

Synthesis of Primary Arylamines Using Bulky Palladium N-Heterocyclic Carbene
Precatalysts

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A Thesis Submitted to the Faculty of Graduate Studies in Partial
Fulfillment of the Requirements for the Degree of Masters of Science

Graduate Program in Chemistry

York University

Toronto, Ontario

January 2017

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Abstract

The synthesis of primary arylamines is an important reaction in organic synthesis due to the pervasiveness of arylamines in biologically and industrially relevant molecules. Historically these molecules have been accessed through non-catalytic methods such as reduction of nitro compounds and nucleophilic aromatic substitution. Recent advancements in catalyst design have allowed the synthesis of primary arylamines to be achieved using ammonia in the Buchwald-Hartwig amination reaction. Ammonia is a low cost and abundant chemical which makes the direct amination desirable.

In this thesis, the reaction between aryl halides and ammonia was investigated using N-heterocyclic carbene (NHC) ligated palladium pre-catalysts. The use of NHCs is well documented for coupling of alkyl and arylamines, but there is little precedent for the coupling of ammonia. Pyridine Enhanced Pre-catalyst Preparation Stabilization Initiation (PEPPSI) and π -allyl NHC pre-catalysts that are sterically demanding were both shown to be effective for this coupling. Only NHCs with the largest alkyl groups projected towards palladium produced the primary arylamine selectively over the diarylamine. NaOtBu base gives the fastest reactions with the highest selectivity for primary arylamine; use of one equivalent relative to the aryl halide allows substrates containing base sensitive functional groups to be isolated in high yield.

Ammonia surrogates are useful coupling partners because they are easier to couple than ammonia and do not produce any undesired diarylamine. Aminotriphenylsilane in combination with LiHMDS and ZnCl₂ was used to couple aryl halides containing base-sensitive groups that were previously considered to be incompatible. Isolation of the silyl protected amine allowed for the selective N-alkylation with primary, benzylic and allylic electrophiles.

Acknowledgements

I would like to express my gratitude to everyone who contributed to my education at York University. The opportunity to be a researcher, student, and teacher to undergraduates simultaneously has been time well invested. I am confident that through the collective contributions of the faculty and students I will be leaving York University a much better chemist than when I arrived.

A special thank you goes to my supervisor Professor Organ whose guidance throughout my master's degree has been most helpful and has also been an excellent role model for myself or any young scientist. I would like to thank Professors Orellana and Lee-Ruff for participating in my supervisory committee throughout my master's degree. Nobody likes not knowing the answer to a question, but it is very useful to have gaps in one's knowledge highlighted so that they can be filled. I would also like to thank Professor Hunter who was tremendously helpful inside and outside of the classroom with NMR spectroscopy.

Thank you to all of the graduate students and postdoctoral researchers for their help and support throughout my time at York University. Thank you Nalin and Sepideh who shared an office with me and were always helpful when it came to discussing research ideas, problem sets, and other topics. Thank you to Greg, Jonathan, Bruce, and Richard who were always supportive and generous with their time. Special thanks to Nalin and Jonathan who synthesized all of the pre-catalysts for this work.

Thank you to my parents for their love and support in my pursuit of a graduate level education and also to my good friend Charlie. Lastly, thank you to my girlfriend turned fiancé

Natasha, for being endlessly patient and supportive of my decision to stay in school after graduating from Ryerson University together.

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List of Abbreviations

Ac = acetate

atm = atmospheric pressure

BHT = 3,5-Di-*tert*-4-butyl-4-methylphenol (butylated hydroxytoluene)

BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene

*t*Bu = *tert*-butyl

dba = dibenzylideneacetone

DCM = dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DME = 1,2-dimethoxyethane

DMF = *N,N*-dimethylformamide

DMSO = dimethylsulfoxide

DPPF = bis(diphenylphosphino)ferrocene

LiHMDS = lithium bis(trimethylsilyl)amide

NHC = N-heterocyclic carbene

*i*Pr = *iso*-propyl

Pd[(*o*-tol)₃P]₂ = bis(tris(*o*-tolyl)phosphine)palladium(0)

Pd(PPh₃)₄ = tetrakis(triphenylphosphine)palladium(0)

Pd(dba)₂ = bis(dibenzylideneacetone)palladium(0)

Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0)

Pd(P^{*t*}Bu₃)₂ = bis(tri-*tert*-butylphosphine)palladium(0)

pK_a = negative logarithmic acid dissociation constant

TBAF = tetrabutylammonium fluoride

THF = tetrahydrofuran

Ts = tosylate

Tf = triflate

Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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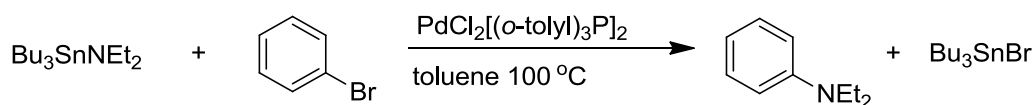
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Chapter 1 Introduction: Synthesis of Primary Arylamines Using Bulky Palladium N-heterocyclic Carbene Pre-catalysts

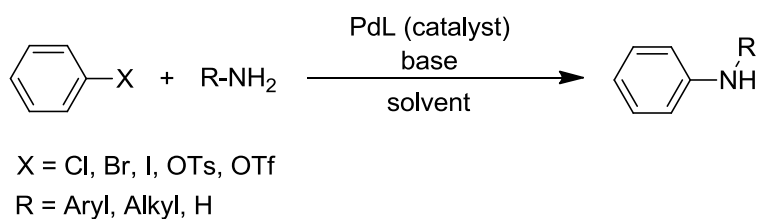
Buchwald-Hartwig Amination

Palladium-catalyzed coupling reactions have become an indispensable method for the formation of carbon-carbon and carbon-heteroatom bonds. The first report of C—N Pd-catalyzed coupling was by Migita and co-workers using aryl bromides and tin amides (Scheme 1).¹ The Pd-catalyzed formation of C—N bonds from aryl halides and amines was first reported by Yagupol'skii and later co-developed by Buchwald and Hartwig (Scheme 2)²⁻⁴.

Scheme 1. The first C—N Pd-catalyzed coupling.¹



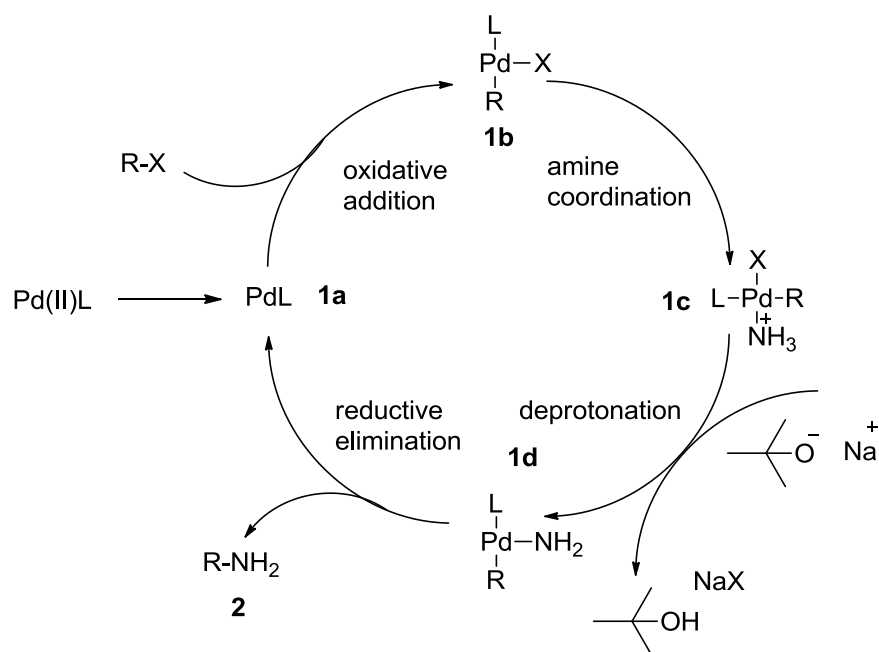
Scheme 2. Generalized Buchwald-Hartwig amination reaction scheme.



In place of a transmetalation from tin to palladium between the amine to be coupled and the Pd-catalyst, this process is broken down into two steps. The first step is amine coordination with palladium (**1c** in Scheme 3). This acidifies the amine sufficiently to allow an external base to deprotonate the Pd-amido complex, thus completing the equivalent of a transmetalation.⁵

Common bases used include: LiHMDS, NaOtBu, KOtBu, Cs₂CO₃, and K₃PO₄. This method of Pd-catalyzed coupling is much more attractive because stoichiometric amounts of tin amides are replaced with stoichiometric base and the amine to be coupled. This is beneficial for ease of synthesis and eliminates the need to handle and dispose of tin-containing materials.

Scheme 3. Putative amination catalytic cycle.



Mechanistic Details of the Buchwald-Hartwig Amination

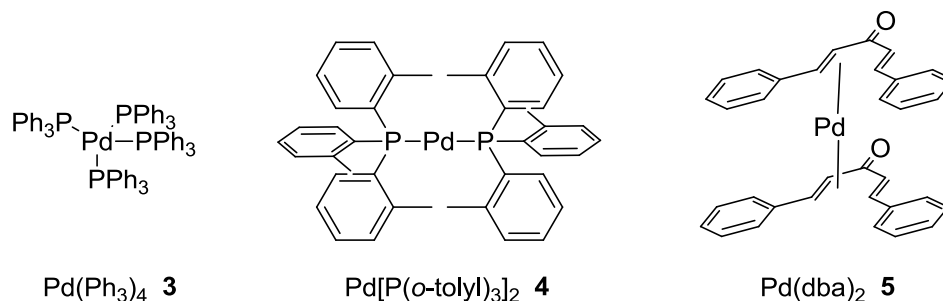
Catalyst Activation

There are several different strategies to generate an active catalyst for amination reactions. The simplest strategy is to use a Pd^0 species such as $\text{Pd(PPh}_3\text{)}_4$ (**3**), $\text{Pd}[(o\text{-tol})_3\text{P}]_2$ (**4**), or Pd(dba)_2 (**5**). While these complexes already contain the desired Pd^0 and could theoretically catalyze reactions directly, triphenylphosphine and dba do not impart the required steric and electronic properties to palladium for good catalyst performance with most substrates.

Therefore, addition of an ancillary ligand with suitable properties for good reactivity is required.

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Scheme 4. Common Pd⁰ reagents for amination.



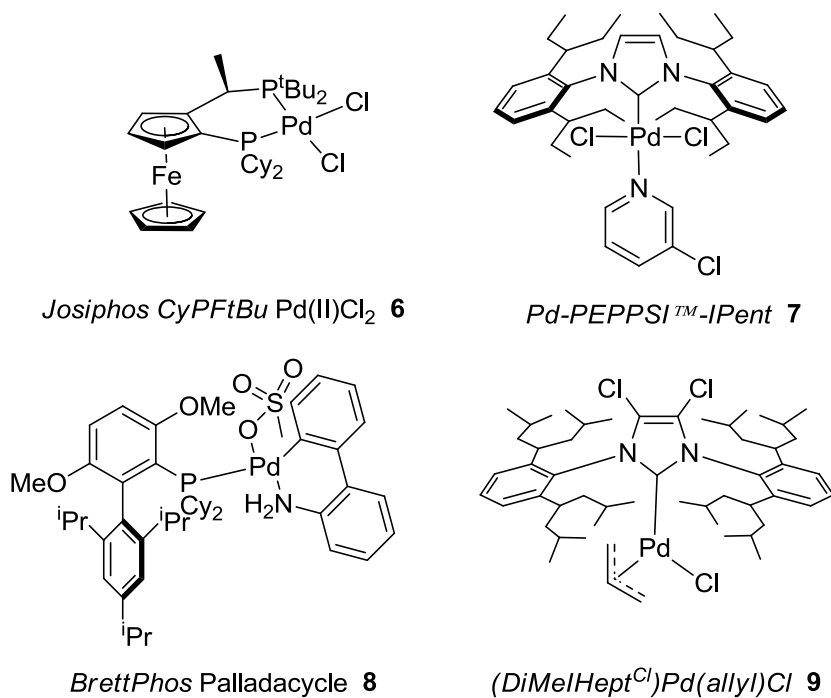
A study by Pend and co-workers revealed Pd(dba)₂ and Pd₂(dba)₃ are equally effective when used in combination with bulky phosphine ligands such as *Xantphos* or *Josiphos* type for amination and sulfination.⁷ This strategy has the advantage of being able to form an active catalyst by simply mixing the Pd⁰ precursor and ligand together at room temperature in solution prior to addition of the other reagents. A drawback is the Pd⁰ complexes are not always air stable and should be stored and weighed out under an inert atmosphere for the best results. Additionally, displacement of dba or P(*o*-tolyl)₃ by the added ligand required for an active catalyst is not always complete, leading to complex mixture of species. Sometimes the most active species is a combination of the ligand originally ligated in the added Pd⁰ complex and the added ligand. For example, reactions catalyzed by the dimer [PdBr(P^{*t*}Bu₃)₂]₂ or a 1:1 ratio of Pd(dba)₂ and P^{*t*}Bu₃ occur at room temperature whereas Pd(P^{*t*}Bu₃)₂ requires an elevated temperature.^{8,9} Conversions and selectivity can also change with different Pd⁰ sources. For example, the selectivity for monoarylation with ammonia can change depending on whether Pd₂(dba)₃ or Pd[(*o*-tol)₃P]₂ is used with the same *Josiphos* ligand.¹⁰ These examples demonstrate how sensitive reactions are to the identity and ratios of Pd⁰ sources to added ligand.

Another strategy for generating an active catalyst is addition of a Pd^{II} species with an added ligand. The most common reagent is Pd(OAc)₂. Assuming the ligand can be weighed out in air, this strategy is much more convenient. As with the addition of Pd⁰, there is sometimes uncertainty about the active catalyst when a Pd^{II} source is used. The Pd^{II} must also be reduced to Pd⁰ before entering the catalytic cycle. Alkylamines that contain β-hydrogens will readily activate the catalyst through β-hydride elimination. Anilines and ammonia do not have β-hydrogens and cannot go through this pathway. It's known that monodentate phosphine ligands are able to reduce Pd(OAc)₂ to Pd⁰ species.¹¹ A process similar to this may be responsible for catalyst activation when a Pd^{II} source is used with anilines or ammonia, although the activation mechanisms are still unclear and likely differ between catalyst systems.¹² In general, reactions with anilines and ammonia require > 80 °C if Pd(OAc)₂ is used.^{10,13,14} In the case of ammonia, incomplete conversion to products was observed using Pd(OAc)₂, but full conversion was achieved with Pd⁰ sources.¹⁰

A popular strategy for catalyst design is the use of a pre-catalyst. A pre-catalyst in the context of Buchwald-Hartwig amination is a Pd^{II} complex that is already coordinated to the ligand responsible for imparting the proper steric and electronic properties for catalysis. Pre-catalysts also contain other stabilizing ligands that are displaced during the reaction or reductively eliminate (see pre-catalyst **8** in Scheme 5) to generate an active catalyst. This strategy has several benefits. The ligand is already bound to palladium so there is no need for an excess of ligand, which is typically many times the cost of palladium. Also, the ligand does not need to displace other ligands from palladium as is the case when Pd⁰ complexes are used with added ligand. Pd^{II} pre-catalysts are typically bench stable which eliminates the need for an inert atmosphere to measure out and store the pre-catalyst. However, the pre-catalysts require

reduction to the active Pd^0 species which is typically achieved by the amines or bases employed in the reaction. If activation is not facile, additives capable of reducing palladium may be used. For example, addition of a reducing agent such as LiOiPr that contains β -hydrogens to β -hydride eliminate on Pd^{II} , generating a $\text{Pd}^{\text{II}}\text{-H}$ species that may reductively eliminate to generate a Pd^0 species.¹⁵ Alternatively, organometallic reagents such as Grignards may activate the catalyst or MOtBu for π -allyl containing pre-catalysts.¹⁶

Scheme 5. A selection of pre-catalysts.



