ligands featuring a dearomatized pyridine anion.[32]



cationic indene-hydride *cyclometallated hydride*

Figure 2.12 Possible intermediate Ru-H involved in TH catalysis when employing zwitterion **2-6**.

In summary, donor-substituted indenes, such as **2-1**, including the deprotonated derivative featured in the zwitterionic complex **2-6** have been established as a promising new class of non-NH ancillary ligands for use in constructing highly active Ru species for the TH of ketones in basic 2-propanol. In fact, **2-6** is one of the most active in a limited series of precatalysts for ketone TH that do not exploit Ru-NH interactions, providing near-quantitative conversions in minutes for a range of ketone substrates at low catalyst loadings with TOF values as high as 300 000 h^{-1}. Interestingly, all previously reported cationic ketone TH precatalysts of the type $[(arene)Ru(P,N)(Cl)]^+X^-$ feature neutral P,N-ligands, and are commonly 10^2 to 10^3 times less active than **2-6**.[33] Such observations, when considered in the context of the diminished catalytic abilities of cationic species

relative to **2-6**, suggest that the anionic nature of the P,N ligand may play an important role in engendering desirable reactivity properties to ketone TH catalysts formed *in situ*.

2.3 Ketone Transfer Hydrogenation Employing Simple, *In Situ* Prepared Iridium(I) Pre-catalysts Supported by 'Non N-H' P,N-Ligands

As described in the preceding sections, Ru-based catalysts have provided major in-roads in the field of metal-mediated transfer hydrogenation. However, significant interest and research effort has also been directed towards the development of catalysts featuring alternative metal centers in hopes of providing improved or complementary reactivity to Ru. Os,[25d, 27] and, more recently, Fe-based[34] catalysts featuring "N-H" ligand sets similar to those employed successfully in Ru-catalyzed TH have been developed, and in a few cases, provide useful levels of activity and selectivity. The catalytic utility in TH chemistry of Rh and Ir complexes that feature an M-NH functionality has also been well demonstrated.[35] Abdur-Rashid and co-workers[35g] have described the use of $IrH_3[(iPr_2PC_2H_4)_2NH]$ (Figure 2.13), which is among the most active of the previously reported Ir pre-catalysts for the TH of ketones in 2-propanol, providing a TOF of 43 000 h^{-1} (at 50 % conversion) for the reduction of acetophenone. Furthermore, the field of Rh- and Ir-mediated asymmetric ketone TH is dominated by pre-catalysts featuring an M-NH linkage, with chiral Cp*(Cl)M(amido-amine) and related species, as well as alternative non-Cp* catalyst systems prepared using chiral tetradentate N-H (or imine) ligands, being among the most effective (Figure 2.13).

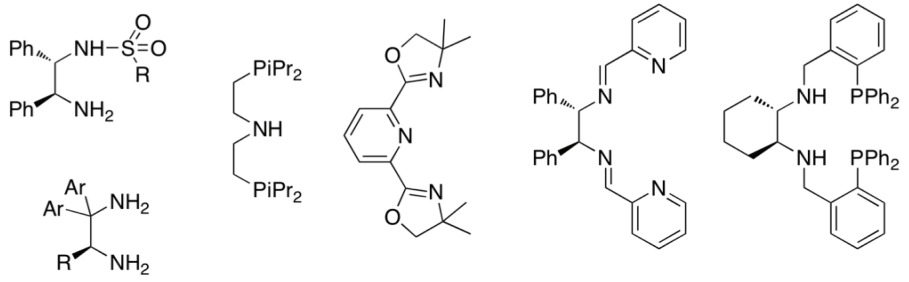


Figure 2.13 Selected ligands for highly active Rh- or Ir-based TH catalysts.

While progress in metal-mediated TH continues to be enabled through the study of pre-catalysts that exploit the now well-established ancillary ligand 'N-H effect', the

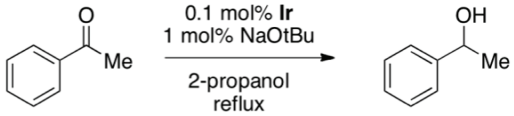
identification of alternative ligation strategies that give rise to highly active and/or selective TH pre-catalysts represents a key step toward new and synthetically useful metal-mediated reactivity. In addition to advances that have been made in Ru-mediated TH chemistry, (NHC)Ir complexes have emerged as promising pre-catalysts for the TH of ketones.[36] For example, Crabtree, Faller and co-workers[36g] have reported an Ir(III) system of this type that is capable of mediating the near quantitative reduction of benzophenone with a TOF of 50 000 h^{-1} (at 50 % conversion). Notwithstanding such developments, (NHC)Ir complexes that exhibit a combination of high TOFs and conversions for a broad range of ketone substrates at low catalyst loadings have yet to be reported, and only modest enantioselectivity has been achieved by use of chiral (NHC)Ir pre-catalysts. Indeed, the quest is ongoing to identify alternative classes of simple and easily prepared 'non N-H' ancillary ligands to support Ir and other ketone TH pre-catalysts that exhibit high efficiency and broad substrate scope.

Encouraged by the catalytic abilities of Ru-complexes derived from ligand **2-1** (see Section 2.2), and building on the Stradiotto research group's previous studies employing the cationic and zwitterionic Ir complexes derived from **2-1** as pre-catalysts in the direct hydrogenation of alkenes,[8d] the utility of these, and related group 9 complexes, in ketone TH was explored.

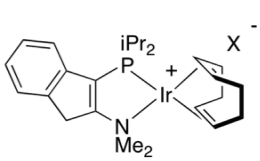
The reduction of acetophenone in basic 2-propanol at reflux temperature was selected as a preliminary test reaction with which to assess the catalytic utility of the Ir cations **2-21**-**2-24** and the zwitterion **2-25** (0.1 mol%) in the TH of ketones (Table 2.4). No catalyst exhibited activity in the absence of base (NaOtBu), and investigations of cationic species featuring the ligand isomer **2-24** were not conducted with other counter anions due to facile isomerization in solution.[8k] The pre-formed cationic complexes, and zwitterionic **2-25** each proved effective in mediating the test transformation, providing good TOFs (0.1 mol% Ir; 36 000–48 000 h^{-1} measured at 30 seconds and 30-40% conversion), and high final conversions to 1-phenylethanol (93–99%; Table 2.4, entries 1 to 5). Poor results were obtained when using the conceptually similar (P,N)-Ir complex, $[(COD)Ir(PCy_3)(pyridine)]^+PF_6^-$ (Crabtree's catalyst) under similar conditions, agreeing with results reported previously.[36i] Negligible conversion was achieved by use of the Rh analogue of **2-25** under similar conditions.[8b] Related catalyst mixtures prepared *in situ*

from $[(COD)IrCl]_2$ and the ligand **2-1** were also found to be effective under analogous conditions (34 000 h^{-1} at 28% conversion; Table 2.5, entry 1). These results are in contrast to the results obtained with Ru, where good catalytic activity was only observed when employing the pre-formed zwitterionic species **2-6**.

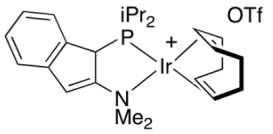
Table 2.4 TH of acetophenone (0.1 M) with Ir-cations and zwitterion **2-25** (0.1 mol%) and NaOtBu (1 mol%) in 2-propanol.



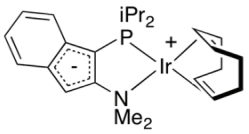
entry	catalyst	t (h)	conv. (%)[a]	TOF, h^{-1} (%)[b]
1	**2-21**	2	96	47000 (39)
2	**2-22**	2	98	42000 (35)
3	**2-23**	2	93	36000 (30)
4	**2-24**	3.25	99	48000 (40)
5	**2-25**	2	95	37000 (31)
6	Crabtree's	2	29	*nd*



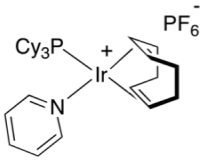
X = PF_6: **2-21**
X = BF_4: **2-22**
X = OTf: **2-23**



2-24



2-25



Crabtree's Catalyst

Conditions: Ir:ketone = 1:1000; 0.8 mmol scale; 0.1 M ketone; 82 °C; 1 mol% NaOtBu in 2-propanol. [a] Conversion determined by GC at stated time. [b] Determined at 30 seconds, with the corresponding conversion given in parentheses.

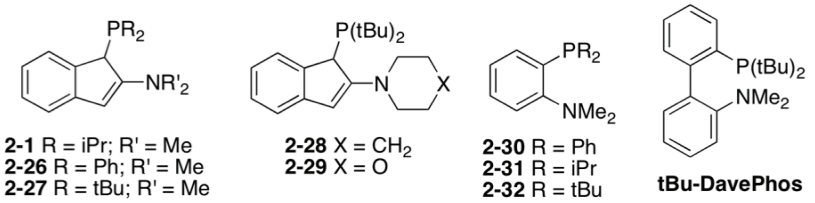
Encouraged by these preliminary findings, the influence of donor-fragment substitution on catalyst performance was explored by examining acetophenone TH mediated by mixtures of $[(COD)IrCl]_2$ and alternative P,N-indene ligands (Table 2.5). Ligands **2-26** and **2-29** could be prepared by treatment of the corresponding lithated-2-aminoindene with the desired chlorophosphine and isolated as a mixture of allylic and vinylic isomers (for clarity only the allylic forms are shown in Table 2.5).[8a] While the PPh_2-variant (**2-26**, entry 2) proved inferior to **2-1**, the closely related $P(tBu)_2$-derivative (**2-27**) gave rise to a significantly more active catalyst system, thereby allowing for the

near quantitative reduction of acetophenone in only 0.25 h (59 000 h^{-1} at 49% conversion; Table 2.5, entry 3). Despite the apparent reactivity advantages of employing a bulky $P(tBu)_2$-substituent in this family of P,N-indene ligands, further elaboration of the N-donor fragment proved deleterious (Table 2.5, entries 4 and 5).

It has been observed previously that the cationic κ^2-*P*,*N*-indene complexes **2-21**-**2-24** can be transformed under basic conditions into the corresponding zwitterionic P,N-indenide complex **2-25** upon loss of HX.[8k] As such, it was interesting to determine if the anionic nature of P,N-indenide ligands formed *in situ* from **2-1** (as in **2-25**) or ligand **2-27** might play a role in facilitating the observed ketone TH chemistry mediated by mixtures of $[(COD)IrCl]_2$ and these P,N-indenes in basic 2-propanol. Toward this end, the catalytic utility of the structurally related phenylene P,N-ligands (*o*-R_2P-C_6H_4)NMe_2 (R = Ph, **2-30**, entry 6; iPr, **2-31**, entry 7; R = tBu, **2-32**, entry 8) was evaluated. Such ligands would represent structurally analogous versions of **2-1** without an acidic proton. It should be noted that ligand **2-30** has been studied in the Ir-catalyzed H_2-hydrogenation of α,β-unsaturated ketones with moderate results.[37] It was found that each of **2-30**, **2-31** and **2-32** were observed to out-perform the corresponding P,N-indene ligand in the Ir-mediated TH of acetophenone under similar conditions, with mixtures of $[(COD)IrCl]_2$, $NaPF_6$, and **2-32** affording a particularly active Ir catalyst system (96%, 0.25 h, 0.05 mol% Ir, TOF = 152 000 h^{-1} at 63% conversion; Table 2.5, entry 9). Conversely, tBu-DavePhos, $P(tBu)_3$, 1:1 mixtures of $P(tBu)_3$/$PhNMe_2$, and PPh_3 (2 equiv.)[38] proved ineffective in supporting similarly active catalyst systems when used in place of **2-32**, as did mixtures of ligand **2-32** and either $[(COD)RhCl]_2$, $[Cp^*IrCl_2]_2$, $[Cp^*RhCl_2]_2$, $RuCl_2(PPh_3)_3$, or $[(p\text{-cymene})RuCl_2]_2$ (0.1 mol% metal, <10%, 0.25 h).

Table 2.5 Ligand optimization for the Ir-catalyzed TH of acetophenone (0.1 M) with NaOtBu (1 mol%) in 2-propanol.

entry	**ligand**	t (h)	conv. (%)[a]	TOF (h^{-1}) (%)[b]
1	**2-1**	2	81	34 000 (28)
2	**2-26**	2	54	*nd*
3	**2-27**	0.25	98	59 000 (49)
4	**2-28**	2	57	*nd*
5	**2-29**	2	39	*nd*
6	**2-30**	2	84	*nd*
7	**2-31**	2	96	42 000 (35)
8[c]	**2-32**	0.25	94	103 000 (43)
9[d]	**2-32**	0.25	96	152 000 (63)
10	tBu-DavePhos	2	4	*nd*
11	$P(tBu)_3$	2	21	*nd*
12	$P(tBu)_3$ / NEt_3	2	14	*nd*
13	2 PPh_3	2	43	*nd*



2-1 R = iPr; R' = Me
2-26 R = Ph; R' = Me
2-27 R = tBu; R' = Me

2-28 X = CH_2
2-29 X = O

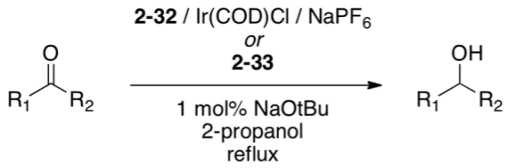
2-30 R = Ph
2-31 R = iPr
2-32 R = tBu

tBu-DavePhos

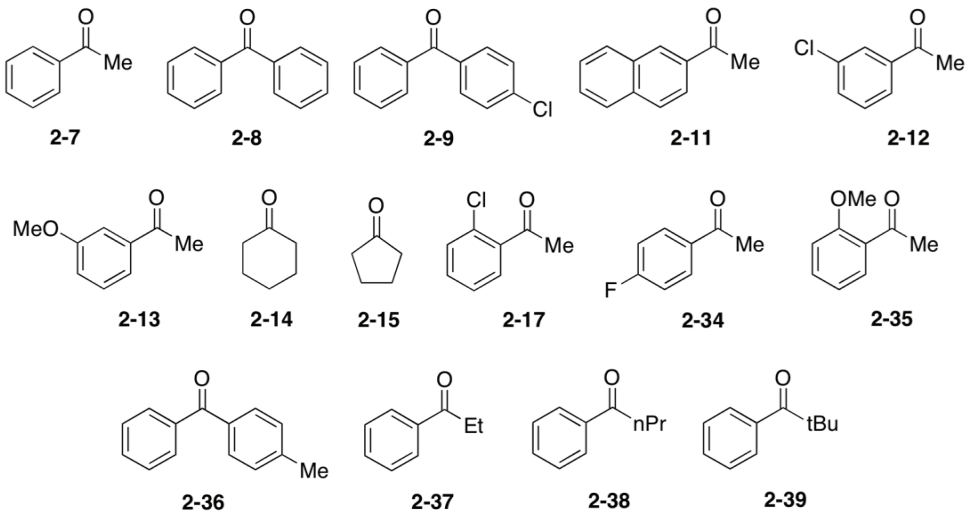
Conditions: Ir:L:ketone = 1:1:1000; 0.8 mmol scale; 0.1 M ketone; 82 °C; 1 mol% NaOtBu in 2-propanol. [a] Based on GC data obtained at stated time. [b] Determined at 30 seconds, with the conversion given in parentheses (*nd* = not determined). [c] Ir:L:ketone = 1:1:2000. [d] With $NaPF_6$:Ir:L:$NaPF_6$:ketone = 1:1:1.1:2000.

Intrigued by the remarkable activity of $[(COD)IrCl]_2$/$NaPF_6$/**2-32** mixtures in mediating the catalytic TH of acetophenone, the reduction of other ketones in basic 2-propanol at reflux temperature was examined (Table 2.6). This *in situ* prepared catalyst mixture proved very effective for the TH of a range of substituted acetophenones and benzophenones, as well as other aryl/alkyl and dialkyl ketones. In the case of cyclohexanone (**2-14**) high conversions in relatively short reaction times were achieved by use of 0.01 mol% Ir (>99%, 0.33 h; Table 2.6, entry 12) and even 0.004 mol% Ir (95%, 1.5 h; entry 13). Sterically demanding substrates, such as 2-substituted acetophenones as well as bulky aryl-alkyl ketones were reduced in relative short reaction times employing 0.1 mol% Ir or less. In preliminary studies, imines and aldehydes were not reduced rapidly under the standard reaction conditions.

Table 2.6 Scope of ketone TH employing $[(COD)IrCl]_2$, **2-32**, and $NaPF_6$, or Ir complex **2-33**.



entry	ketone	Ir:ketone	t (min.)	conv. (%)[a]
1[b]	**2-7**	1:2000	15	96
2[b]	**2-7**	1:4000	60	96
3[c]	**2-7**	1:2000	15	97
4[b]	**2-8**	1:2000	40	90
5[b]	**2-9**	1:2000	15	94
6[b]	**2-11**	1:2000	15	96
7[b]	**2-12**	1:2000	15	98
8[c]	**2-12**	1:2000	15	99
9[b]	**2-13**	1:2000	15	95
10[c]	**2-13**	1:2000	15	97
11[b]	**2-14**	1:2000	15	>99
12[b]	**2-14**	1:10000	20	>99
13[b]	**2-14**	1:25000	90	95
14[c]	**2-14**	1:10000	10	99
15[b]	**2-15**	1:2000	15	98
16[b]	**2-17**	1:1000	5	>99[d]
17[b]	**2-34**	1:2000	15	93
18[c]	**2-35**	1:1000	5	99
19[b]	**2-36**	1:2000	120	91
20[c]	**2-37**	1:1000	60	87
21[b]	**2-38**	1:2000	30	79
22[c]	**2-38**	1:2000	30	83



Conditions: Ir:**2-25**:$NaPF_6$ = 1:1:1.1; 0.8 mmol scale; 0.1 M ketone; 82 °C; 1 mol% NaOtBu in 2-propanol. [a] Based on GC data obtained at stated time. [b] Employing $[(COD)IrCl]_2$, **2-25**, and $NaPF_6$. [c] Using **2-33**. [d] 2.0 mmol scale, 95% isolated yield.

In an effort to provide evidence to support the view that $[(COD)IrCl]_2/NaPF_6$/**2-32** mixtures as giving rise to $[(COD)Ir(\kappa^2\text{-}P,N\text{-}\mathbf{2\text{-}32})]^+PF_6^-$ (**2-33**) as the pre-catalyst in these reactions, the catalytic utility of isolated **2-33** was examined. This compound was prepared as an analytically pure solid in 64% isolated yield by the addition of two equivalents of ligand to $[(COD)IrCl]_2$ followed by addition the of $NaPF_6$. The solution NMR characterization of **2-33** as a traditional square planar $[(\kappa^2\text{-}P,N)Ir(COD)]^+X^-$ complex is entirely consistent with the crystallographically determined structure; an ORTEP[39] diagram of **2-33** is presented in Figure 2.14. Gratifyingly, the catalytic performance of this complex mirrored that of $[(COD)IrCl]_2/NaPF_6$/**2-32** mixtures (Table 2.6), with the TH of acetophenone using **2-33** (Table 2.6, entry 3) proceeding with a TOF of 230 000 h^{-1} (measured at 20 seconds and 63% conversion).

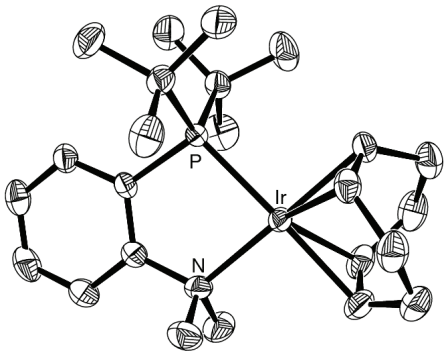
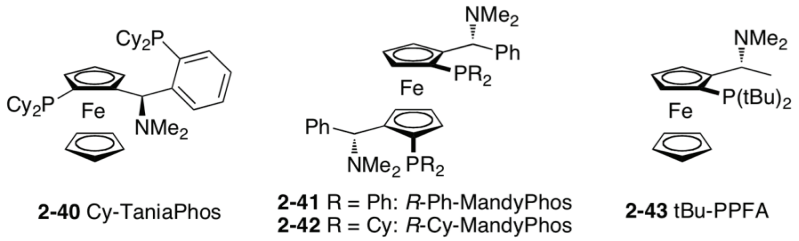


Figure 2.14 ORTEP diagram for **2-33**. The hydrogen atoms and the PF_6^- anion have been omitted for clarity. Selected bond lengths (Å): Ir-P 2.3212(6); Ir-N 2.184(2); Ir-alkene 2.118(3) and 2.166(2) (*trans* to N), 2.168(3) and 2.228(3) (*trans* to P).

Having succeeded in establishing the utility of simple P,N-ligands such as **2-32** in the Ir-mediated TH of ketones, it was hoped to develop asymmetric variants of this reaction by employing structurally related chiral ancillary ligands. Given the pairing of a bulky PR_2 fragment with an NMe_2 donor featured in **2-32**, the commercially available ferrocenyl ligands Cy-Taniaphos and Cy-Mandyphos were identified as attractive ligand candidates for asymmetric TH experiments (Figure 2.15).[40]



2-40 Cy-TaniaPhos

2-41 R = Ph: *R*-Ph-MandyPhos
2-42 R = Cy: *R*-Cy-MandyPhos

2-43 tBu-PPFA

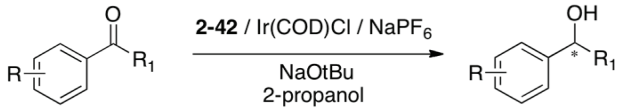
Figure 2.15 Structures of chiral P,N-ligands tested in asymmetric TH.

In a preliminary survey, good conversion (94%, 4.5 h) and enantioselectivity (72% *ee*) were achieved when employing Cy-Mandyphos (**2-42**) for the TH of acetophenone at 40 ºC, by using catalyst mixtures comprised of $[(COD)IrCl]_2$/$NaPF_6$/**2-42** (1.0 mol% Ir; Table 2.7, entry 1). While the use of Cy-Taniaphos (**2-40**) under similar conditions afforded good conversions, poor enantioselectivity (< 50% *ee*) was achieved. In keeping with the inferior performance of catalysts prepared from the PPh_2 ligand **2-26** relative to those featuring the -$P(tBu)_2$ variant **2-27** (*vide supra*), Ph-Mandyphos

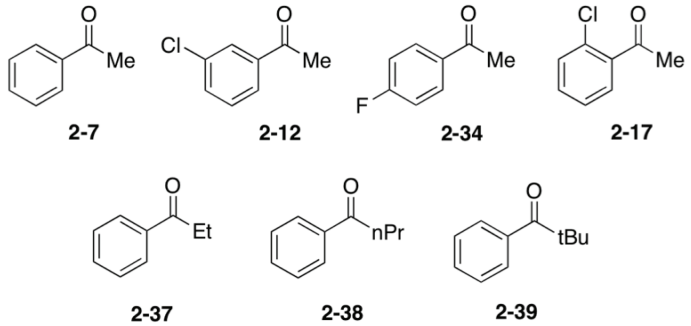
displayed poor activity and selectivity for the reduction of acetophenone under analogous conditions (29% conversion, 37% *ee*, 4.5 h). Interestingly, the P,N-ligand tBu-PPFA (**2-43**) gave only modest conversions and *ee*'s.[41]

Catalyst mixtures of $[(COD)IrCl]_2/NaPF_6$/Cy-Mandyphos (1.0 mol% Ir) proved capable of reducing other aryl/alkyl ketones under relatively mild conditions (Table 2.7). The presence of aryl-halogen substituents appear to affect both the rate and enantioselectivity of the transformation, most notably in the case of 2'-chloroacetophenone (**2-17**) where only a 22% *ee* was observed, despite the relatively short (2.5 h) reaction time. Increasing the steric demand at the alkyl position of aryl/alkyl ketones resulted in increased enantioselectivity (Table 2.7, entries 6-10). This catalyst mixture was found to be particularly effective for the reduction of the sterically encumbered substrate 2,2-dimethylpropiophenone (**2-39**), with excellent conversion (95%, 2 h) and enantioselectivity (93% *ee*; Table 2.7, entry 8). Whereas lowering the reaction temperature from 40 ºC to 30 ºC decreased the extent of reduction without providing any gain in selectivity, slightly enhanced enantioselectivity was achieved by reducing the catalyst loading to 0.5 mol% Ir (95% conversion, 12 h, 95% *ee*; Table 2.7, entry 9). Prior to this work, metal-catalyzed asymmetric TH of **2-39** with such efficiency had not been documented in the literature, thereby highlighting the utility of employing Ir in combination with this class of ligands in addressing challenging asymmetric TH chemistry. Indeed, the efficient Ru-catalyzed hydrogenation of this and related sterically demanding ketone substrates by use of dihydrogen gas has been reported only recently.[42] Attempts to reduce α-branched acetophenone derivatives such as phenylcyclohexyl ketone and phenylisopropyl ketone resulted in low turnover, possibly due to formation of the resulting enolates under basic conditions.

Table 2.7 Scope of asymmetric TH of ketones employing $[(COD)IrCl]_2$, Cy-Mandyphos (**2-42**), and $NaPF_6$.



entry	ketone	t (h)	conv. (%)[a]	*ee*[a]
1	**2-7**	4.5	94	72 (*S*) [b]
2[c]	**2-7**	24	81	70
3	**2-12**	3	95	59
4	**2-34**	22	94	68
5	**2-17**	2.5	98	22
6	**2-37**	14	86	78
7	**2-38**	28	87	81
8	**2-39**	2	95	93
9[c]	**2-39**	12	95	95
10[d]	**2-39**	24	56	95



Conditions: Ir:**2-42**:$NaPF_6$:ketone = 1:1:1.1:100; 0.4 mmol; 0.1 M ketone; 40 °C; 5 mol% NaOtBu in 2-propanol. [a] Conversions and *ee*'s determined by chiral GC data at stated time. [b] Absolute configuration assignment made by comparison to literature data.[21] [c] Reaction conducted at 30 °C. [d] Ir:**2-42**:$NaPF_6$:ketone = 1:1:1.1:200.

In summary, the catalytic utility in ketone TH of Ir complexes supported by various P,N-substituted indene, indenide, or phenylene ligands was evaluated. In a preliminary catalytic survey the cationic and formally zwitterionic complexes **2-21**-**2-24** and **2-25**, as well as related *in situ* prepared Ir catalysts derived from P,N-indenes, were found to be generally effective in mediating the reduction of acetophenone to 1-phenylethanol in basic 2-propanol. Although the catalytic performance of these Ir complexes proved inferior to that of the highly active zwitterionic Ru species **2-6**, related pre-formed or *in situ* prepared Ir complexes supported by the rather simple ancillary

ligand (*o*-tBu_2P-C_6H_4)NMe_2 (**2-32**) afforded a remarkably active catalyst system for the TH of ketones. Notably, these Ir catalysts supported by **2-32** represent a rare example of a ketone TH catalyst system that exhibits TOF values of 10^5 h^{-1}, and which also provides high conversions for a diversity of substrates at low catalyst loadings (0.004–0.1 mol% Ir). In the course of these catalytic studies it was observed that altering the substituents at the donor fragments of the supporting P,N-ligand had a pronounced influence on the catalytic performance of the derived catalysts, with ligands featuring bulky dialkylphosphino donors proving most effective. Building on these observations, chiral catalysts prepared *in situ* from commercially available $[(COD)IrCl]_2$, $NaPF_6$, and the PCy_2-substituted chiral ligand Cy-Mandyphos (**2-42**) proved capable of mediating the asymmetric TH of ketones, including the hindered substrate 2,2-dimethylpropiophenone with unprecedented efficiency (95% conversion, 95% *ee*). Collectively, these results demonstrate that appropriately constructed simple P,N-ligands represent an effective class of often overlooked 'non N-H' ancillary ligands in metal-mediated ketone TH chemistry.

2.4 Summary and Conclusions

The results described in Sections 2 and 3 of this Chapter establish two new classes of highly active transition metal based transfer hydrogenation catalysts. The zwitterionic Ru species **2-6** was found to be an excellent TH catalyst, exhibiting high TOF's and operating under low catalyst loadings, however this catalyst appeared to display a short catalyst lifetime. Structurally related cationic Ru complexes such as **2-2** appeared to be vastly inferior when compared to **2-6**, even though both species gave rise to the same zwitterionic Ru-hydride **2-20** when exposed to catalytic conditions (KOtBu in 2-propanol). It appears that the Ru zwitterion may transform rapidly into a catalytically active species in a manner not accessible to related cations under basic conditions (see Figure 2-13). In any event, the clear benefits of employing pre-catalyst species featuring ligand backbone deprotonation helps to establish these types of complexes as useful compounds for hydrogen transfer reactions.

While cationic and zwitterionic Ir complexes supported by indene-derived ligands such as **2-21** and **2-24** displayed good activity in ketone TH, simple mixtures of $[(COD)IrCl]_2$, $NaPF_6$, and the P,N-phenylene ligand **2-32** provided the best results from a

series of ligands screened. Good conversions at low catalyst loadings were observed for a range of ketone substrates by using either a mixture of Ir, ligand and $NaPF_6$ or by employing the preformed complex **2-33**. Related chiral, ferrocenyl P,N-ligands were explored for activity in enantioselective TH, with Cy-Mandyphos (**2-42**) providing the best results.

Collectively, these results underscore the utility of appropriately designed P,N-ligands in both Ru- and Ir-catalyzed transfer hydrogenation and may provide inroads in the development of alternative classes of hydrogen transfer catalysts.

2.5 Experimental Section

2.5.1 General Considerations

Unless noted, all manipulations were conducted 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 (130 ºC) for 5 d and then evacuated for 24 h prior to use. The non-deuterated solvents diethyl ether, CH_2Cl_2, tetrahydrofuran, pentane and hexane were deoxygenated and dried by sparging with dinitrogen gas, followed by passage through a double-column solvent purification system purchased from mBraun Inc. Diethyl ether, CH_2Cl_2, and tetrahydrofuran were purified over two alumina-packed columns, while pentane and hexane were purified over one alumina-packed column and one column packed with copper-Q5 reactant. Purification of 2-propanol (Aldrich, anhydrous 99.5%) was achieved by sparging with dinitrogen over a period of 0.25 h followed by storage over 4 Å sieves (approximately 10 grams/100 mL) for a minimum of 24 h. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. $CDCl_3$ (Aldrich) was degassed by using three repeated freeze-pump-thaw cycles, dried over CaH_2 for 7 days, distilled *in vacuo* and stored over 4 Å molecular sieves for 24 h prior to use. All ketone substrates were obtained from commercial sources in high purity; solid ketones were dried *in vacuo* for a minimum of 12 h prior to use, while liquid ketones were degassed by use of three repeated freeze-pump-thaw cycles. In the cases of acetophenone, cyclohexanone, and cyclopentanone the ketones were dried over CaH_2 and distilled before degassing. $[(COD)IrCl]_2$,

(COD)Ru(methylallyl)$_2$, [(COD)RhCl]$_2$, [Cp*IrCl$_2$]$_2$ (Cp* = η^5-C$_5$Me$_5$), [Cp*RhCl$_2$]$_2$, RuCl$_2$(PPh$_3$)$_3$, [(*p*-cymene)RuCl$_2$]$_2$, ([(COD)Ir(PCy$_3$)(pyridine)]$^+$PF$_6^-$, as well as all commercially available ligands and bases, in addition to NaPF$_6$ and were dried *in vacuo* for a minimum of 12 h prior to use. Ligands **2-1** and **2-26** were prepared by employing published procedures,[8a, 8k] the preparation of (*o*-Ph$_2$P-C$_6$H$_4$)NMe$_2$ (**2-30**)[43] and **2-21**-**2-25**[8k] have been reported previously. The 2-NR$_2$-indenes used in the preparation of 1-/3-P(tBu$_2$)-2-NMe$_2$-indene (**2-27**), 1/3-P(tBu)$_2$-2-piperidyl-indene (**2-28**), and 1-/3-P(tBu$_2$)-2-morpholino-indene (**2-29**) were prepared according to literature procedures.[44] TOFs were determined at approximately 50% conversion, unless otherwise stated. ^{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) or 85% H$_3$PO$_4$ in D$_2$O (for ^{31}P). ^{1}H and ^{13}C NMR chemical shift assignments are based on data obtained from ^{13}C-DEPT, ^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC NMR experiments. In some cases fewer than expected independent ^{13}C NMR resonances were observed despite prolonged data acquisition times. Unless noted all gas chromatographic data was collected using a Supleco BETA-DEX 120 (30m X 0.25 mm) column.

2.5.2 Experimental Section for Section 2.2

Typical Procedure for the Catalytic Transfer Hydrogenation of Ketones. The pre-catalyst **2-6** (2.7 mg, 5.0 μmol) was dissolved in THF (2.000 mL) and from this freshly prepared stock solution a 162 μL (0.4 μmol) aliquot was delivered by use of an Eppendorf pipette to an Schlenk flask containing a magnetic stir bar. Optimal catalytic performance was observed when the stock solution was prepared and used within 5-10 minutes. The solvent within the Schlenk flask was then removed *in vacuo*, and subsequently 0.8 mmol of ketone followed by 6 mL of 2-propanol was added to the residue within the Schlenk flask. Stirring was initiated and the solution was then heated to reflux temperature for 10 min (measured oil bath temperature = 100(±2) ºC), at which point 2 mL of a 0.004 M solution of KOtBu in 2-propanol was added to the Schlenk flask (**2-6**/KOtBu/ketone = 1:20:2000; [ketone] = 0.1 M), resulting in rapid reduction of the ketone. Reactions were sampled by removing an aliquot of the reaction mixture via

syringe (0.25-0.75 mL) and filtering through a plug of silica. Conversions were determined by use of GC (average of at least catalytic two runs). The identities of the hydrogenation products were confirmed by comparison to authentic samples and/or the use of ^{1}H NMR methods.

Preparative Scale Transfer Hydrogenation of Benzophenone (2-8). Compound **2-6** (3.8 mg, 6.80 μmol) was dissolved in 5 mL of THF and from this stock solution a 358 μL (0.499 μmol) aliquot was delivered by use of an Eppendorf pipette to a round bottom Schlenk flask that contained a magnetic stir bar and that was fitted with a reflux condenser. The solvent was removed *in vacuo* and benzophenone (0.909 g, 4.99 mmol) was added to the flask, followed by 2-propanol (40 mL). Stirring was initiated and the resulting solution was heated to reflux. To the Schlenk flask containing **2-6** and benzophenone in 2-propanol was added 10 mL of a 0.0025 M solution of KOtBu (0.025 mmol) that had been heated to reflux (**2-6**/KOtBu/ketone = 1:50:10 000; [ketone] = 0.1 M). After 3.5 hours the reaction was sampled, and the conversion was determined to be 91% on the basis of GC data. The reaction mixture was allowed to cool to ambient temperature and the remaining procedures were carried out without the rigorous exclusion of air. The solvent was removed *in vacuo* and the crude product was extracted into 50 mL of CH_2Cl_2 and washed with water (3 x 50 mL). The CH_2Cl_2 was removed *in vacuo* and the product was isolated by recrystallization from hot methanol and water (40:60 by volume). Isolated yield: 0.75 g (82%).

2.5.3 Experimental Section for Section 2.3:

Synthesis of 1-/3-P(tBu)$_2$-2-dimethylamino-indene (2-27), 1-/3-P(tBu)$_2$-2-piperidyl-indene (2-28), and 1-/3- P(tBu)$_2$-2-morpholino-indene (2-29). These P,N-substituted indenes were prepared from the corresponding 2-aminoindenes [44] by using synthetic methods directly analogous to those employed in the preparation of the closely related indenes 1-PiPr$_2$-2-NMe$_2$-indene (**2-1**) and 1-PPh$_2$-2-NMe$_2$-indene (**2-26**),[8a, 8b] with the exception that extended reaction times (up to 6 days) at ambient temperatures were required to obtain optimal yields. The propensity of isomerically pure ligands to form a mixture of allylic (1-PR$_2$-2-NR$_2$-indene) and vinylic (3-PR$_2$-2-NR$_2$-indene) isomers upon

standing in solution has been well-documented;[8a, 8k] similarly, **2-27**-**2-29** were each obtained as a mixture of allylic and vinylic isomers. **2-27**: 48% yield. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 51.6 and 14.6 (4.5:1). **2-28**: 47% yield. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 55.3 and 15.7 (20:1). **2-29**: 35% yield. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ 53.2 and 14.9 (4:1). Given that **2-24** has been shown to rapidly isomerize to **2-23** under basic conditions,[S3] it appears that the isomeric form of the ancillary P,N-indene ligand backbone has minimal influence over the performance of the derived catalyst complexes. As such, for simplicity only the allylic form of **2-27**-**2-29** are represented and discussed in this thesis.

Synthesis of (*o*-R_2P-C_6H_4)NMe_2 (R = iPr, 2-31; R = tBu, 2-32). To a glass vial containing *o*-bromo-*N*,*N*-dimethylaniline (218 μL, 1.5 mmol) in 3 mL Et_2O (pre-cooled to -35 ºC), was added nBuLi (625 μL, 1.8 mmol). After 0.5 h at -35 ºC and an additional 0.25 h at room temperature the resulting yellow solid was isolated by removing the solvent by pipette, followed by washing of the solid with cold hexane (2 x 2 mL), after which the volatile materials were then removed *in vacuo*. The resulting solid was dissolved in 3 mL THF and $ClP(iPr)_2$ (238 μL, 1.5 mmol) was added dropwise. The mixture was stirred at room temperature overnight (~18 h). The solvent and volatile materials were then removed *in vacuo*. The resulting mixture was dissolved in CH_2Cl_2 and filtered through a Celite plug. Removal of the CH_2Cl_2 *in vacuo* yielded **2-31** as a pale yellow oil (0.11 g, 0.47 mmol, 31% yield). Compound **2-32** was prepared in a similar manner using *o*-bromo-*N*,*N*-dimethylaniline (288 μL, 2.0 mmol) and nBuLi (759 μL, 2.20 mmol), with the exception that the resulting solid was dissolved in 6 mL Et_2O (rather than 3 mL THF), $ClP(tBu)_2$ (392 μL, 2.0 mmol) was used in place of $ClP(iPr)_2$, and the mixture was stirred at room temperature for 6 days at which point no further conversion of the chlorophosphine was observed (^{31}P NMR). **2-32** was isolated as a beige powder (0.204 g, 0.78 mmol, 39% yield). NMR data for **2-31**: ^{1}H NMR ($CDCl_3$): δ 7.37 (m, 1H, Ar-H), 7.31 (m, 1H, Ar-H), 7.17 (m, 1H, Ar-H), 7.09 (m, 1H, Ar-H), 2.77 (s, 6H, $N(CH_3)_2$), 2.07 (m, 2H, $P(CH(CH_3)_2)_2$), 1.15 (dd, $^{3}J_{PH}$ = 14.2 Hz, $^{3}J_{HH}$ = 7.0 Hz, 6H, $P(CH(CH_3CH_3)_2)$, 0.94 (dd, $^{3}J_{PH}$ = 11.5 Hz, $^{3}J_{HH}$ = 7.0 Hz, 6H, $P(CH(CH_3CH_3)_2)$); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 160.1 (d, J_{PC} = 18.6 Hz), 133.0 (d, J_{PC} = 3.3 Hz), 131.8 (d, J_{PC} = 17.4 Hz), 129.5, 123.2, 119.7 (d, J_{PC} = 4.7 Hz), 45.8 (d, $^{4}J_{PC}$ = 5.2 Hz, $N(CH_3)_2$), 23.6 (d, $^{1}J_{PC}$ =

13.9 Hz, P(*C*H(CH$_3$)$_2$)$_2$), 20.1 (d, $^2J_{PC}$ = 18.6 Hz, P(CH(*C*H$_3$CH$_3$)$_2$), 19.3 (d, $^2J_{PC}$ = 10.5 Hz, P(CH(CH$_3$*C*H$_3$)$_2$); ^{31}P{^{1}H} NMR (CDCl$_3$): δ 3.5. NMR data for **2-32**: ^{1}H NMR (CDCl$_3$): δ 7.70 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 7.21 (m, 1H, Ar-H), 7.06 (m, 1H, Ar-H), 2.76 (s, 6H, N(C*H*$_3$)$_2$), 1.21 (d, 18H, $^3J_{PC}$ = 11.5 Hz, P(C(C*H*$_3$)$_3$)$_2$); ^{13}C{^{1}H} NMR (CDCl$_3$): δ 161.0 (d, J_{PC} = 21.7 Hz), 136.2 (d, J_{PC} = 3.7 Hz), 133.6 (d, J_{PC} = 22.9 Hz), 129.8, 122.7, 120.4 (d, J_{PC} = 3.7 Hz), 46.0 (d, $^4J_{PC}$ = 4.3 Hz, N(*C*H$_3$)$_2$), 32.1 (d, $^1J_{PC}$ = 24.7 Hz, P(*C*(CH$_3$)$_3$)$_2$), 30.7 (d, $^2J_{PC}$ = 15.4 Hz, P(C(*C*H$_3$)$_3$)$_2$); ^{31}P{^{1}H} NMR (CDCl$_3$): δ 17.6.

Synthesis of [(COD)Ir(2-32)]$^+$PF$_6^-$ (2-33). To a glass vial was added [(COD)IrCl]$_2$ (0.067 g, 0.20 mmol), **2-32** (0.053 g, 0.20 mmol), NaPF$_6$ (0.034 g, 0.20 mmol) and CH$_2$Cl$_2$ (8 mL). The resulting mixture was stirred magnetically at room temperature for 24 h, after which the solvent was removed *in vacuo* and the residue was taken up in 5 mL CH$_2$Cl$_2$ and filtered through a plug of silica. The solvent was removed *in vacuo* and the residue was washed with pentane (2 x 2 mL). The product was then dried *in vacuo* to yield **2-33** as an orange solid (0.091 g, 0.13 mmol, 64% yield). ^{1}H NMR (CDCl$_3$): δ 7.97 (m, 1H, Ar-H), 7.91 (m, 1H, Ar-H), 7.73 (m, 1H, Ar-H), 7.47, (m, 1H, Ar-H), 4.70-4.62 (m, 4H, COD), 3.31 (s, 6H, N(C*H*$_3$)$_2$), 2.33-2.27 (m, 4H, COD), 1.85-1.80 (m, 4H, COD), 1.41 (d, $^3J_{PH}$ = 14.5 Hz, 18H, P(C(C*H*$_3$)$_3$)$_2$); ^{13}C{^{1}H} NMR (CDCl$_3$): δ 163.1, 134.7, 128.7 (d, J_{PC} = 5.0 Hz), 123.4 (d, J_{PC} = 8.8 Hz), 89.4 (d, J_{PC} = 11.3 Hz, COD), 62.2 (COD), 53.6 (N(*C*H$_3$)$_2$), 32.9 (d, J_{PC} = 2.5 Hz, COD), 30.7 (d, J_{PC} = 3.8 Hz, P(C(*C*H$_3$)$_3$)$_2$), 29.7 (P(*C*(CH$_3$)$_3$)$_2$), 29.3 (d, J_{PC} = 2.5 Hz, COD); ^{31}P{^{1}H} NMR (CDCl$_3$): δ 52.8. A single crystal of **2-33** suitable for single crystal X-ray diffraction was obtained from vapor diffusion of diethyl ether into a concentrated solution of **2-33** in CH$_2$Cl$_2$.

Typical Procedure for the Catalytic Transfer Hydrogenation of Ketones. A mixture of [(COD)IrCl]$_2$ (3.9 mg, 0.0058 mmol), **2-32** (3.2 mg, 0.0119 mmol), and NaPF$_6$ (2.1 mg, 0.0125 mmol) were vigorously stirred in THF (4.000 mL) for approximately 1 h before a 139 μL (0.4 μmol) aliquot was delivered to a Schlenk flask by use of an Eppendorf pipette. The solvent within the Schlenk flask was then removed *in vacuo*, and subsequently 0.8 mmol of ketone followed by 6 mL of 2-propanol was added to the residue within the Schlenk flask. The solution was then heated at 82 ºC for 10 minutes at

which point 2 mL of a 0.004 M solution of NaOtBu in 2-propanol was added to the Schlenk flask (Ir:**2-32**:$NaPF_6$:NaOtBu/ketone = 1:1:1.1:20:2000; [ketone] = 0.1 M), resulting in rapid reduction of the ketone. Reactions were sampled by removing an aliquot of the reaction mixture via syringe (0.25-1 mL) and filtering through a plug of silica. Conversions were determined by use of GC and the identities of the hydrogenation products were confirmed by use of ^{1}H NMR methods or by comparison to authentic samples. All reported data represent the average of a minimum of two catalytic runs.

Typical Procedure for the Catalytic Asymmetric Transfer Hydrogenation of Ketones. $[(COD)IrCl]_2$ (7.1 mg, 0.01 mmol), Cy-Mandyphos (**2-42**) (18.0 mg, 0.021 mmol) and $NaPF_6$ (4.1 mg, 0.024 mmol) were vigorously stirred in THF (4.000 mL) for approximately 1 h before a 379 μL (0.002 mmol) aliquot was delivered to a Schlenk flask by use of an Eppendorf pipette. The solvent within the Schlenk flask was then removed *in vacuo*, and subsequently 0.4 mmol of ketone followed by 2 mL of 2-propanol was added to the residue within the Schlenk flask. The solution was then heated at 40 ºC for 10 minutes at which point 2 mL of a 0.04 M solution of NaOtBu in 2-propanol was added to the Schlenk flask (Ir:**2-42**:$NaPF_6$:NaOtBu:ketone = 1:1:1.1:10:200; [ketone] = 0.1 M). Conversions and enantiomeric ratios were determined by use of chiral GC (Astec CHIRALDEX G-TA 30m X 0.25mm for all substrates with exception of 2'-chloroacetophenone for which a Supelco Beta-Dex 120 30m X 0.25mm column was employed) and the identities of the hydrogenation products were confirmed by use of ^{1}H NMR methods or by comparison to authentic samples. The *S*-absolute configuration assigned to the major enantiomer of 1-phenylethanol formed in the reduction of **2-7** was determined by comparison to literature data.[21] GC conditions and retention times for enantioselective reductions: acetophenone (**2-7**) (100 ºC; 20 psi): 11.0 min; 1-phenylethanol: t_1= 11.6 min; t_2= 12.4 min; 3-chloroacetophenone (**2-12**) (145ºC; 12 psi): 8.3 min; 1-(2-chlorophenyl)ethanol: t_1= 13.8 min; t_2= 14.8 min; 4-fluoroacetophenone (**2-34**) (110 ºC; 17 psi): 6.8 min; 1-(2-fluorophenyl)ethanol: t_1= 9.7 min; t_2= 10.3 min; 2'-chloroacetophenone (**2-17**) (145 ºC; 12 psi): 8.0 min; 1-(2-chlorophenyl)ethanol: t_1= 10.3 min; t_2= 10.8 min; propriophenone (**2-37**) (110 ºC; 17 psi): 10.6 min; 1-phenylpropan-1-ol: t_1= 12.7 min; t_2= 13.1 min; n-butyrophenone (**2-38**) (125 ºC; 8 psi): 18.0 min; 1-

phenylbutan-1-ol: t_1= 21.7 min; t_2= 22.5 min; 2,2-dimethylpropiophenone (**2-39**) (125 °C; 8 psi): 14.5 min; 2,2-dimethyl-1-phenyl-propanol: t_1= 20.8 min; t_2= 21.5. All reported data represent the average of a minimum of two catalytic runs.

Crystallographic Solution and Refinement Details. Crystallographic data for **2-33** were collected by Dr. Michael Ferguson at the University of Alberta, Department of Chemistry X-Ray Crystallography Laboratory, on a Bruker PLATFORM/SMART 1000 CCD diffractometer using graphite-monochromated Mo K*a* (l = 0.71073 Å) radiation, employing a sample that was mounted in inert oil and transferred to a cold gas stream on the diffractometer (193(±2) K). Programs for diffractometer operation, data collection, data reduction, and absorption correction (including SAINT and SADABS) were supplied by Bruker. The structure of **2-33** was solved by use of direct methods, and refined by use of full-matrix least-squares procedures (on F^2) with R_1 based on $F_o^2 \geq 2s(F_o^2)$ and wR_2 based on $F_o^2 \geq -3s(F_o^2)$. Anisotropic displacement parameters were employed throughout for the non-H atoms. All H-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. Selected crystal data for **2-33**: empirical formula, $C_{24}H_{40}F_6Ir_1N_1P_2$; crystal system, monoclinic; space group, P2(1)/c; unit cell dimensions, a = 9.7092(7) Å, b = 16.0329(12) Å, c = 17.0851(13) Å, a = 90 deg., b = 96.7480(10) deg., g = 90 deg; volume = 2641.2(3) $Å^3$; Z = 4; m = 5.232 mm^{-1}; crystal size = 0.31 x 0.25 x 0.17 mm; f range for data collection = 1.75 to 27.51 deg.; limiting indices, $-12 \leq h \leq 12$, $-20 \leq k \leq 20$, $-22 \leq l \leq 22$; reflections collected / unique, 22776 / 6062 [R(int) = 0.0228]; completeness = 99.6 %; max. and min. transmission, 0.4699 and 0.2938; data / restraints / parameters, 6062 / 0 / 307; goodness-of-fit on F^2, 1.035; final R indices [I>2s(I)], R1 = 0.0200, wR2 = 0.0496; final R indices (all data), R1 = 0.0230, wR2 = 0.0509; largest diff. peak and hole, 1.145 and -0.363 e·$Å^3$. Additional crystallographic information is provided in the deposited CIF (CCDC 683381).

CHAPTER 3. APPLICATION OF PHENYLENE-P,N-LIGANDS IN PALLADIUM-CATALYZED C-N CROSS-COUPLING REACTIONS

3.1 INTRODUCTION

The Pd-catalyzed cross-coupling of aryl or vinyl (pseudo)halides and N-H containing compounds (Buchwald-Hartwig coupling) has emerged as an important method for the construction of C-N bonds in contemporary organic synthesis (Figure 3.1).[45] This method, along with Cu-catalyzed variants,[46] has superseded traditional routes for the synthesis of aryl amines in many cases. The high levels of selectivity, broad substrate scope, and excellent functional group tolerance displayed by state-of-the-art Pd-based catalysts have resulted in the widespread application of this reaction in the synthesis of pharmaceutical intermediates, natural products, and organic materials, both in industrial and academic settings.[47]

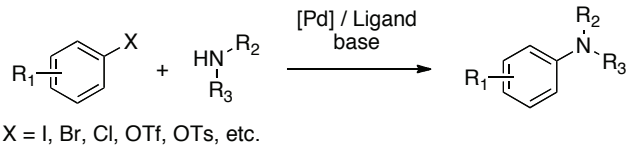


Figure 3.1 General scheme for the Pd-catalyzed cross-coupling of aryl (pseudo)halides and N-H containing compounds.

The general catalytic cycle for C-N cross-coupling reactions employing Pd is analogous to the Pd(0)-Pd(II) cross-coupling reactions of aryl halides and carbon nucleophiles (Figure 3.2).[45c, 48] The active catalytic Pd(0) species are typically generated via *in situ* reduction of Pd(II) complexes, such as L_nPdX_2 (L_n = unspecified number of ligands, X = halide or acetate), or arise from ligand dissociation from higher coordinate Pd(0) species (for example, $Pd_2(dba)_3$/ligand mixtures). After oxidative addition of the aryl halide to the 12- or 14-electron $L_nPd(0)$ species, a Pd(II)aryl(amido) intermediate can be generated by amine binding and subsequent deprotonation. Alternative routes to such Pd(II)amido species involving the protonation of Pd(II)aryl(alkoxide) by amine have also been suggested when employing strong metal alkoxide bases. Reductive elimination of aryl amine to regenerate $L_nPd(0)$ completes the catalytic cycle.

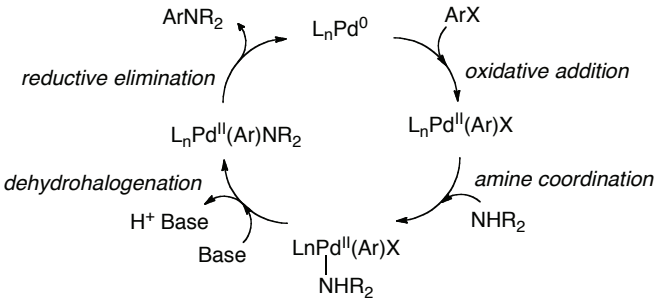


Figure 3.2 General mechanism for the Pd-catalyzed cross-coupling of aryl halides and amines.

Current consensus suggests that aryl halide oxidative addition is the turnover-limiting step in the C-N cross-coupling catalytic cycle, however reactions of the Pd(II)aryl(amido) complexes tend to dictate the scope and yield of the reaction.[48] Common unwanted side-reactions in Pd-catalyzed amine arylation reactions include aryl halide hydrodehalogenation via amine beta-hydride elimination, amine displacement of ligand to render inactive Pd species, and di- or tri-arylation of amine substrates. The general trend with respect to reactivity and efficiency of the X group of the aryl (pseudo)halide is Br > OTf > I > Cl. This observation is not in exact accordance with Ar-X bond dissociation energies (BDE in kcal mol^{-1} for PhX: Cl: 96, Br: 81, I: 65),[49] that typically affect the rate of oxidative addition, due to poisoning effects by iodide, which can be circumvented under certain conditions.[50] Electron poor aryl (pseudo)halides undergo oxidative addition faster than electron rich aryl (pseudo)halides, thus electron poor aryl halides are termed "activated" substrates. Electron rich amines, after forming Pd-amido species, undergo reductive elimination faster than Pd-amides of electron poor amines.[51] While generally speaking, factors controlling the individual steps of Pd-catalyzed cross-coupling reactions are well understood, predicting (or improving) reactivity in real applications becomes difficult due to the myriad of competing processes that influence the reaction.

Insights gained regarding the key mechanistic steps in Pd-catalyzed C-N cross-coupling have enabled the development of several highly active classes of catalysts for the cross-coupling of challenging substrates (unreactive substrates or substrates prone to deleterious side reactions). General themes arising from ligand design studies related to

Buchwald-Hartwig cross-coupling and related Pd-catalyzed reactions can be summarized as follows:[45a, 47c, 52]

1. Sterically demanding ligands that favour the formation of low-coordinate Pd(0) complexes (ideally mono-coordinate or cis-dicoordinate) over multi-ligated Pd-species, which must undergo ligand dissociation, are preferred ancillary ligands.

2. Ligands possessing basic, sterically demanding donor fragments, such as bulky trialkylphosphines or N-heterocyclic carbenes enhance the rates of oxidative addition of aryl halides and broaden reaction scope by generating a more reactive, electron-rich metal center.

3. Increased steric demand at the Pd center increases the rate of reductive elimination from Pd(II)aryl(amido) complexes and may be used to control selectivity. Steric effects generally override electronic effects in C-N reductive eliminations.

4. Ligands featuring secondary metal-ligand interactions appear to help stabilize or activate the metal center in key mechanistic steps, allowing for enhanced reactivity with difficult substrates, increased catalyst lifetime, and/or increased rates of catalysis, beyond what is observed for simple monodentate ligands.

While ligand effects pertaining to aryl halide oxidative addition[53] and C-N reductive elimination[51] at Pd are more well established, the way in which ligand structure affects amine coordination and subsequent dehydrohalogenation, key factors influencing overall reaction efficiency and selectivity, are less well understood.

There now exist several ligand classes that promote difficult C-N cross-coupling reactions, including bulky trialkylphosphines;[54] *N*-heterocyclic carbenes;[55] biaryldialkylphosphines[47c] and chelating bisphosphines;[52c, 56] as well as N- or O-heteroatom functionalized phosphines.[57] Select examples representing the historical development of ligands for C-N cross-coupling are shown in Figure 3.3.

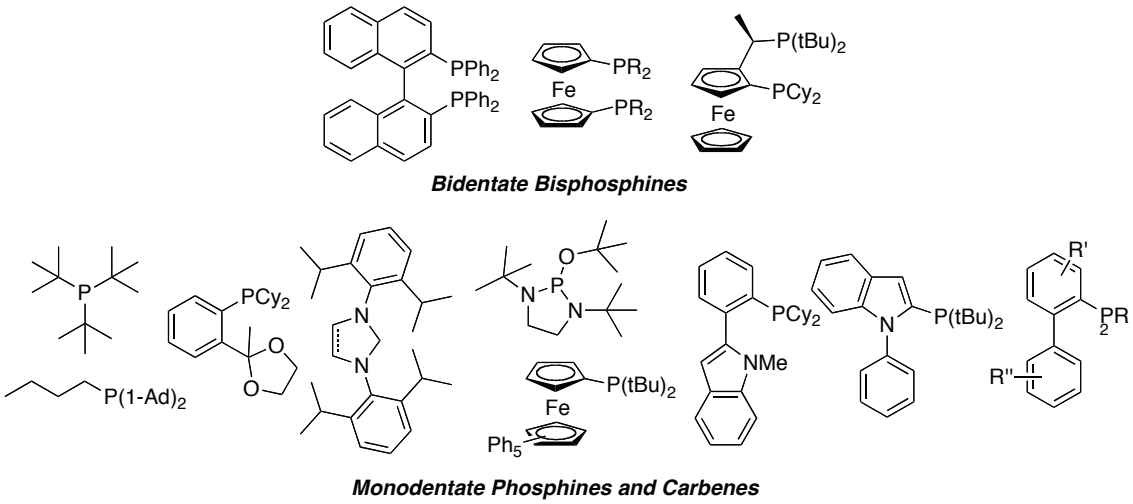


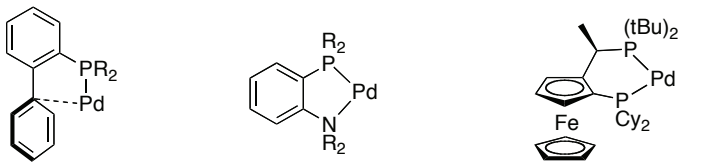
Figure 3.3 Select examples within the evolution of ligands for the Pd-catalyzed cross-coupling of aryl (psuedo)halides and amines.

Challenges addressed by the above described ligands include the use of aryl (pseudo)halide substrates that are reluctant to undergo oxidative additions under relatively mild conditions, such as electron-rich (deactivated) aryl chlorides,[49] as well as the use of phenol derived substrates such as aryl tosylates[52b, 58] and aryl mesylates,[57i, 59] which are less reactive than more commonly employed (but less stable) aryl triflates. Difficulties associated with particularly challenging classes of amine substrates have been addressed by use of specialized 'task-specific' ligands in combination with a judiciously selected Pd precursor. These reactivity challenges include the selective monoarylation of small primary alkyl amines (including methylamine),[59-60] the arylation of poorly nucleophilic[59, 61] or heteroatom-functionalized anilines,[62] the coupling of base-sensitive substrates,[63] the arylation of lithium amides,[64] and the synthesis of anilines from ammonia.[64b, 65]

Despite the tremendous progress made within the field of Pd-catalyzed C-N cross-coupling, there still exist numerous challenges related to the scope and utility of this reaction. A lack of catalyst generality for a broad range of amination processes can make *a priori* selection of optimal Pd/ligand mixtures troublesome. Most catalyst systems that perform well in selected applications with regard to amine substrates, fail with alternative classes of substrates. The development of a "universal catalyst" would greatly improve the utility of the transformation. Furthermore, the scope of Buchwald-Hartwig aminations with small nucleophilic amines such as methylamine, ammonia, hydrazine and

hydroxylamine have either been severely limited with respect to aryl halide scope, or have not been reported. More commonly, surrogates of these types of substrates have been employed to attenuate unwanted side reactions.[66] Lastly, general reactivity and lifetime issues related to C-N cross-coupling catalysts have made the use of relatively high Pd-loadings a requirement for all but the more facile reactions. The pursuit of more active cross-coupling catalysts should allow for the reduction of metal and ligand used in these reactions, making them more attractive in large-scale synthesis.

Motivation for the design and application of the P,N-ligands presented herein for Pd-catalyzed C-N cross-coupling reactions arose from analysis of unarguably the two most productive classes of ligands for Buchwald-Hartwig aminations. Hartwig has reported extensively on the use of the strongly chelated bisphosphine ligand Josiphos (Figure 3.4).[52c] Here, the combined effects of chelation enforced by the ferrocenyl backbone, the steric demand presented by the $P(tBu)_2$ and PCy_2 donor groups, and the high electron density at Pd provide a rationale for the high activity and lifetime associated with Pd-Josiphos catalyzed mixtures when employed in certain C-N cross-coupling reactions. Josiphos has been found to be an excellent ligand for the cross-coupling of aryl and heteroaryl bromides, chlorides, and tosylates to primary alkyl and aryl amines, as well as ammonia and lithium amide. The rigid, chelating nature of the ligand prevents displacement by strongly nucleophilic or heteroatom functionalized amines. Limitations of the Josiphos system include poor reactivity with secondary amines, the requirement of typically high reaction temperatures (~100 °C), poorly defined chemoselectivity, as well as the cost of the ligand. Conversely, Buchwald has introduced a series of ligands based on a biaryl phosphine motif.[47c] These ligands rely on an electron-rich, bulky phosphine donor as well as weak arene-Pd interactions, in which the bottom aryl ring accounts for the exceptional activity and stability of such ligands in comparison to non-biaryl substituted ligands. While a number of challenging cross-coupling reactions have been shown to be possible by employing biaryl phosphine ligands, substrate generality and activity at low catalyst loadings are limitations of this ligand family.



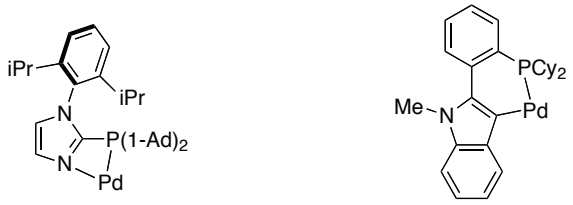
Biaryl Monophosphines (Buchwald)
one strong interaction
one weak interaction

P,N-Ligands
one strong interaction
one moderate interaction

Bisphosphines (Hartwig)
two strong interactions

Figure 3.4 Comparison of metal-ligand interactions in P,N-ligands and other successful classes of ligands for C-N cross-coupling.

At the outset of this thesis research, it was postulated that a ligand motif featuring an electron rich phosphine donor in combination with a weaker amine-donor might act as a useful middle ground between the previously described mono- and bidentate systems. In the course of such studies, two notable reports emerged that have conceptual similarities. Beller and co-workers have developed a catalyst for the mild cross-coupling of hydroxide to aryl halides by employing an imidazole-biaryl phosphine ligand (Figure 3.5).[67] Solution and NMR studies demonstrate that this ligand binds to palladium in a κ^2-P,N fashion, and the presence of the N-donor may offer an explanation for the enhanced reactivity observed. Kwong and co-workers have developed indolyl biaryl phosphine ligands and proved their utility in a number of Pd-catalyzed cross-coupling reactions, including the amination of aryl mesylates.[57i] Here, it appears that rather than N-coodination, ligand cyclometalation occurs at the indole C-X position.



Beller - Imidazole Biaryl
P,N Ligand for OH^- Arylation

Kwong - Indoyl Biaryl
P,C Ligand for Mesylate Amination

Figure 3.5 Related P,N-ligands with structurally characterized Pd-ligand interactions.

Finally, the design of ligands tailored for application in C-N cross-coupling reactions have also found use in a number of other Pd-catalyzed reactions, for example carbonyl α-arylation,[68] Kumada,[69] Negishi,[70] fluoride,[71] trifluoromethyl,[72] and nitro coupling.[73] Thus, the design of new ligand classes to promote more active and efficient

Pd-catalysts for amination reactions may have wide-ranging application involving a range of transformations.

3.2 Development of a Highly Versatile P,N-Ligand for the Cross-Coupling of Aryl Chlorides and Amines

Treatment of 2-lithio-*N*,*N*-dimethylaniline with tBu_2PCl lead to low yields of **2-32** (see Chapter 2, section 3), thus alternative routes for the preparation of sterically demanding P,N-ligands were explored. It was found that **2-32** could be prepared in 71% yield by a catalytic P-C coupling reaction[74] of *o*-Br-*N*,*N*-dimethylaniline and tBu_2PH employing $Pd(OAc)_2$ and DiPPF (1,1'-bis(diisopropylphosphino)ferrocene); the related 1-adamantyl (1-Ad) substituted ligand **3-1** was prepared in an analogous fashion in 74 - 85% yield (Scheme 3.6). Both reactions were observed to proceed to >95% conversion based on ^{31}P NMR and could be isolated conveniently by simply washing or recrystallization of the crude reaction material after filtration through silica. The use of the robust and air-stable secondary phosphine $(1\text{-Ad})_2PH$ in the preparation of **3-1** circumvents the use of highly oxygen- and moisture-sensitive and/or pyrophoric reagents, such as dialkylchlorophosphines, which are commonly required for the synthesis of bulky alkylphosphine ligands. $(1\text{-Ad})_2PH$ can be easily prepared according to literature procedures in good yield in two steps from adamantane and PCl_3.[75] Both **2-32** and **3-1** were found to be stable (as observed by ^1H and ^{31}P NMR) in the solid state for at least two months when stored under air. The ease of synthesis of **2-32** and **3-1** is in contrast to some of the most widely used ligands for challenging Pd-catalyzed C-N coupling reactions, which commonly require multistep syntheses from less readily available and/or costly reagents. **3-1** has been prepared in scales of approximately 10 g in similar yields, without any significant difficulties.

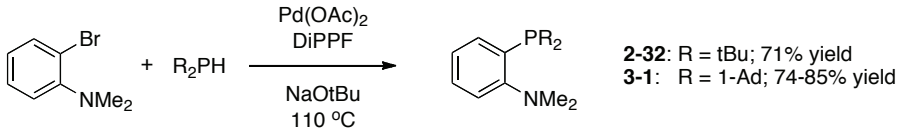


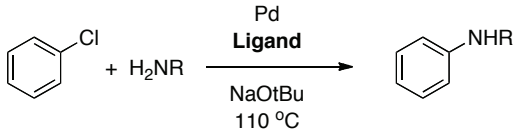
Figure 3.6 Synthesis of *ortho*-dimethylamino phenylphosphine ligands by Pd-catalyzed cross-coupling of secondary phosphines.

The reaction of chlorobenzene and aniline using 0.5 mol% Pd at 100 °C in toluene was selected to assess the catalytic utility of **2-32** and related ligands in Pd-catalyzed C-N coupling. Under these screening conditions, most commonly employed Pd-starting materials including $Pd(OAc)_2$, $PdCl_2$, $PdCl_2(COD)$, $PdCl_2(MeCN)_2$, and $Pd_2(dba)_3$ gave only modest conversions after 4 h. However, it was discovered that $[Pd(allyl)Cl]_2$ and **2-32** afforded an active catalyst system, providing 91% yield of diphenylamine in 4 h with no significant diarylation product (triphenylamine) formed. The use of $[Pd(cinnamyl)Cl]_2$ provided even better catalytic activity (92% yield in 2.5 h; Table 3.1, entry 1), while the use of **3-1** with $[Pd(cinnamyl)Cl]_2$ gave high yields (87%) under similar conditions (Table 3.1, entry 3). The use of two equivalents of **2-32** or **3-1** was found to be ideal under standard conditions and toluene was identified as the solvent of choice, although 1,4-dioxane and dimethoxyethane could also be employed. The influence of the position and substitution of both the P- and N-donor fragments was explored by testing a series of related ligands under the conditions that proved favorable for **2-32** and **3-1**. Ligands possessing less basic or less sterically demanding substituents on phosphorus (**3-2** and **3-3**, Table 3.1, entries 5 and 7) were ineffective for the cross-coupling of chlorobenzene and aniline, each giving less then 10% conversion on the basis of GC data. The importance of the nitrogen donor group was evidenced by the failure of mixtures of $[Pd(cinnamyl)Cl]_2$ and ligands **3-4** or **3-5** to provide the desired cross-coupling product in appreciable yield after 2.5 h. The failure of highly analogous ligands **3-6** and **3-7** to provide significant yields of diphenylamine under our standard conditions was surprising; **3-6** has been demonstrated to be an excellent ligand for the Suzuki-Miyaura reactions of heteroaryl chlorides.[76] Collectively, these results provide compelling evidence in support of the concept that both the basic and sterically demanding phosphine donor and the *ortho*-situated dimethylamino group in **2-32** and **3-1** are necessary for achieving high activity in this particular Pd-catalyzed C-N coupling reaction.

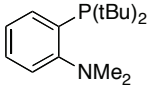
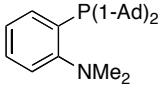
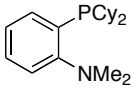
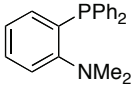
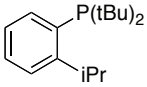
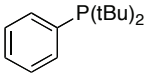
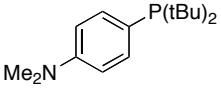
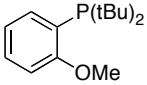
Having established **2-32** and **3-1** as superior ligands for a relatively facile C-N coupling process, their utility in a considerably more difficult transformation was explored. Although the abundance and low cost of ammonia make it an ideal nitrogen source in amine synthesis, the small and highly nucleophilic, deactivating nature of this substrate present considerable challenges with respect to its efficient utilization in metal-

catalyzed C-N coupling reactions. While ammonia cross-coupling with aryl bromides and iodides has been reported using catalysts based on Pd[64b, 65, 77] and Cu,[78] the selective monoarylation of ammonia with aryl chlorides represents a challenging reaction, one that has only started to be addressed very recently by use of specially designed ancillary ligands. Furthermore, selective monoarylation of ammonia employing deactivated aryl chlorides lacking *ortho*-substituents represents a particular challenge. After a brief optimization campaign, it was discovered that employing **3-1** with $[Pd(allyl)Cl]_2$ (2 mol% Pd; Pd:L = 1:4) at 110 ºC in 1,4-dioxane resulted in the complete conversion of chlorobenzene to a mixture of aniline and diphenylamine after 20 h (Table 3.1, entry 4); modest selectivity for the monoarylation product was achieved ($PhNH_2$:Ph_2NH = 2.9:1). It was found that the structural features in **3-1** were prerequisites for obtaining high activity and selectivity, as other related ligands afforded lower conversions and favored diphenylamine, the undesired diarylation product (Table 3.1).

Table 3.1 Ligand screen for the cross-coupling of chlorobenzene with aniline and ammonia.