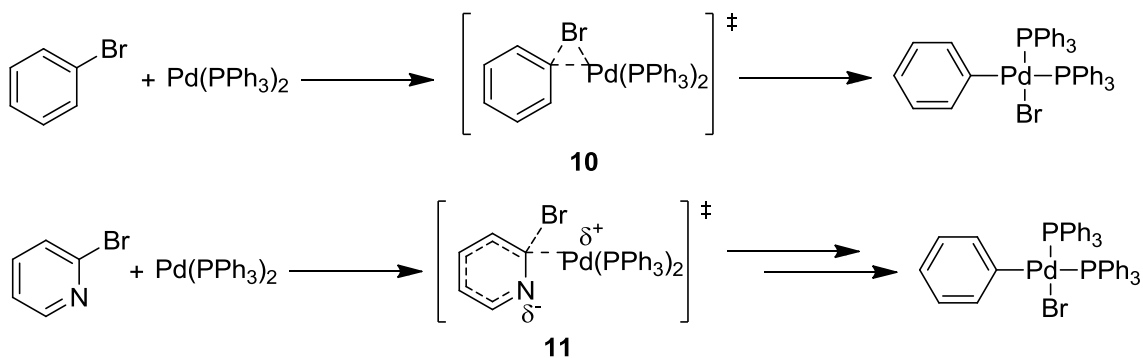
Oxidative Addition

Once a catalytically active species is present, the first step of the cycle is an oxidative addition of a C-X bond to LPd^0 where X can be a halide or sulfonate. The choice of electrophile can be important because the rates of oxidative addition are: $\text{ArI} > \text{ArBr} \approx \text{ArOTf} > \text{ArOTs} > \text{ArCl}$.^{17,18} The ability of Pd^0 complexes to oxidatively add C-X bonds increase with

ligands that make Pd more electron rich and sterically demanding, with electronics playing a more important role.^{17,19,20} The electronic effect is easiest to rationalize. An electron rich palladium will be more nucleophilic and easier to oxidize from Pd⁰ to Pd^{II}. The reason for steric crowding enhancing oxidative addition is less straight-forward. One explanation, for monodentate phosphine ligands, is that sterically demanding ligands help achieve diligated PdL₂ or monoligated PdL species that are responsible for oxidative addition into the more difficult aryl bromides and chlorides, respectively.^{19,21} With the invention of electron rich and sterically hindered alkyl phosphine and NHC ligands, oxidative addition is typically facile and not rate-limiting as is the case with some aryl phosphine ligands.^{12,22,23}

Two proposed mechanisms for oxidative addition are shown in Scheme 6. The first is a concerted mechanism in which there is a 3 coordinate transition state **10** between palladium and the two atoms it is inserting into with no significant ionic character.^{24–26} This is the generally accepted oxidative addition mechanism for palladium. However, there can be exceptions to this mechanism. For example, functionalized 2-chloropyridines and 2-bromopyridines go through a S_NAr-type mechanism where there is a significant charge build up in the transition state **11**.²⁷

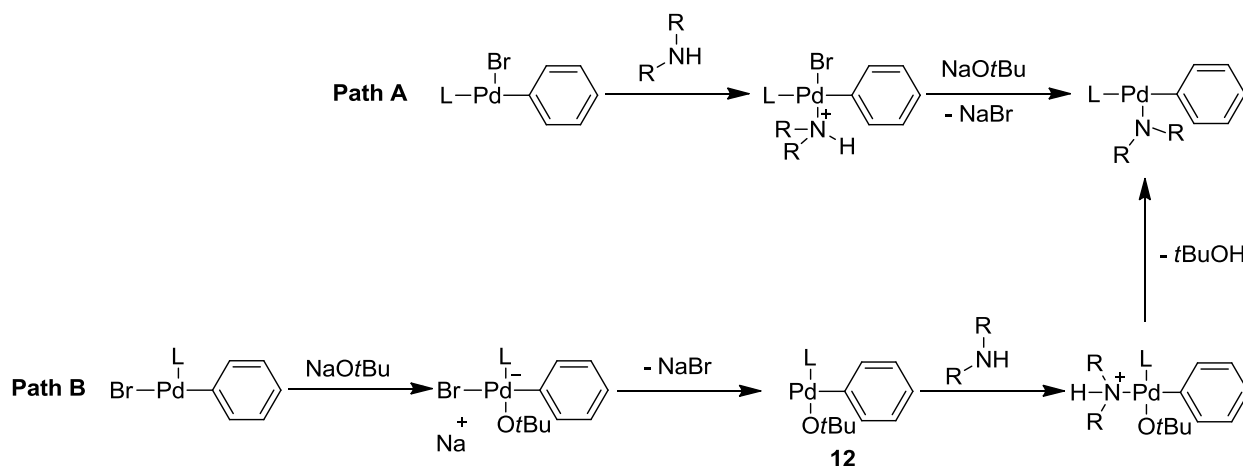
Scheme 6. Oxidative addition mechanism.



Amine Coordination and Deprotonation

The sequence of amine coordination and deprotonation is generally thought to be coordination of the amine to palladium followed by deprotonation by the base (Path A, Scheme 7). Coordination of the amine acidifies the proton on nitrogen sufficiently for deprotonation. Reactions are normally done in non-polar solvents such as toluene, 1,4-dioxane and DME, for which there is little pK_a data. An approximation of the pK_a can be made by looking at the pK_a in DMSO. Alkyl amines and ammonia have a pK_a of approximately 40 while anilines cover a wider range from 21 to 32 depending on the nature of functional groups on the aromatic ring.²⁸ The most common bases for amination are $NaOtBu$ and $KOtBu$ that have a DMSO pK_a of about 30. Other popular and effective bases for amination are phenoxides ($pK_a \sim 18$) and carbonates ($pK_a \sim 18$). The numbers indicate that coordination of the amine to Pd lowers the pK_a by approximately 20 pK_a units. It's not surprising that when *tert*-butoxides are employed as the base the rate of reaction typically increases when compared with phenoxides and carbonates.²⁹ When the weaker phenoxide and carbonate bases are used reaction rates tend to slow down and deprotonation can even become rate limiting; this was found to be the case for coupling of alkylamines with aryl halides using cesium carbonate and Pd-NHC catalysts.^{23,30} Although alkylamines preferably bind to palladium in competition experiments with anilines, when base is added the products are > 99% diarylamine, the product of reductively eliminating the aniline and not the alkylamine.³¹ This result can only be explained by a fast deprotonation of the more acidic aniline since alkylamines are known to reductively eliminate faster than anilines.²²

Scheme 7. Coordination and deprotonation of amines with Pd.³²



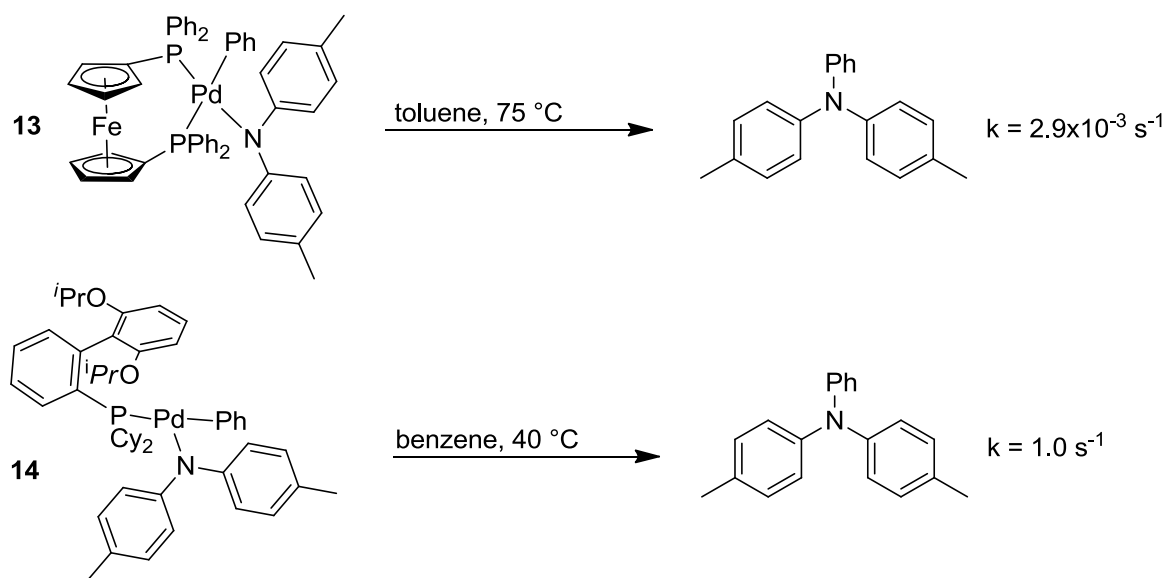
Depending on the ligand, base, and aryl halide, the sequence of events may be different as is shown in Path B. There is computational and experimental evidence that supports Path B in some cases. For example, the resting state of the reaction between ammonium salts and aryl chlorides using NaOtBu as base was found to be a *tert*-butoxide ligated species **12**.³³ Furthermore, a computational study found that in non-polar solvents which are typical for amination, Path B was found to be energetically favourable for the coupling of morpholine, although Path A was also calculated to have low energy barriers.³²

Reductive Elimination

The reductive elimination is the final and crucial C—N bond forming step of the catalytic cycle. The nature of the ligand exerts great influence over the rate of reductive elimination just like it does for oxidative addition. Since reductive elimination is effectively the opposite of oxidative addition, the required electronic properties of the catalyst are also opposite. The ideal ligand for reductive elimination would be sterically demanding while also making palladium electron deficient.³⁴ Although studies have shown that placing electron withdrawing groups on

the aryl rings of DPPF enhances the rate of reductive elimination for intermediate **13** while electron donating groups decrease the rate, the tuning of sterics has had a greater impact.³⁵ Scheme 8 demonstrates the dramatic difference in rate for reductive elimination between DPPF and the sterically hindered alkylphosphine *RuPhos* **14**. Presumably palladium in **13** is more electron deficient than palladium in **14**. Despite the relative electron richness imparted to palladium by *RuPhos*, **14** reacts 340 times faster at a lower temperature than DPPF despite the electron donating cyclohexyl groups. The large difference in rate of reductive elimination is most likely attributed to a more sterically congested palladium.

Scheme 8. Reductive elimination comparison between *RuPhos* and DPPF.^{36,37}



The rate of reductive elimination also depends on electronic and steric properties of the amine and aryl group forming the C—N bond. Amines that are electron rich and large reductively eliminate faster than smaller electron poor amines. For example, adding *p*-OMe groups to aniline increase the rate of reductive elimination while adding a *p*-OMe groups to the oxidative addition partner decreases the rate.³⁸ Addition of an *o*-Me to either the aniline or

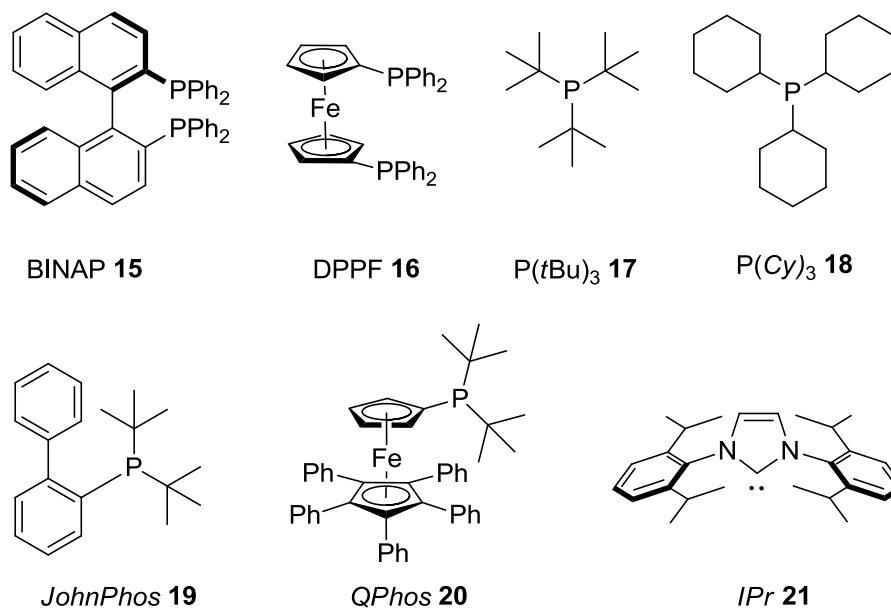
oxidative addition partner will increase the rate. Alkylamines are the fastest type of amine to reductively eliminate, followed by anilines and then ammonia. The small size of ammonia outweighs the fact that it is more electron rich than aniline, causing it reductively eliminate 200 times slower for certain phosphine ligands.³⁸

Ligands for Buchwald-Hartwig Amination

There has been a continuous ligand development since the first reports of coupling free amines with aryl halides in an attempt to improve the process. The two general classes of ligands that have become dominant through 20 years of innovation are phosphine and NHCs. Several problems with Buchwald-Hartwig amination that became apparent early on with simple phosphine ligands were: the tendency of alkylamines to β -hydride eliminate, over-arylation of the amine when primary alkylamines and to a lesser extent primary arylamines are coupled, and the inability of palladium to oxidatively add into aryl chlorides.

The problem of β -hydride elimination was mitigated by the development of tightly chelating bidentate phosphine ligands such as DPPF and BINAP (**15**) (Scheme 9). For the coupling of hexylamine, BINAP is superior at reducing β -hydride elimination and subsequent reduction of the aryl halide compared to DPPF (**16**) (40:1 vs. 13.2:1), respectively. Moreover, BINAP was also more selective for the monoarylated product than DPPF (39:1 vs. 2.2:1), respectively.⁶ However, neither of these aryl phosphine ligands is effective at helping palladium oxidatively add into the less reactive aryl chlorides. For this, alkyl phosphine or NHC ligands that make palladium sufficiently electron rich are required.

Scheme 9. Ligands for Buchwald-Hartwig amination.

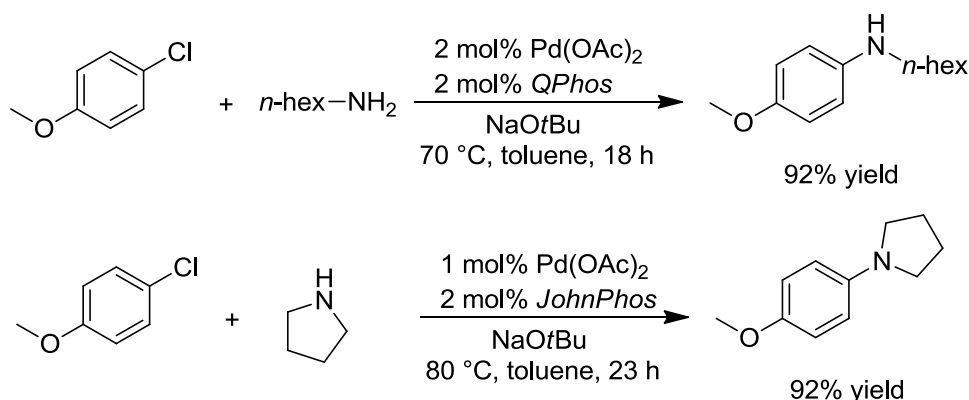


Among the first examples of alkyl phosphines were tri-*tert*-butylphosphine (**17**) and tricyclohexylphosphine (**18**), with **17** proving more effective at minimizing β -hydride elimination than **18**.^{39,40} Both of these ligands are effective for promoting oxidative addition of palladium into aryl chlorides. The drawback of these relatively simple alkyl phosphine ligands is that phosphorus is so electron rich and sterically accessible that it is easily oxidized in air, causing both of these ligands to be pyrophoric. A work-around to this problem is to utilize the air-stable tetrafluoroborate phosphonium salts and allow an *in situ* deprotonation to generate the free phosphine in solution.⁴¹

More sophisticated ligands were then developed by Buchwald, Hartwig, and others in an effort to capture the reactivity of alkyl phosphines and the stability of aryl phosphines. *JohnPhos* (**19**) and *QPhos* (**20**) are both stable in air, with *QPhos* being reported as indefinitely stable in air while *JohnPhos* is stable for 6 months in a desiccator.^{42,43} The air stability of *QPhos* is attributed to sterics rather than electronics.⁴³ Both of these ligands are useful for a wide range of amination

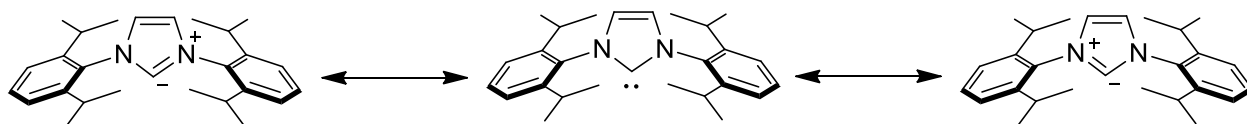
reactions between aryl chlorides and: primary alkylamines, secondary alkylamines, primary arylamines, and secondary arylamines (Scheme 10).

Scheme 10. Amination examples with *JohnPhos* and *QPhos*.^{42,43}



Around the same time phosphine ligands were being optimized for Buchwald-Hartwig amination, NHCs, although first used as ligands in 1968, were being reported for Pd-catalyzed cross couplings including amination.^{44,45} NHCs that are the most useful for Pd-catalyzed amination are imidazole-based dually stabilized carbenes that form strong Pd—C bonds (~25-50 kcal/mol) relative to phosphines (~13 kcal/mol) which tend to be more labile during the course of a reaction.⁴⁶⁻⁴⁹ Stabilization of the carbene carbon comes from π -electron donation from the two neighbouring nitrogen atoms (Scheme 11).

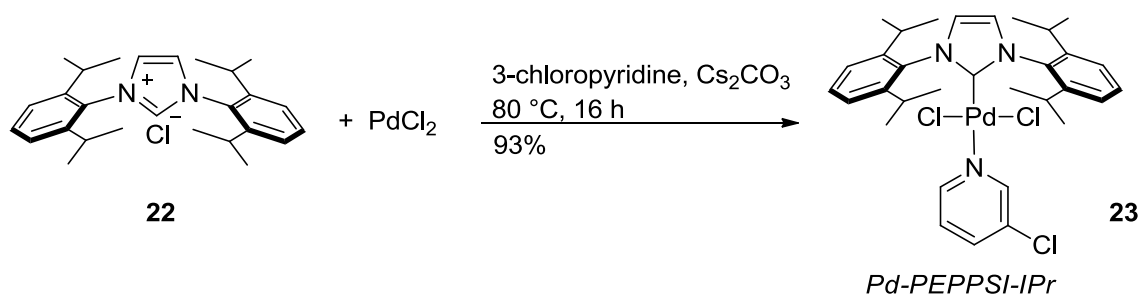
Scheme 11. A stabilized N-heterocyclic carbene.