Condition A: $H_2NR = PhNH_2$ ***Condition B***: $H_2NR = NH_3$

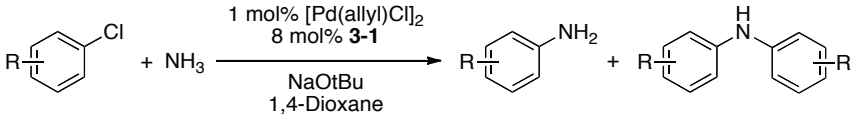
entry		**ligand**	conditions	yield
1	**2-32**		**A**	92%
2			**B**	77% (1:1.3)
3	**3-1**		**A**	87%
4			**B**	>99% (2.9:1)
5	**3-2**		**A**	<10%
6			**B**	13% (1:6)
7	**3-3**		**A**	<10%
8			**B**	*nd*
9	**3-4**		**A**	<10%
10			**B**	*nd*
11	**3-5**		**A**	<10%
12			**B**	56% (1:16)
13	**3-6**		**A**	17%
14			**B**	67% (<1:20)
15	**3-7**		**A**	<10
16			**B**	49% (<1:20)

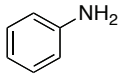
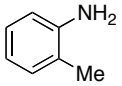
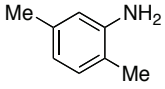
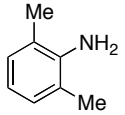
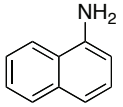
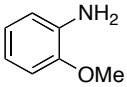
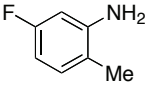
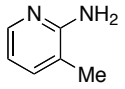
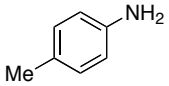
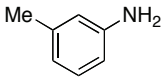
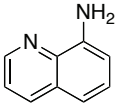
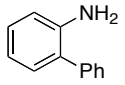
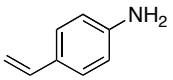
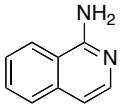
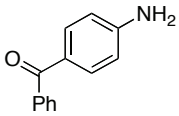
Condition A: ArCl:Aniline:NaOtBu = 1:1.2:1.4, 1.0 mmol scale in 2 mL toluene at 100 °C, 2.5 h, 0.25 mol% $[Pd(cinnamyl)Cl]_2$, Pd:L = 1:2. Yields of isolated product. **Condition B**: ArCl:NH_3:NaOtBu = 1:10:1.4-1.6, [ArCl] = 0.025 M, 1 mol% $[Pd(allyl)Cl]_2$, Pd:L = 1:4, 20 h at 110 °C in 1,4-dioxane. Conversions determined by consumption of chlorobenzene, with $PhNH_2$:Ph_2NH indicated in parenthesis as determined by calibrated GC data (average of two catalytic runs).

The scope of anilines that could be prepared via monoarylation of ammonia employing aryl- or heteroaryl chlorides with $[Pd(allyl)Cl]_2$ and **3-1** was found to be limited to *ortho*-substituted or electron-poor substrates (Table 3.2). The use of *ortho*-substituted aryl or heteroaryl chlorides resulted in high selectivities for monoarylation (generally >20:1), while maintaining high levels of conversion. Presumably, the increased steric demand of the resulting aniline, paired with the bulk of the aryl chloride substrate, prevents subsequent diarylation. The use of the modestly deactivated aryl chloride

substrates 3- and 4-chlorotoluene still gave complete conversion at 4 mol% Pd, however the selectivity for the monoarylation product was reduced substantially (~1:1); in this instance it appears that the use of a chelating bisphosphine ligand can provide better selectivity for electron-rich aryl chlorides.[65c] The activated substrates 4-chlorostyrene and 4-chlorobenzophenone provided high conversions (> 95%) and excellent selectivities for monoarylation (>10:1). For these cases, the reduced nucelophilicity of the resulting aniline product (compared to aniline or 4-methylaniline) presumably inhibits diarylation.

Table 3.2 Cross-coupling of aryl and heteroaryl chlorides with ammonia.



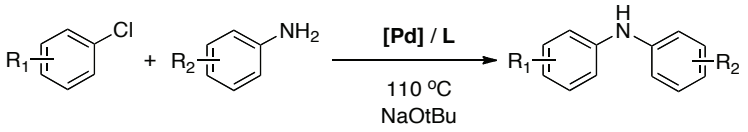
 **3-8** >99% (2.9:1)	 **3-9** >99% (>20:1)	 **3-10** 98% (>20:1)	 **3-11** 98% (>20:1)
 **3-12** 88%[b]	 **3-13** 91% (>20:1)[c]	 **3-14** 98% (>20:1)[c]	 **3-15** 96% (>20:1)[c]
 **3-16** >99% (1.1:1)[d]	 **3-17** >99% (1:1.1)[d]	 **3-18** 84%[a,c]	 **3-19** 90%[a,c]
 **3-20** >99% (>20:1)	 **3-21** 99% (>20:1)[c]	 **3-22** 80%	

Conditions: $ArCl:NH_3:NaOtBu$ = 1:10:1.4-1.6, [ArCl] = 0.025-0.04 M, conversions determined by consumption of ArCl, with $ArNH_2:Ar_2NH$ indicated in parenthesis as determined by calibrated GC data, 16-20 h, 110-120 ºC in 1,4-dioxane. [a] Isolated yield. [b] From ca. 90% pure 1-chloronaphthalene. [c] Using Pd:L = 1:2. [d] Using 4 mol% Pd.

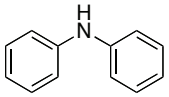
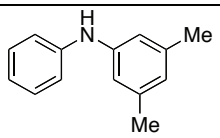
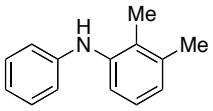
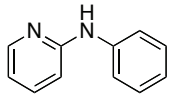
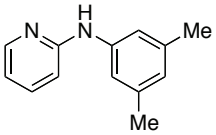
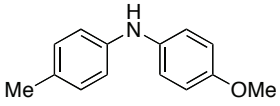
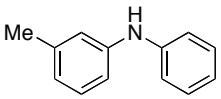
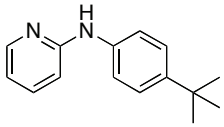
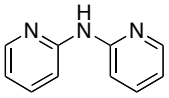
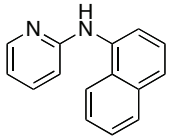
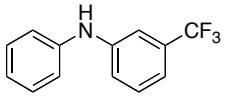
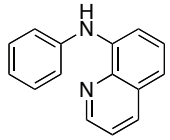
Encouraged by the successful demonstration that **2-32** and **3-1** represent effective ligands for the Pd-catalyzed coupling of chlorobenzene with aniline or ammonia, the

scope of this catalyst system with primary and secondary amines was explored (Tables 3.3 and 3.4, respectively). Throughout these catalytic studies it was observed that **2-32** or **3-1** with either $[Pd(cinnamyl)Cl]_2$ or $[Pd(allyl)Cl]_2$ could be used interchangeably. An initial survey of various aryl or heteroaryl chlorides and anilines revealed this catalyst system to be generally insensitive to the nature of the coupling partners (Table 3.3). Good to excellent yields were obtained for the coupling of a series of substituted aryl chlorides to anilines, including 2-aminopyridine and 8-aminoquinoline, as well electron-poor anilines that are often difficult substrates in C-N coupling reactions (Table 3.3). Lithium amide ($LiNH_2$) could be used as an alternative nitrogen source, providing high yields of the corresponding symmetrical diarylamine under appropriate conditions. Monoarylation was not observed under such conditions, perhaps due to the poor solubility of $LiNH_2$, resulting in low concentrations of amine in solution.

Table 3.3 Pd-catalyzed cross-coupling of aryl chlorides and anilines employing **2-32** or **3-1** as ligands.



[Pd] = $[Pd(allyl)Cl]_2$ *or* $[Pd(cinnamyl)Cl]_2$
L = **2-32** *or* **3-1**

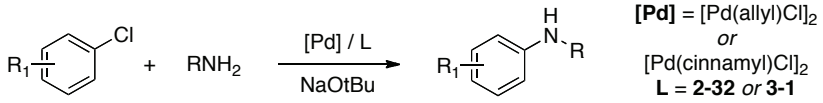
 **3-23** 91% (0.2); 89 (1)[a]	 **3-24** 99% (0.5)	 **3-25** 93% (0.5)	 **3-26** 92% (0.2)
 **3-27** 99% (0.2)	 **3-28** 88% (0.2)	 **3-29** 98% (0.5)	 **3-30** 99% (0.2)
 **3-31** 97% (0.5); 99% (0.5)[a]	 **3-32** 83% (0.2)	 **3-33** 94% (1.0)	 **3-34** 68% (0.5)

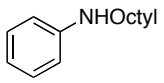
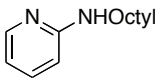
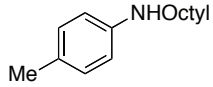
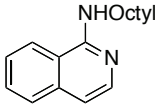
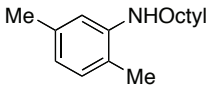
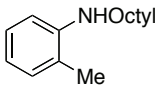
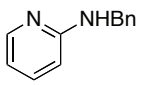
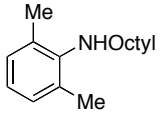
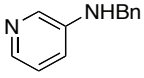
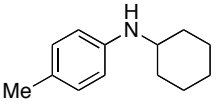
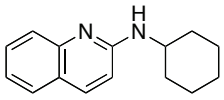
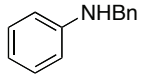
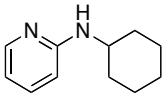
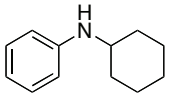
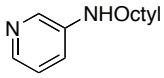
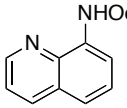
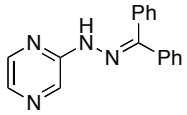
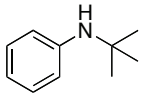
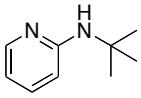
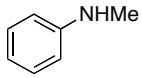
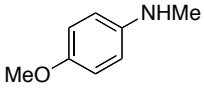
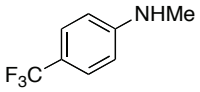
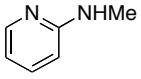
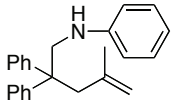
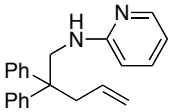
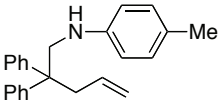
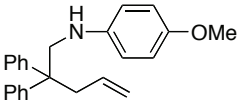
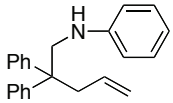
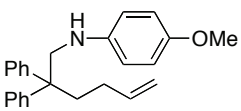
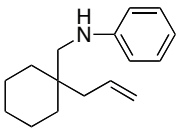
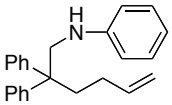
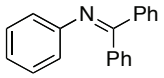
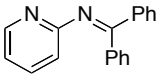
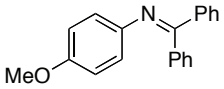
Conditions: ArCl:Amine:NaOtBu = 1:1.2:1.4, 1.0 mmol scale, 3-48 h. Isolated yields are an average of two runs, mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd:L = 1:2). [a] Using 10 equiv. of $LiNH_2$, [ArCl] = 0.2 M.

Electronically neutral or deactivated aryl chlorides could be coupled to simple primary alkyl amines such as octylamine, benzylamine and cyclohexylamine in high yields at catalyst loadings of 0.1 – 0.05 mol% Pd (Table 3.4). It is worthy of mention that while Guram and co-workers[79] have disclosed the use of PR_2-substituted phenylene ligands that are conceptually related to **2-32** and **3-1** in Pd-catalyzed C-N coupling reactions, their optimal ligand configuration required 2 mol% Pd and 6 mol% ligand to achieve a 92% yield of *N*-(2,5-dimethylphenyl)octylamine (**3-39**); by comparison, an 87% isolated yield is achieved by use of our catalyst system employing 20 times less Pd (0.1 mol%). Aryl chlorides substituted at the *ortho*, *meta*, or *para* position each proved to be compatible substrates under standard conditions, with negligible diarylation observed by GC. The coupling of 2- or 3-pyridyl and related *N*-heteroaryl chlorides to primary amines proceeded with high efficiency, allowing catalyst loadings as low as 0.02 mol% Pd to be employed. The broad scope of reactivity when employing **2-32** or **3-1** in Pd-catalyzed

aminations is exemplified by the fact that both the sterically demanding substrate *tert*-butylamine, as well as the unhindered methylamine, could each be cross-coupled in high yield with no significant diarylation. Furthermore, other classes of N-H containing substrates including imines and benzophenone hydrazone could also be cross-coupled in good yields. The cross-coupling of aryl and pyridyl chlorides to amines bearing pendant olefin groups also proved to be feasible. In these cases, good to excellent yields of the *N*-aryl amino-alkene could be achieved without competing isomerization or insertion chemistry at the olefin position.[80]

Table 3.4 Pd-catalyzed cross-coupling of aryl chlorides and alkyl amines employing **2-32** or **3-1** as ligands.



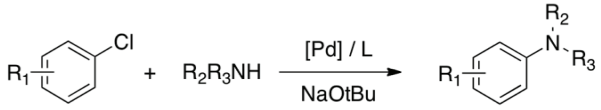
 **3-35** 98% (0.05)	 **3-36** 94% (0.02)	 **3-37** 94% (0.05)	 **3-38** 90% (0.02)
 **3-39** 87% (0.1)	 **3-40** 79% (0.05)	 **3-41** 99% (0.02)	 **3-42** 84% (0.1)
 **3-43** 85% (0.4)	 **3-44** 70% (0.05)	 **3-45** 97% (0.05)	 **3-46** 91% (0.05)
 **3-47** 77% (0.2)	 **3-48** 87% (0.05)	 **3-49** 83% (0.3)	 **3-50** 99% (0.2)
 **3-51** 91% (0.2)	 **3-52** 83% (1.5)	 **3-53** 95% (1)	 **3-54** 99% (2)[c,e]
 **3-55** 89% (2)[d]	 **3-56** 97% (2)[c,e]	 **3-57** 97% (1)[c]	 **3-58** 97% (0.5)[b]
 **3-59** 68% (0.5)[b]	 **3-60** 90% (0.2)[b]	 **3-61** 73% (0.5)[b]	 **3-62** 95% (0.5)[b]
 **3-63** 78% (0.5)[b]	 **3-64** 94% (0.5)[b]	 **3-65** 98% (0.5)[b]	
 **3-66** 98% (0.5)	 **3-67** 97% (0.5)	 **3-68** 80% (1)	

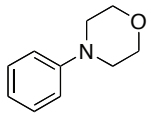
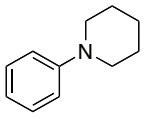
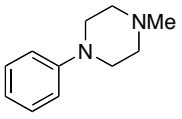
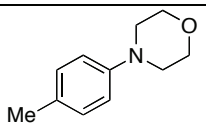
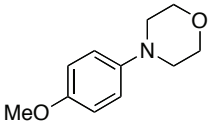
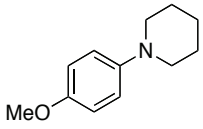
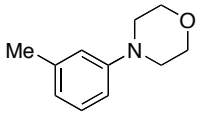
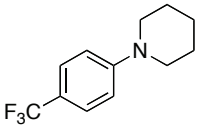
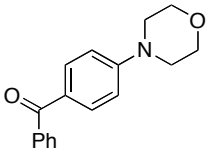
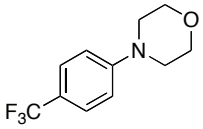
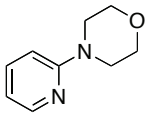
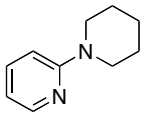
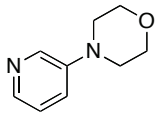
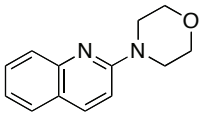
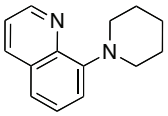
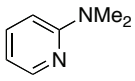
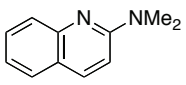
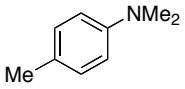
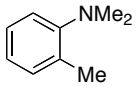
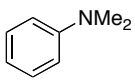
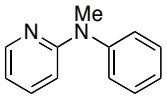
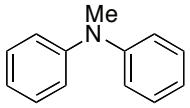
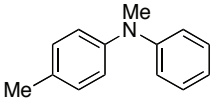
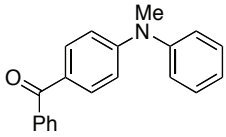
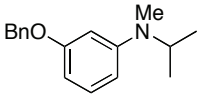
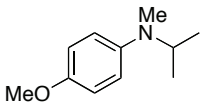
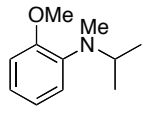
Conditions: ArCl:Amine:NaOtBu = 1:1.2:1.4, 1.0 mmol scale, 3-48 h, mol% Pd employed indicated in parentheses (Pd:L = 1:2). [b] Using 1.05 equiv. of amine. [c]

Conditions (cont.): Using 4 equiv. H_2NMe at 65 ºC. [d] Using 4 equiv. H_2NMe at 85 ºC. [e] Conversion determined by GC. Where ambiguous, the left portion of the product is derived from the aryl chloride.

Given that most catalyst systems for C-N cross-coupling reactions tend to favour drastically either primary or secondary amine substrates with respect to catalyst productivity, it was surprising to discover that **2-32** or **3-1** in combination with $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$ could also couple secondary amines such as morpholine, piperidine, and *N*-methylpiperazine to a diverse set of electronically activated, deactivated, and neutral aryl chlorides, as well as to *N*-heteroaryl chlorides, at low catalysts loadings (0.5-0.05 mol% Pd; Table 3.5). The preparation of *N,N*-dimethylanilines was also successfully achieved by employing dimethylamine as a substrate. The use of dimethylamine as a 2.0 M solution in THF required reactions to be performed at 65 ºC (instead of 100-110 ºC); nonetheless, high isolated yields were obtained by using 2-0.2 mol% Pd. The use of dimethylamine as a coupling partner is uncommon,[81] and the results presented herein represent rare examples in which ubiquitous *N,N*-dimethylanilines have been prepared via cross coupling of aryl chlorides. While secondary *N*-methylanilines represented more challenging substrates for the above described catalyst system, good yields of the corresponding diarylalkyl amines were obtained by modification of the standard conditions (Pd:L = 1:0.9 in 1,4-dioxane; Table 3.5). In this manner, a series of unsymmetrical diarylmethylamines could be prepared – a process that corresponds to a selective two-step diarylation beginning from H_2NMe (Table 3.3). The sterically demanding, acyclic secondary amine *N*-methylisopropyl amine could also be employed as a substrate. (**3-93**-**3-95**) In this case, *para*-, *meta*-, and even challenging *ortho*-substituted, deactivated aryl chloride substrates could be employed, delivering the product amine in acceptable yields. These catalytic results involving secondary amines are particularly impressive in light of the ability of **2-32** and **3-1** to also promote the arylation of much smaller nitrogen substrates such as ammonia and methylamine.

Table 3.5 Pd-catalyzed cross-coupling of aryl chlorides and secondary amines employing **2-32** or **3-1** as ligands.



 **3-69** 99% (0.2)	 **3-70** 88% (0.2)	 **3-71** 86% (0.2)	 **3-72** 81% (0.2)
 **3-73** 83% (0.2)	 **3-74** 94% (0.2)	 **3-75** 94% (0.2)	 **3-76** 98% (0.2)
 **3-77** 89% (0.2)	 **3-78** 84% (0.2)	 **3-79** 80% (0.05)	 **3-80** 92% (0.2)
 **3-81** 95% (0.5)	 **3-82** 96% (0.1)	 **3-83** 94% (0.2)	 **3-84** 87% (0.2)[a]
 **3-85** 93% (0.2)[a]	 **3-86** 89% (0.5)[a]	 **3-87** 83% (2)[a,c]	 **3-88** 91% (0.5)[a,c]
 **3-89** 87% (1)	 **3-90** 80% (1)[b]	 **3-91** 81% (1.5)[b]	 **3-92** 76% (1)[b]
 **3-93** 87% (2.0)	 **3-94** 72% (2.5)	 **3-95** 65% (4.0)	

Conditions: ArCl:Amine:NaOtBu = 1:1.2:1.4, 1.0 mmol scale, 3-48 h. Yields are of isolated material, mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd:L = 1:2). [a] ArCl:$HNMe_2$ = 1:2, at 65 °C in 1:1 toluene/THF. [b] Pd:L = 1:0.9 in 1,4-dioxane. [c] Conversion determined by GC.

While for convenience most cross-coupling experiments were conducted under inert conditions excluding oxygen and moisture by employing an inert-atmosphere

glovebox, the stability of **2-32** or **3-1** allowed for reactions to be conducted under less rigorous conditions. For example, in the coupling of chlorobenzene and octylamine at 0.1 mol% Pd, >99% conversion (by GC) was achieved after 20 h by using a protocol in which the catalyst components ($[Pd(cinnamyl)Cl]_2$ and **2-32** or **3-1**) were weighed out on the benchtop and combined with NaOtBu in anhydrous toluene, followed by placing the reaction vial under an atmosphere of dinitrogen. When the coupling of chlorobenzene and piperidine at 0.2 mol% Pd was conducted in air employing toluene that had not been purified to remove water or oxygen, quantitative conversion to *N*-phenylpiperidine (**3-71**) was still achieved after 24 h (Figure 3.7).

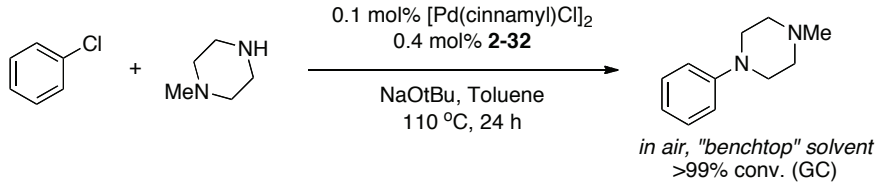
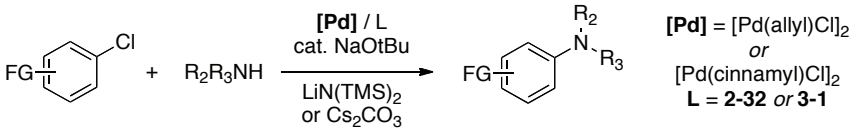
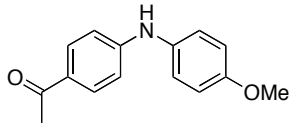


Figure 3.7 Cross-coupling of chlorobenzene and *N*-methylpiperazine in air, employing unpurified solvent.

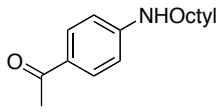
The use of Pd-allyl type starting materials presents a potential drawback – the requirement of a strong nucleophilic base for the rapid *in situ* generation of Pd(0) catalysts.[55a, 82] However, we found that base-sensitive compounds could be employed as substrates by using a catalytic amount of NaOtBu to activate the Pd(allyl)-type precatalyst, and a stoichiometric amount of a more appropriate base such as Cs_2CO_3 or $LiN(SiMe_3)_2$ to facilitate the cross-coupling chemistry. This technique allowed for the cross-coupling of aryl chloride substrates containing enolizable ketones, esters, carboxylic acids, phenols, alcohols, and amides to primary or secondary amines (Table 3.6).

Table 3.6 Pd-catalyzed C-N cross-coupling of base-sensitive substrates.

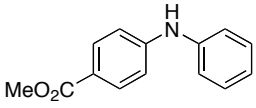




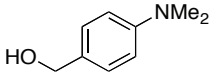
3-96 96% (0.5)[a]



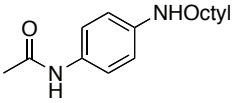
3-97 74% (0.5)[a]



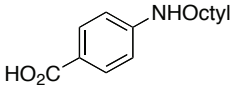
3-98 96% (0.5)[c]



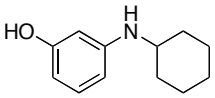
3-99 82% (2.0)[c]



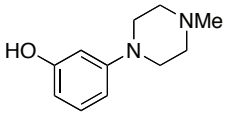
3-100 73% (1.0)[b]



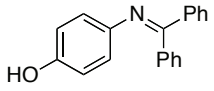
3-101 72% (0.5)[b]



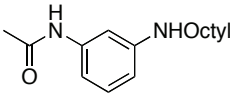
3-102 80% (0.5)[b]



3-103 70% (0.5)[b]



3-104 67% (1.5)[b]



3-105 98% (1.0)[b]

Conditions: ArCl:Amine:Base = 1:1.2:2.2, 0.5-1.0 mmol scale, 2-4 mol% NaOtBu, 2-48 h, 110 °C. Mol% Pd employed (from $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$) indicated in parentheses (Pd:L = 1:2). [a] Using Cs_2CO_3 in 1,4-dioxane. [b] Using LiHMDS in toluene. [c] Using LiHMDS in THF/dioxane at 65 °C.

Despite the high activity displayed by the catalyst system for a wide range of amine substrates, selected intermolecular C-N couplings proceeded chemoselectively. For example, when one equivalent of chlorobenzene was reacted with 1.05 equivalent each of octylamine and morpholine in the presence of 0.125 mol% $[Pd(cinnamyl)Cl]_2$ and **3-1** at 95 °C, 88% conversion of the aryl chloride was observed (on the basis of GC data), favoring the octylamine cross-coupling product in an 18:1 ratio versus the morpholine-derived product (Figure 3.8). Competition experiments between benzylamine and *N*-methylaniline also demonstrated high selectivity for primary amine arylation, giving 85% conversion to *N*-benzylaniline (**3-46**) after 2 h (with only trace amounts of Ph_2NMe) when employing 0.5 mol% Pd. Anilines can also be chemoselectively coupled to chlorobenzene in the presence of secondary amines (e.g. piperidine) with excellent conversions and good selectivities over the course of 1 h employing 1 mol% Pd. Finally, while the current study focused on the cross-coupling of more challenging aryl chloride substrates, aryl iodides

and bromides can also be employed with excellent results. Iodobenzene and octylamine could be coupled with >99% conversion employing 0.05 mol% Pd under standard conditions. Chemoselective amination (100 °C; 0.5 mol% Pd) at the bromide position of 1,4-bromochlorobenzene with 4-anisidine was obtained by using $[Pd(cinnamyl)Cl]_2$ and **3-1** to afford the chloro-functionalized diarylamine **3-106** in 76% isolated yield. The powerful combination of high catalytic activity, broad substrate scope, and excellent chemoselectivity displayed by Pd catalysts featuring **2-32** or **3-1** suggests that these catalyst systems should be of widespread utility in the construction of complex molecular frameworks by use of C-N coupling techniques.

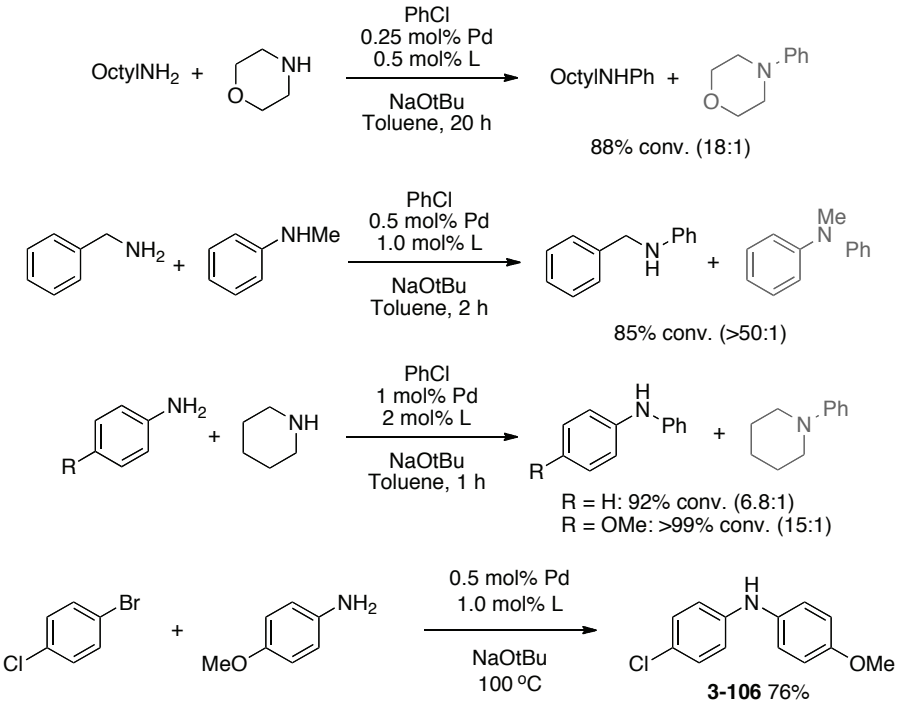


Figure 3.8 Amine competition studies employing chlorobenzene and primary or secondary amines and selective aryl bromide coupling. Pd = $[Pd(cinnamyl)Cl]_2$, L = **3-1**. Conversions and selectivities determined by GC.

Despite the broad scope and good reactivity in C-N cross-coupling reactions displayed by **2-32** and **3-1** in most of the tested applications, some limitations were encountered. Poorly nucleophilic N-H containing molecules such as benzamides, sulfonamides, hydroxylamides, and indole were not suitable reaction partners. In the case of benzamide, good conversions were observed with 2-chloropyridine; however reactivity

with chlorobenzenes was poor, suggesting chelation of amides might inhibit reactivity. Attempts to react sterically demanding substrates, such as 2,6-dimethylchlorobenzene and morpholine, or diphenylamine with chlorobenzene, resulted in low conversions. It appears the catalytic system has a limit with respect to the size of reaction partners it can accommodate. Additionally, all the above-described reactions were conducted at a minimum of 65 ºC, and more generally at 110 ºC. While room temperature (and below) C-N cross-coupling reactions are known, it appears that **2-32** or **3-1** require higher temperatures.

In summary, the results presented in this section show the structurally simple and air-stable ligands **2-32** and **3-1** to be broadly useful for the Pd-catalyzed cross-coupling of aryl and heteroaryl chlorides to amines and related substrates. Good-to-excellent yields can be obtained by using a wide range of amine partners including primary aryl- and alkyl amines, cyclic and acyclic secondary amines, lithium amide, N-H imines, hydrazones, and ammonia. In many cases the reactions can be performed at low catalysts loadings with excellent functional group tolerance and chemoselectivity. Given current limitations associated with established ligand classes with regard to maintaining high activity across the diverse possible range of C-N coupling applications, **2-32** and **3-1** represent an unusually versatile ligand system for the cross-coupling of aryl chlorides and amines and an important contribution towards the development of more general catalyst systems for Pd-catalyzed C-N coupling reactions.

3.3 Development of a "Task-Specific" P,N-Ligand for the Cross-Coupling of Aryl Chlorides and Tosylates with Ammonia

Ammonia represents an abundant and inexpensive nitrogen source that represents an ideal reagent for amine synthesis. Despite its potential to provide more direct and economical routes to nitrogen-containing molecules, the use of ammonia in transition metal-catalyzed reactions has only very recently begun to be realized.[32b, 83]

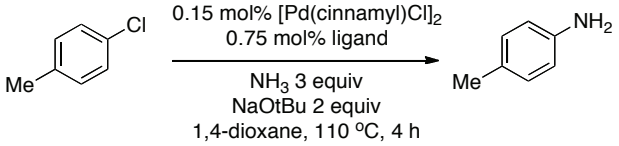
Recent advances in catalyst design have enabled the use of ammonia as a coupling partner in C-N cross-coupling reactions to generate primary aryl amines employing Cu[78, 84] or Pd[64b, 65, 77] catalysts. Despite the success of these initial reports, a number of serious limitations regarding the scope and utility of metal-catalyzed cross-couplings of aryl

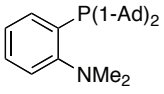
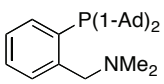
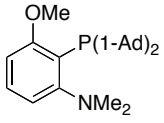
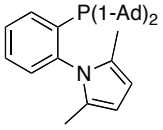
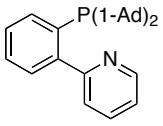
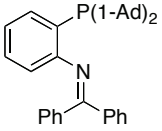
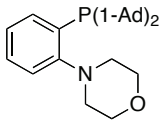
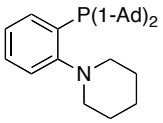
halides and ammonia still exist and must be addressed before this method can be considered a viable alternative to more traditional aniline syntheses. In the case of Cu, high loadings of metal and ligand are typically required (10-50 mol%) and less reactive but more economically attractive aryl chlorides, or more readily accessible pseudo-halides derived from phenols, are poor reaction partners. Limitations regarding the Pd-catalyzed cross-coupling of ammonia include the coupling of electron rich, sterically unbiased aryl chlorides as well as the selective coupling of ammonia in the presence of additional amine functionality (chemoselectivity). In addition, systems known currently require catalyst loadings of 0.5-5 mol% Pd as well as elevated temperatures (70-120 ºC) to maintain reasonable activity for even simple aryl chloride and bromide substrates. The slow rate of oxidative addition of electron-rich aryl chlorides, combined with a reduced tendency for such species lacking *ortho*-substitution to undergo reductive elimination[51] from the requisite $L_nPd(II)$aryl(amido) species, can provide a rationale for the difficulties posed by such reaction partners and the elevated reaction temperatures required for catalyst turnover. This section details the preparation of a suitably designed P,N-ligand that addresses several of the above described challenges in ammonia cross-coupling, including highly chemoselective transformations and the first report of aryl chloride and aryl tosylate coupling with ammonia at room temperature.

While it was found that **3-1** was a broadly useful ligand for the Pd-catalyzed cross-coupling of aryl chlorides and amines (including ammonia), modestly electron-rich substrates lacking *ortho*-substitution gave very poor results, requiring harsh reaction conditions and giving undesired diaryl amines as the major product (see Section 3.2). Indeed, within the field of Pd-catalyzed cross-coupling of ammonia, only Hartwig's Josiphos/Pd[P(*o*-tol)$_3$]$_2$ system has been reported to effect reactions of this type (4-chlorotoluene, 55% yield; 1 mol% Pd at 100 ºC; TOF = 5.5 h^{-1}).[65c] With the aim of addressing some of the outstanding issues in ammonia arylation catalysis, a series of air-stable phenylene-bridged P,N-ligands featuring the bulky di(1-adamantyl)phosphino [P(1-Ad)$_2$] fragment were synthesized (**3-107**-**3-113** in Table 3.7). Ligands **3-107**-**3-113** were all prepared via a similar route, from where the *N*-(2-bromo)aryl compounds were synthesized according to literature protocols and then cross-coupled to HP(1-Ad)$_2$ in a manner similar to that employed in the synthesis of **3-1**. While attempts to cross-couple 4-

chlorotoluene under the challenging test conditions (0.3 mol% Pd, 3 equiv. NH_3; 4 h) afforded poor results for most of the ligands, the variant featuring an *ortho*-morpholino group (**3-112**) gave exceptional results; at 110 ºC, 84% conversion was achieved after 4 h (TOF = 70 h^{-1}), with an excellent mono- to diarylation ratio (14:1). Whereas the piperidine-derived ligand **3-113** performed similarly well exhibiting only a modest decrease in selectivity, a **3-112** variant where the P(1-Ad)$_2$ group was replaced by PCy_2 proved ineffective, yielding only small amounts of diarylated product (~10%). Reactions conducted at 65 ºC with **3-112** were also successful when employing 1.5 mol% Pd (98% at 20 h; 23:1). When reactions were performed with a large excess of ammonia (10 equiv.) or with alternative bases (K_3PO_4 or Cs_2CO_3) inferior results were obtained. Interestingly, the Pd:L ratio appeared less important, with Pd:L ranging from 1:1.5 to 1:4 giving similar results, which suggest that an equilibrium involving (**3-112**)Pd and (**3-112**)$_2$Pd is not important in such Pd-catalyzed ammonia cross-coupling.

Table 3.7 Ligand screening for the Pd-catalyzed cross-coupling of ammonia and 4-chlorotoluene.



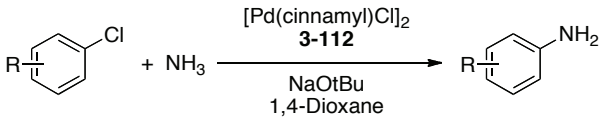
			
3-1	**3-107**	**3-108**	**3-109**
8% (5:1)	22% (1:1.9)	3% (*nd*)	18% (22:1)
			
3-110	**3-111**	**3-112**	**3-113**
14% (10:1)	<1% (*nd*)	84% (14:1)[b]	87% (10:1)

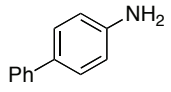
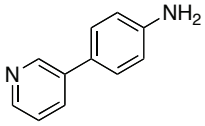
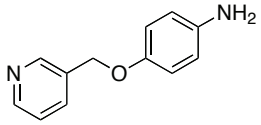
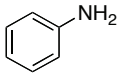
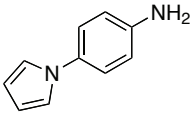
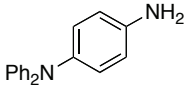
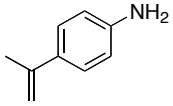
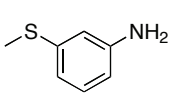
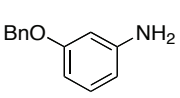
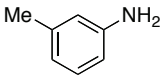
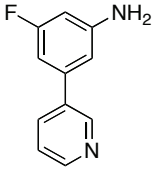
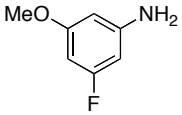
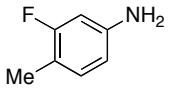
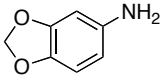
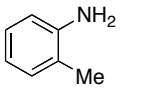
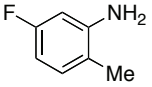
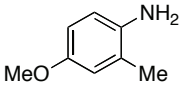
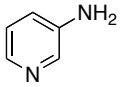
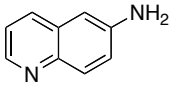
Conditions: ArCl:NH_3:NaOtBu = 1:3:2, 0.15 mmol scale, 0.3 mol% Pd, Pd:L = 1:2.5, 110 ºC, dioxane. Conversions and $ArNH_2$:Ar_2NH ratio (indicated in parenthesis) determined by GC. [b] 99% conversion (15:1) after 16 h.

Having defined a catalyst system and conditions for the cross-coupling of ammonia to a modestly deactivated, sterically unbiased aryl chloride, the scope of

reactivity was explored (Table 3.8). Aryl chloride substrates possessing electron-donating groups at the *para* or *meta* positions were easily cross-coupled at 110 ºC or 65 ºC, including examples containing N-, O-, F- or S- heteroatoms. Catalyst loadings for the coupling of these challenging substrates remained low at 110 ºC (0.3-0.6 mol% Pd) and reasonable at 65 ºC (1.5-4 mol% Pd). Included in the numerous examples in Table 3.8 is the 3-fluoro-5-(3'pyridyl)-functionalized aniline **3-122**, a key intermediate in the synthesis of a potential antidepressant/anxiolytic agent (Figure 3.9).[85] This ammonia cross-coupling methodology (65 ºC; 3 mol% Pd; 87% yield) offers a viable alternative to the reported stoichiometric $SnCl_2$-mediated nitro-reduction protocol.[85] 2-Substituted aryl chlorides were also suitable reaction partners, as were some heteroaromatic aryl chlorides, such as 3-chloropyridine and 6-chloroquinoline. Attempts to cross-couple 2-chloropyridines or 8-chloroquinoline led to nearly exclusive diarylation, possibly due to chelation assistance present in the monoarylation aniline products. Reactions conducted at temperatures as low as 50 ºC still gave excellent results (Table 3.8, **3-17** and **3-123**).

Table 3.8 Scope of Pd-catalyzed cross-coupling of ammonia to aryl chlorides.



			
3-114 A 90% (0.18) B 87% (0.75)	**3-115** A 98% (0.25)	**3-116** A 75 % (0.3)	
			
3-8 A 88% (0.15)[b] B 85% (0.75)[b]	**3-117** A 87% (0.35)	**3-118** A 68% (1.5)	**3-119** B 80% (0.75)
			
3-120 A 60% (0.25)	**3-121** A 90% (0.25)	**3-17** A 87% (0.15) [b] B 95% (1.0) [b] C 90% (2.0) [b]	**3-122** B 87% (1.5)
			
3-123 C 80% (2.0)	**3-124** B 61% (1.0)	**3-125** A 64% (0.25) B 55% (2.0)	**3-9** A 96% (0.3)[b]
			
3-14 A 90% (0.3)	**3-126** B 52% (1.25)	**3-127** B 79% (1.5)	**3-128** B 99% (1.0)

Conditions: ArCl:NH_3:NaOtBu = 1:3-4:2, [Pd]:**3-112** = 1:2, [ArCl] = 0.10 - 0.05 M, (2-48 h). Yields are of isolated material, mol% $[Pd(cinnamyl)Cl]_2$ indicated in parentheses. **A**: T = 110 ºC. **B**: T = 65 ºC. **C**: T = 50 ºC. [b] Yield determined by GC.

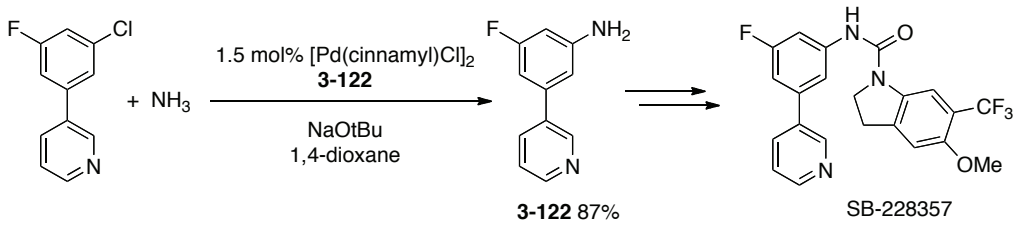
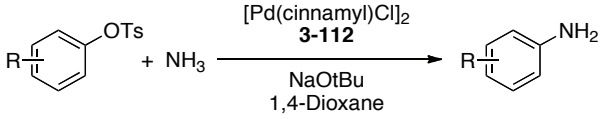
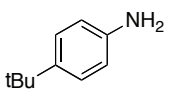
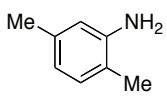
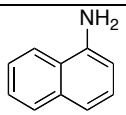
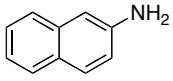


Figure 3.9 Amination of 3-fluoro-5-(3'-pyridyl)-chlorobenzene with ammonia to generate a key intermediate in the preparation of SB-228357, a potential drug for CNS disorders.

Easily prepared and inexpensive aryl tosylates are also suitable partners for ammonia cross-coupling employing $[Pd(cinnamyl)Cl]_2$ and **3-112** (Table 3.9); reactions can be conducted under exceptionally mild conditions (room temperature) with good yields for both unhindered substrates and 2-substituted aryl tosylates. Unfortunately, electron poor aryl tosylates such as 3-CF_3- or 4-benzophenone- substituted substrates, led to significant amounts of the corresponding phenol, as did aryl triflates.

Table 3.9 Room temperature Pd-catalyzed cross-coupling of ammonia with aryl tosylates.



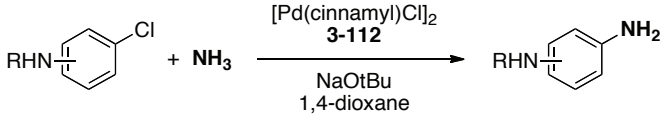
			
3-129	**3-10**	**3-12**	**3-130**
69% (3.0)	79% (2.5)	78% (2.0)	83% (2.0)

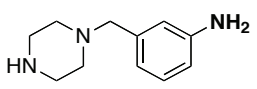
Conditions: ArCl:NH_3:NaOtBu = 1:3-4:2, [Pd]:**3-112** = 1:2, [ArCl] = 0.10 - 0.05 M, (2-48 h), room temperature. Yields are of isolated material, mol% $[Pd(cinnamyl)Cl]_2$ indicated in parentheses.

Given the apparently high affinity for ammonia when conducting coupling reactions employing **3-112** with $[Pd(cinnamyl)Cl]_2$, chemoselective transformations with aminoaryl chlorides containing NH-functionalities were attempted (Table 3.10). Reactions of aminoaryl chlorides featuring secondary aryl/alkyl-, diaryl- or dialkylamines each afforded good to excellent isolated yields (64-98%) of the ammonia-derived arylation product. Even more impressive was the ability of **3-112** and $[Pd(cinnamyl)Cl]_2$

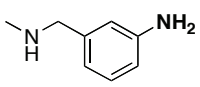
to selectively couple ammonia in the presence of both primary aryl- and alkylamines (Table 3.10).

Table 3.10 Chemoselective Pd-catalyzed cross-coupling of ammonia to amino-aryl chlorides.

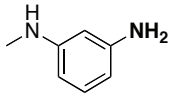




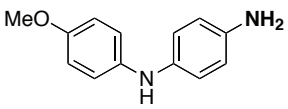
3-131
97% (0.5)



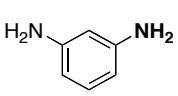
3-132
74% (0.75)



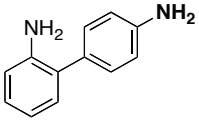
3-133
98% (0.25)



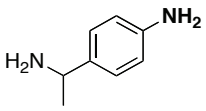
3-134
64% (1.5)



3-135
76% (0.5)[b]



3-136
93% (0.5)



3-137
61% (2.5)[c]

Conditions: AminoarylCl:NH_3:NaOtBu = 1:3-4:2, [Pd]:**3-112** = 1:2, 110 ºC, [ArCl] = 0.10-0.05 M. Yields are of isolated material, mol% $[Pd(cinnamyl)Cl]_2$ indicated in brackets. [b] Isolated as a 8:1 mixture of mono- and diarylation product in 96% combined yield. [c] Reaction conducted at 65 ºC.

Given the unique activity of **3-112** compared to more established bisphosphine[52c, 64b, 65c] or biarylphosphine[47c, 65a, 65b] ligands in the cross-coupling of ammonia, the nature of Pd-ligand interactions under conditions relevant to catalysis was gained via stoichiometric reactions of Pd/ligand mixtures under catalytically relevant conditions. Treatment of $[Pd(cinnamyl)Cl]_2$ and 2 equivalents of **3-112** with NaOtBu in chlorobenzene at room temperature resulted in the quantitative formation (^{31}P NMR) of a new species after 3 h (Figure 3.10). Solution NMR and X-ray crystallographic studies confirmed the identity of this species as being the square planar Pd(II) complex **3-138**, in which **3-112** is coordinated in a k^2-*P,N* fashion with Cl *trans* to P. Complex **3-138** was also prepared successfully from alternative Pd-sources in excellent yield ([CpPd(allyl)], 93%; $[(COD)Pd(CH_2TMS)_2]$, 99%). The analogous 4-anisolyl derivative **3-139** was prepared in a similar manner and displayed solution and solid state characteristics analogous to **3-138**.

Interestingly, no reaction was observed (^{31}P NMR) upon exposure of **3-138** to ammonia (2 or 10 equiv.), suggesting that the N-donor arm of **3-112** is not readily displaced from Pd during catalysis employing ammonia as a substrate. In an effort to examine the reactivity of ammine-ligated (**3-112**)Pd(II) species, the cationic ammonia adducts **3-140** and **3-141** were prepared in high isolated yield via addition of AgOTf to either **3-138** or **3-139** in the presence of NH_3 (Figure 3.10). Treatment of **3-140** with $NaN(TMS)_2$ at room temperature promoted the rapid reductive elimination of aniline from the unobserved intermediate [(**3-112**)Pd(Ph)NH_2][66a, 66b], which in turn regenerated **3-138** as the major species (by ^{31}P NMR) in the presence of chlorobenzene.

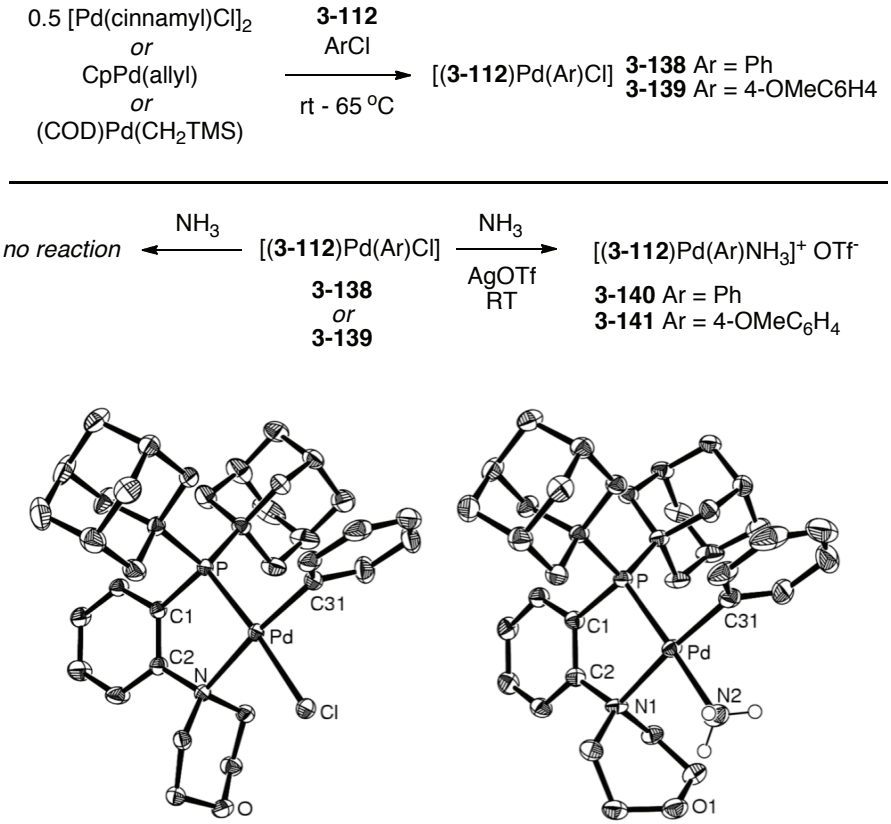
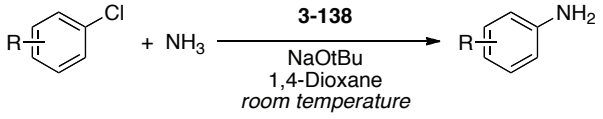
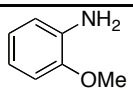
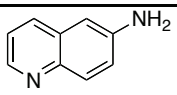
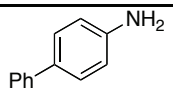
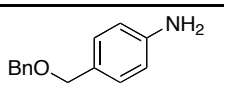
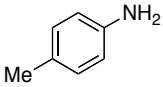
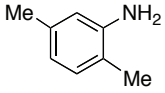
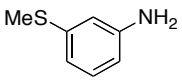
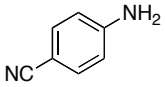
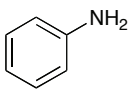
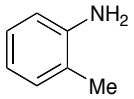
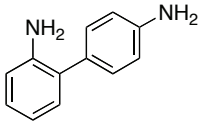
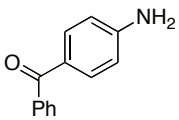


Figure 3.10 Reagents: **3-138**: Route 1: [CpPd(allyl)] and **3-112** in 1:1 PhCl and THF, 65 ºC, 12 h, 93%. Route 2: [(COD)Pd($CH_2TMS)_2$] and **3-112** in PhCl, 40 min., RT, 99%. **3-139**: [CpPd(allyl)] and **3-112** in 1:1 4-chloroanisole and THF, 12 h, 65 ºC, 79%. **3-140** or **3-141**: 3 equiv. NH_3, 1.1 equiv. AgOTf, 30 min., RT (**3-140** 90%; **3-141** 84%). ORTEP diagrams of **3-138** (left) and **3-140** (right) shown with 50% ellipsoids; some H atoms and OTf^- in **3-140** are omitted for clarity.

Employing **3-138** as a precatalyst for ammonia arylation led to striking results: good to excellent conversions were observed for a number of aryl chloride substrates *at room temperature* (Table 3.11). The use of 5 mol% **3-138** enabled the rapid conversion of *ortho*-substituted or electron-poor aryl chlorides (>95% conversion after 1-2 h), however such substrate characteristics were not prerequisites for achieving high conversions and yields at room temperature. While a full understanding of the properties of **3-138** that engender enhanced reactivity under mild conditions is currently lacking, [(**3-112**)Pd(Ar)Cl] species such as **3-138** potentially represent the active catalyst in cross-coupling reactions employing $[Pd(cinnamyl)Cl]_2$/**3-112** precatalyst mixtures; the direct use of **3-138** may serve to by-pass deleterious side reactions that may occur during catalyst activation steps related to ligand binding and the reduction of Pd(cinnamyl)Cl to Pd(0).

Table 3.11 Room temperature Pd-catalyzed cross-coupling of aryl chlorides and ammonia employing **3-138**.



			
3-13	**3-128**	**3-114**	**3-142**
88%	92%	88%	93%
			
3-16	**3-10**	**3-120**	**3-143**
58%[a]	76%	72%	66%
			
3-8	**3-9**	**3-136**	**3-22**
>99%[a]	>99%[a]	83%	70%

Conditions: $ArCl:NH_3:NaOtBu$ = 1:3-4:2, 5 mol% Pd, [ArCl] = 0.10 - 0.05 M, (2-24 h), room temperature. Yields are of isolated material. [a] Yields determined by GC.

In conclusion, an air-stable P,N-ligand (**3-112**) has been prepared that advances the scope and utility of Pd-catalyzed ammonia cross-coupling. A variety of aryl chloride

and aryl tosylate substrates can be coupled efficiently, most notably electron-rich species lacking *ortho*-substitution under a range of conditions. The unique preference for ammonia coupling when using Pd/**3-112** mixtures can be exploited in chemoselective arylations, and for the first time, the room temperature Pd-catalyzed cross-coupling of ammonia has been achieved.

3.4 Development of the Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Tosylates with Hydrazine

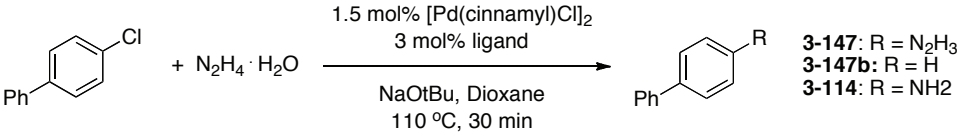
Aryl hydrazines are highly valuable intermediates in the synthesis of a number of important nitrogen heterocyclic frameworks such as indoles (via Fischer indole synthesis),[86] indazoles, arylpyrazoles, and aryltriazoles.[87] In some cases, hydrazine reacts with haloarenes directly in nucleophilic aromatic substitution reactions; however, such reactions typically occur at high temperatures and/or only with highly electron deficient haloarenes or at select positions of halogenated heterocycles.[88] The prevailing method for the preparation of aryl hydrazines relies on the stoichiometric oxidation of anilines to their corresponding diazonium salts followed by reduction.[89] The transition metal catalyzed cross-coupling of aryl halides and hydrazine represents an attractive alternative to traditional aryl hydrazine synthesis. Nonetheless, despite the tremendous progress made in the field of Buchwald-Hartwig aminations over the past decade,[45a, 45b, 45d, 47a, 47c, 52c,] no such process has been reported.

Hydrazine presents a number of potential problems in Pd-catalyzed cross-coupling reactions. First, hydrazine is an aggressive reductant of both organic and inorganic substrates,[90] and could reduce key Pd(II)aryl(X) species, thereby promoting the generation of catalytic inactive Pd(0) aggregates, as well as reducing aryl halide substrates via hydrodehalogenation.[91] Second, aryl hydrazines can undergo metal-mediated N-N bond cleavage,[92] resulting in the formation of undesired aniline byproducts. Lastly, and most importantly, the product aryl hydrazines still possess three reactive N-H bonds that can undergo further C-N cross-coupling leading to polyarylated products. Some of these challenges have been circumvented by the use of hydrazine surrogates with attenuated reactivity such as benzophenone hydrazone[66c, 93] or protected hydrazides,[94] although such strategies are not ideal from efficiency or economic

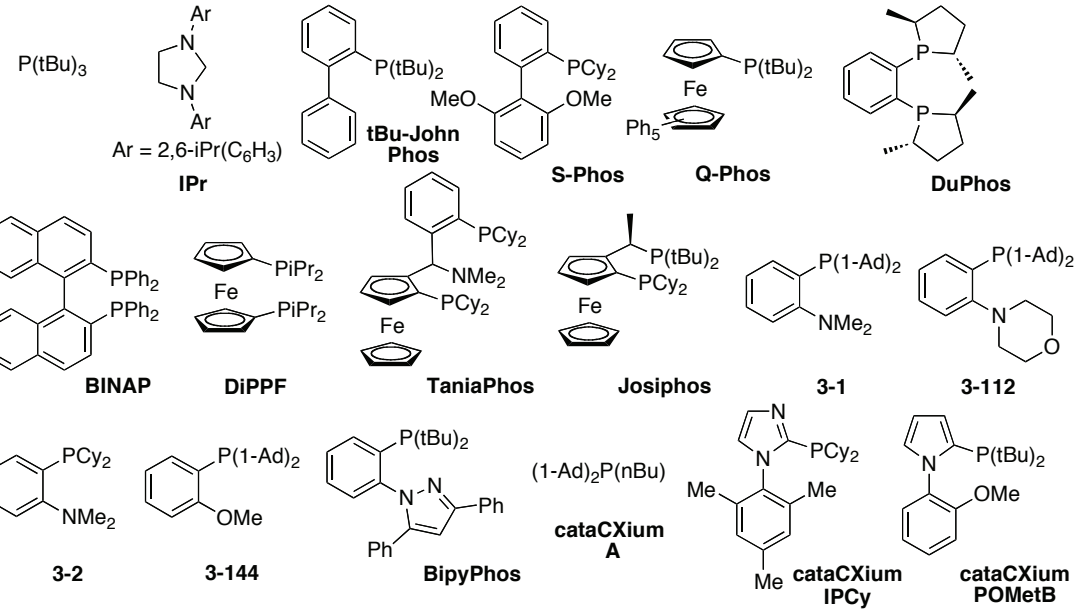
standpoints. Additionally, aryl- or alkyl-substituted hydrazines, which are less prone to undergo some of the above described detrimental side reactions, have been employed as substrates.[95] This section documents the identification of a Pd-catalyst system and conditions that allow, for the first time, the cross-coupling of aryl chlorides and tosylates with hydrazine. Reactions proceed rapidly under relatively mild conditions with excellent monoarylation selectivity, providing direct access to aryl hydrazines.

A variety of ligands (Table 3.12) and conditions (Table 3.13) were screened in the hopes of effecting the cross-coupling of 4-phenylchlorobenzene with readily available hydrazine sources. A series of structurally diverse phosphine and N-heterocyclic carbene ligands were tested employing 1.5 mol% $[Pd(cinnamyl)Cl]_2$ and 3 mol% ligand at 110 °C in 1,4-dioxane with 2 equivalents of hydrazine hydrate and NaOtBu. Electron-rich monophosphines or carbenes including $P(tBu)_3$, IPr, tBu-JohnPhos, SPhos, Q-Phos, as well as bisphosphines DuPhos, BINAP, DiPPF, and Taniaphos all gave poor results, either resulting in low conversions of the starting aryl chloride, or providing mainly the hydrodehalogenated product. The electron-rich bisphosphine ligand Josiphos or P,N-ligands (**3-1** and **3-112**) provided a breakthrough in reactivity: high conversions with reduced amounts of arene side product were achieved. Other related P-phenyl ligands such as **3-2** and **3-144**, as well as cataCXium ligands A, PICy, POMetB were ineffective, demonstrating the extreme sensitivity of the reaction to ligand structure. Notably, in most reactions significant darkening and black precipitate was observed over the course of the reactions.

Table 3.12 Ligand screen for the Pd-catalyzed cross-coupling of 4-phenylchlorobenzene and hydrazine.



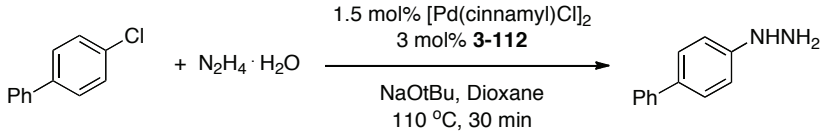
entry	ligand	**3-147**	**3-147b**	**3-114**
1	none	0	99	0
2	$P(tBu)_3$	4	85	0
3	IPr	21	71	4
4	tBu-JohnPhos	23	12	0
5	S-Phos	0	26	0
6	Q-Phos	0	25	0
7	DuPhos	0	7	0
8	BINAP	0	95	0
9	DiPPF	23	12	0
10	Taniaphos	5	10	0
11	Josiphos	73	16	10
12	**3-1**	54	30	15
13	**3-112**	72	15	10
14	**3-2**	0	16	0
15	**3-144**	0	47	0
16	BipyPhos	0	31	0
17	cataCXium A	3	44	0
18	cataCXium PICy	25	25	0
19	cataCXium POMetB	35	33	0



Conditions: ArCl:N_2H_4:NaOtBu = 1:2:2, 0.2 mmol scale, 3 mol% Pd, Pd:L = 1:1, 110 °C, dioxane. Yields determined by GC.

The coupling of 4-phenylchlorobenzene proved to be sensitive to the reaction conditions. When employing **3-112**, toluene or 1,4-dioxane could be used interchangeably, but the use of *N*,*N*-dimethylacetamide (DMA) or 1,2-dichloroethane (DCE) inhibited the transformation (Table 3.13, entries 4 and 5). The use of excess $N_2H_4 \cdot H_2O$ or NaOtBu both resulted in diminished conversions and yields. Other bases such as KOH and Cs_2CO_3 were inferior to NaOtBu. Interestingly, aryl chlorides appear to be superior substrates compared to aryl bromides, where incomplete conversion of 4-phenylbromobenzene and 45% yield of the desired product was observed (Table 3.13, entry 11). This result suggests that aryl halide oxidative addition is not directly related to the reaction's overall efficiency, and processes related to amine binding/deprotonation or reductive elimination are turnover-limiting.[71, 73, 78a] Conveniently, solid $N_2H_4 \cdot HCl$ could also be employed with additional base. Reactions with $N_2H_4 \cdot 2HCl$ were significantly less productive, possibly due to solubility issues. The palladium source proved less important, with $[Pd(cinnamyl)Cl]_2$ only slightly out-performing $PdCl_2(MeCN)_2$ or $Pd(dba)_2$ (Table 3.13, entries 14 and 15).

Table 3.13 Optimization of the Pd-catalyzed cross-coupling of 4-phenylchlorobenzene and $N_2H_4 \cdot H_2O$.



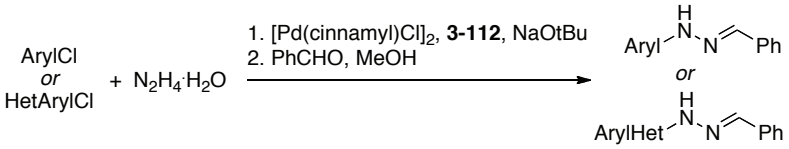
entry	variation from standard conditions	conv.	yield (%)
1	none	>99	73
2	9 mol% **3-112**	>99	61
3	toluene instead of 1,4-dioxane	>99	79
4	DMA instead of 1,4-dioxane	<10	0
5	DCE instead of 1,4-dioxane	0	0
6	0.3 M ArCl instead of 0.1 M	65	35
7	4 equiv. hydrazine instead of 2 equiv.	51	24
8	3 equiv. NaOtBu instead of 2 equiv.	90	66
9	KOH instead of NaOtBu	45	24
10	Cs_2CO_3 instead of NaOtBu	65	14
11	ArBr instead of ArCl	95	45
12[a]	$N_2H_4 \cdot HCl$ instead of $N_2H_4 \cdot H_2O$	>99	80
13[a]	$N_2H_4 \cdot HCl$ instead of $N_2H_4 \cdot H_2O$, 65 °C	99	76
14[a,b]	$PdCl_2(MeCN)_2$ instead of Pd(cinnamyl)Cl	>99	69
15[a,b]	$Pd(dba)_2$ instead of Pd(cinnamyl)Cl	99	60
16	no Pd, no ligand	<10	0

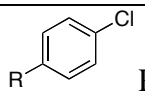
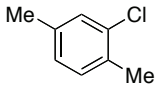
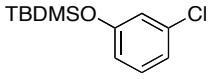
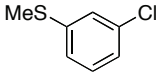
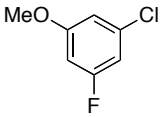
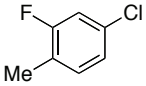
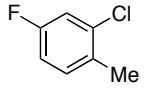
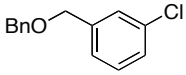
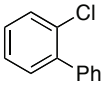
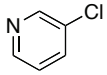
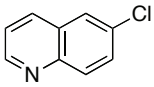
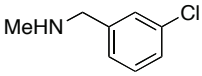
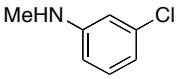
Conditions: 0.2 mmol scale, 2 equiv. $N_2H_4 \cdot H_2O$ and NaOtBu, 110 °C, in 1,4-dioxane (0.1 M). Conversions and yields determined by GC. [a] Employing $N_2H_4 \cdot HCl$ and 3.5 equiv. NaOtBu. [b] At 90 °C.

Having defined a catalyst system and conditions allowing for the cross-coupling of aryl chlorides and hydrazine, the scope of the reaction was explored (Table 3.14). The product aryl hydrazines were isolated as their corresponding hydrazones after treatment with benzaldehyde to simplify isolation and purification. Aryl hydrazones can be hydrolyzed under acidic conditions to retrieve the aryl hydrazine.[66c] Cross-coupling of electron-neutral aryl chlorides proceeded with good yields employing 5 mol% Pd at 90 °C, including biaryl substrates with ether and $-CF_3$ substituents, as well as heterocycles such as pyrrole and pyridine. The electron-poor substrate 4-(trifluoromethyl)chlorobenzene (Table 3.14, entry 7) gave poorer yields due to increased amounts of hydrodehalogenation, while the electron rich substrate 4-chloroanisole (Table 2, entry 9) reacted sluggishly. 4-Fluorochlorobenzene could be employed as a substrate with moderate success (49% yield) when the reaction was conducted in 1,4-dioxane; in

toluene significant amounts of the net hydrodefluorinated product were observed. It is difficult to determine whether this observation is the result of nucleophilic substitution of hydrazine at fluorine, followed by hydrodechlorination, or cross-coupling at chlorine and hydrodefluorination, although no 4-chlorophenyl hydrazine was observed by use of GC. Other examples of aryl chlorides substituted at the 3-position with alkyl, oxygen, sulfur, or fluoro-groups resulted in good yields (72–88%). *ortho*-Substitution was also tolerated; 2-chloro-*p*-xylene was cross-coupled cleanly to give the desired product after derivatization in 88% yield (Table 3.14, entry 11), while the bulky substrate 2-phenylchlorobenzene could be employed with success using 10 mol% Pd. Chloropyridine and quinoline substrates such as 3-chloropyridine and 6-chloroquinoline (Table 3.14, entries 19 and 20) were also suitable substrates. Importantly, unlike 2- or 4-halopyridines, such chloro-heterocycles are not amenable to nucleophilic aromatic substitution with hydrazine, indicating such cross-coupling strategies to be complimentary to established methods that employ hydrazine. Aminoaryl chloride substrates were also readily cross-coupled in moderate to good yields (Table 3.14, entries 21 and 22) without significant interference from the pendant NH-functionality. This protocol is also suitable for larger-scale reactions; for example, 92% yield (2.09 g) of **3-155** was obtained when conducting reactions on a 10 mmol scale (Figure 3.11).

Table 3.14 Scope of the Pd-catalyzed cross-coupling of aryl chlorides and hydrazine.



entry	ArCl	mol % Pd	temp/time (°C/h)	yield (%)[a]
1	 R = H	5	90/1	**3-145** 86
2	R = Me	5	90/1	**3-146** 93
3	R = Ph	3	90/1	**3-147** 86
4	R = 4-OMeC$_6$H$_4$	5	90/0.5	**3-148** 82
5[b]	R = 4-CF$_3$C$_6$H$_4$	3	90/0.5	**3-149** 83
6	R = *N*-pyrrole	5	90/1	**3-150** 78
7	R = CF$_3$	5 (2.5)	90/1	**3-151** 50 (44)[c]
8	R = 3-pyridine	5	65/2	**3-152** 97
9[b]	R = OMe	10	110/1	**3-153** 27
10[b,d]	R = F	5	90/0.33	**3-154** 49
11		5	90/1	**3-155** 88
12[c,e]		5	90/0.5	**3-156** 83
13		10	110/0.5	**3-157** 95
14		5	90/1	**3-158** 72
15		5	90/1	**3-159** 77
16		5	90/0.5	**3-160** 75
17		5	65/1	**3-161** 83
18[b]		10	90/1	**3-162** 71
19		5	65/1.5	**3-163** 69
20[e]		3	65/1	**3-164** 81
21		5	90/0.5	**3-165** 75
22		5	90/0.5	**3-166** 58

Conditions: ArCl:$N_2H_4 \cdot H_2O$:NaOtBu = 1:2:2-1.8, [Pd] = $[Pd(cinnamyl)Cl]_2$, [Pd]:**3-112** = 1:1.5, in toluene (0.1 M). [a] Isolated yield. [b] Employing $N_2H_4 \cdot HCl$ and 3.5 equiv. NaOtBu. [c] >95% conv. of ArCl, yield at 2.5 mol% Pd in brackets. [d] In 1,4-dioxane. [e] Isolated aryl hydrazine.

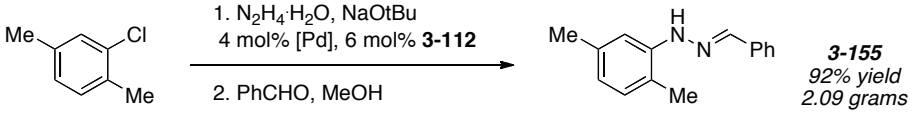
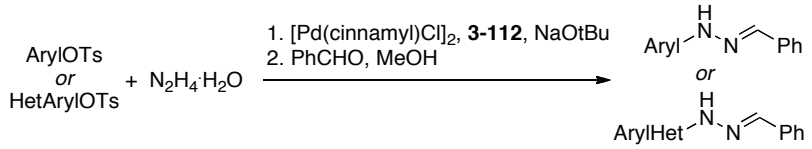
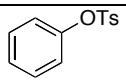
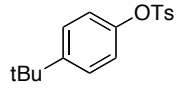
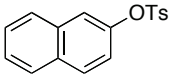
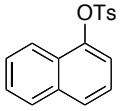
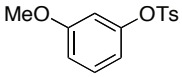
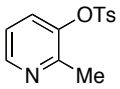
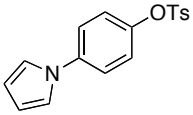


Figure 3.11 Large scale preparation of aryl hydrazone **3-155**, via Pd-catalyzed hydrazine cross-coupling, followed by condensation with benzaldehyde.