NHCs are singlet carbenes, with two electrons paired in the same orbital and electron donation from the two nitrogen atoms helping to stabilize the empty p orbital. The bonding

situation of metal-carbene complexes is difficult to capture in a single skeletal structure, so a single bond is drawn between the carbene carbon and the metal to represent the two electron donation to the metal and minimal π -back bonding (Scheme 12).^{49,50} Pd-NHC complexes are typically synthesized by reaction of an azolium salt (e.g. **22**) in the presence of base, palladium, and supporting ligands to generate stable Pd^{II} complexes that function as good pre-catalysts for a variety of Pd-catalyzed reactions.^{20,51–53}

Scheme 12. Synthesis of a N-heterocyclic carbene pre-catalyst.⁵²



The strong σ -electron donation of NHC ligands makes palladium sufficiently electron rich to oxidatively add into electron rich aryl chlorides at room temperature.⁵³ In addition to the favourable electronic properties imparted to palladium, NHC ligands project their steric bulk towards palladium rather than away like phosphines (Figure 1). This projection of steric bulk towards palladium is thought to be responsible for enhanced rates of reductive elimination for Pd-NHC complexes, with flexible bulk (branched alkyl chains) proving to be particularly effective.^{54–56} Two measures of steric bulk are the Tolman cone angle and percent buried volume. The Tolman cone angle is formed with the metal at the vertex and extending the cone outwards so that it fully encapsulates the ligand (Figure 1), whereas percent buried volume measures the amount of volume a ligand fills in a sphere of defined radius.⁵⁷ There are reports of percent buried volume correlating well with catalyst reactivity within a series of NHC ligands,

but it is sometimes difficult to draw direct correlations between either of these metrics and catalyst reactivity.⁵⁶

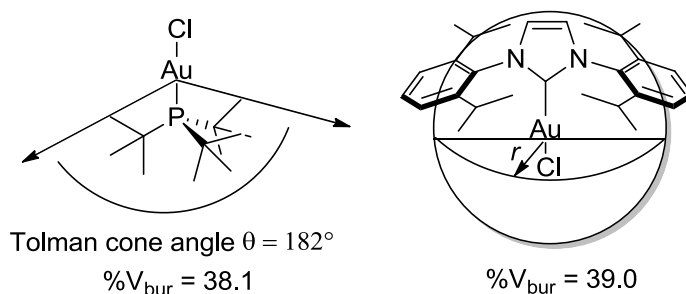
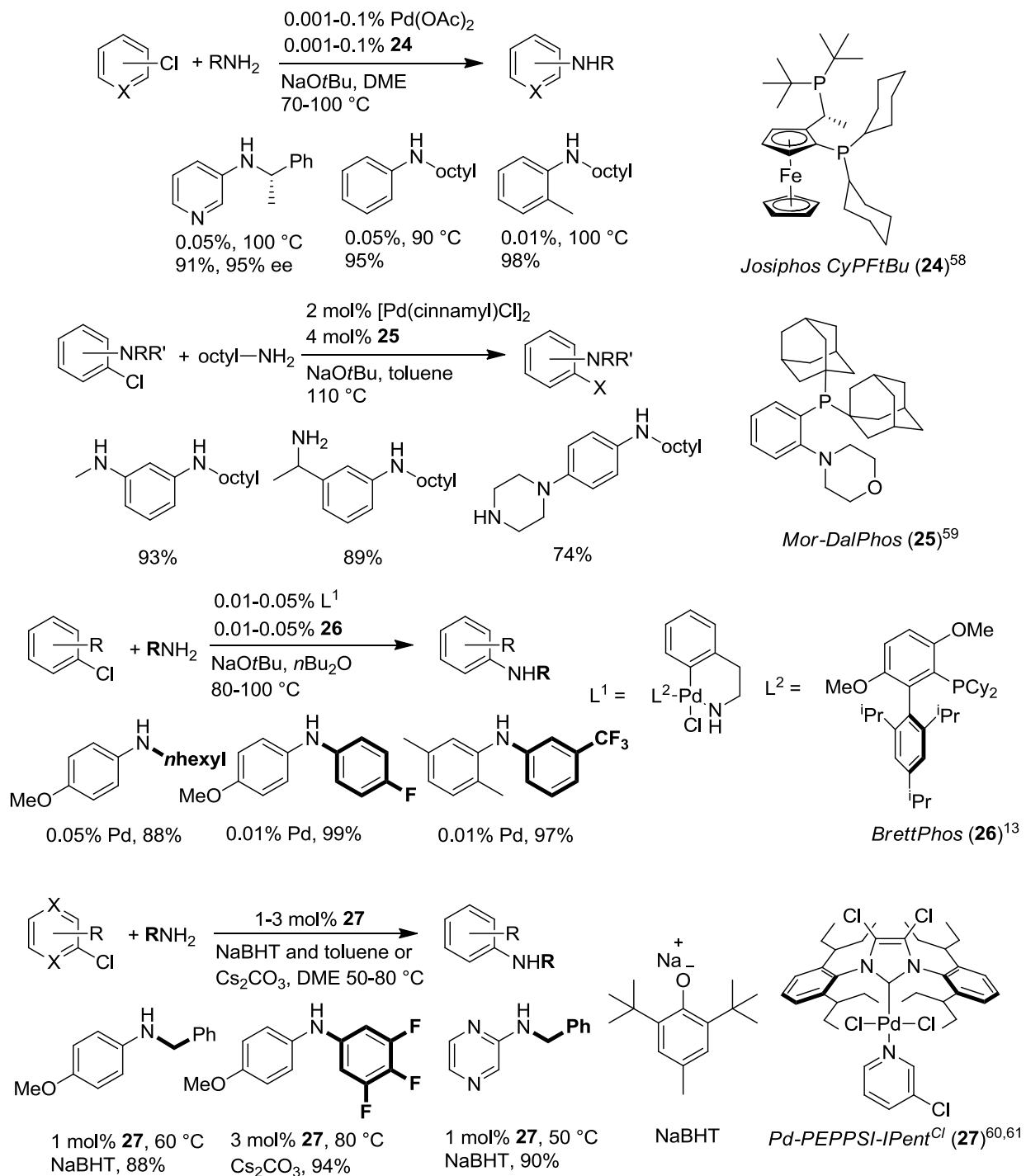


Figure 1. Tolman cone angle and percent buried volume at 2.28 \AA .^{56,57}

The state of the art catalysts for amination feature sterically hindered phosphine or NHC ligands, although for less demanding couplings ligands such as DPPF, BINAP, and *IPr* can give excellent results. A selection of catalysts capable of facilitating the couplings of difficult reactions is presented in Scheme 13. *Josihpos* (**24**) is able to resist β -hydride elimination and produce monoarylated product in high yield while requiring remarkably low catalyst loadings. *Mor-DalPhos* (**25**) has excellent chemoselectivity for primary alkylamines to produce coupled products in high yield. *BrettPhos* (**26**) has similar capabilities to **24** and has also shown to be effective for the difficult coupling of electron rich aryl halides with electron poor anilines. *Pd-PEPPSI-IPent^{Cl}* (**27**) is able to couple primary alkylamines and electron deficient anilines with electron rich 4-chloroanisole using milder bases and lower temperatures than typically required by other catalysts.

Scheme 13. Examples of difficult Pd-catalyzed amination reactions.^{13,58-61}



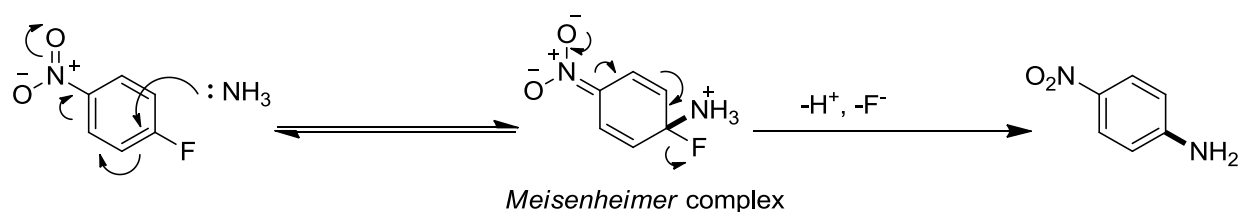
Methods to Synthesize Primary Arylamines

Buchwald-Hartwig amination has been widely implemented in the synthesis of molecules for pharmaceuticals, agricultural products, and advanced materials.⁶² There are a number of other routes to primary arylamines that include: copper catalyzed Ullmann-type reaction, reduction of nitro compounds, nucleophilic aromatic substitution, and more recently nickel catalyzed amination.

Nucleophilic Substitution

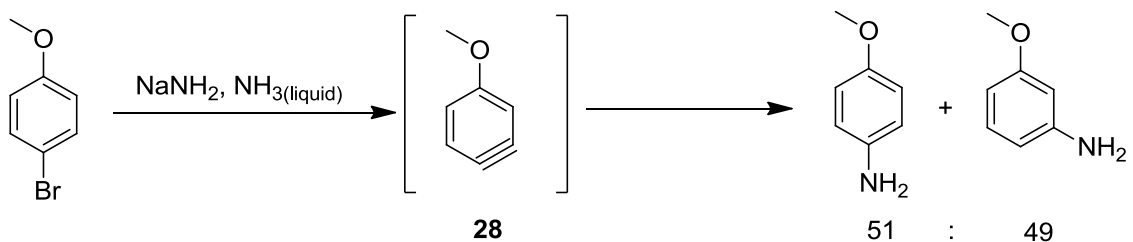
Perhaps the simplest way of synthesizing anilines is through nucleophilic aromatic substitution of ammonia and an aryl halide. These reactions generally require that the aryl halide contains an electron withdrawing group to stabilize the *Meisenheimer* complex (Scheme 14).⁶³ The halide also has a large effect on reaction rate with $F > Cl > Br > I$ due to slow formation of the *Mesenheimer* complex with less electronegative substituents; this is the exact opposite order of reactivity for metal catalyzed reactions that go through an oxidative addition.⁶³ For example, an alcoholic solution of ammonia reacts with 4-nitrofluorobenzene at room temperature and 4-nitrochlorobenzene requires 100 °C.^{64,65}

Scheme 14. Nucleophilic aromatic substitution between ammonia and 4-nitrofluorobenzene.



For substrates that aren't activated towards direct nucleophilic aromatic substitution with ammonia, reaction with NaNH₂ in liquid ammonia is effective. These reactions proceed through aryne intermediates (**28** in scheme 15). A consequence of the mechanism is the formation of regioisomers in the absence of a directing group. For example, reaction of 4-bromoanisole produces 49:51 ratio of *meta* to *para* substituted products whereas 3-bromoanisole gives almost exclusively *meta* substituted product. The methoxy group acidifies the *ortho*-hydrogen on the aryl ring and stabilizes the negative charge after addition to the aryne intermediate.⁶⁶

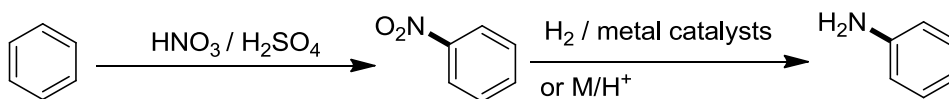
Scheme 15. Elimination-addition (benzyne) mechanism between NaNH₂ and 4-bromoanisole.⁶⁶



Reduction of Nitroaromatic Compounds

Nitration of aromatic compounds takes place in the presence of concentrated nitric acid and sulfuric acid for electron poor deactivated substrates or nitric acid in acetic acid for electron rich aromatics (Scheme 16).⁶⁷ The strongly acidic conditions and the generation of different regioisomers limit the synthetic utility of this transformation. There are many methods to reduce the nitro group to an amine. Metals such as Fe (Bechamp reduction),⁶⁸ Zn, Sn, Ti, and Sm⁶⁹ in acidic conditions will reduce aromatic nitro groups.⁶⁷ Reduction also takes place in the presence of a H₂ source and a metal catalyst such as: Pd/C, PtO₂ (Adam's catalysts), or Raney nickel.^{67,70,71} Selective reduction of the nitro group can be difficult when carbonyl, cyano, chloro and alkenyl groups are present.⁷²

Scheme 16. Nitration and reduction to produce primary arylamines.

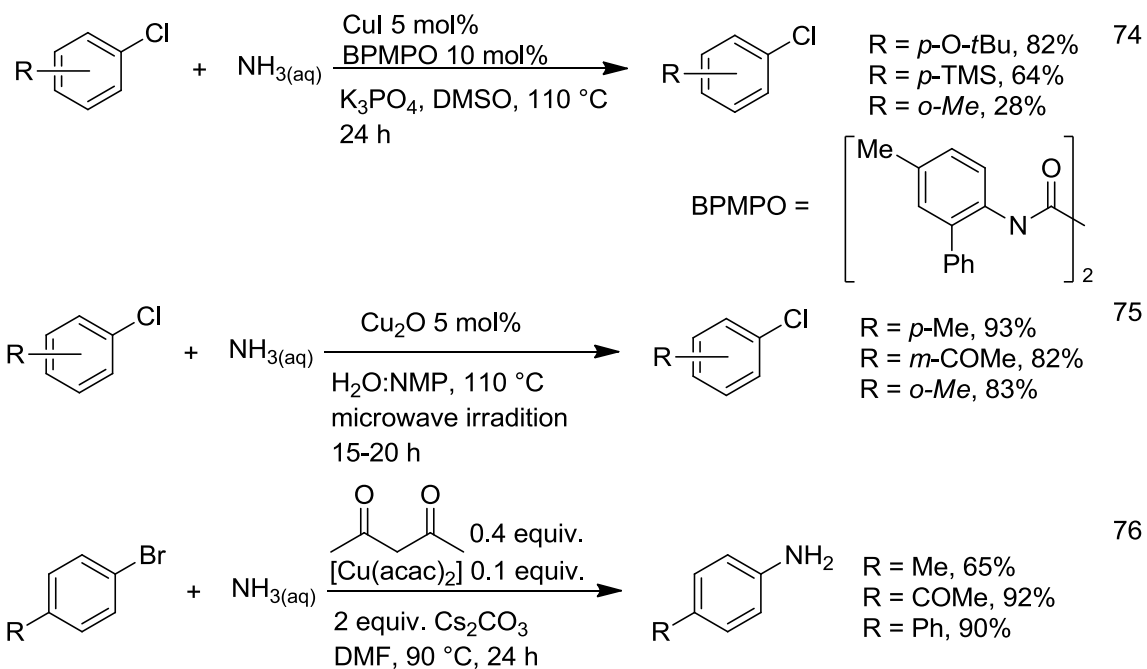


Copper-Catalyzed Amination with Ammonia

The Cu-catalyzed reaction between an amine and an aryl halide has many similarities to Pd-catalyzed Buchwald-Hartwig amination. Both are believed to proceed through oxidative addition and reductive elimination, although many have proposed alternative mechanisms to the Cu⁺/Cu³⁺ catalytic cycle.^{73,74} Copper catalyzed reactions employ metal and ligand loadings anywhere from 2% to 20% depending on the substrate. While these catalyst loadings are high, copper is relatively cheap and the ligands required are inexpensive (Scheme 17).⁷⁴⁻⁷⁶

As with palladium, Cu-catalyzed reactions are most facile with aryl iodides followed by bromides and chlorides. Copper reactions also require higher temperatures; for example aryl chlorides require > 100 °C to react whereas the analogous Buchwald-Hartwig amination can be done at room temperature. Substrate scopes are generally good with copper. A wide variety of base-sensitive groups (ketone, ester, aldehyde, nitro) are tolerated in most methodologies. The reactions can be sensitive to sterics, with yields decreasing and reaction times increasing significantly for certain catalyst systems.

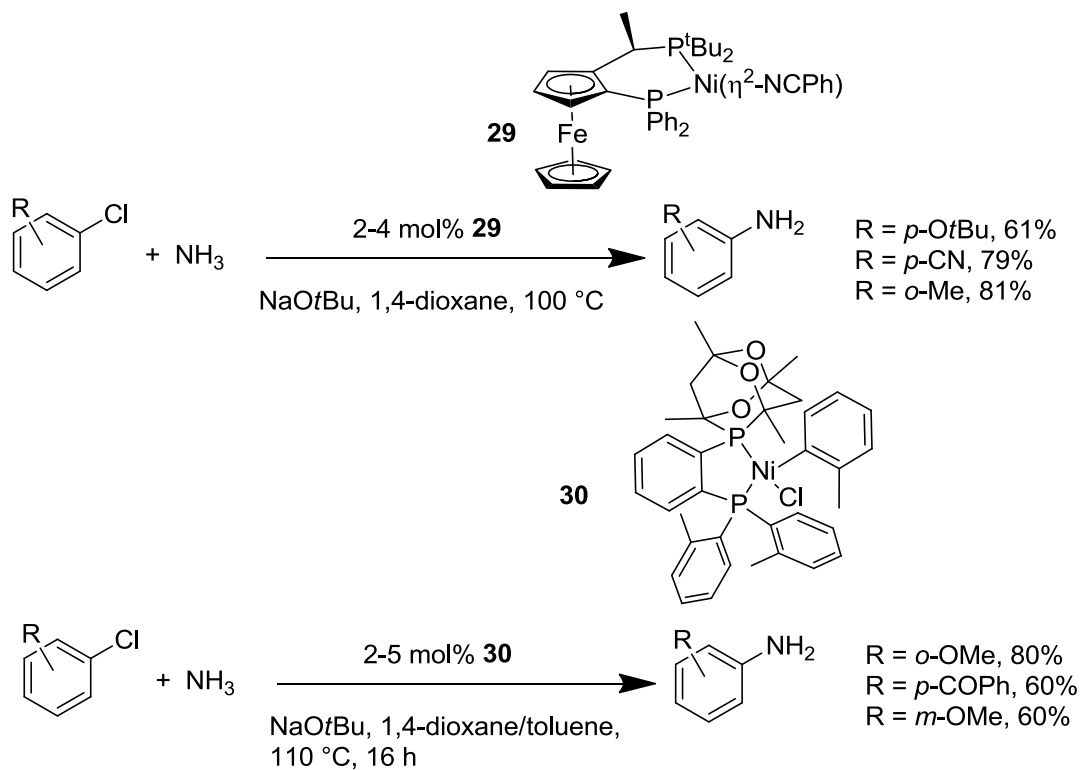
Scheme 17. Examples of Copper-catalyzed couplings between ammonia and aryl halides.⁷⁴⁻⁷⁶



Nickel Catalyzed Amination with Ammonia

Recent reports from Hartwig⁷⁷ and Stradiotto^{78,79} have demonstrated nickel catalyzed amination between ammonia or ammonium salts and aryl halides or pseudo halides. This methodology is virtually identical to the palladium catalyzed reactions, likely because the reports are relatively recent and comes from research groups that developed the Pd-catalyzed reactions (Scheme 18). Nickel, being cheaper and more abundant than palladium, has the potential of becoming a more economical alternative to palladium.

Scheme 18. Nickel-catalyzed amination with ammonia.^{77,79}

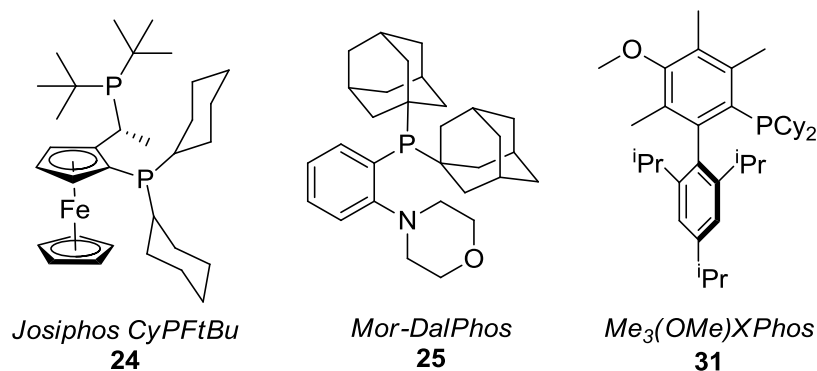


The propensity of the primary anilines to react competitively with ammonia has forced the development of highly specialized ligands to combat this problem. The cost to synthesize these ligands is only known to the manufacturers, but they are 20 to 100 times more expensive per mole than palladium to purchase from commercial suppliers. In order to truly become a more cost effective than palladium, Ni-catalyzed methods need to utilize less expensive ligands or work at a lower catalyst loading than the 0.1-2 mol% required with palladium. To date neither of those goals has been achieved, although the bisphosphine *PAd-DalPhos* (**30**) and future derivatives have potential to achieve this goal.