Aryl tosylates, readily available and easily prepared from phenols, could also be employed using a similar catalytic protocol (Table 3.15). Moderate to excellent yields (51-97%) for a range of aryl tosylate substrates were obtained, including *o*-, *m*-, and *p*-substituted derivatives, although electron rich aryl tosylates were less successful, as were aryl triflates and mesylates. Heteroaromatic substrates such as 2-methyl-3-pyridyl tosylate were also suitable reaction partners (Table 3.15, entry 6).

Table 3.15 Pd-catalyzed cross-coupling of aryl tosylates and hydrazine.



entry	ArOTs	mol % Pd	temp/time (°C/h)	yield (%)[a]
1[b]		5	65/1	**3-145** 64
2[b]		5	65/1	**3-167** 73
3		5	65/0.5	**3-168** 67
4[c]		5	65/0.5	**3-169** 97
5		5	65/0.5	**3-170** 51
6		5	50/0.5	**3-171** 79
7		5	65/0.5	**3-150** 59

Conditions: ArCl:$N_2H_4 \cdot H_2O$:NaOtBu = 1:2:2-1.8, in toluene (0.1 M). [a] Isolated yield. [b] Employing $N_2H_4 \cdot HCl$ and 3.5 equiv. NaOtBu. [c] Isolated aryl hydrazine.

Diarylation of hydrazine was anticipated to be a potential challenge to overcome; however, throughout both screening experiments as well as during substrate scope studies, no significant amount of material arising from multiple arylations of hydrazine was observed. This observation is interesting in light of the fact that [Pd(cinnamyl)Cl]$_2$ / **3-112** is a highly capable catalyst for the cross-coupling of aryl hydrazines. For example 2-chloro-*p*-xylene could be coupled to phenyl hydrazine to give **3-172** in 68% yield under standard conditions (Figure 3.12); however in the presence of $N_2H_4 \cdot H_2O$ the only product that was observed was 2,5-dimethylphenylhydrazine. Given the similar steric environment of hydrazine and phenyl hydrazine at the terminal nitrogen position, the origin of high chemoselectivity when employing [Pd(cinnamyl)Cl]$_2$/**3-112** is postulated to be primarily electronic in nature, with the more nucleophilic hydrazine substrate reacting preferentially. This postulate agrees generally with the results obtained with other amine substrates when employing **3-1** or **3-112** throughout this Chapter.

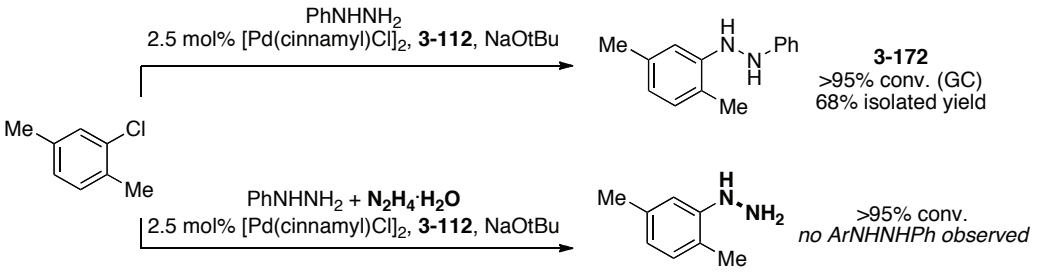
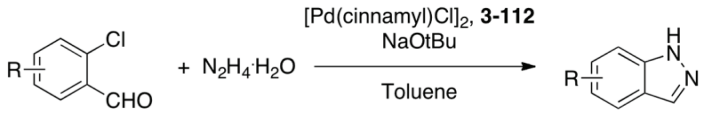
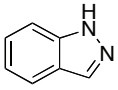
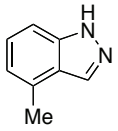
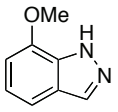


Figure 3.12 Pd-catalyzed cross-coupling of $PhNHNH_2$ and $N_2H_4{\cdot}H_2O$. **Conditions:** 1.2 equiv. $RNHNH_2$, 1.3 equiv. NaOtBu, 0.075 equiv. **3-112**, toluene (0.1 M), 90 ºC, 30 min.

Lastly, the newly developed methodology was exploited to prepare 1*H*-indazoles directly from 2-chlorobenzaldehydes and hydrazine in a tandem cross-coupling/condensation strategy (Table 3.16). While there exist many metal-catalyzed tandem indazole syntheses in the literature,[96] this protocol allows for the generation of substituted NH-indazoles, which are attractive substrates for further elaboration. Moderate to good yields were observed in short reaction times (1-1.5 h) and under relatively mild conditions (65-90 ºC). When similar reactions were performed employing 2-chloroacetophenone or tosyl salicylaldehyde, complex mixtures were observed by use of GC.

Table 3.16 Indazole synthesis via cross-coupling/condensation reactions employing 2-chlorobenzaldehydes and hydrazine.



		
3-173	**3-174**	**3-175**
73% (5) 1.5 h	51% (10) 1 h[a]	76% (5) 1.5 h

Conditions: $ArCl:N_2H_4{\cdot}H_2O:NaOtBu = 1:2:2$, [Pd]:**L** = 1:1.5, [ArCl] = 0.20 M in toluene at 65 ºC, mol% Pd employing indicated in brackets. [a] Employing $N_2H_4{\cdot}HCl$ and 3.5 equiv. NaOtBu at 90 ºC.

In conclusion, the first Pd-catalyzed cross-coupling of aryl chlorides and tosylates with hydrazine has been developed. The reaction relies on the use of appropriately designed ligands to overcome the difficulties associated with the use of hydrazine and proceeds rapidly under mild conditions with excellent chemoselectivity. Given the readily available nature of aryl chlorides and tosylates, and the importance of aryl hydrazines in heterocycle synthesis, this methodology should find widespread application.

3.5 Summary and Conclusions

The results documented in this chapter demonstrate that ligands featuring appropriately functionalized P- and N-donor groups are highly effective ligands for Pd-catalyzed C-N cross-coupling reactions of aryl chlorides and tosylates. Ligands **2-32** and **3-1** were shown to be broadly effective in the cross-coupling of aryl chlorides to a wide range of N-H containing substrates, such as primary aryl and alkyl amines, cyclic and acyclic secondary amines, hydrazones, N-H imines, and lithium amide. The diversity of substrates amenable to cross-coupling when employing **2-32** or **3-1** compared favourably to other established ligands for C-N cross-coupling, which are typically only effective for certain amine substrates. While **3-1** proved capable of ammonia arylation, high catalyst loadings and poor yields for deactivated substrates provided motivation for the preparation of a "second generation" P,N-ligand, **3-112**, which exhibited excellent performance in the Pd-catalyzed cross-coupling of aryl chlorides and tosylates and ammonia. Reactions could be performed at low catalyst loadings (generally <1 mol% Pd) or under exceptionally mild conditions (room temperature). Ligand **3-112** also provided inroads in the development of the first example of the Pd-catalyzed cross-coupling of aryl chlorides and tosylates with hydrazine. Collectively, these results clearly indicate that P,N-ligands are particularly well-suited for applications in Pd-catalyzed C-N cross-coupling reactions, and may provide a useful middle ground between previously established classes of ligands.

3.6 EXPERIMENTAL SECTION

3.6.1 GENERAL CONSIDERATIONS

Unless noted, all reactions were setup inside a dinitrogen-filled inert atmosphere glovebox. Toluene was deoxygenated by sparging with dinitrogen followed by passage through a double column solvent purification system purchased from mBraun Inc. THF and 1,4-dioxane (Aldrich) was dried over Na/benzophenone followed by distillation under an atmosphere of dinitrogen. 1,2-Dimethoxyethane was deoxygenated by sparging with dinitrogen gas followed by storage over activated 4 Å molecular sieves for 48 h prior to use. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Aniline was distilled under reduced pressure prior to use. $[Pd(cinnamyl)Cl]_2$,[97] diphenyl-2-dimethylaminophenylphosphine (**3-3**),[43] di(tert-butyl)-2-(isopropylphenyl) phosphine (**3-4**),[98] di(tert-butyl)phenylphosphine (**3-5**),[98a] di-1-adamantylphosphine,[99] $(COD)Pd(CH_2TMS)_2$,[100] CpPd(allyl),[101] aryl tosylates,[58, 102] and amino alkene substrates[103] were prepared according to literature procedures. Di(tert-butyl)-2-(methoxyphenyl)phosphine (**3-7**) was prepared in a manner similar to **3-1**, and the spectroscopic features of the isolated complex agreed with those reported previously.[76b] Pd starting materials as well as NaOtBu and Cs_2CO_3 were evacuated under reduced pressure for 24 h prior to use and stored in an inert atmosphere glove box. All other reagents were used as received from commercial sources. Conversions based on gas chromatography data obtained for the arylation of aniline and ammonia were determined by calibration with standards of chlorobenzene, aniline and diphenylamine; product identity was confirmed on the basis of ^1H NMR, GC-MS data, and/or by comparison with authentic samples. Anilines **3-8**-**3-22** (excluding **3-19**) NMR data agreed with that of commercially available material. Flash column chromatography was performed on silica gel (SiliaFlash P60). ^1H, ^{13}C, and ^{31}P NMR characterization data were collected at 300 K on a Bruker AV-500 spectrometer operating at 500.1, 125.8, and 202.5 MHz (respectively) or a Bruker/Tecmag AC-250 spectrometer operating at 250.1, 62.9, and 101.3 MHz (respectively), with chemical shifts reported in parts per million downfield of $SiMe_4$ for ^1H and ^{13}C or 85% H_3PO_4 in D_2O for ^{31}P, as referenced to residual NMR solvent signals.

3.6.2 Experimental Section for Section 3.2

Improved synthesis of 2-32. In an analogous manner to the synthesis of **3-1** (*vide infra*), the title compound was prepared by Pd-catalyzed cross-coupling of tBu_2PH and bromo-*N*,*N*-dimethylaniline. The product was isolated in 71% yield after recrystallization from hexane at -35 ºC. The spectral properties agreed with those reported in Chapter 2, Section 3.

3-1. $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) was added to a glass vial and dissolved in toluene (2 mL). This solution was then transferred to a vial containing DiPPF; 14.2 mg, 0.034 mmol) and was left to stir for 10 minutes. To a separate glass vial containing NaOtBu (192 mg, 2.0 mmol) was added a solution of $(1\text{-Ad})_2PH$ (410 mg, 1.36 mmol) in 2 mL toluene, followed by 2-bromo-*N*,*N*-dimethylaniline (230 μL, 1.4 mmol), and the $Pd(OAc)_2$/DiPPF solution, after which the vial was sealed with a cap containing a PTFE septum. The mixture was stirred for 20 h at 110 ºC, at which point the reaction was deemed complete on the basis of ^{31}P NMR data obtained from an aliquot of the reaction mixture. The reaction mixture was then allowed to cool and was passed through a plug of silica, followed by washing of the plug with 40 mL of CH_2Cl_2. The combined eluent was collected and the solvent was removed *in vacuo*. The resulting pale orange solid was washed with cold hexanes (2 x 4 mL). Removal of volatile materials *in vacuo* yielded the product as an off-white powder (0.424 g, 1.01 mmol; 74 % yield). ^1H NMR ($CDCl_3$): δ 7.71 (m, 1H, Ar-H), 7.32 (m, 1H, Ar-H), 7.20 (m, 1H, Ar-H), 7.05 (m, 1H, Ar-H), 2.71 (s, 6H, $N(CH_3)_2$), 2.01-1.89 (m, 18H, 1-Ad), 1.67 (s, 12H, 1-Ad). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.6 (d, J_{PC} = 21.6 Hz, C_{quat}), 137.4 (d, J_{PC} = 3.3 Hz), 131.1 (d, J_{PC} = 22.9 Hz, C_{quat}), 129.6, 122.2, 120.6 (d, J_{PC} = 3.9 Hz), 46.1 (d, J_{PC} = 4.2 Hz, $N(CH_3)_2$), 41.8 (d, J_{PC} = 13.0 Hz, CH_2), 37.1 (CH_2), 29.0 (d, J_{PC} = 8.6 Hz, CH). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 20.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{28}H_{40}N_1P_1$: 422.2971. Found: 422.2978. Anal. Calcd for $C_{28}H_{40}P_1N_1$: C 79.77; H 9.56; N 3.32. Found: C 79.47; H 9.46; N 3.31.

3-2. To a glass vial containing 2-bromo-*N*,*N*-dimethylaniline (288 μL, 2.0 mmol) in 3 mL Et_2O (pre-cooled to -35 ºC), was added n-BuLi (759 μL, 2.2 mmol). After 30 minutes at -35 ºC and an additional 15 minutes at room temperature, the resulting yellow

precipitate was isolated by removing the solvent by using a pipette, followed by washing of the remaining solid with cold hexanes (3 x 2 mL), after which the volatile materials were removed *in vacuo*. The resulting solid was dissolved in 6 mL Et_2O and $ClPCy_2$ (440 μL, 2.0 mmol) was added dropwise. The mixture was stirred magnetically at room temperature for 48 h. The solvent and volatile materials were then removed *in vacuo*. The resulting mixture was dissolved in CH_2Cl_2 and washed with 10 mL of saturated $NaHCO_3$ and 10 mL of water. The organic layer was extracted, dried *in vacuo* and passed through a plug of silica as a pentane solution. Removal of the solvent *in vacuo* yielded the product as a white solid (0.162 g, 0.51 mmol, 25% yield). ^{1}H NMR ($CDCl_3$): δ 7.35 (dt, *J* = 7.6, 1.9 Hz, 1H), 7.28 (m, 1H), 7.13 (ddd, *J* = 8.0, 4.3, 1.2, 1H), 7.05 (dt, *J* = 7.4, 1.3, 1H), 2.72 (s, 6H), 1.90-1.74 (m, 12H), 1.30-0.99 (m, 10H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.8, 133.8 (d, *J* = 2.7 Hz), 132.0, 129.8, 123.6, 120.2 (d, *J* = 2.9 Hz), 46.4 (d, *J* = 5.0 Hz), 34.2 (d, *J* = 14.3), 30.8 (d, *J* = 16.6 Hz), 29.6 (d, *J* = 8.9 Hz), 27.8 (d, *J* = 11.6 Hz), 27.7 (d, *J* = 7.6 Hz), 27.0. ^{31}P{^{1}H} NMR ($CDCl_3$): δ -12.7

3-6. The title compound was prepared in a manner similar to Guram *et al*,[76b] only using 4-iodo-*N*,*N*-dimethylaniline instead of 4-bromo-*N*,*N*-dimethylaniline. This ligand is commercially available from Aldrich, however the spectroscopic properties have not been disclosed. ^{1}H NMR ($CDCl_3$): δ 7.54 (m, 2H), 6.68 (d, *J* = 8.7 Hz, 2H), 2.98 (s, 6H), 1.20 (d, *J* = 11.2 Hz, 18H). ^{13}C{^{1}H} NMR ($CDCl_3$): 150.9, 129.3 (d, *J* = 101.7 Hz), 122.0 (d, *J* = 15.5 Hz), 111.4 (d, *J* = 9.1 Hz), 40.3, 32.1 (d, *J* = 19.3 Hz), 30.7 (d, *J* = 14.2 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 36.7.

Representative procedure for the coupling of primary or secondary amines with aryl chlorides. In an inert atmosphere glovebox, $[Pd(cinnamyl)Cl]_2$ (0.67 mg, 0.0013 mmol, from a toluene stock solution) and **3-1** (2.2 mg, 0.0052 mmol) were mixed in a total of 2.000 mL toluene for 10 minutes. From this stock solution, 383 μL was added to a vial containing NaOtBu (135 mg, 1.4 mmol), followed by 600 μL of additional toluene. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. Chlorobenzene (103 μL, 1.0 mmol) and octylamine (200μL, 1.2 mmol) were added by use of a microlitre syringe. The reaction mixture was heated at 110 ºC and

periodically monitored by use of TLC or gas chromatography. Upon completion of the reaction, the product was purified by use of column chromatography on silica (20:1 Hex:EtOAc) and isolated as a colorless oil (0.203 g, 99% yield). Alternatively, samples of $[Pd(cinnamyl)Cl]_2$, ligand, and NaOtBu stored under N_2 could be weighed out on the benchtop into a vial. Following addition of chlorobenzene, octylamine and anhydrous toluene, the vial was sealed with a cap containing a PTFE septum, purged with N_2 and heated at 110 ºC, with results similar to those obtained from reactions setup in a glovebox (99% conversion on the basis of GC data at 0.1 mol% Pd). Reaction times are noted in parentheses for individual products below.

Representative procedure for the coupling of ammonia with aryl chlorides. In an inert atmosphere glovebox, $[Pd(allyl)Cl]_2$ (2.2 mg, 0.006 mmol) and **3-1** (10.1 mg, 0.024 mmol) were vigorously mixed in 4 mL of dioxane for 10 minutes. From this stock solution, 1.000 mL was added to a vial containing 20 mg NaOtBu. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox. 2-Chloro-3-methylpyridine (16 μL, 0.15 mmol) was added by use of a microlitre syringe, followed by 3 mL of a 0.5 M solution of NH_3 in 1,4-dioxane. The reaction mixture was stirred at 110 ºC and monitored by use of gas chromatography. Products were identified by comparison with authentic samples and/or GC-MS.

2-Phenylaniline (3-19).[56] (20 h) ^{1}H NMR ($CDCl_3$) δ: 7.49-7.39 (m, 4H), 7.37 (m, 1H), 7.17 (m, 2H), 6.86 (dt, *J* = 1.1, 7.5 Hz, 1H), 6.79 (dd, *J* = 1.0, 8.0 Hz, 1H), 3.78 (broad s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 143.6, 139.6, 130.5, 129.2, 128.8, 128.5, 127.7, 127.2.

Diphenylamine (3-23). (20 h) NMR data agrees with commercially available material.

***N*-Phenyl-3,5-dimethylphenylamine (2-24).**[104] (20 h) ^{1}H NMR ($CDCl_3$): δ 7.40-7.37 (m, 2H), 7.18 (m, 2H), 7.05 (m, 1H), 6.83 (s, 2H), 5.73 (broad s, 1H), 2.41 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 143.4, 143.1, 139.1, 129.4, 123.0, 120.8, 118.0, 115.7, 21.5.

***N*-Phenyl-2,3-dimethylphenylamine (3-25).** (22 h) ^{1}H NMR ($CDCl_3$): δ 7.37-7.33 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.3, 1H), 7.00-6.96 (m, 3H), 5.46 (s, 1H), 2.45 (s, 3H) 2.28 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 145.1, 140.9, 137.9, 129.3, 128.7, 126.6, 124.8, 119.8, 118.9, 116.6, 20.8, 13.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{16}N_1$: 198.1277. Found: 198.1281.

***N*-(2-Pyridyl)aniline (2-26).**[56] (24 h) ^{1}H NMR ($CDCl_3$): δ 8.23 (m, 1H), 7.50 (m, 1H), 7.37 (m, 2H), 7.30 (m, 2H), 7.18 (broad s, 1H), 7.07 (m, 1H), 6.90 (d, *J* = 8.4, 1H), 6.73 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.3, 148.5, 140.7, 137.8, 129.4, 122.9, 120.5, 115.0, 108.3.

***N*-(2-Pyridyl)-3,5-dimethylphenylamine (2-27).**[62c] (48 h) ^{1}H NMR ($CDCl_3$): 8.22 (m, 1H), 7.49 (m, 1H), 7.00 (broad s, 1H), 6.95 (s, 2H), 6.91 (d, *J* = 4.0 Hz, 1H), 2.30 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.4, 148.5, 140.5, 139.0, 137.2, 124.8, 118.4, 114.8, 108.2, 21.5.

***N*-(4-Tolyl)-4-anisidine (3-28).**[56] (48 h) ^{1}H NMR ($CDCl_3$): 7.09 (m, 4H), 6.91 (m, 4H), 5.46 (broad s, 1H), 3.86 (s, 3H), 2.35 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 154.9, 142.5, 136.7, 129.8, 129.4, 121.2, 116.6, 114.7, 55.7, 20.6.

***N*-Phenyl-3-methylphenylamine (3-29).**[57a] (3 h) ^{1}H NMR ($CDCl_3$): δ 7.38 (m, 2H), 7.27 (m, 1H), 7.18 (m, 2H), 7.06-6.99 (m, 3H), 6.87 (d, *J* = 7.3 Hz), 5.72 (broad s, 1H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 143.4, 143.2, 139.3, 129.4, 129.3, 122.0, 121.0, 118.6, 117.9, 115.1, 21.6.

***N*-(2-Pyridyl)-4-tert-butylaniline (3-30).**[105] (24 h) ^{1}H NMR ($CDCl_3$): δ 8.24 (broad d, *J* = 4.2 Hz, 1H), 7.51 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.25 (broad s, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.74 (m, 1H), 1.39 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.7, 148.4, 146.0, 137.9, 137.7, 126.2, 120.7, 114.6, 107.9, 34.4, 31.5.

2,2'-Dipyridylamine (3-31). (1 h) NMR data agrees with commercially available material.

***N*-(2-Pyridyl)-α-naphthylamine (3-32).**[56] (24 h) ^{1}H NMR ($CDCl_3$): δ 8.18 (m, 2H), 7.94 (d, J = 8.2 Hz, 1H), 7.87-7.74 (m, 2H), 7.63 (d, J = 7.4 Hz, 1H), 7.59-7.47 (m, 3H), 7.43 (m, 1H), 6.71 (t, J = 5.3 Hz, 1H), 6.66 D, J (8.3 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 158.1, 148.5, 137.8, 136.3, 134.8, 129.5, 128.5, 126.4, 126.0, 125.3, 124.9, 122.6, 120.7, 114.5, 107.7.

***N*-Phenyl-3-(trifluoromethyl)aniline (3-33).**[106] (20 h) ^{1}H NMR ($CDCl_3$): δ 7.37-7.32 (m, 3H), 7.28 (s, 1H), 7.21-7.11 (m, 4H), 7.05 (t of t, J = 7.4, 1.1 Hz, 1H), 5.81 (broad s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.1, 141.8, 131.8 (q, J_{CF} = 31.8 Hz) , 129.9, 129.6, 124.6 (q, J_{CF} = 270.7 Hz), 122.4, 119.8, (q, J_{CF} = 1.5 Hz), 119.1, 117.0 (q, J_{CF} = 3.9 Hz), 113.2 (q, J_{CF} = 3.9 Hz).

8-*N*-Phenylaminoquinoline (3-34).[107] (18 h) ^{1}H NMR ($CDCl_3$) δ: 8.80 (dd, J = 1.7Hz, 4.2 Hz, 1H), 8.27 (bs, 1H), 8.12 (dd, J = 1.7, 8.7 Hz, 1H), 7.50 (dd, J = 1.2, 7.8 Hz, 1H), 7.41-7.35 (m, 6H), 7.22 (dd, J = 1.2, 8.2 Hz, 1H), 7.05 (tt, J = 1.5, 7.0 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.0, 142.0, 140.4, 138.7, 136.4, 129.5, 129.0, 127.5, 122.3, 121.7, 120.2, 116.7, 107.9.

***N*-Phenyloctylamine (3-35).**[56] (20 h) ^{1}H NMR ($CDCl_3$): δ 7.07 (m, 2H), 6.59 (m, 1H), 6.50 (m, 2H), 3.47 (broad s, 1H), 3.00 (t, J = 7.2 Hz, 2H), 1.51, (quint, J = 7.0 Hz, 2H), 1.33-1.20 (m, 10H), 0.81 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.7, 129.3, 117.14, 112.8, 44.1, 32.0, 29.7, 29.6, 29.4, 27.3, 22.8, 14.2.

***N*-Octyl-2-aminopyridine (3-36).**[56] (20 h) ^{1}H NMR ($CDCl_3$): δ 8.06 (d of q, J = 5.0, 0.8 Hz, 1H), 7.40 (m, 1H), 6.53 m (1H), 6.35 (m, 1H), 4.60 (broad s, 1H), 3.22 (m, 2H), 1.61 (quint, J = 7 Hz, 2H), 1.42-1.27 (m, 10H), 0.88 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H}

NMR ($CDCl_3$): δ 159.1, 148.3, 137.5, 112.6, 106.4, 42.4, 31.9, 29.7, 29.5, 29.3, 27.2, 22.7, 14.2.

***N*-(4-Methylphenyl)octylamine (3-37).**[108] (24 h) ^1H NMR ($CDCl_3$): δ 7.05 (m, 2H), 6.60 (m, 2H), 3.57 (broad s, 1H), 3.15 (m, 2H), 2.31 (s, 3H), 1.66 (m, 2H), 1.50-1.36 (m, 10H), 0.96 (m, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.4, 129.8, 126.3, 113.0, 44.5, 31.9, 29.7, 29.5, 29.4, 27.3, 22.8, 20.4, 14.2.

***N*-Octyl-1-aminoisoquinoline (3-38).**[62b] (48 h) ^1H NMR ($CDCl_3$): δ 8.01 (d, J = 5.9 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.56 (m, 1H), 7.43 (m, 1H), 6.90 (d, J = 5.92 Hz, 1H), 5.27 (broad s, 1H), 3.59 (m, 2H), 1.72 (quint, J = 7.2 Hz, 2H), 1.45-1.20 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 155.3, 141.5, 137.1, 129.6, 127.2, 125.7, 121.4, 118.2, 110.6, 42.0, 31.9, 29.6, 29.5, 29.3, 27.3, 22.7, 14.1.

***N*-(2,5-Dimethylphenyl)octylamine (3-39).**[79] (36 h) ^1H NMR ($CDCl_3$): δ 7.17 (d, J = 7.4 Hz, 1H), 6.71 (d, J = 7.4 Hz, 1H), 6.68 (s, 1H), 3.54 (broad s, 1H), 3.38 (t, J = 7.2 Hz, 2H), 2.55 (s, 3H), 2.32 (s, 3H), 1.88 (quint, J = 7.0 Hz, 2H), 1.70-1.50 (m, 10H), 1.18 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.4, 136.6, 129.9, 118.7, 117.3, 110.6, 44.0, 32.0, 29.8, 29.6, 29.4, 27.4, 22.8, 21.6, 17.0, 14.2.

***N*-(2-Methylphenyl)octylamine (3-40).**[56] (48 h) ^1H NMR ($CDCl_3$): δ 7.20 (m, 1H), 7.13 (d, J = 7.3 Hz, 1H), 6.75-6.70 (m, 2H), 3.45 (broad s, 1H), 3.16 (t, J = 7.2 Hz, 2H), 2.14 (s, 3H), 1.66 (m, 2H), 1.51-1.34 (m, 10H), 0.99 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 146.3, 130.2, 127.2, 121.9, 117.0, 110.0, 44.2, 32.0, 29.7, 29.6, 29.5, 27.4, 22.8, 20.1, 17.6, 14.2.

***N*-(2-Pyridyl)-benzylamine (3-41).**[109] (24 h) ^1H NMR ($CDCl_3$): δ 8.13 (d, J = 5.0 Hz, 1H), 7.45-7.36 (m, 5H), 7.31 (m, 1H), 6.62 (dd, J = 7.1, 5.1 Hz, 1H), 6.41 (d, J = 8.4 Hz, 1H), 5.12 (broad s, 1H), 4.54 (d, J = 5.8 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 158.7, 148.3, 139.3, 137.5, 128.7, 127.4, 127.3, 113.4, 106.8, 46.3.

***N*-(2,6-Dimethylphenyl)octylamine (3-42).**[56] (48 h) ^{1}H NMR ($CDCl_3$): δ 7.02 (d, *J* = 7.5 Hz, 2H), 6.84 (m, 1H), 3.02 (m, 3H), 2.32 (s, 6H), 1.62 (m, 2H), 1.41-1.32 (m, 10H), 0.93 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.2, 129.2, 128.9, 121.6, 48.8, 31.9, 31.3, 29.6, 29.4, 27.2, 22.7, 18.6, 14.2.

***N*-(2-Pyridyl)cyclohexylamine (3-43).**[56] (44 h) ^{1}H NMR ($CDCl_3$): δ ^{1}H NMR ($CDCl_3$): δ 8.05 (dd, *J* = 1.1, 5.0 Hz, 1H), 7.38 (m, 1H), 6.51 (ddd, *J* = 0.7, 5.0, 7.0 Hz, 1H), 6.34 (d, *J* = 8.5 Hz, 1H), 4.46 (s, 1H), 3.52 (m, 1H), 2.02 (m, 2H), 1.73 (m, 2H), 1.61 (m, 1H), 1.38 (m, 2H) 1.28-1.16 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 158.2, 148.3, 137.3, 112.4, 106.7, 50.1, 39.4, 25.8, 24.9.

***N*-(4-Methylphenyl)cyclohexylamine (3-44).**[110] (28 h) ^{1}H NMR ($CDCl_3$): δ 6.99 (d, *J* = 8.5 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 2H), 3.37 (broad s, 1H), 3.28-3.23 (m, 1H), 2.26 (s, 3H), 2.07 (m, 2H), 1.81-1.77 (m, 2H), 1.69-1.66 (m, 1H), 1.44-1.35 (m, 2H), 1.30-1.12 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 145.2, 129.8, 126.2, 113.6, 52.1, 33.7, 26.1, 25.2, 20.5.

***N*-Cyclohexyl-2-aminoquinoline (3-45).** [56] (48 h) ^{1}H NMR ($CDCl_3$): δ 7.81 (d, *J* = 8.9 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.52 (m, 1H), 7.19 (m, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 4.80 (broad s, 1H), 3.85 (m, 1H), 2.13 (m, 2H), 1.79 (2H), 1.66 (m, 1H), 1.50-1.41 (m, 2H), 1.30-1.21 (m 3H). $^{3}C\{^{1}H\}$ NMR ($CDCl_3$): δ 156.5, 148.2, 137.5, 129.6, 127.5, 126.0, 123.4, 121.9, 111.1, 50.0, 33.6, 25.9, 25.0.

***N*-Benzylaniline (3-46).**[56] (48 h) ^{1}H NMR ($CDCl_3$): δ 7.48-7.42 (m, 4H), 7.38 (m, 1H), 7.30-7.26 (m, 2H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 2H), 4.41 (s, 2H), 4.10 (broad s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.3, 139.5, 129.4, 128.7, 127.6, 127.3, 116.6, 112.9, 48.4.

***N*-3-Pyridylbenzylamine (3-47).**[56] (24 h) ^{1}H NMR ($CDCl_3$) δ: 8.07 (s, 1H), 7.96 (d, *J* = 4.3 Hz, 1H), 7.37-7.26 (m, 5H), 7.06 (dd, *J* = 4.7, 8.3 Hz, 1H), 6.86 (ddd, *J* = 1.3,

2.9, 8.3 Hz, 1H), 4.34 (s, 2H), 4.20 (bs, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 144.1, 139.0, 138.6, 136.3, 128.9, 127.6, 127.5, 123.8, 118.7, 48.0.

***N*-Phenylcyclohexylamine (3-48).**[56] (26 h) ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 2H), 6.68 (m, 1H), 6.62 (m, 2H), 3.55 (broad s, 1H), 3.26 (m, 1H), 2.11-2.08 (m, 2H), 1.82-1.78 (m, 2H), 1.70-1.67 (m, 1H), 1.45-1.36 (m, 2H), 1.30-1.15 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.5, 129.4, 117.0, 113.3, 51.8, 33.6, 26.1, 25.2.

***N*-3-Pyridyloctylamine (3-49).**[56] (24 h) ^{1}H NMR ($CDCl_3$) δ: 8.01 (d, *J* = 2.9 Hz, 1H), 7.93 (dd, *J* = 1.3, 4.7 Hz, 1H), 7.07 (dd, *J* = 4.7, 8.3 Hz, 1H), 6.84 (ddd, *J* = 1.4, 2.9, 8.3 Hz, 1H), 3.72 (broad s, 1H), 3.10 (t, *J* = 7.0 Hz, 2H), 1.62 (quint, *J* = 7.0 Hz, 2H), 1.42-1.27 (m, 10H), 0.87 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 144.5, 138.2, 136.1, 123.8, 118.4, 43.7, 31.9, 29.5, 29.4, 29.3, 27.2, 22.7, 14.2.

***N*-8-Octylaminoquinoline (3-50).**[58] (18 h) ^{1}H NMR ($CDCl_3$) δ: 8.71 (dd, *J* = 1.7, 4.2 Hz, 1H), 8.05 (dd, *J* = 1.5, 1H), 7.36 (m, 2H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.66 (d, *J* = 7.7 Hz, 1H), 6.12 (broad s, 1H), 3.30 (t, *J* = 7.1 Hz, 2H), 1.89 (q, *J* = 7.3 Hz, 2H), 1.50 (m, 2H), 1.40-1.24 (8H, m), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.8, 145.1, 136.2, 128.8, 128.0, 121.4, 113.5, 104.6, 43.6, 32.0, 29.6, 29.5, 29.4, 27.5, 22.8, 14.3.

***N*-2-Pyrazyl Benzophenone Hydrazone (3-51).**[111] (4 h) ^{1}H NMR ($CDCl_3$): δ 8.93 (d, *J* = 1.4 Hz, 1H), 8.10 (broad s, 1H), 8.05 (d, *J* = 2.7 Hz, 1H), 7.97 (dd, *J* = 1.6, 1.1 Hz, 1H), 7.63-7.52 (m, 5H), 7.37-7.33 (m, 5H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 152.3, 148.4, 141.5, 137.5, 136.2, 132.3, 132.0, 129.9, 129.8, 129.1, 128.8, 128.4, 127.1.

***N*-2-tert-Butylaniline (3-52).**[112] (48 h) ^{1}H NMR ($CDCl_3$): δ 7.19 (m, 2H), 6.79 (m, 3H), 3.42 (broad s, 1H), 1.38 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.1, 129.1, 118.5, 117.6, 51.6, 30.3.

***N*-2-tert-Butylaminopyridine (3-53).**[113] (6 h) ^{1}H NMR ($CDCl_3$): δ 8.07 (m, 1H), 7.34 (m, 1H), 6.51 (m, 1H), 6.42 (d, *J* = 8.5 Hz, 1H), 4.49 (broad s, 1H), 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 158.6, 148.3, 136.9, 112.5, 108.8, 50.8, 29.7.

***N*-Methylaniline (3-54).** NMR data agrees with commercially available material.

***N*-Methylanisidine (3-55).**[59] (30 h) ^{1}H NMR ($CDCl_3$): 6.86 (m, 2H), 6.64 (m, 2H), 3.80 (s, 3H), 3.49 (broad s, 1H), 2.85 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 152.2, 143.8, 115.0, 113.7, 56.0, 31.7.