Buchwald-Hartwig Amination with Ammonia

The Buchwald-Hartwig amination reaction with ammonia is the most challenging of the aminations.⁸⁰ The first challenge is finding a catalyst system that is catalytically active because ammonia will displace phosphine ligands such as tri(*o*-tolyl)phosphine from palladium.^{4,81} Only catalyst systems that contain ligands that resist displacement by ammonia are catalytically active. Ligands that have been previously successful are highly sterically hindered phosphines shown in Scheme 19.

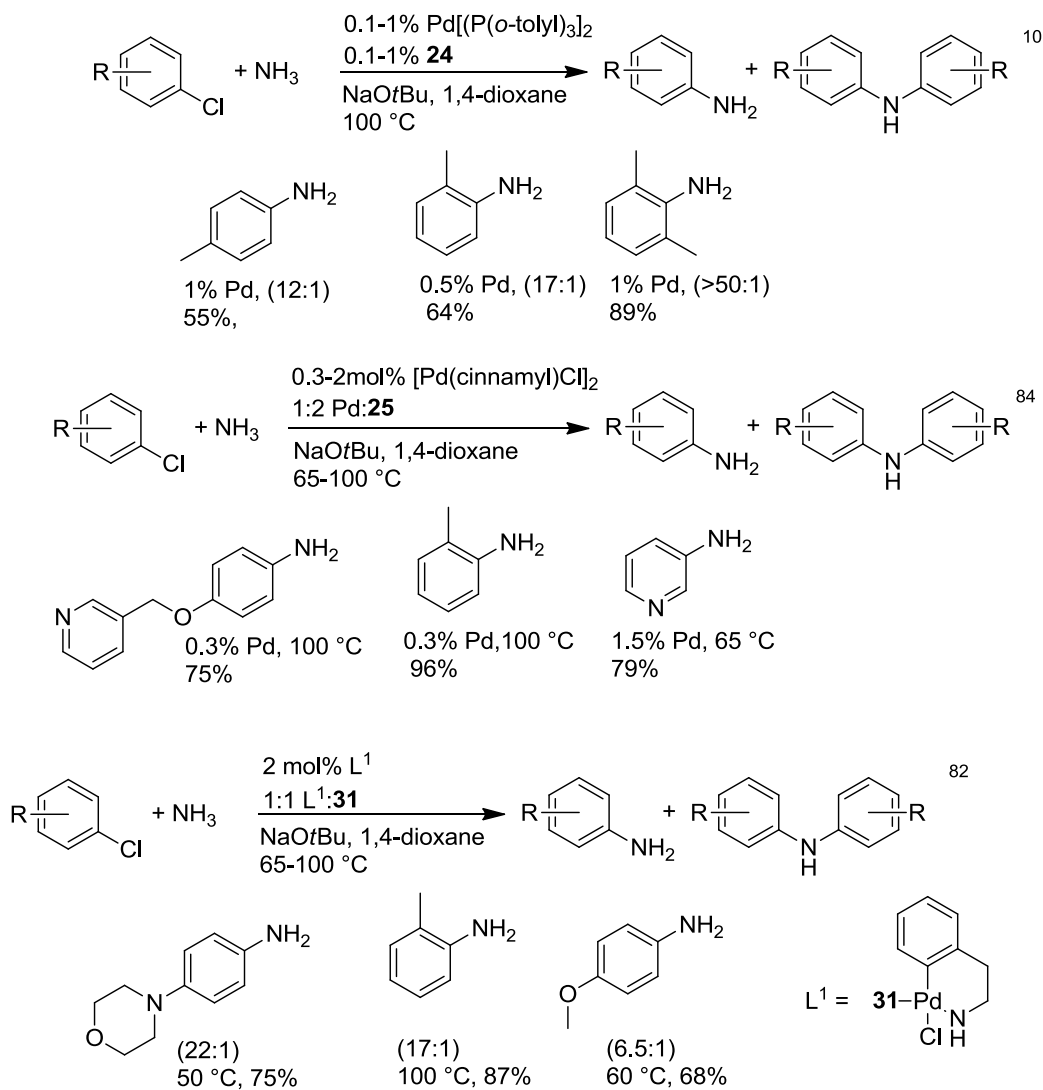
Scheme 19. Ligands for the Buchwald-Hartwig amination with ammonia.^{10,82,83}



The second challenge with coupling ammonia is reductive elimination of the primary arylamine from the palladium amido intermediate. This intermediate has been isolated with ligand **24** and it reductively eliminates slowly at room temperature.²² Other ligands such as DPPF and BINAP do not give C—N coupled products.²² The third challenge is producing the primary arylamine selectively. The desired primary arylamine product will couple faster than ammonia and produce a substantial amount of the diarylamine unless the ligand on Pd is tremendously bulky. The structure of the aryl halide matters greatly with respect to the selectivity for monoarylation. Aryl halides that are electron poor or are substituted in the *ortho* position are more selective due to the decreased ability of the aniline product to re-enter the

catalytic cycle. A Pd-complex containing ligand **24** has been used successfully with ammonia in 1,4-dioxane solutions for aryl chlorides, bromides, and iodides (Scheme 20).¹⁰ This Pd-complex has also been used for palladium and nickel-catalyzed reactions with ammonium sulfate for coupling of aryl chlorides in 1,4-dioxane or 2-methyltetrahydrofuran.^{33,77} A Pd-complex containing ligand **31** will couple a wide variety of aryl halides, although 6 membered heterocyclic and *ortho*-substituted aryl halides each require a slight change to the ligand structure.⁸² The choice of base for these reactions is NaOtBu in all literature examples with the exception of one procedure that uses K₃PO₄, but requires 200 psi of ammonia to compensate for a loss in selectivity due to K₃PO₄.¹⁰ Not all functional groups can tolerate NaOtBu at elevated temperatures (e.g. esters, aldehydes, enolizable ketones, nitrile, nitro). Only a few of these substrates have been reported with ammonia with low to moderate yields.⁸²

Scheme 20. Examples of Buchwald-Hartwig amination with ammonia (monoarylamine: diarylamine).^{10,82,84}



Research Objectives

The Buchwald-Hartwig amination reaction using ammonia in 1,4-dioxane solution works well for non-base-sensitive substrates achieving moderate to high selectivity for monoarylation with electron rich sterically hindered phosphine ligands. The excess of NaOtBu is responsible for the limited substrate scope. The use of ammonium salts in place of a saturated

ammonia solution greatly improved the convenience while lowering the cost of the reaction, but selectivity for monoarylation was only maintained for aryl chlorides and *ortho*-substituted aryl bromides.³³ A single protocol that works well for all aryl halides has not been developed. The goal of this research is to develop a single protocol for monoarylation of ammonia that tolerates a broad range of functional groups and substitution patterns.

Pd pre-catalysts that utilize N-heterocyclic carbene ligands have demonstrated extremely high catalytic reactivity in a wide variety of couplings including arylation of anilines and alkylamines. Despite the excellent reactivity for amination, there are very few reports of catalysts that utilize an NHC ligand for amination with ammonia and none that are monoligated by a NHC. The Pd-PEPPSI (PEPPSI = pyridine enhanced pre-catalyst preparation, stabilization and initiation) catalyst family is effective for Buchwald-Hartwig amination. It has been found that increasing the steric bulk around Pd through lengthening of alkyl chains and chlorination of the imidazole backbone makes *Pd-PEPPSI-IPent^{Cl}* (**27**) more selective for the amination with primary alkylamines than catalysts with shorter alkyl chains and no substituents on the imidazole backbone.⁶⁰ Since primary alkylamines are the closest coupling partner to ammonia, **27** or bulkier versions of this catalyst may be effective at promoting the selective coupling of ammonia with aryl halides under mild conditions.

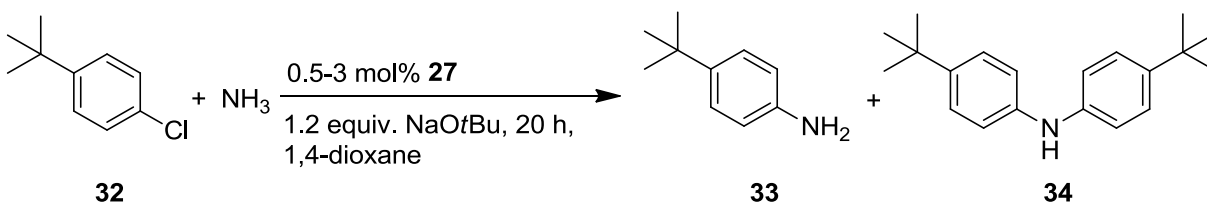
Results and Discussion

Investigating the Reactivity of *Pd-PEPPSI-IPent*^{Cl}

The starting point of the project was finding a set of reaction conditions to couple ammonia and aryl chlorides with *Pd-PEPPSI-IPentCl* (**27**). The substrate chosen was 4-*tert*-butylchlorobenzene (**32**) because it is a moderately electronically deactivated coupling partner. Electron rich aryl chlorides are slow to undergo oxidative addition. Reductive elimination is also slower for electron rich sterically unhindered aryl halides. Aryl chloride **32** yields a slightly electron rich sterically unhindered aniline **33** that is likely to go through the coordination/deprotonation sequence to couple again and produce the diarylamine product **34**. Therefore, if **32** can be converted to **33** in high yield and selectivity for monoarylation, the procedure should be applicable to a wide range of aryl halides.

The initial reaction conditions for the model reaction (entry 1, Table 1) were a combination of literature procedures that utilize a commercially available 0.5 M ammonia in 1,4-dioxane solution with sodium *tert*-butoxide base and reaction conditions for the amination with alkylamines using **27**. Unfortunately, 60 °C and 3 mol% of **27** (entry 1, Table 1) was insufficient to convert all of **32** to products. Raising the temperature to 100 °C (entry 2, Table 1) allowed the reaction to reach completion with a moderate 2.7:1 ratio of **33:34** when 10 equivalents of ammonia are used. Dropping the catalyst loading to 1 mol% (entry 4, Table 1) caused the reaction to only reach 35% conversion and the selectivity to increase. The increase in selectivity for monoarylation is expected for reactions that do not reach completion because there is less of the monoarylated product to compete with ammonia for the catalyst and generate the diarylamine.

Table 1. Optimization study for the Pd-catalyzed amination of 4-*tert*-butylchlorobenzene with ammonia using *Pd-PEPPSI-IPent*^{Cl} [a]



| Entry | 27 (mol%) | Temp. (°C) | LiOiPr (mol%) | [32] (M) | NH ₃ (equiv.) | Conv. (%) ^[b] | 33/34 ^[c] |
|-------------------|------------------|------------|---------------|-------------------|--------------------------|--------------------------|-----------------------------|
| 1 | 3 | 60 | - | 0.05 | 10 | 15 | - |
| 2 | 3 | 100 | - | 0.05 | 10 | 100 | 2.7:1 |
| 3 | 3 | 100 | - | 0.025 | 20 | 100 | 5.4:1 |
| 4 | 1 | 100 | - | 0.05 | 10 | 35 | 5:1 |
| 5 | 3 | 100 | - | 0.1 | 5 | 100 | 1.7:1 |
| 6 ^[d] | 3 | 100 | - | 0.05 | 5 | 100 | 1.4:1 |
| 7 | 1 | 100 | 5 | 0.1 | 5 | 100 | 1.5:1 |
| 8 | 0.5 | 100 | 5 | 0.1 | 5 | 100 | 1.3:1 |
| 9 | 1 | 100 | 10 | 0.05 | 10 | 100 | 2.7:1 |
| 10 ^[e] | 1 | 70 | 10 | 0.1 | 5 | 100 | 1:1 |
| 11 ^[e] | 1 | 30 | 10 | 0.1 | 5 | 100 | 0.5:1 |

[a] Reactions were performed on a 0.25 mmol scale in duplicate. [b] Percentage conversion was determined by ¹H NMR spectroscopy of the crude reaction mixture. [c] Product ratios of **33** to **34** were determined by ¹H NMR spectroscopy of the crude reaction mixture. [d] Reaction was diluted with 1,4-dioxane to achieve a [0.05 M]. [e] NaOtBu, **27**, and LiOiPr were heated at 95 °C for 5 minutes and then cooled to their respective reaction temperatures before addition of the aryl halide and ammonia.

Next, the selectivity for monoarylation and amount of ammonia used was investigated more thoroughly. There is a doubling in selectivity (2.7:1 to 5.4:1) when the equivalents of ammonia doubles from 10 to 20. In order to double the equivalents, twice the amount of solvent was required because ammonia comes in 0.5 M 1,4-dioxane solutions. To determine whether the extra ammonia or dilution of the reaction is responsible for the increased selectivity, a reaction

was diluted with 1,4-dioxane (entry 6, Table 1). If the selectivity of the diluted reaction matches the reaction with an equal concentration of **32** (entry 2, Table 1), then it could be concluded diluting the reaction increases selectivity. However, it was found that these two reactions do not have the same selectivity. The diluted reaction (entry 6, Table 1) more closely matches the selectivity of the reaction that contains the same 5 equivalents of ammonia at a higher concentration of **32** (entry 5, Table 1). The conclusion from these experiments is that selectivity for monoarylation is almost directly proportional to the equivalents of ammonia used.

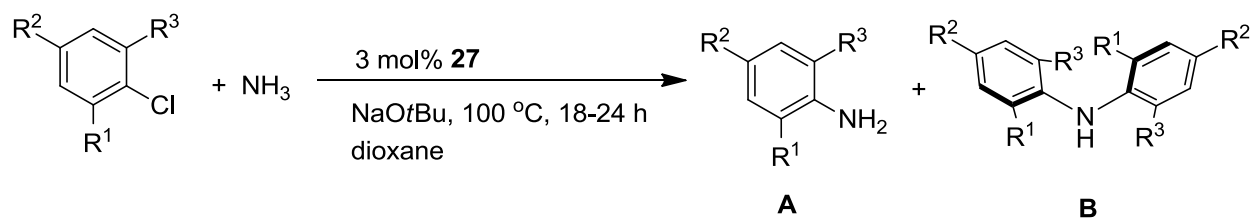
Considering **27** is able to catalyze the reaction of 4-chloroanisole and 1-octylamine at room temperature with a 1 mol% catalyst loading when NaOtBu is used as the base, it is unusual that ammonia should require such a large increase in temperature and catalyst loading. It was hypothesized that the problem with ammonia wasn't with any steps of the catalytic cycle, but with the process of catalyst activation. Since ammonia contains no β -hydrogens and neither does NaOtBu, the typical low temperature β -hydride elimination observed with alkylamines is not a viable catalyst activation pathway. Perhaps there is a high energy barrier catalyst activation process that can take place when the reaction is heated (e.g., β -hydride elimination from 1,4-dioxane); this would allow some catalyst to come on cycle and be consistent with the observed increase in temperature and catalyst loading.

To test the activation problem hypothesis, small amounts of LiOtPr (5-10%) were added to the reaction (entries 7-11, Table 1). LiOtPr had been previously used in sulfination chemistry with PEPSI catalysts where it was shown to be effective for catalyst activation *via* β -hydride elimination.¹⁵ When 5 mol% of LiOtPr was added to a reaction containing 1 mol% of **27**, the reaction reached 100% conversion of **32** (entry 7) compared to the 35% conversion (entry 4) reached without LiOtPr. The catalyst loading could be further lowered to 0.5% without a drop in

conversion. To further test the idea of slow catalyst activation, **27** was pre-activated by heating it in 1,4-dioxane at 95 °C for 5 minutes. The reactions were then successfully run at reduced temperatures of 70 °C and 30 °C, albeit with a drop in selectivity for monoarylation. These results support the idea that catalyst activation of **27** is problematic for amination with ammonia and that **27** is capable of navigating the catalytic cycle at 30 °C once activated.

The functional groups on the aryl halide have a large effect on the selectivity. This can be rationalized by looking at the effect the functional groups have on the primary arylamine products ability to bind with the catalyst to produce a diarylamine. Functional groups that increase the electron density on the nitrogen of the primary arylamine are increasing its nucleophilicity and ability to bind to palladium. Functional groups that decrease electron density on nitrogen decrease the nucleophilicity and ability to bind to palladium. Entries 1 to 5 in Table 2 demonstrate clearly the effect of electron withdrawing and electron donating groups when placed in the *para* position. The electron withdrawing trifluoromethyl group is coupled with approximately three times the selectivity for monoarylation than the electron donating methoxy group.

Even more pronounced than the electronic effect is the steric effect. Functional groups that are in the *ortho* position act as a steric block and decrease the nucleophilicity of the primary arylamine. A single methyl group in the *ortho* position increases selectivity nearly 20 times and two methyl groups make the amount of diarylamine produced negligible. Entry 9 is an excellent example of sterics overcoming electronics to give the primary arylamine selectively.