***N*-Methyl(4-trifluoromethyl)aniline (3-56).** NMR data agrees with commercially available material.

***N*-2-(Methylamino)pyridine (3-57).**[114] (4 h) ^{1}H NMR ($CDCl_3$): δ 8.09 (m, 1H), 7.43 (m, 1H), 6.57 (ddd, *J* = 7.2, 5.1, 0.9 Hz, 1H), 6.38 (dt, *J* = 8.4, 0.9 Hz, 1H), 4.50 (broad s, 1H), 2.92 (d, *J* = 5.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 159.8, 148.8, 137.6, 113.0, 106.4, 29.3.

***N*-Phenyl-4-methyl-2,2-diphenylhex-4-en-1-amine (3-58).** (4 h) ^{1}H NMR ($CDCl_3$): δ 7.36 (m, 4H), 7.32-7.26 (m, 6H), 7.19 (m, 2H), 6.73 (m, 1H), 6.61 (m, 2H), 4.88 (m, 1H), 4.61 (m, 1H), 3.86 (s, 2H), 3.27 (broad s, 1H), 3.07 (s, 2H), 1.14 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.6, 146.6, 142.5, 129.3, 128.4, 128.3, 126.7, 117.7, 116.0, 113.4, 49.9, 49.5, 45.0, 24.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{24}H_{26}N_1$: 328.2060. Found: 328.2037.

***N*-(2-Pyridyl)-2,2-diphenylpent-4-en-1-amine (3-59).** (8 h) ^{1}H NMR ($CDCl_3$): 8.09 (m, 1H), 7.40-7.32 (m, 5H), 7.30-7.24 (m, 6H), 6.57 (m, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 5.51-5.43 (m, 1H), 5.00 (m, 2H), 4.11 (m, 1H), 4.02 (d, *J* = 5.7, 2H), 3.02 (d, *J* = 7.1 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 158.8, 148.1, 145.6, 137.2, 134.1, 128.2, 128.0, 126.4, 118.4, 112.8, 107.0, 50.2, 48.2, 41.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_{22}H_{23}N_2$: 315.1856. Found: 315.1863.

***N*-(4-Methylphenyl)-2,2-diphenylpent-4-en-1-amine (3-60).** (44 h) ^{1}H NMR ($CDCl_3$): δ 7.42-7.36 (m, 4H), 7.34-7.28 (m, 6H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.56 (d, *J* = 8.5 Hz, 2H), 5.28 (m, 1H), 5.13-5.03 (m, 2H), 3.80 (s, 2H), 3.17 (br s, 1H), 3.10 (d, *J* = 7.5 Hz, 2H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.2, 145.8, 134.3, 128.6, 128.2, 128.0, 126.8, 126.4, 118.3, 113.3, 50.6, 50.0, 42.1, 20.3. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{24}H_{26}N$: 328.2060. Found: 328.2040.

***N*-(4-Methoxyphenyl)-2,2-diphenylpent-4-en-1-amine (3-61).** (24 h) ^{1}H NMR ($CDCl_3$): δ 7.38-7.32 (m, 4H), 7.31-7.24 (m, 6H), 6.81-6.76 (m, 2H), 6.58-6.54 (m, 2H), 5.44 (m, 1H), 5.09-4.99 (m, 2H), 3.77 (s, 3H), 3.73 (s, 2H), 2.07 (d, *J* = 7.0 Hz, 2H), 2.99 (br s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.1, 145.9, 142.8, 134.6, 128.2, 128.0, 126.4, 118.3, 114.8, 114.5, 55.8, 51.4, 50.0, 42.1. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{24}H_{26}NO$: 344.2009. Found: 344.1993.

***N*-Phenyl-2,2-diphenylpent-4-en-1-amine (3-62).**[115] (4 h) ^{1}H NMR ($CDCl_3$): δ 7.39-7.33 (m, 4H), 7.31-7.25 (m, 6H), 7.21-7.15 (m, 2H), 6.75-6.69 (m, 1H), 6.62-6.57 (m, 2H), 5.49-5.39 (m, 1H), 5.09-4.99 (m, 2H), 3.78 (s, 2H), 3.27 (br s, 1H), 3.06 (s, *J* = 7.0 Hz, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.5, 145.7, 134.2, 129.1, 128.3, 128.0, 126.4, 118.4, 117.4, 113.1, 50.2, 50.0, 42.1.

***N*-(4-methoxyphenyl)-2,2-diphenylhex-5-en-1-amine (3-63).** (3 h) ^{1}H NMR ($CDCl_3$ δ 7.35 (m, 4H), 7.27 (m, 6H), 6.78 (m, 2H), 6.56 (m, 2H), 5.79 (m, 1H), 4.94 (m, 2H), 3.77 (s, 3H), 3.76 (s, 2H), 3.03 (broad s, 1H), 2.36 (m, 2H), 1.85 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.7, 146.6, 143.4, 139.2, 129.8, 128.7, 128.5, 126.8, 115.4, 114.9, 56.4, 52.0, 50.8, 37.3, 29.2. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{25}H_{27}NO$: 358.2165. Found: 358.2172.

(1-Allylcyclohexylmethyl)-*N*-phenylamine (3-64). (4 h) ^{1}H NMR ($CDCl_3$ δ 7.19 (m, 2H), 6.70 (m, 1H), 6.64 (m, 2H), 5.86 (m, 1H), 5.08 (m, 2H), 3.63 (s, 1H), 3.00 (s, 2H), 2.00 (d, *J* = 7.6 Hz, 2H), 1.52-1.39 (m, 10H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.3,

134.9, 129.4, 117.6, 117.1, 112.9, 50.9, 40.7, 37.0, 34.0, 26.5, 21.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_{16}H_{24}N_1$: 230.1903. Found: 230.1881.

***N*-Phenyl-2,2-diphenylhex-5-en-1-amine (3-65).** (3 h) ^{1}H NMR ($CDCl_3$): 7.38 (m, 4H), 7.32 (m, 6H), 7.22 (m, 2H), 6.75 (t, *J* = 7.3 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 2H), 5.80 (m, 1H), 4.97 (m, 2H), 3.84 (d, *J* = 2H, 2H), 3.30 (m, 1H), 2.38 (m, 2H), 1.88 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.9, 146.4, 139.0, 129.3, 128.7, 128.4, 126.8, 117.9, 114.9, 113.5, 50.8, 50.6, 37.3, 29.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{24}H_{26}N_1$: 328.2060. Found: 328.2038.

***N*-Phenyl Benzophenone Imine (3-66).**[58] (3 h) ^{1}H NMR ($CDCl_3$): 7.53 (m, 2H), 7.24 (m, 1H), 7.17 (m, 2H), 4.05-7.00 (m, 3H), 6.93-6.88 (m, 4H), 6.69 (m, 1H), 6.50 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.3, 151.4, 139.8, 136.3, 130.8, 129.6, 129.4, 128.7, 128.6, 128.3, 128.0, 123.3, 121.1.

***N*-2-Pyridyl Benzophenone Imine (3-67).**[56] (18 h) ^{1}H NMR ($CDCl_3$): 8.31 (ddd, *J* = 1.0, 1.9, 5.0 Hz, 1H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.51 (m, 1H), 7.48-7.39 (m, 3H), 7.30-7.23 (m, 3H), 7.16 (m, 2H), 6.84 (ddd, 1.0, 5.0, 7.4 Hz, 1H), 6.59 (dt, 1.0, 8.1 Hz 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 170.2, 163.0, 148.6, 138.9, 137.2, 136.2, 131.2, 129.8, 129.3, 128.8, 128.2, 127.9, 188.5, 115.4.

***N*-4-Anisole Benzophenone Imine (3-68).**[116] (48 h) ^{1}H NMR ($CDCl_3$): 7.77 (m, 2H), 7.49 (m, 1H), 7.43 (m, 2H), 7.33-7.29 (m, 3H), 7.16 (m, 2H), 6.72 (d, *J* = 1.4 Hz, 4H), 3.77 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 168.0, 156.1, 144.6, 140.2, 136.9, 130.7, 129.8, 129.4, 128.7, 128.3, 128.2, 122.8, 114.0, 55.5.

***N*-(Phenyl)morpholine (3-69).** (20 h) NMR data agrees with commercially available material.

***N*-(Phenyl)piperidine (3-70).**[117] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.32-7.28 (m, 2H), 7.00-6.88 (m, 2H), 6.86 (m, 1H), 3.21-3.19 (m, 4H), 1.78-1.74 (m, 4H), 1.65-1.61 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 152.4, 129.1, 119.3, 116.6, 50.8, 26.0, 24.4.

1-Methyl-4-phenylpiperazine (3-71).[118] (15 h) ^{1}H NMR ($CDCl_3$): δ 7.31 (m, 2H), 6.98 (m, 2H), 6.89 (m, 1H), 3.26 (m, 4H), 2.62 (m, 4H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 151.3, 129.1, 119.7, 116.1, 55.2, 49.1, 46.2.

***N*-(4-Methylphenyl)morpholine (3-72).**[56] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.11 (d, J = 8.6 Hz, 2H), 6.87-6.84 (m, 2H), 3.88 (m, 4H), 3.12 (m, 4H), 2.30 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 149.3, 129.8, 129.6, 116.1, 67.1, 50.0, 20.5.

***N*-(4-Methoxyphenyl)morpholine (3-73).**[57f] (24 h) ^{1}H NMR ($CDCl_3$): δ 6.90-6.84 (m, 4H), 3.86 (m, 4H), 3.77 (s, 3H), 3.05 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 154.1, 145.8, 118.0, 114.7, 67.2, 55.7, 50.9.

***N*-(4-Methoxyphenyl)piperidine (3-74).**[118] (24 h) ^{1}H NMR ($CDCl_3$): δ 6.94 (m, 2H), 6.86 (m, 2H), 3.79 (s, 3H), 3.05 (m, 4H), 1.76 (m, 4H), 1.57 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.6, 147.0, 118.8, 114.4, 55.6, 52.3, 26.2, 24.3.

***N*-(3-Methylphenyl)morpholine (3-75).**[119] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.21 (t, J = 7.9 Hz, 1H), 6.78-6.74 (m, 3H), 4.89 (m, 4H), 3.18 (m, 4H), 2.37 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 151.5, 139.0, 129.2, 121.1, 116.7, 113.0, 67.1, 49.6, 21.9.

***N*-(4-Trifluoromethylphenyl)piperidine (3-76).**[57f] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.47 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 3.28 (t, J = 5.3 Hz, 4H), 1.73-1.61 (m, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.9, 126.3 (q, J_{CF} = 3.8 Hz), 124.0 (q, J_{CF} = 268.8 Hz), 114.7 (q, J_{CF} = 32.4 Hz), 49.5, 25.6, 24.4.

***N*-(4-Benzoylphenyl)morpholine (3-77).**[120] (25 h) ^{1}H NMR ($CDCl_3$): δ 7.83-7.79 (m, 2H), 7.76-7.74 (m, 2H), 7.56-7.53 (m, 1H), 7.49-7.45 (m, 2H), 6.90 (m, 2H), 3.87 (m,

4H), 3.33 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 195.3, 154.1, 138.9, 132.6, 131.7, 129.7, 128.2, 127.9, 113.3, 66.7, 47.7.

***N*-(4-Trifluoromethylphenyl)morpholine (3-78).**[57f] (18 h) ^{1}H NMR ($CDCl_3$): δ 7.51 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.7, 2H), 3.87 (m, 4H), 3.24 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 153.4, 126.4 (q, J_{CF} = 3.7 Hz), 124.8 (q, J_{CF} = 268.5 Hz), 121.9 (q, J_{CF} = 34.5 Hz), 114.3, 66.6, 48.2.

***N*-(2-Pyridyl)morpholine (3-79).**[121] (22 h) ^{1}H NMR ($CDCl_3$): δ 8.16 (m, 1H), 7.44 (m, 1H), 6.62-6.59 (m, 2H), 3.77 (m, 4H), 3.45 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 159.6, 148.0, 137.5, 113.8, 106.9, 66.7, 45.6.

***N*-(2-Pyridyl)piperidine (3-80).**[55e] (20 h) ^{1}H NMR ($CDCl_3$): δ 8.15 (m, 1H), 7.39 (m, 1H), 6.60 (m, 1H), 6.51 (m, 1H), 3.49 (m, 4H), 1.61 (m, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 159.7, 147.9, 137.3, 112.4, 107.1, 46.3, 25.5, 24.8.

***N*-(3-Pyridyl)morpholine (3-81).**[56] (20 h) ^{1}H NMR ($CDCl_3$): δ 8.25 (m, 1H), 8.08 (m, 1H), 7.13 (m, 2H), 3.82 (m, 4H), 3.13 (m, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.0, 141.1, 138.3, 123.6, 122.2, 66.7, 48.6.

***N*-2-Quinolylmorpholine (3-82).**[122] (20 h) ^{1}H NMR ($CDCl_3$): δ 7.94 (d, J = 9.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.65 (m, 1H), 7.59 (m, 1H), 7.30 (m, 1H), 6.98 (d, J = 9.1 Hz, 1H), 3.89 (t, J = 4.7 Hz, 4H), 3.75 (t, J = 5.2 Hz, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 157.6, 147.8, 137.7, 129.7, 127.3, 126.8, 123.4, 122.8, 109.4, 67.0, 45.7.

8-Piperidylquinoline (3-83).[107] (18 h) ^{1}H NMR ($CDCl_3$): 8.89 (dd, J = 4.2, 1.8 Hz, 1H), 8.07 (dd, J = 8.2, 1.8 Hz, 1H), 7.44-7.37 (m, 2H), 7.33 (dd, J = 8.2, 4.2 Hz, 1H), 7.14 (dd, J = 7.4, 1.5 Hz, 1H), 3.32 (t, J = 5.3 Hz, 4H), 1.91 (m, 4H), 1.66 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 150.9, 148.2, 143.1, 136.4, 129.7, 126.7, 121.2, 120.7, 116.1, 53.8, 26.3, 24.8.

2-(Dimethylamino)pyridine (3-84).[123] (4 h) ^{1}H NMR ($CDCl_3$): δ 8.20 (m, 1H), 7.46 (m, 1H), 6.56 (m, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 3.11 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 159.7, 147.7, 136.9, 111.2, 105.6, 37.9.

2-(Dimethylamino)quinoline (3-85).[124] (18 h) ^{1}H NMR ($CDCl_3$): δ 7.86 (d, *J* = 9.1 Hz, 1H), 7.75 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.55 (m, 1H), 7.21 (m, 1H), 6.89 (m, 1H), 3.24 (s, 6H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 157.7, 148.2, 137.2, 129.4, 127.3, 126.4, 122.5, 121.6, 109.1, 38.1.

***N*-(4-Methyl)dimethylaniline (3-86).**[125] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 8.7 Hz, 2H), 2.97 (s, 6 H), 2.33 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 149.0, 129.7, 126.2, 113.3, 41.2, 20.4.

***N*-Methyl-2-pyridylphenylamine (3-89).**[56] (24 h) ^{1}H NMR ($CDCl_3$): δ 8.27 (ddd, *J* = 0.8, 1.8, 5.0 Hz, 1H), 7.44 (m, 2H), 7.36-7.30 (m, 3H), 7.25 (m, 1H), 6.65 (m, 1H), 6.57 (d, *J* = 8.6 Hz, 1H), 3.52 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 158.9, 147.9, 146.0, 136.7, 129.8, 126.5, 125.6, 113.2, 109.3, 38.6.

Methyldiphenylamine (3-90).[57g] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.32 (m, 4H), 7.07 (m, 4H), 7.00 (m, 2H), 3.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 149.2, 129.3, 121.4, 120.6, 40.4.

Methylphenyl-4-tolylamine (3-91).[126] (48 h) ^{1}H NMR ($CDCl_3$): δ 7.27 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.96 (m, 2H), 6.91 (m, 1H), 3.33 (s, 3H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 149.5, 146.7, 132.1, 130.0, 129.1, 122.6, 119.9, 118.3, 40.4, 20.8.

***N*-Methyl-*N*-4-benzophenonephenylamine (3-92).**[127] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.78 (m, 4H), 7.56 (m, 1H), 7.46 (m, 4H), 7.27 (m, 3H), 6.83 (dt, *J* = 2.1, 9.1 Hz, 2H), 3.43 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 195.2, 152.6, 147.3, 139.0, 132.4, 131.3, 129.9, 129.5, 128.1, 126.8, 126.2, 125.7, 113.4, 40.3.

***N*,*N*-Methylisopropylamine (3-93).** (20 h) ^{1}H NMR ($CDCl_3$) δ: 7.48 (m, 2H), 7.41 (m, 2H), 7.34 (m, 1H), 7.16 (t, *J* = 8.2 Hz, 1H), 6.46 (m, 2H), 6.37 (dd, *J* = 2.0, 8.2 Hz, 1H), 5.08 (s, 2H), 4.10 (sept, *J* = 6.6 Hz, 1H), 2.75 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.2, 151.7, 137.6, 129.8, 128.6, 127.9, 127.6, 106.7, 102.0, 100.8, 70.0, 49.0, 30.0, 19.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{17}H_{22}N_1O_1$: 256.1696. Found: 256.1703.

***N*-(4-Methoxyphenyl)methylisopropylamine (3-94).** (3 h) ^{1}H NMR ($CDCl_3$) δ: 6.84–6.80 (4H), 3.90 (sept. *J* = 6.6 Hz, 1H), 3.77 (s, 3H), 2.67 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 152.3, 145.3, 116.8, 114.7, 55.9, 51.2, 31.1, 19.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{18}N_1O_1$: 180.1383. Found: 180.1370.

N-(2-Methoxyphenyl)methylisopropylamine (3-95). (14 h) ^{1}H NMR ($CDCl_3$) δ: 6.95 (m, 2H), 6.91 (m, 1H), 6.84 (m, 1H), 3.85 (s, 3H), 3.70 (sept, *J* = 6.5 Hz, 1H), 2.67 (s, 3H), 1.09 (d, *J* = 6.6 Hz, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 153.0, 141.9, 122.4, 120.8, 120.6, 111.2, 55.5, 51.9, 32.0, 18.6. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{18}N_1O_1$: 180.1383. Found: 180.1381.

1-(4-(4'-Methoxyphenylamino)phenyl)ethanone (3-96).[61a] (12 h) ^{1}H NMR ($CDCl_3$): δ 7.82 (m, 2H), 7.14 (m, 2H), 6.91 (m, 2H), 6.81 (m, 2H), 5.98 (broad s, 1H), 3.83 (s, 3H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 196.3, 156.7, 150.1, 133.2, 130.7, 128.2, 124.6, 118.8, 113.2, 55.6, 26.1.

4-*N*-Octylaminoacetophenone (3-97).[56] (24 h) ^{1}H NMR ($CDCl_3$): δ 7.78 (m, 2H), 6.54 (m, 2H), 4.20 (broad s, 1H), 3.17 (m, 2H), 2.49 (s, 3H), 1.65 (m, 2H), 1.41-1.27 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 196.4, 169.4, 152.5, 130.9, 126.6, 111.4, 43.5, 31.9, 29.5, 29.4, 29.3, 27.2, 26.1, 22.8, 14.2.

***N*-(4-Benzoic acid methyl ester)phenylamine (3-98).**[128] (20 h) ^{1}H NMR ($CDCl_3$): δ 7.92 (d, *J* = 8.8 Hz, 2H), 7.34 (m, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.06 (m, 1H),

6.98 (m, 2H), 6.07 (broad s, 1H), 3.88 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): 167.1, 148.2, 141.0, 131.6, 129.6, 123.2, 121.2, 120.6, 114.7, 51.8.

***N*-(4-Hydroxybenzyl)dimethylamine (3-99).**[129] (18 h) ^{1}H NMR ($CDCl_3$) δ δ 7.28 (m, 2H), 6.77 (m, 2H), 4.60 (s, 2H), 2.99 (s, 6H), 1.95 (broad s, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 150.4, 129.1, 128.7, 112.8, 65.3, 40.8.

4-*N*-Octylaminoacetanilide (3-100).[56] (14 h) ^{1}H NMR ($CDCl_3$) δ: 7.26 (m, 2H), 7.21 (bs, 1H), 6.55 (m, 2H), 3.07 (t, *J* = 7.1 Hz, 2H), 2.12 (s, 3H), 1.59 (quint, *J* = 7.3 Hz, 2H), 1.40-1.28 (10 H), 0.89 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 168.3, 145.8, 128.0, 122.5, 113.0, 44.5, 31.9, 29.6, 29.5, 29.3, 27.3, 24.4, 22.8, 14.2.

4-*N*-Octylaminobenzoic acid (3-101).[56] (3 h) ^{1}H NMR ($CDCl_3$) δ 7.92 (m, 2H), 6.55 (m, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 1.63 (quint, *J* = 7.1 Hz, 2H), 1.41-1.26 (m, 12H), 0.88 (t, *J* = 6.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 172.1, 152.8, 132.4, 117.0, 111.4, 43.4, 31.9, 29.4, 29.4, 29.3, 27.2, 22.7, 14.2.

***N*-(3-Hydroxyphenyl)cyclohexylamine (3-102).**[56] (18 h) ^{1}H NMR ($CDCl_3$) δ: 6.99 (t, *J* = 8 Hz, 1H), 6.19 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.15 (dd, *J* = 2.3, 8.0 Hz, 1H), 6.09 (t, *J* = 2.3 Hz, 1H), 4.20 (br s, ca. 2H), 3.20 (m, 1H), 3.04 (m, 2H), 1.76 (m, 2H), 1.65 (m, 1H), 1.33 (m, 2H), 1.14 (m, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 156.9, 149.0, 130.3, 106.6, 104.2, 100.2, 52.0, 33.5, 26.0, 25.1.

N-(3-Hydroxyphenyl)methylpiperazine (3-103). (20 h) ^{1}H NMR ($CDCl_3$) δ: 7.09 (t, *J* = 8.1 Hz, 1H), 6.48 (dd, *J* = 2.2 Hz, 8.2 Hz, 1H), 6.37 (t, *J* = 2.3 Hz, 1H), 6.30 (dd, *J* = 2.2 Hz, 7.9 Hz, 1H), 3.20 (t, *J* = 5.0 Hz, 4H), 2.61 (t, *J* = 5.1 Hz, 4H), 2.37 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 157.2, 152.9, 130.2, 108.7, 107.2, 103.6, 55.1, 48.9, 46.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{17}N_2O_1$: 193.1335. Found: 193.1322.

***N*-(4-Hydroxyphenyl)benzophenone imine (3-104).** (24 h) ^{1}H NMR (CD_3OD) δ: 7.62 (m, 2H), 7.47 (m, 1H), 7.41 (m, 2H), 7.30 (m, 3H), 7.10 (m, 2H), 6.57 (d, *J* = 2.1 Hz,

4H). $^{13}C\{^{1}H\}$ NMR (CD_3OD): δ 170.7, 155.1, 144.2, 141.3, 138.0, 131.8, 130.8, 130.2, 129.8, 129.3, 129.2, 123.9, 116.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{19}H_{16}N_1O_1$: 274.1226. Found: 256.1230.

3-*N*-Octylaminoacetanilide (3-105).[56] (2.5 h) ^{1}H NMR ($CDCl_3$) δ: 7.16 (broad s, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.04 (m, 1H), 6.61 (dd, *J* = 1.3, 8.0 Hz, 1H), 6.36 (dd, *J* = 1.8, 8.0 Hz, 1H), 3.09 (t, *J* = 7.1 Hz, 2H), 2.14 (s, 3H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.40-1.28 (10H), 0.89 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 168.3, 149.3, 139.0, 129.7, 108.7, 108.4, 104.3, 44.0, 31.9, 29.6, 29.5, 29.3, 27.2, 24.9, 22.7, 14.2.

***N*-(4-Chloro)-4-anisidine (3-106).**[130] (2 h) ^{1}H NMR ($CDCl_3$): 7.15 (m, 2H), 7.05 (d, 2H), 6.87 (m, 2H), 6.81 (m, 2H), 5.46 (broad s, 1H), 3.80 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.9, 144.2, 135.5, 129.4, 124.2, 122.8, 116.9, 115.0, 55.8.

3.6.3 Experimental Section for Section 3.3

Standard procedure of the cross-coupling of di(1-adamantyl)phosphine to aryl halides. Using a protocol analogous to that reported for the synthesis of **3-1**, in a glovebox $Pd(OAc)_2$ (typically 2 mol%) and DiPPF (Pd:L ~ 1:1.2) were combined in 2 mL toluene and stirred for 10 minutes. This solution was then added to a vial containing di(1-adamantyl)phosphine and NaOtBu, followed by the addition of the aryl halide; the vial was then capped and removed from the glovebox. The resulting mixture was heated at 110 ºC until complete consumption of the phosphine was achieved, as judged on the basis of ^{31}P NMR data. The solution was then cooled and filtered through a plug of silica, which in turn was washed with CH_2Cl_2. Removal of the solvent from the combined eluent afforded products that were further purified by recrystallization or by washing with appropriate solvents (*vide infra*). All ligands were worked up in air and were found to be stable when handled on the benchtop.

3-107. Prepared by the coupling of $(1\text{-Ad})_2PH$ and *N*,*N*-dimethyl-(2-bromobenzyl)amine via the standard procedure employing 4 mol% Pd and 4.4 mol%

ligand in 68% yield (295 mg, 0.68 mmol) as a pale yellow powder. ^{1}H NMR ($CDCl_3$): δ 7.73 (d, J = 7.7 Hz, 1H), 7.67 (dd, J = 3.4 , 7.7 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 3.96 (d, J = 3.4 Hz, 2H), 2.31 (s, 6H), 1.99-1.85 (m, 18H), 1.67 (s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.2 (d, J_{PC} = 2.8 Hz), 133.2 (d, J_{PC} = 24.8 Hz), 129.0 (d, J_{PC} = 6.2 Hz), 128.8, 124.7, 61.9 (d, J_{PC} = 30.6 Hz), 45.7, 41.9 (d, J_{PC} = 12.3 Hz), 37.2 (d, J_{PC} = 22.6 Hz), 37.0, 28.9 (d, J_{PC} = 8.6 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 14.5. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{29}H_{43}NP$: 436.3128. Found: 436.3130.

3-108. Prepared by the coupling of $(1\text{-Ad})_2PH$ and 2-methoxy-6-*N*,*N*-dimethylaminoiodobenzene via the standard procedure employing 4 mol% Pd and 4.4 mol% ligand in 36% yield (70 mg, 0.16 mmol) as a white solid after recrystallizing from hexanes at -35 ºC. ^{1}H NMR ($CDCl_3$): δ 7.29 (t, J = 8.1 Hz, 1H), 6.82 (ddd, J = 0.8, 4.6, 8.0 Hz, 1H), 6.64 (d, J = 8.1 Hz, 1H), 3.80 (s, 3H), 2.72 (s, 6H), 1.99-1.87 (m, 18H), 1.69-1.64 (m, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 163.8 (d, J_{PC} = 22.6 Hz), 162.2 (d, J_{PC} = 4.2 Hz), 130.8, 118.7 (d, J_{PC} = 36.9 Hz), 112.9 (d, J_{PC} = 3.5 Hz), 105.9, 53.9, 46.2 (d, J_{PC} = 5.4 Hz), 41.9 (d, J_{PC} = 14.2 Hz), 37.4 (d, J_{PC} = 27.4 Hz), 37.3, 29.4 (d, J_{PC} = 36.2). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 33.9. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{29}H_{43}NOP$: 452.3077. Found: 452.3102.

3-109. Prepared by the coupling of $(1\text{-Ad})_2PH$ and 2-(2',5'-dimethylpyrrole)bromobenzene via the standard procedure employing 10 mol% Pd and 11 mol% ligand in 26% yield (122 mg, 0.26 mmol) as a beige powder. ^{1}H NMR ($CDCl_3$): δ 7.91 (d, J = 7.4 Hz, 1H), 7.40 (m, 2H), 7.10 (ddd, J = 1.7, 3.9, 7.6 Hz, 1H), 5.91 (s, 2H), 2.06 (s, 6H), 1.95-1.89 (m, 18H), 1.66 (s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.1 (d, J_{PC} = 26.1 Hz), 138.0 (d, J_{PC} = 7.6 Hz), 135.2 (d, J_{PC} = 34.8 Hz), 130.8 (d, J_{PC} = 3.9 Hz), 129.3, 129.2, 126.2, 105.8, 41.9 (d, J_{PC} = 12.8 Hz), 37.5 (d, J_{PC} = 26.4 Hz), 37.0, 29.0 (d, J_{PC} = 8.8 Hz), 14.6 (d, J_{PC} = 3.6 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 21.9. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{32}H_{43}NP$: 472.3128. Found: 472.3111.

3-110. Prepared by the coupling of $(1\text{-Ad})_2PH$ and 2-(2-bromophenyl)pyridine via the standard procedure employing 7.5 mol% Pd and 8 mol% ligand in 74% yield (220

mg, 0.48 mmol) as a white solid after recrystallizing from hexanes at -35 °C. ^{1}H NMR ($CDCl_3$): δ 8.62 (d, J = 4.8 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1), 7.65 (dt, J = 1.7, 7.6 Hz, 1H), 7.45-7.37 (m, 4H), 7.20 (ddd, J = 1.1, 4.9, 7.5 Hz, 1H), 1.90-1.83 (m ,18H), 1.64 (s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 161.4 (d, J_{PC} = 6.1 Hz), 150.6 (d, J_{PC} = 31.6 Hz), 148.6, 136.6 (d, J_{PC} = 2.8 Hz), 134.5, 132.8, 132.6, 130.2 (d, J_{PC} = 6.6 Hz), 128.7 (d, J_{PC} = 1.3 Hz), 126.8, 126.3 (d, J_{PC} = 7.7 Hz), 121.4, 41.9 (d, J_{PC} = 15.3 Hz), 37.3 (d, J_{PC} = 24.5 Hz), 37.0, 28.9 (d, J_{PC} = 8.6 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 21.4. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{31}H_{39}NP$: 456.2815. Found: 456.2809.

3-111. Prepared by the coupling of $(1\text{-Ad})_2PH$ and *N*-(2-bromophenyl)benzhydrylideneamine via the standard procedure employing 6 mol% Pd and 7 mol% ligand in 70% yield (233 mg, 0.42 mmol) as a pale orange powder. ^{1}H NMR ($CDCl_3$): δ 7.74 (d, J = 7.3 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.45-7.39 (m, 3H), 7.30-7.18 (m, 6H), 6.92 (td, J = 1.0, 7.8, 1H), 6.81 (ddd, J = 1.1, 4.3, 7.9 Hz, 1H), 1.85 (s, 12H), 1.74 (m, 6H), 1.65 (s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 165.2, 158.2 (d, J_{PC} = 25.6 Hz), 140.2, 137.3, 137.2, 130.5, 130.3, 129.8, 128.6, 128.5, 128.2, 127.7, 122.1 (d, J_{PC} = 25.7 Hz), 121.5 (d, J_{PC} = 4.5 Hz), 121.3, 41.6 (d, J_{PC} = 12.6 Hz), 37.1, 36.9, 28.9 (d, J_{PC} = 8.5 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 18.3. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{39}H_{45}NP$: 558.3284. Found: 558.3245.

3-112. Prepared by the coupling of $(1\text{-Ad})_2PH$ and *N*-(2-bromophenyl)morpholine employing 3 mol % $Pd(OAc)_2$ and 3.3 mol % ligand in 79 % yield (1.939 g) as an off-white solid after washing with Et_2O. ^{1}H NMR ($CDCl_3$): δ 7.70 (d, J = 7.5 Hz, 1H), 7.30 (m, 1H), 7.04 (m, 2H), 3.83 (app. t, J = 4.5 Hz, 4H), 3.04 (app. t, J = 4.5 Hz, 4H), 1.97 – 1.89 (m, 18H), 1.67 (s, 12H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.5 (d, J_{PC} = 20.5 Hz, C_{quat}), 137.5 (d, J_{PC} = 3.1 Hz), 131.2 (d, J_{PC} = 27.2 Hz, C_{quat}), 129.5, 122.1, 120.0 (d, J_{PC} = 3.8 Hz), 67.2, 53.5 (d, J_{PC} = 5.8 Hz), 42.0 (d, J_{PC} = 13.2 Hz), 37.0, 36.8 (d, J_{PC} = 27 Hz) 28.9 (d, J_{PC} = 8.4 Hz). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 20.4. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{30}H_{43}NOP$: 464.3077. Found: 464.3088.

3-113. Prepared by the coupling of $(1\text{-Ad})_2PH$ and *N*-(2-bromophenyl)piperidine via the standard procedure employing 2 mol% Pd and 2.4 mol% ligand in 66% yield (310 mg, 0.68 mmol) as a pale yellow powder. ^1H NMR ($CDCl_3$): δ 7.68 (m, 1H), 7.27 (m, 1H), 7.05 (ddd, J = 1.0, 4.5, 8.0, 1H), 7.00 (td, J = 1.1, 7.4 Hz, 1H), 2.92 (s, 4H), 1.98-1.88 (m, 18H), 1.71-1.68 (m, 16H), 1.54 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.4 (d, J_{PC} = 21.0 Hz), 137.4 (d, J_{PC} = 2.7 Hz), 131.6 (d, J_{PC} = 26.5 Hz), 129.3, 121.5, 120.4 (d, J_{PC} = 3.3 Hz), 54.8 (d, J_{PC} = 5.4 Hz), 42.0 (d, J_{PC} = 13.5 Hz), 37.3, 36.8 (d, J_{PC} = 27.6 Hz), 29.1 (d, J_{PC} = 8.3 Hz), 26.2, 24.5. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 21.6. HRMS (ESI/$[M+H]^+$) calcd. for $C_{31}H_{45}NP$: 462.3284. Found: 462.3276.

3-114. Prepared from *N*-(2-lithiophenyl)morpoline, prepared *in situ* by treatment of *N*-(2-bromophenyl)morpoline with *n*-BuLi, and chlorodicyclohexylphosphine in Et_2O in 68% yield (200 mg, 0.56 mmol) as a white solid. The air and moisture sensitivity of this ligand was not established. ^1H NMR ($CDCl_3$): δ 7.35-7.28 (m, 2H), 7.10-7.07 (m, 2H), 3.84 (app. t, J = 4.4 Hz, 4H), 3.04 (app. t, J 4.4 Hz, 4H), 1.95-1.82 (m, 4H), 1.78-1.75 (m, 2H), 1.70-1.62 (m, 6H), 1.34-1.07 (m, 8H), 1.04-0.94 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 158.2 (d, J_{PC} = 17.5 Hz), 133.1, 132.1 (d, J_{PC} = 19.8 Hz), 129.3, 123.6, 120.1, 67.4, 53.4 (d, J_{PC} = 5.0 Hz), 33.2 (d, J_{PC} = 15.1 Hz), 30.2 (d, J_{PC} =15.6 Hz), 29.3 (d, J_{PC} = 9.8 Hz), 27.6 (d, J_{PC} = 11.2 Hz), 27.3 (d, J_{PC} = 7.8 Hz), 26.6. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ -11.2.