Table 2. The effect of functional groups on the selectivity for monoarylation.

| Entry | R ¹ | R ² | R ³ | Conversion to A ^[a] | Selectivity (A : B) ^[b] |
|-------|-------------------|-----------------------------------|------------------|---------------------------------------|--|
| 1 | H | -OCH ₃ | H | 35% | 1.4: 1 |
| 2 | H | -CH ₃ | H | 50% | 2.2: 1 |
| 3 | H | -C(CH ₃) ₃ | H | 50% | 2.7: 1 |
| 4 | H | H | H | 55% | 3: 1 |
| 5 | H | -CF ₃ | H | 45% | 5: 1 |
| 6 | -CH ₃ | H | H | 90% | 40: 1 |
| 7 | -OCH ₃ | H | H | 50% | > 50: 1 |
| 8 | -CH ₃ | H | -CH ₃ | 90% | > 50: 1 |
| 9 | -CH ₃ | -OCH ₃ | -CH ₃ | 100% | > 50: 1 |

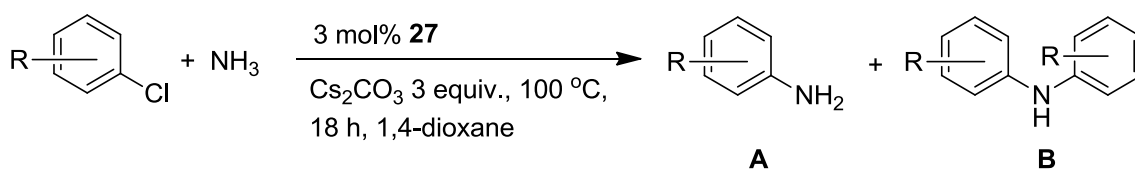
[a] Determined by ¹H NMR spectroscopy with 1,4-bis(trichloromethyl)benzene internal standard. [b] Determined by ¹H NMR spectroscopy.

Milder Bases for Amination.

NaOtBu is ubiquitous in amination reactions, especially amination with ammonia where other bases have failed to yield good results. The desire to move away from the cheap, but highly effective *tert*-butoxide bases comes from the tendency for it to react with many functional groups under amination reaction conditions (entry 6, Table 3). Cesium carbonate has been used successfully for amination with anilines and alkylamines containing functional groups incompatible with *tert*-butoxide. For example, methyl *p*-chlorobenzoate (entry 5, Table 3) is converted completely to monoarylamine and diarylamine products with no loss of material with Cs₂CO₃. When NaOtBu is used, the selectivity increases from 0.8:1 to 4.8:1, however, the

amount of monoarylamine product generated is the same because NaOtBu also reacts directly with the starting material and products to generate carboxylic acids. All other substrates failed to fully convert to amine products with Cs₂CO₃, which is much weaker and also less soluble than NaOtBu. On top of incomplete conversion, the selectivity for monoarylation drops significantly for all but 2,6-dimethylchlorobenzene, which generates an aniline that is too bulky to readily couple again.

Table 3. Amination of aryl halides with ammonia using Cs₂CO₃.



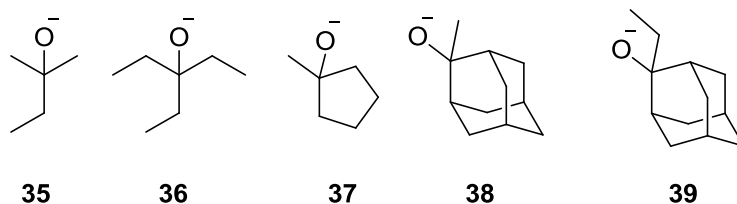
| Entry | Aryl-Cl | Base | Equiv. NH ₃ | Conversion to Products ^[a] | Selectivity (A:B) ^[b] |
|-------|------------------------------|---------------------------------|------------------------|---------------------------------------|----------------------------------|
| 1 | <i>p</i> -OMe | Cs ₂ CO ₃ | 5 | 5% | B only |
| 2 | <i>p</i> -CF ₃ | Cs ₂ CO ₃ | 10 | 15% | 1:1 |
| 3 | <i>o</i> -Me | Cs ₂ CO ₃ | 5 | 40% | 2:1 |
| 4 | <i>o</i> -Me, <i>o</i> -Me | Cs ₂ CO ₃ | 5 | 40% | >50:1 |
| 5 | <i>p</i> -CO ₂ Me | Cs ₂ CO ₃ | 5 | 100% | 0.8:1 |
| 6 | <i>p</i> -CO ₂ Me | NaOtBu | 10 | 35% | 4.8:1 |

[a] Determined by ¹H NMR spectroscopy with 1,4-bis(trichloromethyl)benzene internal standard. [b] Determined by ¹H NMR spectroscopy.

In an effort to increase the selectivity for monoarylation using **27** and improve functional group tolerance, bulkier tertiary alkoxides were investigated (Scheme 21). Alkoxides **35-37** are prepared by from their commercially available alcohols by deprotonation with NaH. The precursor alcohols to **38** and **39** were prepared by addition of a methyl and ethyl Grignard to the

corresponding ketone. Alkoxide **38** was readily formed by deprotonation with NaH in 1,4-dioxane, the solvent for coupling reaction. However, deprotonation to form alkoxide **39** was surprisingly difficult.

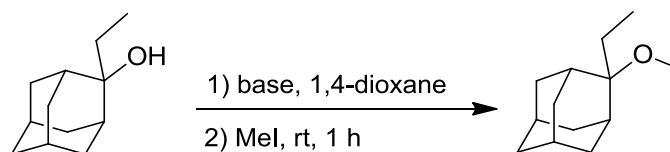
Scheme 21. Bulky tertiary alkoxides.



The amount of alkoxide formed was estimated by methylating it with methyl iodide and calculating the conversion to the methyl ether as determined by ¹H NMR spectroscopy. Typically, stirring an alcohol in ether with NaH at room temperature is sufficient for deprotonation. This was unsuccessful for **39** (entry 6, Table 4), there was no sign of hydrogen gas evolution and the failure to methylate confirmed the failure to deprotonate. Na metal, KH, and NaNH₂ also failed to deprotonate at room temperature. The deprotonation was then attempted in 1,4-dioxane so the temperature could be raised and the resulting alkoxide solution could be transferred directly to the amination. Na metal was unable to deprotonate the alcohol. KH and NaNH₂ were able to partially deprotonate the alcohol within a few hours (entries 2 and 3, Table 4). Heating at 90 °C with NaH for 24 hours gives an 85% conversion to the alkoxide which is suitable for testing the effect of this base on amination. Although KH and NaNH₂ deprotonate quicker than NaH, the Na⁺ counter ion sometimes gives better results than K⁺ for *tert*-butoxide, and using NaNH₂ contaminates the solution with ammonia. Ammonia contamination would actually be beneficial for amination with ammonia, but for the purpose of

looking for differences caused by the base, it's an extra variable that will complicate interpretation of the results.

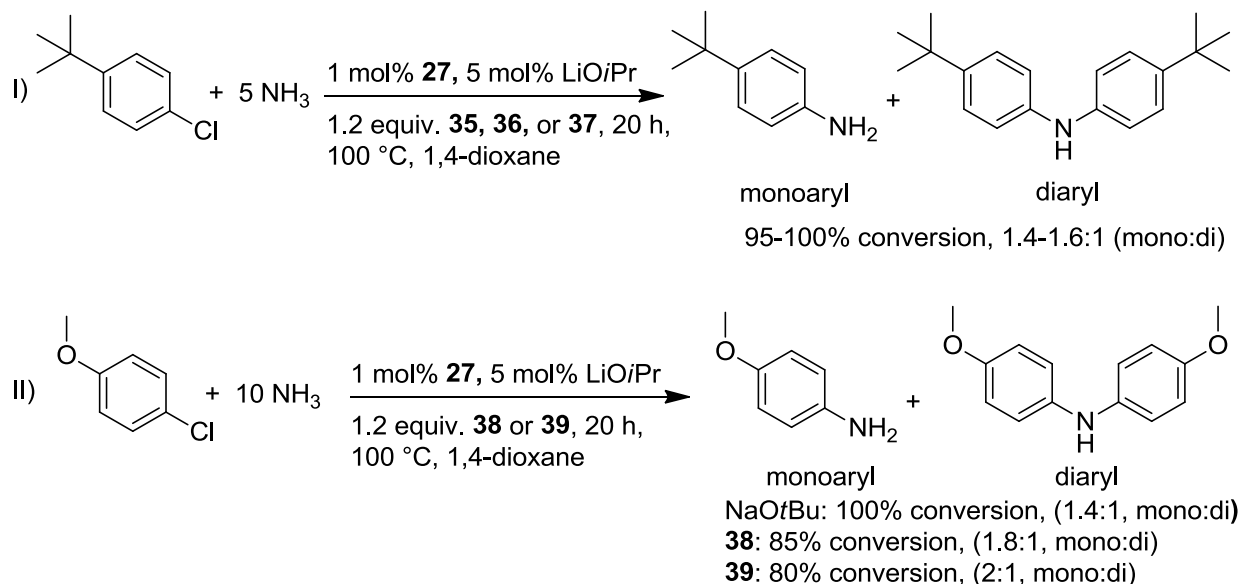
Table 4. Deprotonation and methylation experiments.



| Entry | Base | Conditions | % Conversion |
|-------|-------------------|-------------------|--------------|
| 1 | NaH | 90 °C, 24 h | 85 |
| 2 | NaNH ₂ | 80 °C, 2 h | 65 |
| 3 | KH | 60 °C, 1 h | 50 |
| 4 | NaH | 60 °C, 24 h (THF) | 16 |
| 5 | Na ⁰ | 80 °C, 24 h | 0 |
| 6 | NaH | rt, 24 h (ether) | 0 |

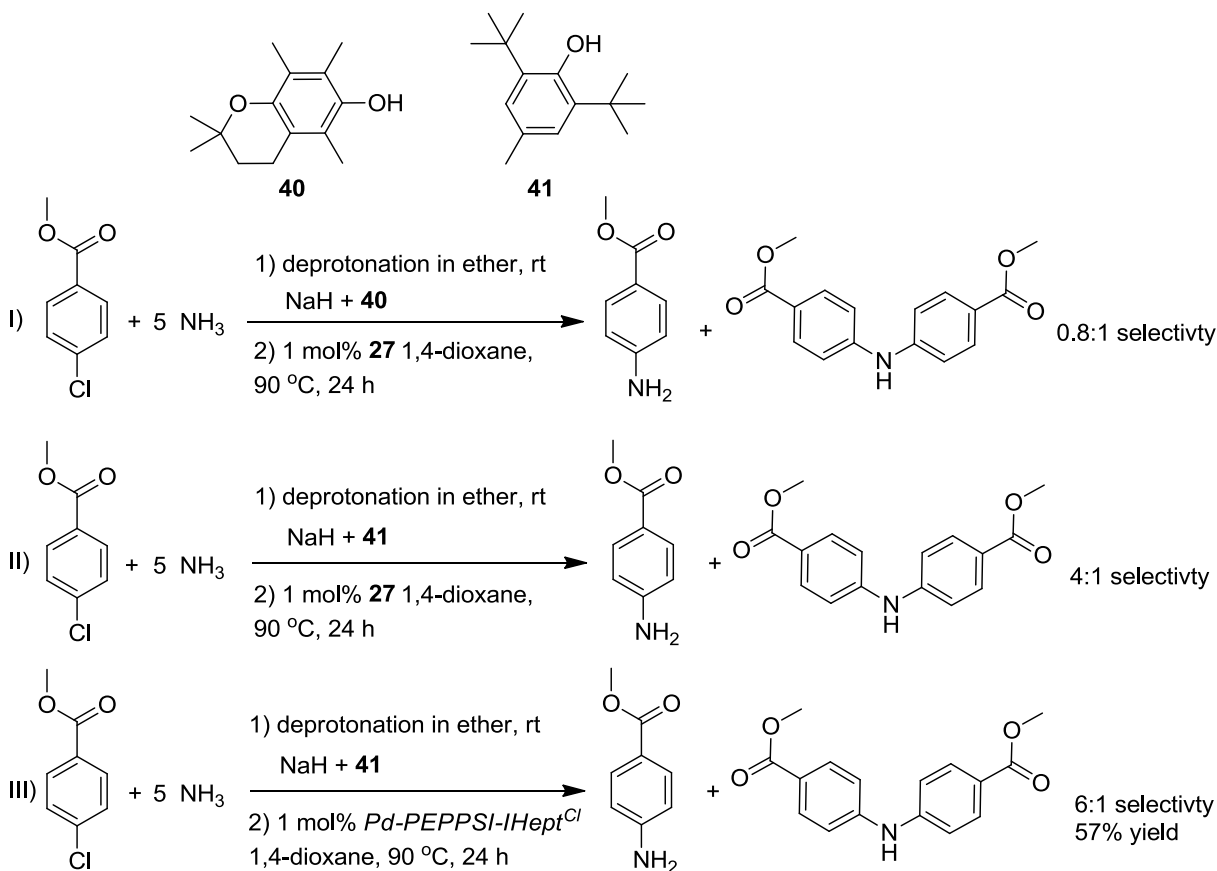
Given the difficulty in the deprotonation to make **39** (**38** only requires 2 hours at 90 °C), it would seem that these alkoxides react significantly slower than *tert*-butoxide. Unfortunately this wasn't able to benefit amination with ammonia. Reactions with aldehydes, esters, ketones, and nitriles generated complicated mixture of products as they do with *tert*-butoxide. Extending the alkyl chains (bases **35** and **36**) did not increase the selectivity or functional group tolerance. Alkoxide **37** gives the same selectivity as *tert*-butoxide for amination of **32**. The adamantane bases **38** and **39** also reacted with aldehyde, ester, ketone, and nitrile functional groups when tested. However, they did show a slight increase in selectivity for monoarylation (Scheme 22).

Scheme 22. Amination reactions with different tertiary alkoxides.



Since all of the tertiary alkoxides are equally incompatible with many functional groups, phenoxides were investigated as a milder alternative. Two phenoxide bases that have been used previously for amination with PEPPSI catalysts are **40** and **41**.^{29,60} Both bases were capable of facilitating the coupling of methyl *p*-chlorobenzoate, but **41** was five times more selective for the monoarylated product (reaction I and II, Scheme 23). When the monoarylamine product was isolated, the yield (57%) was lower than theoretical 75% yield which assumes all of the aryl chloride was converted to monoarylamine and diarylamine products (reaction III, Scheme 23). This was consistently observed for different esters with different Pd-NHC catalysts when the sodium salt of **41** is used as the base.

Scheme 23. Reaction of methyl *p*-chlorobenzoate using phenoxide bases.



To investigate why the yields with esters are consistently low, a base compatibility test was done (Figure 1). Reaction of the sodium salt of **41** with methyl *p*-chlorobenzoate in deuterated benzene generates a brown precipitate upon heating. While precipitates cannot be observed by ¹H NMR spectroscopy during the course of the reaction, the loss of the starting methyl ester can be tracked by comparing the integral of the methyl group singlet with the resonance signal of the methyl group from **41**. Within two hours 15% of methyl *p*-chlorobenzoate has been converted to a precipitate with a final conversion of 25% after the typical 20 hour duration of an amination reaction using this base. The identity of the precipitate

was later revealed to be a carboxylate when the crude reaction mixture was dissolved in deuterated DMSO.

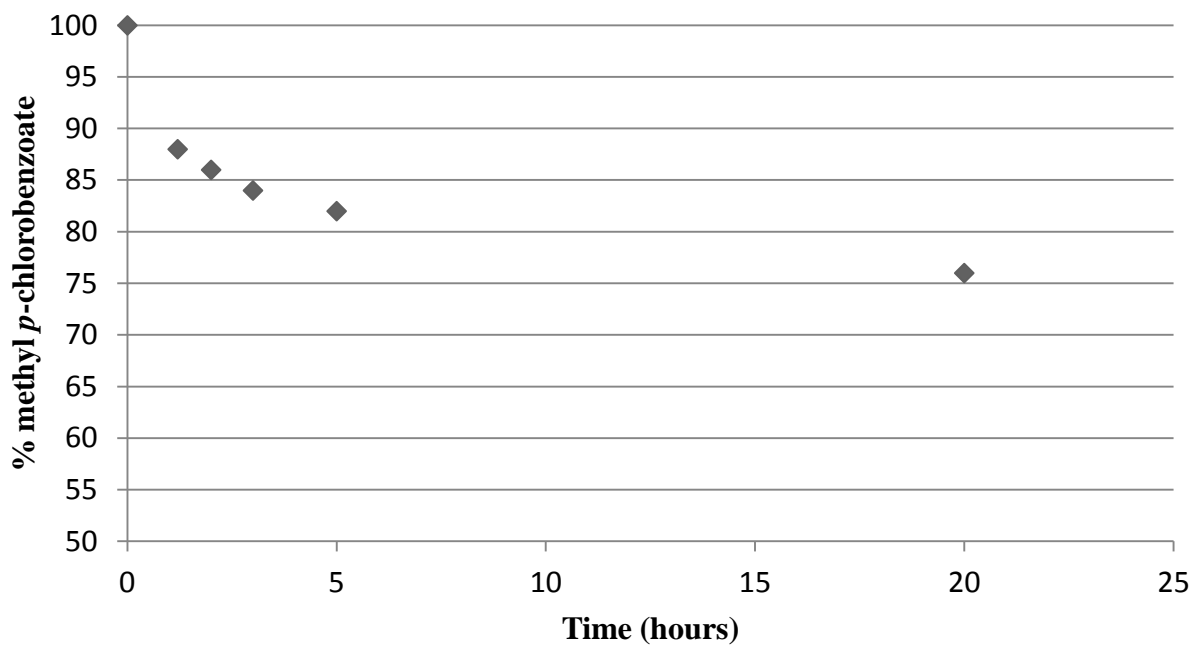
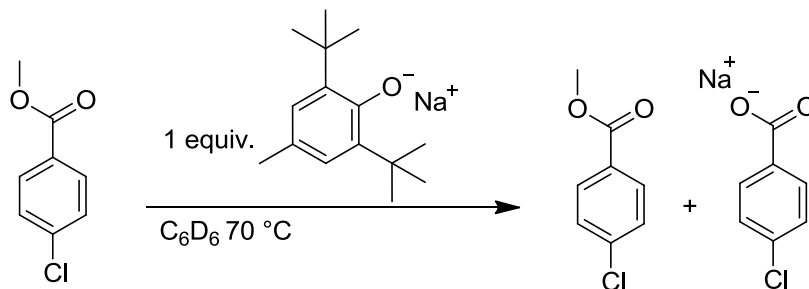
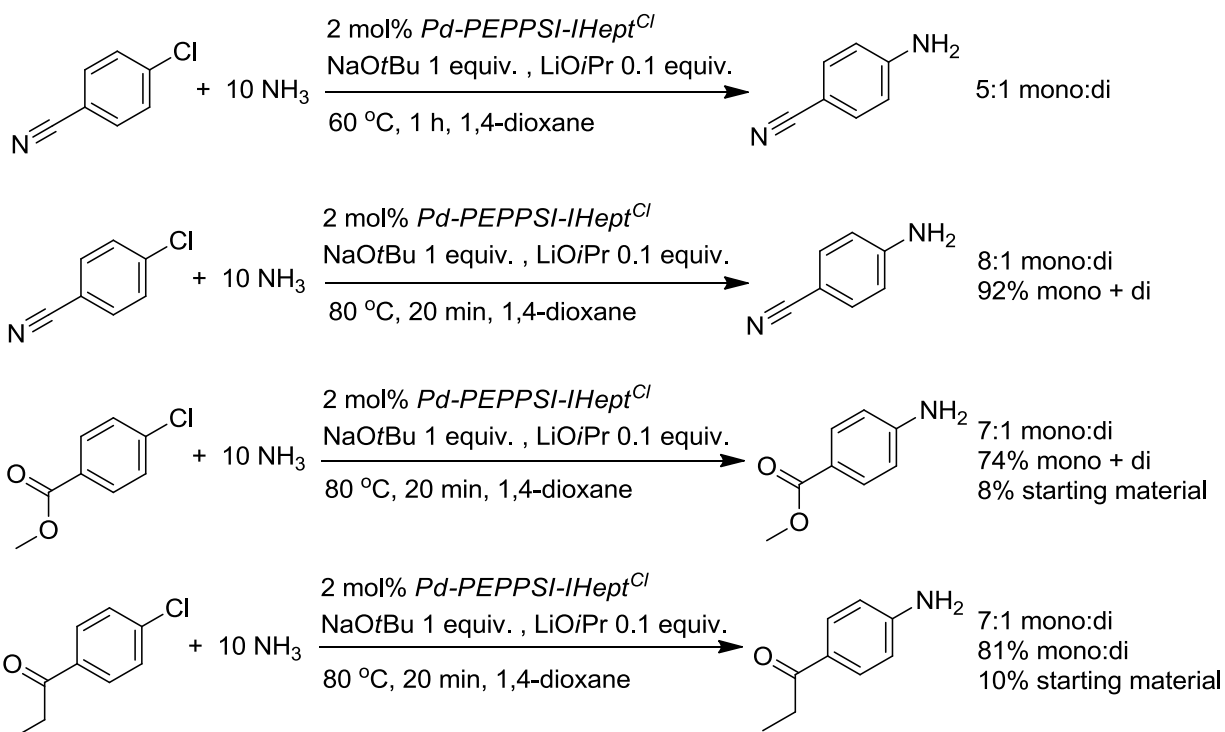


Figure 2. Reaction of the sodium salt of **41** with methyl *p*-chlorobenzoate.

Given that the only bases to give good selectivity for monoarylation will also react with many functional groups, the approach was changed to minimize side reactions rather than finding a base that does not react with the substrate at all. Use of NaOtBu was optimized first because it is a more convenient reagent to use compared to the sodium salt of **41**, which must be made fresh

each time by deprotonation in ether with NaH. In order to minimize contact between the base and substrate, a 1:1 base to substrate ratio was used. Normally a 20 to 100% excess of base is used, likely because bases are typically inexpensive so it makes sense to ensure conversion from starting material to product does not stop from a lack of base. An excess of base will increase the rate of reaction as well when it is involved in the rate limiting step as is the case with carbonate base.³⁰ The small amount of aryl chloride not converted to product with the 1:1 ratio of base to aryl chloride only slightly reduces the yield with base sensitive substrates. Since there is little to no loss from side reactions between the base and sensitive functional groups the monoarylated product yield is higher (Scheme 24). Reactions carried out at 80 °C with a selection of electron poor, sterically unhindered aryl chlorides consume most of the aryl halide within 20 minutes when using 2 mol% of *Pd-PEPPSI-IHept^{Cl}*. Loss of product due to reaction with NaOtBu is less than 10 percent for the nitrile and ketone, and approximately 18% for the ester.

Scheme 24. Amination with base-sensitive substrates and one equivalent of NaOtBu.



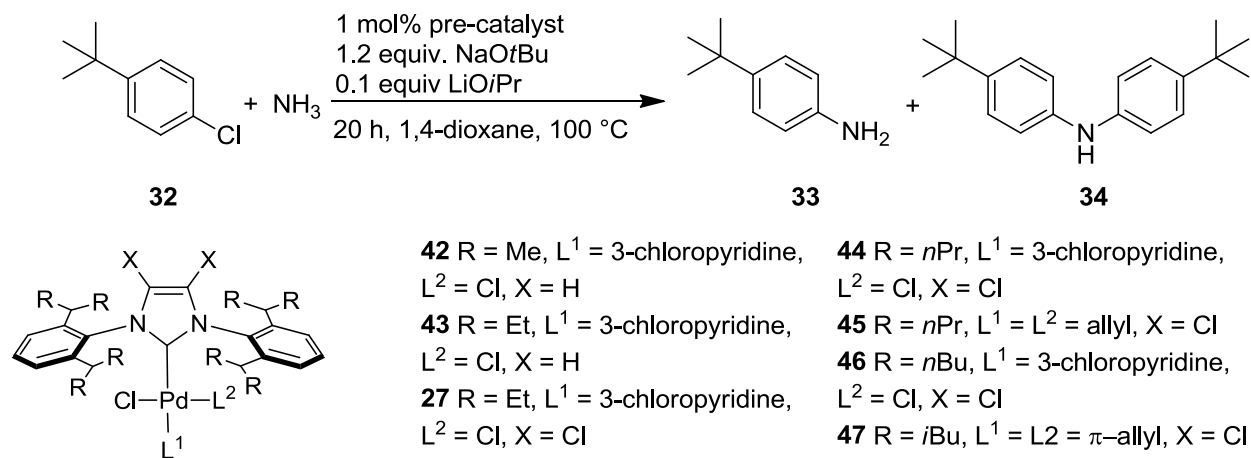
Structure-Activity Relationships of NHC Ligands for Amination with Ammonia

The success of Buchwald-Hartwig amination with ammonia is very reliant on the ligand. Ligands that successfully reductively eliminate alkylamines and arylamines can fail to reductively eliminate ammonia.²² Not only does the Pd-ligand complex need to promote reduction elimination, it needs to be selective for ammonia over the primary arylamine product. Presumably the only way to do this is to have a large ligand that disfavours coordination of primary arylamines in favour of coordination with ammonia.

In order to make Pd-NHC pre-catalysts of the general motif shown in Scheme 25 more bulky, there are two options. The first is to make the R groups bigger. It's known that in order

to maintain high catalyst reactivity, the R groups not only need to be large, but they must also be flexible.^{55,56,85} This conclusion comes from the fact that R groups that are branched alkyl chains generally out-perform catalysts where R = Ph, there is no branching of the alkyl group, or where the imidazole nitrogen atoms are substituted with bulky, but rigid adamantyl groups.^{54,86} The effect of longer alkyl chains is evident by comparing pre-catalysts **42** and **43** (Scheme 25). The *i*Pr group of **42** does not provide enough bulk to generate the C—N coupled product whereas the 3-pentyl group of **43** does. Comparisons can also be made between entries 3-7, where the selectivity increases when the aryl groups are substituted with 4-heptyl instead of 3-pentyl groups, decrease with 5-nonyl groups, and increase drastically with highly branched 4-(2,6-dimethylheptyl) group. There is no effect on selectivity by switching between π -allyl and 3-chloropyridine pre-catalysts. The π -allyl pre-catalyst is used for the highly branched ligand in **47** because the activation does not require LiO*i*Pr and attempts to make a PEPPSI pre-catalyst bearing the same NHC ligand were low yielding. The only outlier of the group is **46** which contain 5-nonyl groups. While there is no percent buried volume data for this exact NHC ligand, percent buried volumes were calculated for a similar series of NHC ligands with no chlorine substituted on the imidazole ring. The percent buried volume of the 5-nonyl ligand was less than the 4-heptyl, which aligns with the selectivity presented in Scheme 25 (i.e., the ligand with the largest percent buried volume is the most selective for monoarylation).⁵⁶

Scheme 25. Effect of catalyst steric bulk on selectivity for monoarylation.



| Entry | Pre-catalyst | Conv. (%) ^[b] | 33/34 ^[c] |
|------------------|---|--------------------------|----------------------|
| 1 | 42 Pd-PEPPSI-IPr | 0 | - |
| 2 | 43 Pd-PEPPSI-IPent | 90 | 1:33 |
| 3 | 27 Pd-PEPPSI-IPent ^{Cl} | 100 | 2.7:1 |
| 4 | 44 Pd-PEPPSI-IHept ^{Cl} | 100 | 4.6:1 |
| 5 ^[d] | 45 | 100 | 4.6:1 |
| 6 | 46 Pd-PEPPSI-INon ^{Cl} | 100 | 3.2:1 |
| 7 ^[d] | 47 | 100 | 40:1 |

[a] Reactions were performed in duplicate on a 0.25 mmol scale. [b] Percentage conversion was determined by ¹H NMR spectroscopy of the crude reaction mixture. [c] Product ratios of **33** to **34** were determined by ¹H NMR spectroscopy of the crude reaction mixture. [d] Reaction performed in the absence of LiOiPr.

The other way to increase ligand bulk is to replace the two hydrogens on imidazole with larger substituents that will push the aryl rings closer to Pd. Examples include: phenyl, dimethylamino, methyl, chloro, bromo.^{87–89} In the PEPPSI series of pre-catalysts that contain an imidazole NHC, a Cl-substituted imidazole backbone has been shown to increase catalytic activity (i.e., **27** is a more active amination catalyst than **43**). For ammonia, Cl-substitution is able to reverse the selectivity from producing 97% diarylamine to 58% monoarylamine as the

major product. The combination of flexible bulky R groups and backbone substitution makes **47** highly selective for amination with ammonia.

It's worth highlighting that the reaction presented in Scheme 25 provides a unique opportunity for measuring NHC ligand bulk through experimental results. Most other cross-coupling reactions stop benefitting from additional ligand bulk somewhere around pre-catalysts **43** and **27**. The only other beneficial use of ligands as hindered as **47** that have been investigated to date is the Negishi reaction of secondary alkyl zincs where the bulk of **44** and **47** suppress β -hydride elimination and migratory insertion that leads to unwanted isomers.^{90,91}

Selective Amination of Hetero(aryl)halides with Ammonia

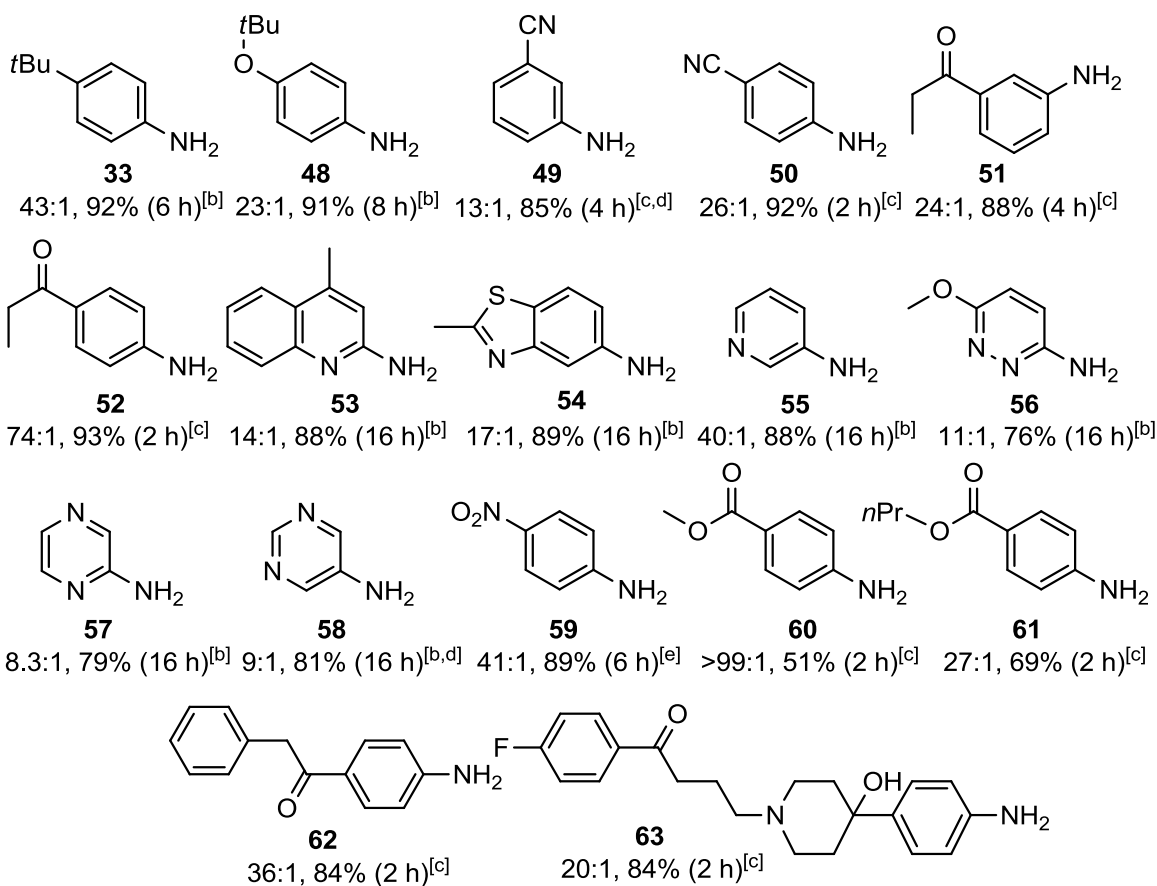
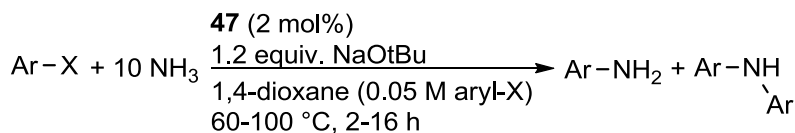
With the highly selective **47** in hand, the substrate scope of BHA amination with ammonia was examined (Scheme 26). The optimal catalyst loading and temperature vary between substrates. In general, for substrates lacking *tert*-butoxide sensitive functional groups, 100 °C with 1.2 equivalents of base and 2 mol% loading of **47** is sufficient to completely convert the starting material to product. Some substrates (e.g. **33** and **48**) couple well with just 1 mol% of pre-catalyst. 6-Membered heterocyclic aryl halides featuring one or more heteroatoms couple in good yield and monoselectivity. 5-Membered heterocycles gave poor conversions to product when coupled with **45** or **47**. It is likely that **47** is insufficiently bulky to facilitate the reductive elimination of the smaller and more electron rich aromatic rings with ammonia.

The *tert*-butoxide sensitive substrates leading to products (**49-52**, and **59-63**) couple best with heating at 80 °C, which is about the maximum temperature the reaction can be run at without generating large quantities of side products; reactions at 90 °C generally gave lower conversion to products. The temperature can certainly be lowered, but there is a loss in

selectivity and increase in reaction time. It can be deduced from the obtained yields that with the exception of esters, the *tert*-butoxide is consumed faster in the amination than by side reactions with the substrate or products. Methyl ester **60** was only obtained in 51% yield, but the slightly larger propyl ester **61** was coupled in 69% yield. The base-sensitive aryl halides do not need to be activated by *para*-substituted groups that are electron withdrawing through resonance to couple. A *meta*-substituted ketone (**51**) and slightly electron rich **63** (from the amination of haloperidol) were obtained in > 80% yield.

The trends in selectivity for monoarylation that can be rationalized using steric/electronic properties of the aryl halide using pre-catalyst **27** are less pronounced with **47**. This is likely because the ability of palladium to coordinate the aniline product through a functional group (e.g. cyano, N-containing heterocycles) or chelate with an amino group and a near-by oxygen or nitrogen atom now has a significant influence on selectivity for monoarylation. The aryl halides were also coupled at different temperatures which is known to influence selectivity for monoarylation. In addition, the unwanted side reactions involving *tert*-butoxide and base-sensitive groups may occur at different rates with diarylamine and monoarylamine products. These are all factors to consider when rationalizing why a particular substrate is more selective for monoarylation than another substrate.

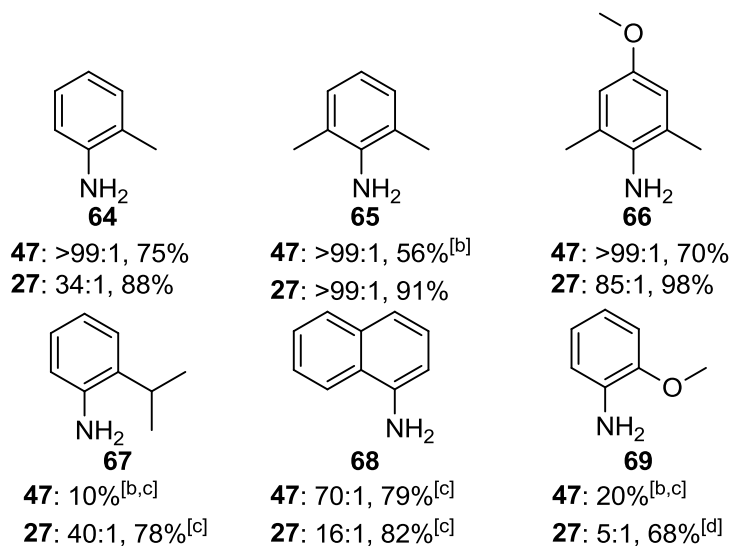
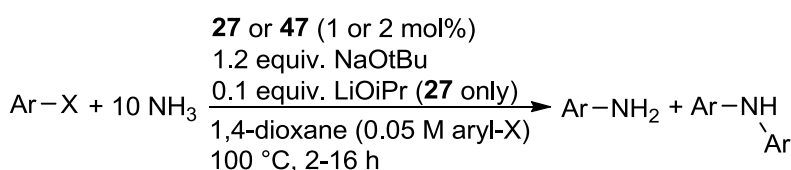
Scheme 26. Substrate scope and selectivity for the monoarylation of (hetero)aryl halides with ammonia using **47**.^[a]



[a] Yields of isolated material, X = Cl, ratio of mono:di determined by ¹H-NMR spectroscopy of the crude product mixture. [b] 100 °C, 1.2 equiv. NaOtBu. [c] 80 °C, 1 equiv. NaOtBu. [d] X = Br. [e] 60 °C, 1 equiv. NaOtBu

Ortho-substituted aryl halides present a less difficult challenge to couple selectively. Although *ortho*-substituted aryl halides still require a very sterically hindered ligand, **47** now becomes overly bulky and conversion to product decreases, but selectivity remains high (Scheme 27). The less bulky **27** gives the monoarylamine in high selectivity and yield for a variety of substrates. Difficulties arise for products (e.g., **69**) than can chelate to Pd, causing selectivity to drop, requiring an increase in catalyst loading for complete conversion to products.