3-138. Route 1. To a vial containing CpPd(allyl) (330 mg, 1.55 mmol) was added **3-112** (690 mg, 1.49 mmol) followed by 6 mL THF and 6 mL chlorobenzene. The vial was sealed, removed from the glovebox and heated at 65 ºC for 12 h. The reaction was concentrated to approximately 6 mL and the resulting slurry was washed with pentane (3 X 5 mL) and dried to yield **3-138** as a pale grey powder in 93% yield (943 mg, 1.38 mmol). **Route 2.** To a vial containing $(COD)Pd(CH_2TMS)_2$ (100 mg, 0.239 mmol) was added **3-112** (110 mg, 0.239 mmol) and chlorobenzene (3 mL). The resulting solution was stirred at room temperature for 40 minutes, after which time ^{31}P NMR indicated the complete conversion to **3-138**, which was isolated in 99% yield (164 mg, 0.239 mmol) by the removal of volatile material under vacuum. Crystals of **3-138**·CH_2Cl_2 suitable for X-

ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a CH_2Cl_2 solution of **3-138**. ^{1}H NMR ($CDCl_3$): δ 8.23 (dd, *J* = 3.4, 8.3 Hz, 1H, ArH), 7.84 (t, *J* = 7.0 Hz, 1H, ArH), 7.64 (t, *J* = 7.7 Hz, 1H, ArH), 7.54 (d, *J* = 7.7 Hz, 2H, Pd-Ph), 7.39 (t, *J* = 7.7 Hz, 1H, ArH), 7.00 (t, *J* = 7.6 Hz, 2H, Pd-Ph), 6.86 (t, *J* = 7.2 Hz, 1H, Pd-Ph), 5.27 (m, 2H, morph CH_2), 4.13 (m, 2H, morph CH_2), 4.00 (m, 2H, morph CH_2), 3.05 (m, 2H, morph CH_2), 2.29 (m, 6H, 1-Ad CH), 2.00 (m, 12H, 1-Ad CH), 1.68 (br s, 12H, 1-Ad CH). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.6 (d, J_{PC} = 12.6 Hz, aryl C_{quat}), 141.7 (Pd-Ph C_{quat}), 138.9 (Pd-Ph CH), 136.2 (aryl CH), 132.6 (aryl CH), 128.9 (d, J_{PC} = 29.9 Hz, aryl CH), 127.7 (d, J_{PC} = 28.5 Hz, aryl C_{quat}), 126.6 (Pd-Ph CH), 126.0 (d, J_{PC} = 4.3 Hz, aryl CH), 122.9 (Pd-Ph CH), 62.0 (morph CH_2), 55.2 (morph CH_2) , 40.8 (1-Ad CH_2), 36.4 (1-Ad CH_2), 28.7 (1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 59.3. Anal. Calcd for $C_{36}H_{47}Pd_1Cl_1P_1N_1O_1$: C 63.32; H 6.94; N 2.05. Found: C 63.03; H 6.92; N 2.05.

3-139. To a vial containing CpPd(allyl) (125 mg, 0.59 mmol) was added **3-112** (270 mg, 0.58 mmol) followed by 1.5 mL THF and 1.5 mL 4-chloroanisole. The vial was sealed, removed from the glovebox and heated at 65 ºC for 12 h, at which time ^{31}P NMR confirmed complete conversion to **3-139**. The reaction mixture was concentrated to approximately 1.5 mL and the resulting slurry was washed with pentane (3 X 3 mL) and dried under vacuum to yield **3-139** as a pale grey powder in 79% yield (331 mg, 0.46 mmol). Crystals of **3-139**·CH_2Cl_2 suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a CH_2Cl_2 solution of **3-139**. ^{1}H NMR ($CDCl_3$): δ 8.23 (dd, *J* = 2.9, 7.8 Hz, 1H, ArH), 7.84 (m, 1H, ArH), 7.63 (m, 1H, ArH), 7.40 – 7.36 (m, 3H, ArH), 6.68 (m, 2H, ArH), 5.25 (m, 2H, morph CH_2), 4.13 (m, 2H, morph CH_2), 3.99 (m, 2H, morph CH_2), 3.75 (s, 3H, OCH_3), 3.05 (m, 2H, morph CH_2), 2.29 (m, 6H, 1-Ad), 2.00 – 1.94 (12H, 1-Ad), 1.68 (br s, 12 H, 1-Ad). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.6 (d, J_{PC} = 12.5 Hz, aryl C_{quat}), 156.2 (Pd-aryl C_{quat}), 138.5 (Pd-aryl CH), 136.2 (aryl CH), 132.6 (aryl CH), 128.9 (d, J_{PC} = 7.5 Hz, aryl CH), 127.6 (d, J_{PC} = 28.2 Hz, (Pd-aryl C_{quat}), 125.9 (d, J_{PC} = 4.4 Hz, aryl CH), 112.8 (Pd-aryl CH), 62.0 (morph CH_2), 55.2 (morph CH_2), 55.0 (OCH_3), 43.2 (d, J_{PC} = 14.1 Hz, 1-Ad C_{quat}), 40.8 (1-Ad CH_2), 36.4 (1-Ad CH_2), 28.6 (d, J_{PC} = 9.3 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 59.6. Anal. Calcd for $C_{36}H_{49}Pd_1Cl_1P_1N_1O_2$: C 62.34; H 6.93; N 1.97. Found: C 62.44; H 6.86; N 1.72.

3-140·CH_2Cl_2**.** A vial was charged with **3-138** (341 mg, 0.50 mmol) followed by 5 mL CH_2Cl_2. The vial was sealed, transferred out of the glovebox and NH_3 (0.5 M in 1,4-dioxane, 3.00 mL, 1.50 mmol) was added. The solution was stirred briefly, and then was transferred back into the glovebox, at which point AgOTf (141 mg, 0.55 mmol) was added. The resulting mixture was stirred for 30 minutes at room temperature during which time a gray precipitate formed. ^{31}P NMR analysis of the reaction mixture indicated complete conversion to a single new phosphorus-containing species. The precipitate was removed by filtration over Celite and the solution was concentrated under vacuum. The resulting solid was washed with pentane/CH_2Cl_2 (5 x 2 mL) and concentrated to afford **3-140**·CH_2Cl_2 as a light brown solid in 90% yield (406 mg, 0.45 mmol). Crystals of **3-140**·CH_2Cl_2 suitable for X-ray diffraction analysis were obtained from vapor diffusion of diethyl ether into a CH_2Cl_2 solution of **3-140**. ^{1}H NMR ($CDCl_3$): δ 8.13 (m, 1H, ArH), 7.83 (t, J = 6.6 Hz, 1H, ArH), 7.69 (t, J = 7.6 Hz, 1H, ArH), 7.52 (d, J = 7.9 Hz, 2H, Pd-Ph), 7.45 (t, J = 7.5 Hz, 1H, ArH), 7.06 (t, J = 7.5 Hz, 2H, Pd-Ph), 6.93 (t, J = 7.1 Hz, 1H, Pd-Ph), 4.33 (m, 2H, morph CH_2), 4.07 (br s, 4H, morph CH_2), 3.24 (m, 2H, morph CH_2), 2.64 (br s, 3H, NH_3), 2.25-2.23 (m, 6H, 1-Ad), 1.97 (br s, 12H, 1-Ad), 1.68 (br s, 12H, 1-Ad). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.6 (m, aryl C_{quat}), 143.2 (Ph C_{quat}), 137.7 (Pd-Ph CH), 135.9 (aryl CH), 133.3 (aryl CH), 127.8 (Pd-Ph CH), 127.1 (d, J_{PC} = 7.5 Hz, aryl CH), 126.6 (aryl CH), 124.0 (Pd-Ph CH), 61.6 (morph CH_2), 55.6 (morph CH_2), 43.1 (d, J_{PC} = 5.4 Hz, 1-Ad C_{quat}), 40.6 (1-Ad CH_2), 36.1 (1-Ad CH_2), 28.4 (d, J_{PC} = 0.5 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 61.7. Anal. Calcd for $C_{38}H_{52}Pd_1Cl_2P_1N_2O_4S_1F_3$: C 50.80; H 5.84; N 3.12. Found: C 50.84; H 5.90; N 3.30.

3-141·CH_2Cl_2**.** A vial was charged with **3-139** (75 mg, 0.105 mmol) followed by 3 mL CH_2Cl_2. The vial was sealed, transferred out of the glovebox and NH_3 (0.5 M in 1,4-dioxane, 0.631 mL, 0.316 mmol) was added. The solution was stirred briefly, and then was transferred back into the glovebox, at which point and AgOTf (30 mg, 0.116 mmol) was added. The resulting mixture was stirred for 30 minutes at room temperature during which time a gray precipitate formed. ^{31}P NMR analysis of the reaction mixture indicated complete conversion to a single new phosphorus-containing species. The precipitate was

removed by filtration over Celite and the solution was concentrated under vacuum. The resulting solid was washed with pentane/CH_2Cl_2 (5 x 2 mL) to afford **3-141**·CH_2Cl_2 as a gray solid in 84% yield (82 mg, 0.088 mmol). ^{1}H NMR ($CDCl_3$): δ 8.12 (dd, *J* = 2.9, 8.0 Hz, 1H, ArH), 7.82 (t, *J* = 6.5 Hz, 1H, ArH), 7.69 (t, *J* = 7.4 Hz, 1H, ArH), 7.45 (t, *J* = 7.4 Hz, 1H, ArH), 7.38 (d, *J* = 7.5 Hz, 2H, Pd-Ph), 6.73 (d, *J* = 8.6 Hz, 2H, Pd-Ph), 4.32 (m, 2H, morph CH_2), 4.06 (m, 4H, morph CH_2), 3.75 (s, 3H, OCH_3), 3.23 (m, 2H, morph CH_2), 2.62 (br s, 3H, NH_3), 2.23 (m, 6H, 1-Ad), 1.95 (m, 12H, 1-Ad), 1.68 (br s, 12H, 1-Ad). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.7 (d, J_{PC} = 9.0 Hz, aryl C_{quat}), 157.0 (Pd-Ph C_{quat}), 137.6 (Pd-Ph CH), 135.9 (aryl CH), 133.3 (aryl CH), 130.5 (Pd-Ph C_{quat}), 127.1 (d, J_{PC} = 6.8 Hz, aryl CH), 126.6 (aryl CH), 113.9 (Pd-Ph CH), 61.7 (morph CH_2), 55.7 (morph CH_2), 55.1 (OCH_3), 43.1 (d, J_{PC} = 5.4 Hz, 1-Ad C_{quat}), 40.6 (1-Ad CH_2), 36.1 (1-Ad CH_2), 28.4 (d, J_{PC} = 9.4 Hz, 1-Ad CH). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 62.1. Anal. Calcd for $C_{39}H_{54}Pd_1Cl_2P_1N_2O_5S_1F_3$: C 50.45; H 5.87; N 3.02. Found: C 50.11; H 5.74; N 2.99.

Representative Example for the Cross-Coupling of Aryl Chlorides and Ammonia. From a stock solution in 1,4-dioxane, 1.9 mg (0.0037 mmol) of [Pd(cinnamyl)Cl]$_2$ was added to a vial containing **3-112** (6.9 mg, 0.0149 mmol) and diluted to 3.000 mL with additional 1,4-dioxane then stirred for 5 minutes. From this solution, 880 μL (0.0021 mmol Pd) was added to a vial containing 4-phenylchlorobenzene (113 mg, 0.6 mmol) and NaOtBu (115 mg, 1.2 mmol), which was then diluted with 7.5 mL of 1,4-dioxane. The vial was sealed with a cap containing a PTFE septum and removed from the glovebox, followed by the addition of NH_3 as a 0.5 M solution in 1,4-dioxane (3.6 mL, 1.8 mmol). The solution was heated at 110 ºC and the reaction progress was monitored by TLC. After complete consumption of the aryl chloride (1 h at 110 ºC, 20 h at 65 ºC, 14 h at room temperature using **3-138**), the reaction was cooled, diluted with 10 mL of water and extracted with CH_2Cl_2 (3 X 25 mL). The organic fractions were dried with Na_2SO_4, evaporated and the resulting material was purified by column chromatography (10:1, Hex:EtOAc) to yield 4-phenylaniline (**3-114**) as a white solid in 90% yield (91 mg, 0.54 mmol). ^{1}H NMR ($CDCl_3$): δ 7.60 (m, 2H), 7.49 – 7.43 (m, 4H), 7.32 (m, 1H), 6.79 (dt, *J* = 2.7, 8.5 Hz, 2H), 3.74 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 145.0, 141.3, 131.6, 128.8, 128.1, 126.5, 126.4, 115.5.[131]

4-(3'-Pyridyl)phenylamine (3-115).[132] Reaction time 1 h. ^{1}H NMR ($CDCl_3$): δ 8.81 (d, *J* = 2.1 Hz, 1H), 8.52 (dd, *J* = 1.5, 4.8 Hz, 1H), 7.81 (m, 1H), 7.41 (dt, *J* = 2.8, 8.5 Hz, 2H), 7.31 (ddd, *J* = 0.6, 4.8, 7.9 Hz, 1H), 6.79 (dt, *J* = 2.8, 8.5 Hz, 2H), 3.80 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.9, 147.6, 146.8, 136.7, 133.6, 128.2, 128.0, 123.6, 115.3.

4-(Pyridin-3-ylmethoxy)phenylamine (3-116). Reaction time 24 h. ^{1}H NMR ($CDCl_3$): δ 8.66 (d, *J* = 1.8 Hz, 1H), 8.57 (dd, *J* = 1.4, 4.8, 1H), 7.76 (m, 1H), 7.31 (m, 1H), 6.80 (m, 2H), 6.65 (m, 2H), 5.00 (s, 2H), 3.18 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 151.6, 149.4, 149.1, 140.8, 135.4, 133.1, 123.6, 116.9, 116.3, 68.6. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{13}N_2O$: 201.1022. Found: 201.1022.

***N*-(4-Aminophenyl)pyrrole (3-117).**[133] Reaction time 4 h. ^{1}H NMR ($CDCl_3$): δ 7.20 (dt, *J* = 3.2, 8.6 Hz, 2H), 6.98 (t, *J* = 2.1 Hz, 2H), 6.73 (dt, *J* = 3.2, 8.6, 2H), 6.32 (t, *J* = 2.2 Hz, 2H), 3.69 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.7, 133.1, 122.5, 119.8, 115.8, 109.6.

***N*,*N*-Diphenylbenzene-1,4-diamine (3-118).**[134] Reaction time 24 h. ^{1}H NMR ($CDCl_3$): δ 7.22 – 7.18 (m, 4H), 7.03 (m, 4H), 6.97 (m, 2H), 6.91 (t, *J* = 7.3 Hz, 2H), 6.64 (d, *J* = 8.6 Hz, 2H), 3.69 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.4, 143.1, 139.1, 129.1, 127.1, 122.7, 121.6, 116.3.

4-Amino(α-methylstyrene) (3-119). Reaction time 16 h. ^{1}H NMR ($CDCl_3$): δ 7.33 (m, 2H), 6.66 (m, 2H), 5.27 (m, 1H), 4.94 (quint, *J* = 1.5 Hz, 1H), 3.70 (br s, 2H), 2.13 (dd, *J* = 0.8, 1.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.0, 142.9, 131.7, 126.6, 114.9, 109.5, 22.0. HRMS (ESI/$[M+H]^+$) $C_9H_{12}N_1$: 134.0964. Found: 134.0970.

3-(Methylthio)aniline (3-120). Reaction time 18 h. NMR data agrees with commercially available material.

3-Benzyloxylphenylamine (3-121).[65b] Reaction time 6 h. ^{1}H NMR ($CDCl_3$): δ 7.47 – 7.39 (m, 4H), 7.35 (m, 1H), 7.09 (t, J = 8.0 Hz, 1H), 6.43 (dd, J = 2.3, 8.2 Hz, 1H), 6.35 (t, J = 2.3 Hz, 1H), 6.33 (m, 1H), 5.05 (s, 2H), 3.67 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 160.1, 147.9, 137.4, 130.2, 128.7, 128.0, 127.6, 108.3, 105.0, 102.1, 69.9.

3-Fluoro-5-(3'pyridyl)phenylamine (3-122). Reaction time 24 h. ^{1}H NMR ($CDCl_3$): δ 8.79 (dd, J = 0.9, 2.4 Hz, 1H), 8.59 (dd, J = 1.7, 4.9 Hz, 1H), 7.81 (ddd, J = 1.7, 2.4, 7.9 Hz, 1H), 7.35 (ddd, J = 0.9, 4.8, 7.9 Hz, 1H), 6.67 – 6.63 (m, 2H), 6.42 (dt, J = 2.2, 10.4 Hz, 1H), 3.96 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 167.0 (d, J_{CF} = 242 Hz), 149.0, 148.5 (d, J_{CF} = 11 Hz), 148.3, 140.7 (d, J_{CF} = 10 Hz), 136.0, 134.4, 123.7, 109.4, 104.2 (d, J_{CF} = 23 Hz), 101.6 (d, J_{CF} = 26 Hz). HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{11}H_{10}F_1N_2$: 189.0823. Found: 189.0827.

3-Fluoro-5-methoxyphenylamine (3-123). Reaction time 16 h. ^{1}H NMR ($CDCl_3$): δ 6.03 (m, 1H), 6.02 – 5.99 (m, 2H), 3.75 (br s 2H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 164.0 (d, J_{CF} = 240.3 Hz), 161.9 (d, J_{CF} = 13.5 Hz), 148.7 (d, J_{CF} = 13.5 Hz), 96.7, 95.1 (d, J_{CF} = 25.0 Hz), 92.0 (d, J_{CF} = 25.5 Hz), 55.5. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_7H_9F_1N_1O_1$:142.0663. Found: 142.0669.

3-Fluoro-4-methylaniline (3-124). Reaction time 20 h. ^{1}H NMR ($CDCl_3$): δ 6.94 (t, J = 8.8 Hz, 1H), 6.39 - 6.36 (m, 2H), 3.60 (br s, 2H), 2.16 (d, J = 1.6 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 162.0 (d, J_{CF} = 241 Hz), 146.0 (d, J_{CF} = 11 Hz), 131.9 (d, J_{CF} = 7 Hz), 114.3 (d, J_{CF} = 18 Hz), 110.7 (d, J_{CF} = 2 Hz), 102.3 (d, J_{CF} = 25 Hz), 13.8 (d, J_{CF} = 3 Hz). HRMS (ESI/[M+H]$^{+}$) calcd. for $C_7H_9F_1N_1$: 126.0714. Found: 126.0721.

1,3-Benzodioxol-5-amine (3-125).[135] Reaction time 18 h at 110 ºC, 20 h at 65 ºC. ^{1}H NMR ($CDCl_3$): δ 6.62 (d, J = 8.2 Hz, 1H), 6.29 (d, J = 2.3 Hz, 1H), 6.14 (dd, J = 2.3, 8.2 Hz, 1H), 5.86 (s, 2H), 3.44 (br s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.4, 141.6, 140.5, 108.7, 107.0, 100.8, 98.2.

2-Methyl-4-methoxyaniline (3-126). Reaction time 24 h. ^{1}H NMR ($CDCl_3$): δ 6.67 (d, *J* = 8.4 Hz, 1H), 6.56 - 6.50 (m, 2H), 3.77 (s, 3H), 3.29 (br s, 2H), 2.18 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 151.3, 139.7, 127.8, 118.7, 113.2, 111.7, 56.1, 16.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_8H_{12}N_1O_1$: 138.0913. Found: 138.0923.

3-Aminoquinoline (3-127). NMR data agrees with commercially available material.

6-Aminoquinoline (3-128).[136] Reaction time 20 h at 110 ºC, 12 h at room temperature. ^{1}H NMR ($CDCl_3$): δ 8.69 (dd, *J* = 1.6, 4.2 Hz, 1H), 7.95 – 7.91 (m, 2H), 7.29 (dd, *J* = 4.2, 8.3 Hz, 1H), 7.18 (dd, *J* = 2.6, 8.9 Hz, 1H), 6.92 (d, *J* = 2.6 Hz, 1H), 3.93 (br s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.9, 144.7, 143.6, 133.9, 130.7, 129.9, 121.7, 121.5, 107.5.

4-tert-Butylaniline (3-129). Reaction time 48 h. NMR data agrees with commercially available material.

2-Aminonaphthalene (3-130). Reaction time 20 h. NMR data agrees with commercially available material.

1-(3-Aminobenzyl)piperazine (3-131). Reaction time 20 h. ^{1}H NMR ($CDCl_3$): δ 7.09 (t, *J* = 7.6, 1H), 6.70 (m, 2H), 6.59 (m, 1H), 3.65 (br s, 2H), 3.41 (s, 2H), 2.91 (t, *J* = 4.9 Hz, 4H), 2.44 (s, 5H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.5, 139.4, 129.2, 119.7, 115.9, 114.0, 63.8, 54.3, 46.0. HRMS (ESI/$[M+H]^+$) calcd. for $C_{11}H_{18}N_3$:192.1502. Found: 192.1498.

3-(*N*-Methylaminomethyl)phenylamine (3-132). Reaction time 18 h. ^{1}H NMR ($CDCl_3$): δ 7.12 (t, *J* = 7.7 Hz, 1H), 6.69 (m, 2H), 6.59 (dd, *J* = 2.4 Hz, 7.9 Hz, 1H), 3.68 (s, 2H), 3.60 (br s, 2H), 2.46 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.7, 141.0, 129.5, 118.6, 115.0, 114.0, 56.0, 35.9. HRMS (ESI/$[M+H]^+$) calcd. for $C_8H_{13}N_2$: 137.1073. Found: 137.1076.

***N*-Methylbenzene-1,3-diamine (3-133).** Reaction time 18 h. ^{1}H NMR ($CDCl_3$): δ 6.99 (t, *J* = 7.9 Hz, 1H), 6.09 (m, 2H), 5.97 (t, *J* = 2.2 Hz, 1H), 3.60 (br s, 3H), 2.81 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 150.7, 147.3, 130.1, 104.9, 103.8, 99.2, 30.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_7H_{11}N_2$: 123.0917. Found: 123.0926.

***N*-(4-Methoxyphenyl)benzene-1,4-diamine (3-134).** NMR data agrees with commercially available material.

1,3-Phenyldiamine (3-135). Reaction time 8 h. ^{1}H NMR ($CDCl_3$): δ 6.94 (t, *J* = 7.9 Hz, 1H), 6.12 (dd, *J* = 2.1, 7.9 Hz, 2H), 6.03 (t, *J* = 2.1 Hz, 1H), 3.54 (br s, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.7, 130.3, 106.1, 102.0. HRMS (ESI/$[M+H]^+$) calcd. for $C_6H_9N_2$: 109.0760. Found: 109.0761.

(3,3'-Bisamino)diphenylamine (3-135b). Reaction time 8 h. ^{1}H NMR ($CDCl_3$): δ 7.03 (t, *J* = 8.0 Hz, 2H), 6.47 – 6.42 (m, 4H), 6.26 (m, 2H), 5.60 (br s, 1H), 3.54 (br s, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 147.6, 144.4, 130.2, 109.0, 108.2, 104.6. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{14}N_3$: 200.1182. Found: 200.1182.

Biphenyl-2,4'-diamine (3-136). Reaction time 24 h. ^{1}H NMR ($CDCl_3$): δ 7.29 (m, 2H), 7.18 – 7.14 (m, 2H), 6.85 (td, *J* = 1.2, 7.4 Hz, 1H), 6.80 (m, 3H), 3.75 (br s, 4H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 145.6, 143.8, 130.6, 130.2, 129.7, 128.0, 127.9, 118.7, 115.6, 115.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{12}H_{13}N_2$: 185.1073. Found: 185.1066.

4-(1-Aminoethyl)phenylamine (3-137). Reaction time 18 h. ^{1}H NMR (DMSO-d_6): δ 6.99 (m, 2H), 6.48 (m, 2H), 4.84 (s, 2H), 3.82 (q, *J* = 6.6 Hz, 1H), 2.10 (br s, 2H), 1.17 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO-d_6): δ 147.0, 135.5, 126.3, 113.6, 50.1, 26.0. HRMS (EI/$[M+H]^+$) calcd. for $C_8H_{13}N_2$: 137.1073. Found: 137.1076

4-Benzyloxymethyl-phenylamine (3-142).[137] Reaction time 28 h. ^{1}H NMR ($CDCl_3$): δ 7.39 – 7.35 (m, 4H), 7.30 (m, 1H), 7.18 (m, 2H), 6.69 (dt, *J* = 2.0, 8.4 Hz,

2H), 4.53 (s, 2H), 4.45 (s, 2H), 3.68 (br s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 146.2, 138.7, 129.7, 128.5, 128.3, 128.0, 127.7, 115.2, 72.2, 71.8.

4-Aminobenzonitrile (3-143). Reaction time 1 h. NMR data agrees with commercially available material.

3.6.4 Experimental Section for Section 3.4

General Catalytic Protocols. In an inert atmosphere glovebox, $[Pd(cinnamyl)Cl]_2$ and **3-112** (generally 5 mol% Pd and 7.5 mol% ligand) were added to a vial sealed with a cap containing a PTFE septum and stirred in toluene for 5 min, after which NaOtBu (1.8-2.0 equiv.) was added along with the aryl chloride substrate (1 equiv.) if it was a solid. After removing the vial from the glovebox the aryl chloride was added if it was a liquid, along with hydrazine hydrate (2.0 equiv.). Alternatively, if hydrazine hydrochloride was employed (2.0 equiv.), 3.5 equiv. NaOtBu was used. The reaction was stirred at the desired temperature for 0.5-2 h. Generally, after a short period of time reactions were observed to darken and considerable black precipitate was formed. After the completion of the reaction, the solution was allowed to cool and filtered through a short plug of neutral alumina, which was washed with CH_2Cl_2/MeOH (50:1). The resulting eluent solution was concentrated, diluted with MeOH and acidified with acetic acid or HCl in MeOH. This solution was then added portion-wise to a vial containing benzaldehyde in MeOH (1 equiv.). After completion of the reaction, as measured by TLC (generally <10 min.), the solution was concentrated and the resulting residue was purified by column chromatography. Typical reaction scales were 0.4 -1.0 mmol. Attempts to directly purify the aryl hydrazine product by column chromatography occasionally led to products that were contaminated by **3-112**. Product hydrazones were unstable at room temperature and were stored at -4 ºC.

***N*-Benzylidene-*N'*-phenylhydrazine (3-145).** Prepared from chlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 86% yield as a light yellow solid (101 mg, 0.52 mmol) after column chromatography (20:1 → 10:1 Hex:EtOAc), or alternatively from phenyl tosylate in 63% yield (63 mg, 0.32 mmol). ^{1}H

NMR (DMSO): δ 10.34 (s, 1H), 7.86 (s, 1H), 7.64 (m, 2H), 7.38 (m, 2H), 7.29 (tt, *J* = 1.3, 7.3 Hz, 1H), 7.22 (m, 2H), 7.06 (m, 2H), 6.74 (tt, *J* = 1.1, 7.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (DMSO): δ 145.4, 136.6, 135.9, 129.2, 128.6, 128.1, 125.7, 118.9, 112.1. HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{13}N_2$: 197.1073. Found: 197.1082.

***N*-Benzylidene-*N'*-(4-tolyl)hydrazine (3-146).** Prepared from 4-chlorotoluene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 93% yield as a light yellow solid (117 mg, 0.56 mmol) after column chromatography (10:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.68-7.65 (m, 3H), 7.50 (br s, 1H), 7.38 (m, 2H), 7.30 (tt, *J* = 7.3, 1.9 Hz, 1H), 7.10 (d, 8.2 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 2.31 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 142.5, 136.8, 135.5, 129.9, 129.5, 128.7, 128.3, 126.2, 112.9, 20.7. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{14}H_{14}N_2Na_1$: 233.1049. Found: 233.1034.

***N*-Benzylidene-*N'*-biphenyl-4-yl-hydrazine (3-147).** Prepared from 4-phenylchlorobenzene via the standard protocol employing 3 mol% Pd at 90 ºC for 1 h in 86% yield as a light yellow solid (96 mg, 0.35 mmol) after column chromatography (20:1 → 10:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.75-7.69 (m, 4H), 7.59 (m, 2H), 7.55 (m, 2H), 7.45-7.38 (m, 4H), 7.32 (m, 2H), 7.20 (m, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 144.1, 141.1, 137.7, 135.3, 133.1, 128.8, 128.7, 128.6, 128.1, 126.6 (2), 126.3, 113.2. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{19}H_{16}N_2Na_1$: 295.1206. Found: 295.1209.

***N*-Benzylidene-*N'*-(4'-methoxybiphenyl-4-yl)hydrazine (3-148).** Prepared from 4-chloro-(4'-methoxybiphenyl) via the standard protocol employing 5 mol% Pd at 90 ºC for 0.5 h in 82% yield as a pale yellow solid. (112 mg, 0.37 mmol) after column chromatography (10:1 → 5:1 Hex:EtOAc). ^{1}H NMR (DMSO): δ 10.45 (br s), 7.89 (s, 1H), 7.66 (d, *J* = 7.3 Hz, 2H), 7.51 (m, 4H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.29 (m, 1H), 7.13 (m, 2H), 6.97 (m, 2H), 3.77 (s, 3H). $^{13}C\{^{1}H\}$ NMR (DMSO): δ 158.0, 144.2, 136.6, 135.8, 132.8, 130.4, 128.7, 128.0, 126.9, 126.8, 125.6, 114.3, 112.4, 55.1. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{20}H_{18}N_2Na_1O_1$: 325.1311. Found: 325.1319.

***N*-Benzylidene-*N'*-(4'-trifluoromethylbiphenyl-4-yl)hydrazine (3-149).** Prepared from 4-chloro-(4'-trifluoromethylbiphenyl) via the standard protocol using hydrazine hydrochloride, employing 3 mol% Pd at 90 ºC for 0.5 h in 83% yield as a pale yellow solid. (112 mg, 0.37 mmol) after recrystallization from CH_2Cl_2/Et_2O. ^1H NMR (DMSO): δ 10.60 (s, 1H), 7.92 (s, 1H), 7.83 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.69-7.64 (m, 4H), 7.40 (m, 2H), 7.31 (m, 1H), 7.19 (m, 2H). $^{13}C\{^1H\}$ NMR (DMSO): δ 145.6, 144.2, 137.5, 135.6, 128.7, 128.6, 128.2, 127.9, 126.4 (q, J_{CF} = 32 Hz), 126.2, 125.8, 125.6 (q, J_{CF} = 4 Hz), 124.6 (q, J_{CF} = 272 Hz), 112.5. HRMS (ESI/$[M+H]^+$) calcd. for $C_{20}H_{16}F_3N_2$: 341.1260. Found: 341.1234.

***N*-Benzylidene-*N'*-(4-pyrrol-1-ylphenyl)hydrazine (3-150).** Prepared from 4-(*N*-pyrrole)chlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 78% yield as a pale yellow solid (101 mg, 0.39 mmol) after column chromatography (10:1 Hex:EtOAc), or alternatively from 4-(*N*-pyrrole)phenyl tosylate in 59% yield (73 mg, 0.28 mmol). ^1H NMR ($CDCl_3$): δ 7.71 (s, 1H), 7.69 (m, 2H), 7.40 (m, 2H), 7.33 (m, 7.33, 3H), 7.18 (m, 2H), 7.04 (t, J = 2.2 Hz, 2H), 6.35 (t, J = 2.2 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.9, 137.9, 135.2, 134.1, 128.7 (2), 126.3, 122.3, 119.7, 113.5, 109.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_{17}H_{16}N_3$: 262.1339. Found: 262.1330.

***N*-Benzylidene-*N'*-(4-trifluoromethylphenyl)hydrazine (3-151).** Prepared from 4-trifluoromethylchlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 50% yield as a pale yellow solid (66 mg, 0.25 mmol) after column chromatography (20:1 → 5:1 Hex:EtOAc), or alternatively employing 2.5 mol% Pd at 90 ºC for 1 hr in 44% yield. ^1H NMR ($CDCl_3$): δ 7.79 (br s, 1H), 7.75 (s, 1H), 7.68 (m, 2H), 7.52 (d, J = 8.6 Hz, 2H), 7.41 (m, 2H), 7.35 (m, 1H), 7.17 (d, J = 8.5 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.3, 139.0, 135.3, 128.7, 128.6, 126.5 (q, J_{CF} = 3 Hz), 126.1, 125.1 (q, J_{CF} = 270 Hz), 118.6 (q, J_{CF} = 32 Hz), 111.7. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{12}F_3N_2$: 265.0947. Found: 265.0943.

***N*-Benzylidene-*N'*-[4-(3-pyridinyl)phenyl]hydrazine (3-152).** Prepared from 4-(3'-pyridinyl)chlorobenzene via the standard protocol employing 5 mol% Pd at 65 ºC for

2 h in 97% yield as a light yellow solid (141 mg, 0.50 mmol) after column chromatography (CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.88 (s, 1H), 8.57 (d, *J* = 3.6 Hz, 1H), 7.98 (s, 1H), 7.89 (dt, *J* = 1.8, 7.9 Hz, 1H), 7.77 (s, 1H), 7.71 (m, 2H), 7.56 (m, 2H), 7.44-7.34 (m, 4H), 7.26 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 147.5, 147.2, 144.9, 138.0, 136.6, 135.2, 133.8, 129.0, 128.7, 128.6, 128.0, 126.3, 123.7, 113.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{18}H_{16}N_3$: 274.1339. Found: 274.1348.

***N*-Benzylidene-*N'*-(4-methoxyphenyl)hydrazine (3-153).** Prepared from 4-chloroanisole via the standard protocol using hydrazine hydrochloride, employing 10 mol% Pd at 110 ºC for 1 h in 27% yield as a pale purple solid which darkens over time (61 mg, 0.27 mmol) after column chromatography (10:1 → 5:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.65 (m, 3H), 7.50 (br s, 1H), 7.38 (m, 2H), 7.30 (tt, *J* = 7.3, 1.3 Hz, 1H), 7.08 (m, 2H), 6.89 (m, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 153.9, 138.9, 136.7, 135.6, 128.7, 128.3, 126.1, 114.9, 114.1, 55.8. HRMS (ESI/$[M+Na]^+$) calcd. for $C_{14}H_{14}N_2Na_1O_1$: 249.0998. Found: 249.0992.

***N*-Benzylidene-*N'*-(4-fluorophenyl)hydrazine (3-154).** Prepared from 4-fluorochlorobenzene via the standard protocol using hydrazine hydrochloride, employing 5 mol% Pd at 90 ºC for 0.5 h in 49% yield as a pale yellow solid (106 mg, 0.49 mmol) after column chromatography (10:1 → 5:1 Hex:EtOAc). ^{1}H NMR (DMSO): δ 10.34 (s, 1H), 7.84 (s, 1H), 7.65 (m, 2H), 7.39 (m, 2H), 7.30 (tt, *J* = 1.3, 6.8 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 2H), 7.06 (s, 2H). ^{13}C{^{1}H} NMR (DMSO): δ 155.9 (d, J_{CF} = 234 Hz), 142.0, 136.5, 135.8, 128.7, 128.0, 125.6, 115.6 (d, J_{CF} = 22 Hz), 112.9 (d, J_{CF} = 7 Hz). HRMS (ESI/$[M+H]^+$) calcd. for $C_{13}H_{12}F_1N_1$: 215.0979. Found: 215.0977.

***N*-Benzylidene-*N'*-(2,5-dimethylphenyl)hydrazine (3-155).** Prepared from 2,5-dimethylchlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 88% yield as a pale yellow solid (79 mg, 0.35 mmol) after column chromatography (10:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.80 (s, 1H), 7.70 (m, 2H), 7.50 (br s, 1H), 7.42-7.39 (m, 3H), 7.33 (tt, *J* = 7.4, 1.3 Hz, 1H), 6.99 (d. *J* = 7.5 Hz, 1H), 6.66 (m, 1H), 2.38 (s, 3H), 2.22 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.3, 138.1, 137.2, 135.4, 130.3, 128.7,

128.5, 126.3, 120.6, 117.3, 113.5, 21.6, 16.8. HRMS (ESI/[M+H]$^+$) calcd. for $C_{15}H_{17}N_2$: 225.1366. Found: 225.1386.

3-(tert-Butyldimethylsilyloxy)phenylhydrazine (3-156). Prepared from 3-(tert-butyldimethylsilyloxy)-chlorobenzene using hydrazine hydrochloride, employing 5 mol% Pd at 90 ºC for 0.5 h in 83% yield as a thick colourless oil (69 mg, 0.29 mmol) after column chromatography (CH_2Cl_2 → 50:1 CH_2Cl_2:MeOH). ^{1}H NMR ($CDCl_3$): δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.42 (ddd, *J* = 0.9, 2.2, 8.0 Hz, 1H), 6.34 (t, *J* = 2.2 Hz, 1H), 6.32 (ddd, *J* = 0.9, 2.2, 7.9 Hz, 1H), 4.20 (br s, 3H), 0.99 (s, 9H), 0.21 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 156.9, 152.8, 129.9, 111.2, 105.5, 104.1, 25.8, 18.3, -4.3. HRMS (ESI/[M+H]$^+$) calcd. for $C_{12}H_{23}N_2O_1Si_1$: 239.1574. Found: 239.1561.

***N*-Benzylidene-*N'*-(3-thioanisole)hydrazine (3-157).** Prepared from 3-chlorothioanisole via the standard protocol employing 10 mol% Pd at 110 ºC for 0.5 h in 95% yield as a white solid (104 mg, 0.43 mmol) after column chromatography (10:1→ 5:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.69-7.66 (m, 3H), 7.61 (br s, 1H), 7.39 (m, 2H), 7.32 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.19 (t, 7.9 Hz, 1H), 7.09 (t, *J* = 1.9 Hz, 1H), 6.85 (ddd, *J* = 8.1, 2.1, 0.7 Hz, 1H), 6.77 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 145.1, 139.7, 137.8, 135.2, 129.7, 128.7 (2), 126.3, 118.1, 110.6, 109.8, 15.8. HRMS (ESI/[M+Na]$^+$) calcd. for $C_{14}H_{14}N_2Na_1S_1$: 265.0770. Found: 265.0775.

***N*-Benzylidene-*N'*-(3-fluoro-5-methoxyphenyl)hydrazine (3-158).** Prepared from 3-fluoro-5-methoxychlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 72% yield as a white solid (88 mg, 0.36 mmol) after column chromatography (10:1 → 5:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.67-7.65 (m, 3H), 7.61 (br s, 1H), 7.39 (m, 2H), 7.33 (m, 1H), 6.50 (dt, *J* = 10.6, 2.0 Hz, 1H), 6.46 (t, *J* = 1.7 Hz, 1H), 6.17 (dt, *J* = 10.6, 2.3 Hz, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 164.5 (d, J_{CF} = 242 Hz), 161.8 (d, J_{CF} = 13 Hz), 146.8 (d, J_{CF} =14 Hz), 138.3, 134.9, 128.9, 128.7, 126.4, 94.3, 93.3 (d, J_{CF} = 26 Hz), 92.9 (d, J_{CF} =27 Hz), 55.6. HRMS (ESI/[M+H]$^+$) calcd. for $C_{14}H_{14}F_1N_2O_1$: 245.1085. Found: 245.1069.

***N*-Benzylidene-*N'*-(3-fluoro-4-methylphenyl)hydrazine (3-159).** Prepared from 3-fluoro-4-methylchlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 1 h in 77% yield as a pale yellow solid (88 mg, 0.39 mmol) after column chromatography (20:1 → 10:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.67-7.64 (m, 3H), 7.56 (br s, 1H), 7.39 (m, 2H), 7.33 (m, 1H), 7.05 (t, J = 8.5 Hz, 1H), 6.93 (dd, J = 11.7, 2.2 Hz, 1H), 6.71 (dd, J = 8.2, 2.2 Hz, 1H), 2.22 (d, J = 1.5 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 162.5 (d, J_{CF} = 243 Hz), 144.3 (d, J_{CF} = 11 Hz), 137.6, 135.1, 131.8 (d, J_{CF} = 7 Hz), 128.7 (2), 126.3, 115.7 (d, J_{CF} = 11 Hz), 108.1, 100.1, 13.9 (d, J = 3Hz). HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{14}H_{14}F_1N_2$: 229.1136. Found: 229.1137.

***N*-Benzylidene-*N'*-(3-fluoro-2-methylphenyl)hydrazine (3-160).** Prepared from 3-fluoro-2-methylchlorobenzene via the standard protocol employing 5 mol% Pd at 90 ºC for 0.5 h in 75% yield as a thick colourless oil which solidifies over time (85 mg, 0.37 mmol) after column chromatography (20:1 → 10:1 Hex:EtOAc). ^{1}H NMR (DMSO): δ 9.74 (s, 1H), 8.19 (s, 1H), 7.68 (m, 2H), 7.41 (m, 2H), 7.33 (tt, J = 1.3, 7.4 Hz, 1H), 7.15 (dd, J = 2.8, 12.0 Hz, 1H), 7.05 (m, 1H), 6.47 (td, J = 2.8, 8.4 Hz, 1H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR (DMSO): δ 161.8 (d, J_{CF} = 238 Hz), 145.2 (d, J_{CF} = 11 Hz), 139.8, 135.9, 131.8 (d, J_{CF} = 9 Hz), 129.1, 128.8, 126.4, 116.8, 104.8 (d, J_{CF} = 21 Hz), 99.0 (d, J = 3Hz), 17.2. HRMS (ESI/[M+H]$^{+}$) calcd. for $C_{14}H_{14}F_1N_2$: 229.1136. Found: 229.1122. The title compound could also be prepared in large scale (92% yield, 2.09 g, 9.2 mmol) employing the same protocol.

***N*-Benzylidene-*N'*-(3-benzyloxymethylphenyl)hydrazine (3-161).** Prepared from 3-benzyloxymethyl-chlorobenzene via the standard protocol employing 5 mol% Pd at 65 ºC for 1 h in 83% yield as a white solid (131 mg, 0.41 mmol) after column chromatography (10:1 → 5:1 Hex:EtOAc). ^{1}H NMR (DMSO): δ 10.38 (s, 1H), 7.86 (s, 1H), 7.64 (d, J = 7.3 Hz, 2H), 7.40-7.35 (m, 6H), 7.31 (m, 2H), 7.20 (t, J = 7.7 Hz, 1H), 7.10 (s, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 4.54 (s, 2H), 4.50 (s, 2H). ^{13}C{^{1}H} NMR (DMSO): 145.4, 139.4, 138.5, 136.5, 135.8, 129.1, 128.7, 128.3, 128.0, 127.5, 127.4, 125.6, 117.9, 111.2, 110.8, 71.6, 71.3. HRMS (ESI/[M+Na]$^{+}$) calcd. for $C_{21}H_{20}N_2Na_1O_1$: 339.1468. Found: 339.1445.

***N*-Benzylidene-*N'*-biphenyl-2-yl-hydrazine (3-162).** Prepared from 2-chlorobiphenyl via the standard protocol using hydrazine hydrochloride, employing 10 mol% Pd at 90 ºC for 1 h in 71% yield as a white solid (61 mg, 0.27 mmol) after column chromatography (20:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.76 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.64 (m, 2H), 7.55 (s, 1H), 7.44 (m, 2H), 7.43-7.40 (m, 3H), 7.37 (t, *J* = 7.2 Hz, 3H), 7.30 (m, 1H), 7.16 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.95 (td, *J* = 7.4, 1.2 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 141.3, 138.5, 138.0, 135.4, 130.3, 129.4, 129.2, 128.9, 128.7, 128.5, 127.7, 126.2, 126.0, 119.8, 113.3. HRMS (ESI/[M+H]$^+$) calcd. for $C_{19}H_{17}N_2$: 273.1386. Found: 273.1376

***N*-Benzylidene-*N'*-(3-pyridinyl)hydrazine (3-163).** Prepared from 3-chloropyridine via the standard protocol employing 5 mol% Pd at 65 ºC for 1.5 h in 69% yield as a light yellow solid (109 mg, 0.55 mmol) after recrystallization from MeOH, followed by washing with cold Et_2O. ^{1}H NMR (MeOD): δ 8.31 (d, *J* = 2.6 Hz, 1H), 7.93 (dd, *J* = 1.3, 4.8 Hz, 1H), 7.84 (s, 1H), 7.66 (m, 2H), 7.55 (ddd, *J* = 1.3, 2.6, 8.4, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.28 (m, 2H). ^{13}C{^{1}H} NMR (MeOD): δ 144.0, 140.5, 140.1, 136.9, 134.9, 129.6 (2), 127.2, 125.6, 120.7. HRMS (ESI/[M+H]$^+$) calcd. for $C_{12}H_{12}N_3$: 198.1026. Found: 198.1024.

6-Quinolinylhydrazine (3-164). Prepared from 6-chloroquinoline without hydrazone formation employing 3 mol% Pd at 65 ºC for 1 h in 81% yield as a light yellow solid (128 mg, 0.81 mmol) after recrystallization from toluene. ^{1}H NMR (MeOD): δ 8.51 (dd, *J* = 1.6, 4.3 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 4.3, 8.3 Hz, 1H), 7.30 (m, 1H), 7.15 (s, 1H), 4.68 (s, 3H). ^{13}C{^{1}H} NMR (MeOD): δ 154.3, 149.4, 146.8, 139.0, 134.1, 125.3, 124.3, 106.8. HRMS (ESI/[M+H]$^+$) calcd. for $C_9H_{10}N_3$: 160.0869. Found: 160.0862.

3-(*N*-Benzylidenehydrazino)benzyl-*N'*-methylamine (3-165). Prepared from 3-chloro-*N*-methylbenzylamine via the standard protocol employing 5 mol% Pd at 90 ºC for 0.5 h in 75% yield as a thick light yellow oil (85 mg, 0.35 mmol) after filtration through a

plug of silica (4 cm) (CH_2Cl_2 → 200:10:1 CH_2Cl_2:MeOH:NH_4OH). ^1H NMR (MeOD): δ 7.81 (s, 1H), 7.68 (m, 2H), 7.40-7.14 (m, 5H), 7.02 (m, 1H), 6.78 (m, 1H), 3.74 (s, 2H), 2.45 (s, 3H). $^{13}C\{^1H\}$ NMR (MeOD): 147.4, 140.4, 138.2, 137.7, 130.4, 129.7, 129.1, 127.0, 120.5, 113.5, 112.7, 56.4, 35.3. HRMS (ESI/$[M+H]^+$) calcd. for $C_{15}H_{18}N_3$: 240.1495. Found: 240.1484.

3-(*N'*-Benzylidenehydrazino)phenyl-*N*-methylamine (3-166). Prepared from 3-chloro-*N*-methylaniline via the standard protocol employing 5 mol% Pd at 90 ºC for 0.5 h in 58% yield as a light yellow solid (57 mg, 0.25 mmol) after column chromatography (5:1 Hex:EtOAc). ^1H NMR (DMSO): δ 10.14 (s, 1H), 7.81 (s, 1H), 7.62 (m, 2H), 7.38 (t, J = 7.1 Hz, 1H), 7.29 (m, 1H), 6.92 (t, J = 7.8 Hz, 1H), 6.30 (m, 2H), 6.00 (m, 1H), 5.55 (m, 1H), 2.67 (d, J = 5.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (DMSO): 150.8, 146.0, 136.1, 135.3, 129.4, 128.6, 127.6, 125.4, 103.4, 100.5, 95.3, 29.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_{14}H_{16}N_3$: 226.1339. Found: 226.1338.

***N*-Benzylidene-*N'*-(4-*tert*-butylphenyl)hydrazine (3-167).** Prepared from 4-*tert*-butylphenyl tosylate via the standard protocol employing 5 mol% Pd at 65 ºC for 1 h in 73% yield as a light yellow solid (92 mg, 0.37 mmol) after column chromatography (20:1 Hex:EtOAc). ^1H NMR (DMSO): δ 10.26 (s, 1H), 7.85 (s, 1H), 7.63 (m, 2H), 7.38 (m, 2H), 7.29-7.24 (m, 3H), 7.02 (dt, J = 2.0, 4.7 Hz, 2H), 1.26 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.9, 141.0, 136.0, 135.8, 128.6, 127.7, 125.7, 125.5, 111.7, 33.7, 31.4. HRMS (ESI/$[M+Na]^+$) calcd. for: $C_{17}H_{20}N_2Na_1$: 275.1519. Found: 275.1508.

***N*-Benzylidene-*N'*-(2-napthyl)hydrazine (3-168).** Prepared from 2-napthyl tosylate via the standard protocol employing 5 mol% Pd at 65 ºC for 0.5 h in 67% yield as a light yellow solid (84 mg, 0.34 mmol) after column chromatography (5:1 Hex:EtOAc). ^1H NMR (DMSO): δ 10.61 (s, 1H), 7.96 (s, 1H), 7.80 (d, J = 8.9 Hz, 1H), 7.75-7.71 (m, 4H), 7.45-7.31 (m, 6H), 7.23 (m, 1H). $^{13}C\{^1H\}$ NMR (DMSO): δ 143.0, 137.3, 135.7, 134.6, 128.9, 128.7, 128.1 128.0, 127.6, 126.4, 126.1, 125.8, 122.3, 115.4, 105.2. HRMS (ESI/$[M+H]^+$) calcd. for $C_{17}H_{15}N_2$: 247.1230. Found: 247.1213.

2-Napthylhydrazine (3-169). Prepared from 1-napthyl tosylate via the standard protocol employing 5 mol% Pd at 65 ºC for 0.5 h in 97% yield as a light yellow solid (84 mg, 0.53 mmol) after column chromatography (500:10:1 CH_2Cl_2:MeOH:NH_4OH). ^{1}H NMR (DMSO): δ 8.10 (d, *J* = 10 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.45-7.30 (m, 4H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.3, 1H), 4.08 (s, 2H). ^{13}C{^{1}H} NMR (DMSO): δ 147.5, 133.7, 127.8, 126.7, 125.5, 123.9, 121.9, 121.4, 116.1, 103.6. HRMS (ESI/$[M+H]^+$) calcd. for: $C_{10}H_{11}N_2$: 159.0917. Found: 159.0913

***N*-Benzylidene-*N'*-(3-methoxyphenyl)hydrazine (3-170).** Prepared from 3-methoxyphenyl tosylate via the standard protocol employing 5 mol% Pd at 65 ºC for 0.5 h in 51% yield as a white solid (58 mg, 0.25 mmol) after column chromatography (5:1 Hex:EtOAc). ^{1}H NMR (DMSO): δ 10.36 (s, 1H), 7.86 (s, 1H), 7.66 (m, 2H), 7.39 (m, 2H), 7.30 (m, 1H), 7.12 (t, *J* = 8.1, 1H), 6.68 (t, *J* = 2.3 Hz, 1H), 6.64 (ddd, *J* = 8.0, 1.9, 0.8 Hz, 1H), 6.34 (ddd, *J* = 8.1, 2.5, 0.8 Hz, 1H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR (DMSO): δ 160.4, 146.6, 136.5, 135.8, 129.9, 128.7, 128.0, 125.7, 104.8, 104.4, 97.5, 54.8. HRMS (ESI/$[M+H]^+$) calcd. for: $C_{14}H_{15}N_2O_1$: 227.1179. Found: 227.1165.

***N*-Benzylidene-*N'*-(2-methyl-3-pyridyl)hydrazine (3-171).** Prepared from 2-methyl-3-pyridyl tosylate via the standard protocol employing 5 mol% Pd at 50 ºC for 0.5 h in 79% yield as a white solid (92 mg, 0.43 mmol) after column chromatography (500:10:1 CH_2Cl_2:MeOH:NH_4OH). ^{1}H NMR (MeOD): δ 8.06 (s, 1H), 7.87-7.84 (m, 2H), 7.67 (m, 2H), 7.37 (m, 2H), 7.30 (tt, *J* = 6.6, 1.3 Hz, 1H), 7.19 (m, 1H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (MeOD): δ 142.8, 141.9, 141.8, 139.3, 137.1, 129.7 (2), 127.3, 123.6, 120.8, 19.8. HRMS (ESI/$[M+H]^+$) calcd. for: $C_{13}H_{14}N_3$: 212.1182. Found: 212.1179.

N-(2,5-Dimethylphenyl)-N'-phenylhydrazine (3-172). Prepared from 2,5-dimethylchlorobenzene and phenylhydrazine employing 5 mol% Pd at 90 ºC for 0.5 h in 68% yield as a light yellow solid (144 mg, 0.68 mmol) after column chromatography (20:1 → 10:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 7.27 (m, 2H), 7.00 (d, *J* = 7.3 Hz, 1H), 6.89-6.80 (m, 4H), 6.61 (d, *J* = 7.5 Hz, 1H), 5.58 (br s, 1H), 5.51 (br s, 1H), 2.25 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.1, 146.3, 137.1, 130.4, 129.5, 120.2, 119.9,

118.2, 112.4, 111.9, 21.6, 19.9. HRMS (ESI/$[M+H]^+$) calcd. for: $C_{14}H_{17}N_2$: 213.1386. Found: 213.1384.

1-*H*-Indazole (3-173). Prepared from 2-chlorobenzaldehyde employing 5 mol% Pd at 65 ºC for 1.5 h in 73% yield (85 mg, 0.73 mmol) as a light yellow solid after column chromatography (10:1 → 1:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 10.76 (br s, 1H), 8.14 (s, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 0.8, 8.4 Hz, 1H), 7.41 (m, 1H), 7.20 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 140.1, 134.9, 126.9, 123.3, 121.1, 121.0, 109.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_7H_7N_2$: 119.0604. Found: 119.0598.

3-Methyl-1-*H*-Indazole (3-174). Prepared from 2-chloro-6-methylbenzaldehyde employing 10 mol% Pd at 90 ºC for 1 h in 51% yield (40 mg, 0.30 mmol) as a light yellow solid after column chromatography (5:1→ 2:1 Hex:EtOAc). ^{1}H NMR ($CDCl_3$): δ 10.95 (br s, 1H), 8.15 (s, 1H), 7.36-7.28 (m, 2H), 6.96 (dt, *J* = 0.9, 6.8 Hz, 1H), 2.64 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 140.1, 133.7, 131.4, 127.0, 123.8, 120.9, 107.2, 18.8. HRMS (ESI/$[M+H]^+$) calcd. for $C_8H_9N_2$: 133.0760. Found: 133.0768.

7-Methoxy-1-*H*-Indazole (3-175). Prepared from 2-chloro-3-methoxybenzaldehyde employing 5 mol% Pd at 65 ºC for 1.5 h in 76% yield (80 mg, 0.54 mmol) as a pale orange solid after column chromatography (CH_2Cl_2 → 50:1 CH_2Cl_2:MeOH). ^{1}H NMR ($CDCl_3$): δ 10.67 (br s, 1H), 8.08 (s, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 4.01 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 145.3, 135.6, 132.3, 124.8, 121.8, 112.9, 105.0, 55.5. HRMS (ESI/$[M+Na]^+$) calcd. for $C_8H_8N_2Na_1O_1$: 171.0529. Found: 171.0529.

CHAPTER 4. CONCLUSIONS

4.1 CHAPTER 2: SUMMARY AND CONCLUSIONS

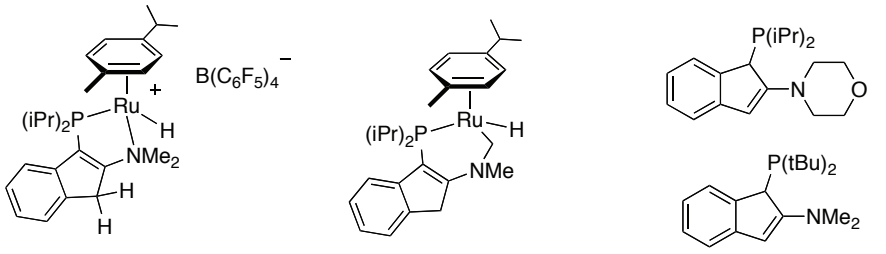
The results detailed in Chapter 2 of this thesis establish two distinct types of highly productive TH catalysts, both featuring 'non-NH' P,N-ligands. In Section 2.2, the Ru-zwitterion **2-6** was found to rapidly (TOFs generally >100 000 h^{-1}) reduce a number of diaryl, aryl-alkyl and dialkyl ketone substrates in basic 2-propanol at low catalyst loadings (0.05 mol% Ru), which was in marked contrast to the catalytic activity of structurally related Ru-cations such as **2-2**, where poor activity was observed under similar conditions (<15% conv. at 0.05 mol% Ru at 15 min). The Ru-hydride species **2-20** generated under catalytic conditions from either **2-2** or **2-6** (KOtBu in 2-propanol) was found to represent a catalyst decomposition product, rather than the active hydrogenation species when employing **2-6**. Evidently, **2-6** must access a key intermediate in a manner not observed when employing related cationic species, so as to presumably generate a highly reactive Ru-hydride, perhaps in a manner assisted by the anionic indenide ligand backbone.

Section 3 of Chapter 2 documented the development of an Ir-based catalyst system for ketone TH. When employing both cationic and zwitterionic species such as **2-21** or **2-25** good catalytic activity was observed (TOFs ~40 000 h^{-1}); however, after the screening of a number of related ligands, it was found that the simple P,N-phenylene ligand **2-32** in combination with $[Ir(COD)Cl]_2$ and $NaPF_6$ provided the best catalytic activity among the species examined. The pairing of a bulky, electron-donating phosphine group and an *ortho*-dimethylamino donor appeared to be essential for good catalytic performance. TOFs up to 230 000 h^{-1} were observed and catalyst loadings as low as 0.004 mol% Ir could be employed with select substrates. The extension of this chemistry to enantioselective TH proved possible by the use of the structurally related ferrocenyl P,N-ligand Cy-Mandyphos, where moderate *ee* values were observed for most of the tested acetophenone derivatives, but excellent values (95% conv. and 95% *ee*) were obtained for the sterically demanding substrate **2-39**. Thus, P,N-ligands such as **2-32** and Cy-Mandyphos represent an effective class of perhaps overlooked 'non N-H' ancillary ligands in metal-mediated ketone TH chemistry.

4.2 CHAPTER 2: FUTURE WORK

There exist still several unanswered questions regarding the origin of high catalytic activity in ketone TH when employing the Ru-zwitterion **2-6**. Studies directed towards the synthesis of potential catalytic intermediates should allow for a more detailed understanding of the mechanism of hydrogen transfer. Towards this end, a collaboration with Prof. D. Goussev (Wilfred Laurier University) has been initiated to explore such processes computationally. Additionally, potential catalytic intermediates such as the cationic Ru-hydride **4-1** and the cyclometalated Ru-hydride **4-2** have been prepared and are currently under scrutiny to determine their viability as species relevant to TH catalysis when employing **2-6**.

The synthesis of new Ru-zwitterions featuring ligands such as those shown in Figure 4.1 will allow for an understanding of how the donor fragments of the indenide ligand affect catalytic performance. The use of alternative $[RuCl_2(arene)]_2$ starting materials such as $[RuCl_2(C_6H_6)]_2$ and $[RuCl_2(C_6Me_6)]_2$ should demonstrate if the electron richness of the arene ancillary co-ligand affects catalysis. Combined, these studies will contribute to a more through comprehension of the chemistry of Ru-zwitterions and should lead to the rational development of Ru-based catalyst systems with increased activity and lifetime in ketone TH.



4-1 *cationic indene-hydride*

4-2 *cyclometallated hydride*

new P,N indene ligands

Figure 4.1 Potential intermediates in Ru-catalyzed ketone TH when employing **2-6** and new P,N-indene ligands.

With regards to the Ir TH-catalyst system, the simple and robust nature of the ligand framework suggests the potential application of these catalysts to related hydrogen transfer processes. Potential examples include the preparation of amides, esters, and imines from amines and alcohols via dehydrogenation.[32a, 32b, 32d, 32f, 138] A number of related

P,N-ligands (including those reported in Chapter 3) could be prepared in the aim of enhancing reactivity in TH processes compared to **2-32**. A study of related tri- and tetradentate ligands, such as those shown in Figure 4.2 might be valuable as such polydentate ligands could confer additional stability and activity to Ir-based TH catalysts.

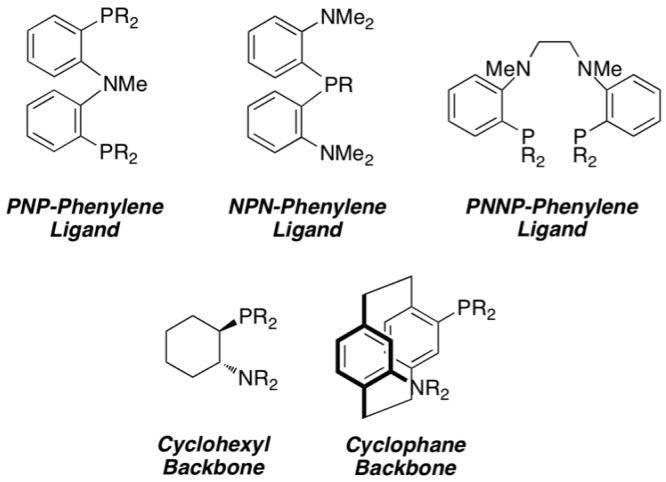


Figure 4.2 Tri- and tetradentate phenylene ligands and chiral P,N-ligands based on **2-32**.

The development of chiral ligands related to **2-32** may also provide continued inroads to the enantioselective TH of sterically demanding ketones. Cyclohexyl- and cyclophane-derived ligands such as those displayed in Figure 4.2 can be prepared starting from commercially available chiral materials, and could provide a starting point for the further extension of "non-NH" P,N-ligands in asymmetric transfer hydrogenation.

4.3 Chapter 3: Summary and Conclusions

Chapter 3 of this thesis explored the utility of P,N-phenylene ligands in the Pd-catalyzed cross-coupling of aryl (pseudo)halides and NH-containing substrates. Section 3.2 demonstrated that **2-32** and **3-1** were highly effective and versatile ligands when employed with $[Pd(allyl)Cl]_2$ or $[Pd(cinnamyl)Cl]_2$ for a range of amination processes. Structurally related ligands that lacked an *ortho*-dimethylamino group or featured less sterically demanding or less basic phosphine donors proved inferior in test reactions. It was found that the ligands **2-32** or **3-1** could enable Pd-catalyzed cross-coupling of electron-rich, -neutral, and -poor aryl or heteroaryl chlorides with primary aryl and alkyl

amines, cyclic and acyclic secondary amines, hydrazones, NH-imines, lithium amide and ammonia. In many cases, low catalyst loadings (0.02-0.2 mol% Pd) could be employed and good functional group tolerance was observed when employing either $LiN(TMS)_2$ or Cs_2CO_3 as the base. Reactions with primary alkyl amines appeared to be the most productive, and the chemoselective arylation of primary alkyl and aryl amines in the presence of secondary amines was observed with good selectivity (>6:1).

While **3-1** proved capable of supporting active Pd species for ammonia arylation, relative high catalyst loadings (2 mol% Pd, 8 mol% ligand) were required and effectively no selectivity for the mono-arylation of electron-rich aryl chlorides could be achieved. A series of new P,N-phenylene ligands were synthesized and tested in ammonia cross-coupling, and it was found that the ligand **3-112** gave excellent conversions and good mono-arylation selectivities. The scope of aryl chlorides that could be coupled when using **3-112** in combination with $[Pd(cinnamyl)Cl]_2$ was broad; substrates possessing electron-donating groups at the *para* or *meta* positions, including examples containing N, O, F, or S heteroatoms, as well as certain heterocyclic aryl chlorides could be converted into their corresponding anilines in yields of 52-99%. Electron-rich or electron-neutral aryl tosylates were also suitable reaction partners and could be coupled at room temperature. Chemoselective arylation of ammonia with aminoaryl chlorides possessing primary or secondary aryl or alkyl amines was also achieved, affording the corresponding diamines in 61-98% yield. Stoichiometric reactions with **3-112** and various Pd-sources and aryl chlorides generated square-planar, [(κ^2-*P,N*-**3-112**)Pd(aryl)Cl] complexes, such as **3-138**, that, without base did not undergo further reactions when exposed to ammonia. Remarkably, **3-138** was found to catalyze the cross-coupling of electron poor or electron neutral aryl chlorides and ammonia at room temperature for the first time.

The first example of the Pd-catalyzed cross-coupling of aryl chlorides and tosylates with hydrazine was accomplished by the use of **3-112** and $[Pd(cinnamyl)Cl]_2$. A diverse series of ligands were screened for the transformation, with most either providing low conversions of the starting aryl chloride or giving the hydrodehalogenated product. Under appropriate conditions, Pd/**3-112** mixtures catalyzed the amination of a range of aryl chloride substrates using hydrazine hydrate at 5 mol% Pd to deliver the mono-arylated hydrazine products in generally good yields (58-97%). Reactions with electron-

rich substrates such as 4-chloroanisole or electron-poor substrates like 4-(trifluoromethyl)chlorobenzene were less successful. Heterocyclic aryl chlorides and tosylates were also suitable partners. Selective hydrazine arylation in the presence of other NH-functionality was achieved with secondary amines, additionally hydrazine hydrate was found to react in preference to phenylhydrazine, despite the fact phenylhydrazine was proven to be a viable reaction partner in independent experiments. NH-indazoles could be prepared in 51-76% yield using 5-10 mol% Pd from their corresponding 2-chlorobenzaldehydes, highlighting the utility of this newly developed amination methodology in heterocycle synthesis.

Collectively, the results in Chapter 3 demonstrate that properly constructed P,N-ligands afford active and selective catalysts for challenging Pd-catalyzed cross-coupling reactions, and compare favourably to other well-established classes of ligands for such transformations. A rationale for the success of this ligand class could be attributed to the presence of the weakly coordinating arylamine donor, which could allow for the facile generation of a three-coordinate [(κ^1-**L**)Pd(aryl)(amido)] species, postulated to be required for C-X reductive elimination, while still stabilizing low-coordinate Pd(0) intermediates with respect to diarylation or bimolecular decomposition. While no evidence of hemilability under catalytic conditions has been observed to date, such a postulate would help explain the origin of both high activity and versatility displayed by these P,N-phenylene ligands.

4.4 Chapter 3: Future Work

The use of ammonia in Pd-catalyzed cross-coupling reactions can provide an opportunity for additional elaboration of the resulting aniline to generate more complex molecules from a feedstock nitrogen source. For example, previous research with alternative classes of amines, such as bulky alkyl amines and anilines, have shown that C-N cross-coupling reactions can be performed in tandem with alkyne amination[139] or a second amination reaction starting from 2-halo-β-halostyrenes[140] to generate indoles. If ammonia could be employed as the nitrogen source, unprotected indoles could be prepared in a single step (Figure 4.3).[141] Studies currently underway in the Stradiotto group suggest that such reactions are possible under appropriate conditions.

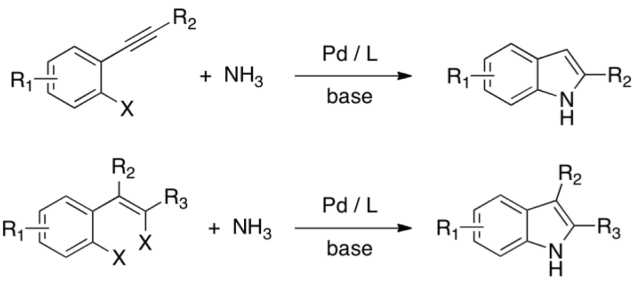


Figure 4.3 Synthesis of indoles from ammonia and 2-haloalkynes or 2-halo-β-halostyrenes via Pd-catalyzed cross-coupling.

Given the remarkable activity of **3-1** and **3-112** in Pd-catalyzed C-N cross-coupling reactions, particularly with small, nucleophilic amines, a number of alternative substrates could be envisioned as potential nucleophiles in Pd-mediated cross-couplings. Hydroxylamine, sodium sulfide, and acetone each represent challenging reaction partners for mono-arylation that have not been documented in the literature; Pd/**3-112** mixtures might prove to be useful for such transformations (Figure 4.4).

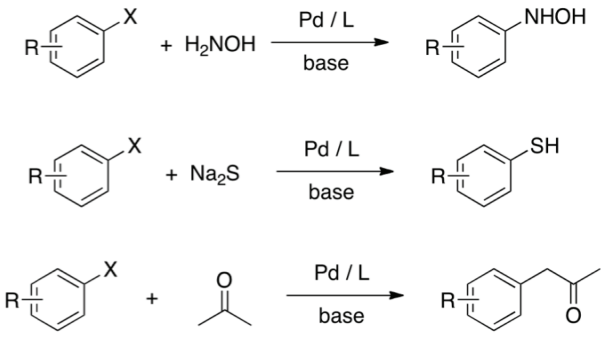


Figure 4.4 Selective mono-arylation of hydroxylamine, sodium sulfide, and acetone via Pd-catalyzed cross-coupling.

Further efforts focused on ligand design in Pd-catalyzed amination should provide additional advances in the utility of P,N-ligands in such processes. Increasing the basicity of the donor groups by employing a cyclohexyl ligand backbone, or increasing the steric profile of the ligand by incorporating cyclophane or ferrocenyl moeities might enhance catalyst performance and lifetime, particularly in challenging reactions such as hydrazine arylation, where catalyst loadings remain high. Comparing the reactivity of phosphine/amine ligand sets with carbene/amine ligand sets might be informative,

especially considering the ubiquity of carbenes in Pd-catalyzed cross-coupling reactions.[55g] The preparation of water-soluble variants of **3-112**, for example the sulfonated ligand depicted in Figure 4.5, would be a worthwhile endeavor, as it might allow reactions to be performed in biphasic, aqueous ammonia or hydrazine solutions, and would help facilitate product purification, particularly on large scales.

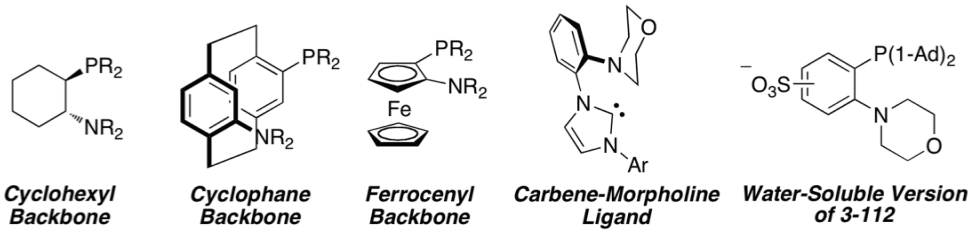


Figure 4.5 Potential new ligands for enhanced reactivity in Pd-catalyzed C-N cross-coupling reactions.

Lastly, given the favourable reactivity patterns displayed by ligands of the type **3-1** and **3-112** when compared to biaryl monophosphines and N-heterocyclic carbenes, it is plausible that these P,N-ligands might also be suitable for other transition-metal catalyzed reactions for which Buchwald-type ligands and carbenes have been employed with success.[142] Indeed, **3-112** has been shown to be an excellent ligand when supporting gold in alkyne hydroamination reactions,[143] suggesting the ligand set developed in this thesis may have wide-spanning application throughout metal-mediated homogeneous catalysis.

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