Scheme 27. Selective monoarylation of *ortho*-substituted aryl halides with ammonia.^[a]



[a] Yields of isolated material, X = Cl, ratio of mono:di determined by ¹H-NMR spectroscopy of the crude reaction mixture. Reactions with **47** were run with 2 mol% catalyst whereas reactions with **27** used 1 mol% catalyst. [b] Percent conversion determined by ¹H NMR spectroscopy of the crude reaction mixture. [c] X = Br. [d] 2 mol% of **27** was used.

Conclusions

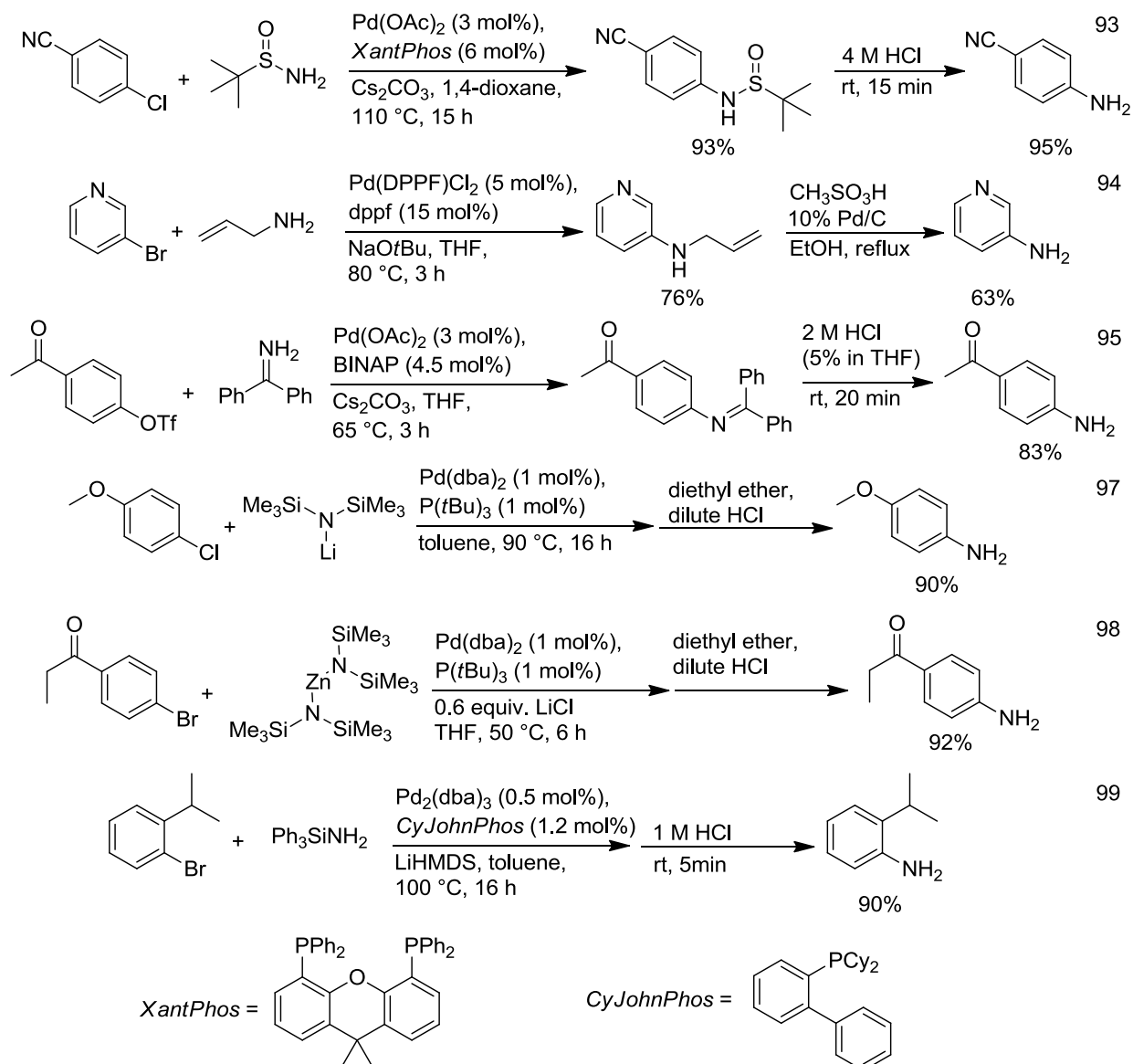
Pre-catalyst **47** is an air and moisture stable complex that is able to catalyze the arylation of ammonia with high selectivity for monoarylated products. Pre-catalyst **27** features a less sterically demanding NHC ligand than **47**, which is better matched for the amination of *ortho*-substituted aryl halides with ammonia. Taken together, they represent the first monoligated Pd-NHC catalysts to accomplish selective amination with ammonia. When base sensitive functional groups are present, (hetero)arylamine products may be obtained in high yield using 1.0 equivalent of NaOtBu.

Chapter 2 Introduction: Pd-catalyzed Amination Using Silylamines and Selective N-alkylation to Produce N-alkylated Arylamine Products

Ammonia Equivalents

In the past decade there has been tremendous progress in the Pd-catalyzed coupling of primary alkylamines and ammonia with aryl halides and pseudo halides.^{58,92} Reports of the direct reaction with ammonia in Pd-catalyzed coupling reactions did not appear until 2006, over 20 years after the first reports of Pd-catalyzed C—N couplings of free amines.^{3,80} In order to access primary arylamines from aryl halides or sulfonates, a number of methods were invented that use an ammonia equivalent or surrogate in place of ammonia. The ammonia equivalents would first be coupled to an aryl halide in the same way as an alkyl and arylamines, after which the ammonia carrier is then removed to yield the primary arylamine. The following reagents (see Scheme 28 for examples) have been successfully used as ammonia equivalents: *tert*-butyl sulfonamide,⁹³ allylamine,⁹⁴ benzophenone imine,^{95,96} lithium bis(trimethylsilyl)amide (LiHMDS),⁹⁷ zinc bis(trimethylsilyl)amide (ZnHMDS),⁹⁸ and aminotriphenylsilane.⁹⁹

Scheme 28. Examples of ammonia equivalents for Pd-catalyzed amination.



The advantage of ammonia is that it is very cheap, widely available, and atom economical compared to ammonia equivalents that only transfer the amino group. However, the reaction as a whole needs to be evaluated, not just one reagent. If the examples in Scheme 28 are compared to the examples with ammonia from Chapter 1, a few advantages of ammonia equivalents can be found.

One difference is the equivalents of nitrogen used in the reaction. Ammonia equivalents do not require 3-10 equivalents of nitrogen like ammonia, a 1:1 ratio of ammonia equivalent to aryl halide or slight excess is all that is required. The ammonia equivalents also do not suffer the problem of product loss due to over-arylation because the product is less reactive than the ammonia equivalent. An exception to this is allylamine which readily over-arylates generating tertiary amines, although the extra allyl group is easily removed in the next step.

The bases used for ammonia equivalents also vary widely compared to amination with ammonia. For example, benzophenone imine and *tert*-butyl sulfinamide both couple using Cs₂CO₃ as the base which extends the substrate scope to include base-sensitive substrates. This is an advantage over ammonia which still requires aggressive NaOtBu that necessitates careful monitoring to minimize unwanted side reactions. Ammonia equivalents LiHMDS and ZnHMDS do not require added base and while the substrate scope is somewhat limited with LiHMDS, ZnHMDS tolerates a wide variety of base-sensitive groups.

Catalysts required for coupling with ammonia equivalents are different than those with ammonia. Ammonia equivalents can utilize simpler, less expensive ligands (eg. P(*t*Bu)₃, DPPF, BINAP). The less sterically demanding ligands are likely a consequence of more facile reductive eliminations with ammonia equivalents and the resulting products inability to re-enter the catalytic cycle to any meaningful extent.

Aminotriphenylsilane (**70**) has been used in Buchwald-Hartwig amination as an ammonia equivalent.⁹⁹ The single triphenylsilyl group is less bulky than the two trimethylsilyl groups of LiHMDS, which is too sterically hindered to couple with *ortho*-substituted aryl halides. Unlike LiHMDS, compound **70** couples well with *ortho*-substituted aryl halides.⁹⁹

Ammonia equivalents need to be removed in a subsequent reaction to yield the free amine. The removal is often done with the crude reaction mixture which makes the process less of an inconvenience. The conditions required to remove what is effectively a protecting group vary between groups. *Tert*-butyl sulfinamide and allylamine are arguably more difficult to remove, requiring 4 M HCl or refluxing methanesulfonic acid with Pd/C, respectively.^{93,94} Although coupling with allylamine and *tert*-butyl sulfinamide have good functional group tolerance, the deprotections steps place restrictions on what functional groups can be tolerated in the overall process. Benzophenone imine requires addition of 2 M HCl to a THF solution to hydrolyze, which is mild enough to tolerate esters, ketones, and acetals among other functional groups.⁹⁵

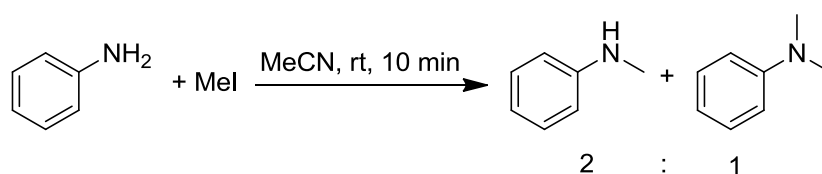
The mildest deprotections involve removal of silyl groups from the corresponding silylated amines. It is possible to remove trimethylsilyl groups by acidifying an ethereal solution with one drop of 1 M HCl for small scale 0.5 mmol reactions. The triphenylsilyl group is removed almost as easily as trimethylsilyl requiring addition of a few mL of 1 M HCl to the crude reaction mixture for 0.5 mmol reactions. Triphenylsilyl groups will also come off by simply passing the product through a column of silica, although basification of the silica with triethylamine is sufficient to stabilize triphenylsilylated amines. If the substrate contains functionality that is extremely sensitive to acid, TBAF may be used to remove the silyl protecting groups.

N-Alkylation

Alkylation of amines, like Buchwald-Hartwig amination, is an important reaction for the synthesis of amine-containing molecules. Reaction of an amine nucleophile with a good electrophile (e.g., primary alkyl bromide, iodides, tosylates) to form a new C—N bond is a facile

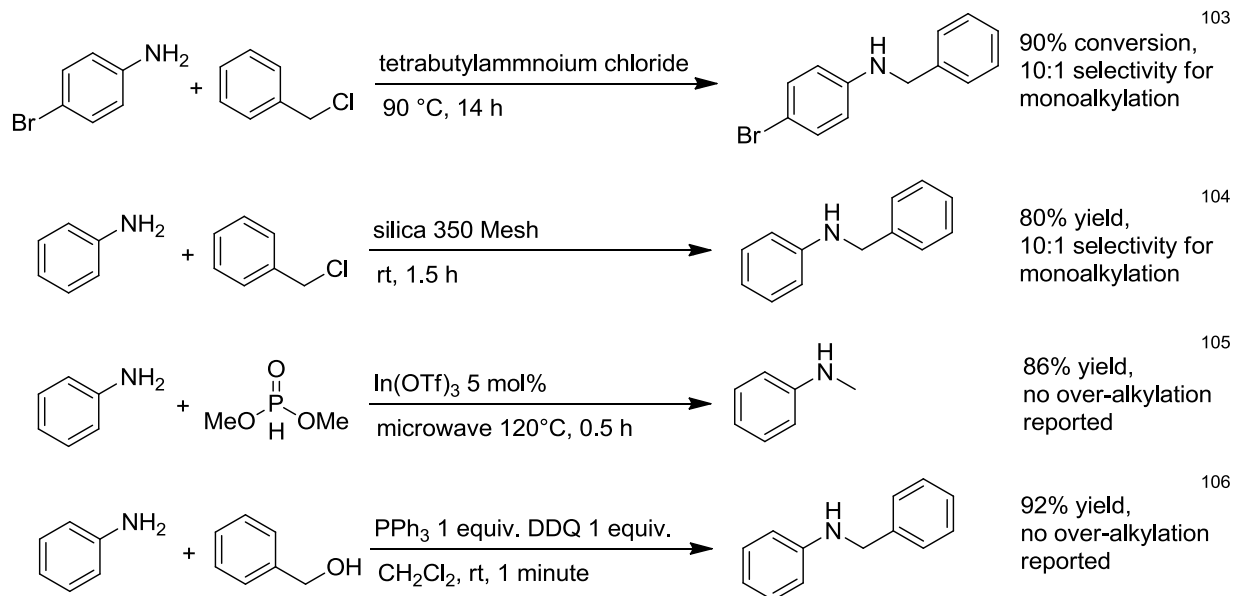
reaction that normally takes place under mild conditions (Scheme 29). Also demonstrated in Scheme 29 is the over-alkylation problem with amines. The product of N-alkylation of a primary amine is a secondary amine that has increased nucleophilicity from an electronic perspective and decreased nucleophilicity from a steric perspective. Alkylation of primary, allylic, and benzylic electrophiles with primary alkyl or aryl amines produce substantial amounts of the over-alkylated product.

Scheme 29. Methylation of aniline.¹⁰⁰



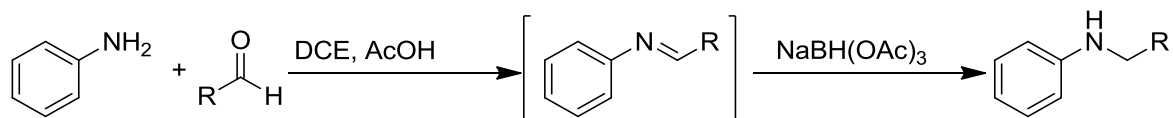
Over the years there have been numerous procedures developed to make N-alkylation more selective for monoalkylated product. These strategies include: special bases like CsOH,^{101,102} ionic liquid solvents,^{100,103} reactions on silica,¹⁰⁴ dialkylphosphites or a mixture of alcohol/triphenylphosphine/DDQ to generate more selective alkyl electrophiles,^{105,106} and biocatalyzed reactions,¹⁰⁷. These alkylation procedures are able to provide increased selectivity for monoalkylation without resorting to using the amine in large excess to favour monoalkylation (Scheme 30).

Scheme 30. N-alkylation with increased selectivity for monoalkylation.^{103–106}

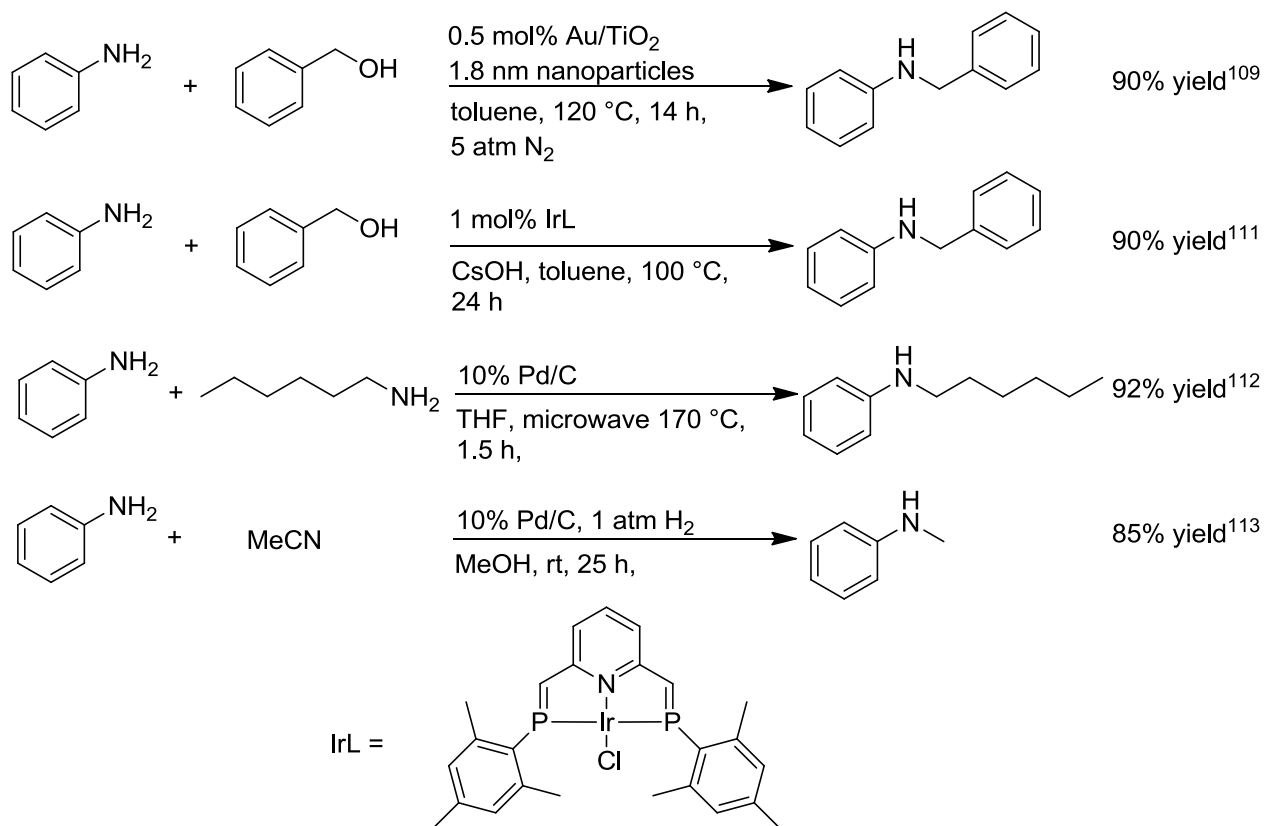


Another approach to obtaining N-alkylated products is reductive alkylation. In reductive alkylation, an amine is condensed with an aldehyde or ketone to form an imine and then reduced to provide the desired alkylamine (Scheme 31). This concept has been expanded to include reactions with nitriles, alcohols, and alkyl amines that are made possible by the addition of a transition metal catalyst. The transition metal catalyst (containing Pd, Au, Ag, Ru, or Ir) is thought to oxidize the alcohol or amine by β -hydride elimination to an aldehyde or imine. The aldehyde or imine will then condense with the amine to yield an imine that is reduced by the catalyst.^{108–113} In the case of nitriles, coordination with Pd facilitates the addition of the amine to the nitrile, which then undergoes a condensation reaction to generate an imine that gets reduced to the amine.^{114,115}

Scheme 31. Generalized reductive alkylation between aniline and an aldehyde.



Scheme 32. Selective alkylation of aniline.^{110,112–114}

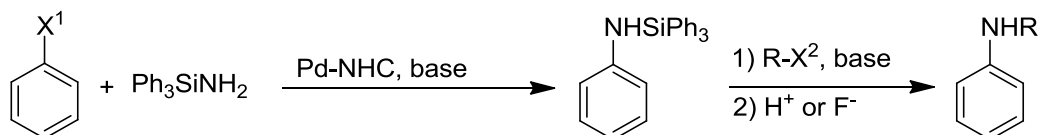


Research Objectives

Using highly active Pd-NHC catalysts, the scope of amination with aminotriphenylsilane will be explored and the silylated products will be isolated. If the silylated products can be successfully isolated, they will be subjected to alkylation with the goal of preventing over-alkylation of the arylamine by primary electrophiles. This method would prevent over-arylation

at the coupling stage and over-alkylation of the product amine. The net result is an alternative to Buchwald-Hartwig amination with alkylamines and alkylation of a primary arylamines to obtain a secondary amine (Scheme 33).

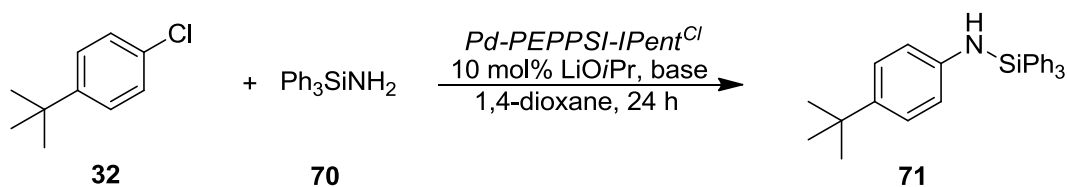
Scheme 33. Amination, alkylation and silyl group removal.



Results and Discussion

Pd-catalyzed Coupling of Aryl Halides and Silylated Amines

The coupling of **70** with aryl chlorides was first attempted with a selection of bases previously used in Buchwald-Hartwig amination (Table 5). NaOtBu gives conversion to product, but the triphenylsilyl group of the reactant or product is slowly removed, releasing ammonia or the aniline, respectively. The ammonia or aniline then enters the catalytic cycle and produces significant quantities of 4-*tert*-butyl aniline and diarylamine. Weaker bases (entries 1-4, Table 5) give little or no conversion to products whereas LiHMDS provided 100% conversion to **71**. The reason for the effectiveness of LiHMDS may be that **70** is deprotonated prior to coordination to palladium, making deprotonation of the highly sterically hindered Pd-amido intermediate unnecessary.⁹⁹

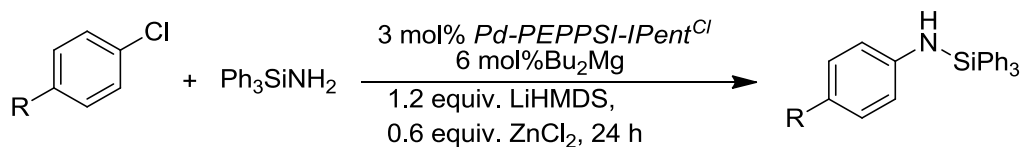
Table 5. Reaction conditions optimization for coupling of 4-*tert*-butylchlorobenzene with **70**.

| Entry ^[a] | Mol (%) | base | Temp. (°C) | Conversion (%) |
|----------------------|---------|---------------------------------|------------|-------------------|
| 1 | 1 | Cs ₂ CO ₃ | 80 | 0 |
| 2 | 1 | Cs ₂ CO ₃ | 100 | 0 |
| 3 | 3 | K ₃ PO ₄ | 100 | 0 |
| 4 | 1 | NaH + 41 (BHT) | 90 | < 5 |
| 5 ^[b] | 1 | NaO ^t Bu | 30 | < 5 |
| 6 | 1 | NaO ^t Bu | 100 | 10 ^[c] |
| 7 | 3 | NaO ^t Bu | 100 | 45 ^[d] |
| 8 | 3 | LiHMDS | 100 | 100 |

[a] 0.1 M aryl-Cl, conversion determined by ¹H NMR spectroscopy. [b] Pre-catalyst was activated by stirring with LiOiPr at 95 °C for 5 minutes. [c] Fourty percent of aryl-Cl was converted to bis(4-(*tert*-butyl)phenyl)amine. [d] Thirty-five percent of aryl-Cl was converted to bis(4-(*tert*-butyl)phenyl)amine.

With LiHMDS as the base, reaction conditions were further optimized in an attempt to allow substrates that are not stable to LiHMDS at 100 °C to be coupled (Table 6). Reactions employing the slightly electronically deactivated **32** went to completion using *Pd-PEPPSI-Pent^{Cl}* in toluene at 100 °C or at room temperature. In order lower the temperature significantly, pre-catalyst activation with dibutylmagnesium was required (entry 1, Table 6). Room temperature reactions were not able to negate the effects of LiHMDS on base-sensitive substrates like methyl *p*-chlorobenzoate where no coupled product was formed.

Table 6. Optimization of the reaction conditions with ZnHMDS for base-sensitive substrates.



| Entry ^[a] | R | Solvent | ZnCl ₂ (equiv.) | Temp. (°C) | Conversion (%) |
|----------------------|---|---------------------|-------------------------------|------------|----------------|
| 1 | -C(CH ₃) ₃ (32) | Toluene | - | rt | 100 |
| 2 | -COOCH ₃ | Toluene | - | rt | 0 |
| 3 | -COOCH ₃ | Toluene | 0.6 | rt | 0 |
| 4 | -COOCH ₃ | THF | 0.6 | rt | 45 |
| 5 | -COOCH ₃ | DME | 0.6 | rt | 50 |
| 6 | -COOCH ₃ | DME | 0.6 | 80 | 65 |
| 7 | -COOCH ₃ | 1:1 THF/ Toluene | 0.6 | 60 | 65 |

[a] 0.625 M 4-*tert*-butylchlorobenzene, conversion determined by ¹H NMR spectroscopy. The pre-catalyst was activated by stirring with Bu₂Mg at rt in toluene for 10 min. ZnHMDS was formed by stirring LiHMDS and ZnCl₂ in THF for 20 min.

Prior to Buchwald-Hartwig amination with ammonia, ZnHMDS was reported as a functional group tolerant substitute for LiHMDS.⁹⁸ Although unreactive in the absence of added salts, ZnHMDS can be made *in situ* by the addition of ZnCl₂ to LiHMDS and was successful in suppressing the reactivity of LiHMDS towards base-sensitive functional groups (entries 4-7, Table 6). The solvent was switched from toluene to an etheral solvent to dissolve ZnCl₂. DME or a 1:1 mixture of toluene and THF worked equally well (entries 6 & 7, Table 6),

but the co-solvent was chosen for convenience as pre-catalyst activation works well in toluene and both LiHMDS and ZnCl₂ are available commercially as THF solutions.

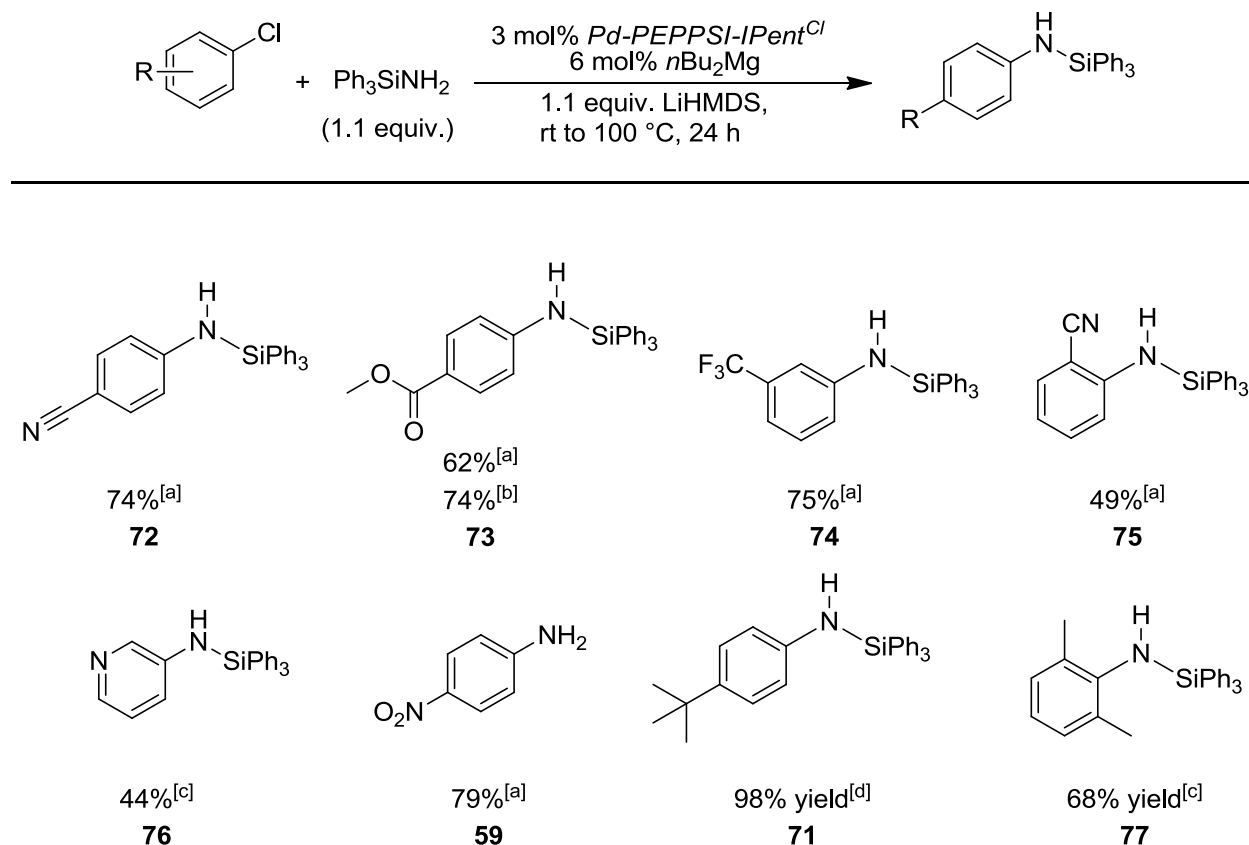
The presence of LiCl, either as a by-product of the cation exchange between LiHMDS and ZnCl₂, or as an additive to ZnHMDS is essential for the coupling of the HMDS group to an aryl halide.⁹⁸ It is possible that by mixing LiHMDS and ZnCl₂ together, there is an equilibrium that favours formation of the unreactive ZnHMDS. The small amount of LiHMDS present is enough to deprotonate **70** and allow the catalytic cycle to turn over.

Using two procedures, one employing ZnCl₂ for base sensitive substrates and one without, **70** was coupled to a variety of sterically and electronically diverse aryl halides (Scheme 34). Aryl halides featuring electron withdrawing groups in the *para* or *meta* position coupled in good yield with addition of ZnCl₂. For **73**, there was a slight increase in yield going to the more bulky *Pd-PEPPSI-IHept*^{Cl} pre-catalyst; other substrates gave similar yields between the two pre-catalysts. Compound **76** was obtained in a relatively low 44% yield, the highest yield obtained for nitrogen-containing heterocycles. Product **71** was obtained in excellent yield and the sterically hindered **77** was obtained in 68% yield to demonstrate that *ortho*-substituted aryl halides can be coupled with this protocol. Substrates without base-sensitive functional groups have been previously reported for the coupling of **70** (although silylated products were never isolated)⁹⁹, so the substrate scope was not extensively explored.

The desilylated product **59** was obtained in 79% yield after the initial silylated product hydrolyzed on silica. The *p*-nitro group makes **59** a good leaving group which accelerates the rate of hydrolysis. In order to minimize hydrolysis on silica, columns were run with at least 1% triethylamine in the eluent, which was sufficient to maintain the silylated group in all products

except for **59**. Although the products hydrolyze easily in dilute acid, they are bench top stable with no loss of triphenylsilyl group (observed by ^1H NMR spectroscopy) after one year for products **71** and **73**.

Scheme 34. Amination reactions with Ph_3SiNH_2 and aryl halides.

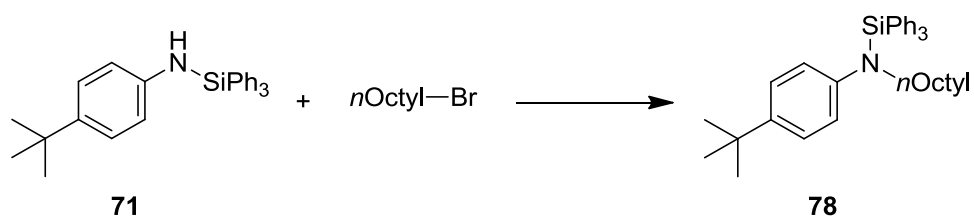


[a] 0.625 M aryl-Cl, 0.55 equiv. ZnCl_2 , 65°C , 1:1 toluene:THF [b] 3 mol% $\text{Pd-PEPPSI } i\text{Hept}^{\text{Cl}}$. [c] 100°C . [d] Toluene, rt.

With a group of silylated products in hand, alkylation of **71** was attempted with 1-bromooctane (Table 7). Reactions with potassium or cesium carbonate in refluxing methylene chloride or acetonitrile resulted in no reaction (entries 1-3, Table 7). Reactions in DMF resulted in partial desilylation of the reactant, allowing the free amine to over-alkylate in the absence of

the protecting group. Since the direct alkylation was unsuccessful, the strategy was changed to deprotonate the silylamine first to generate a better nucleophile. Deprotonation in THF with NaH caused partial loss of the silyl group before alkylation was complete, resulting in over-alkylation. Deprotonation with LiHMDS in THF at room temperature followed by addition of 1-bromooctane gave 60% conversion to alkylated product (entry 8, Table 7).

Table 7. Optimizing of alkylation reaction conditions with **71** and 1-bromooctane.



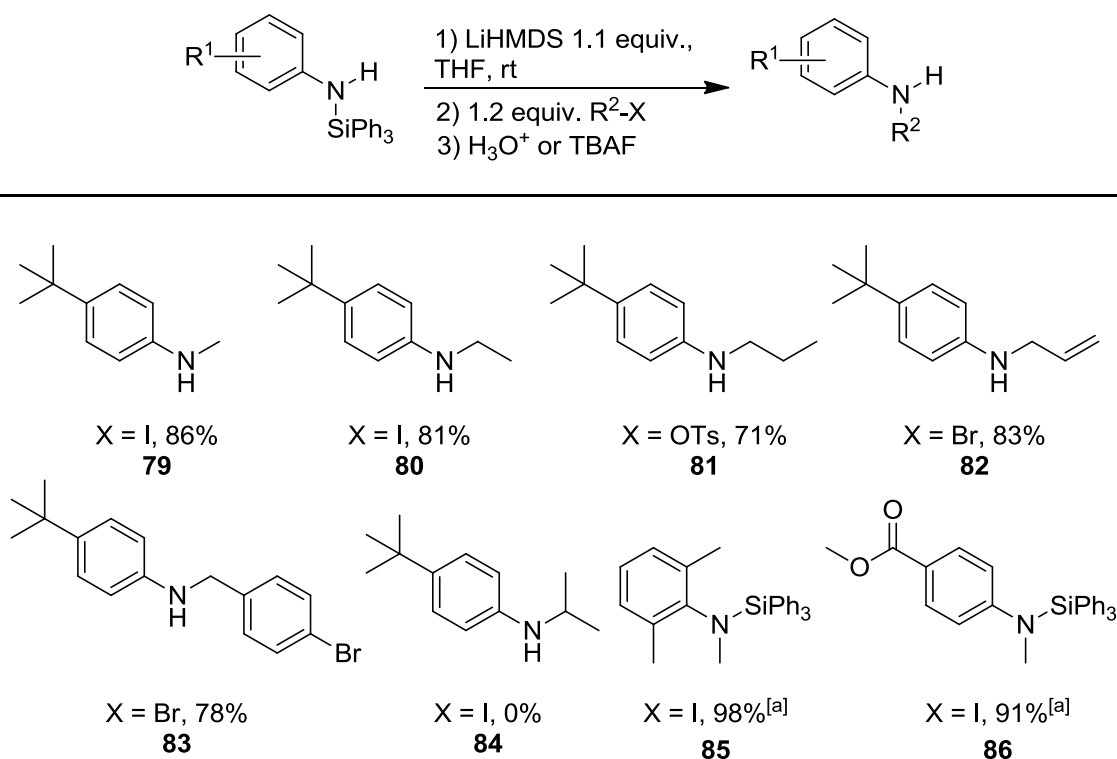
| Entry ^[a] | base | Solvent | Temp. (°C) | Conversion (%) |
|----------------------|---------------------------------|---------|------------|-------------------|
| 1 | Cs ₂ CO ₃ | DCM | 40 | 0 |
| 2 | K ₂ CO ₃ | MeCN | reflux | 0 |
| 3 | Cs ₂ CO ₃ | MeCN | reflux | 0 |
| 4 | K ₂ CO ₃ | DMF | 120 | 0 |
| 5 | Cs ₂ CO ₃ | DMF | 120 | 0 |
| 6 | NaH | THF | 60 | < 5 |
| 7 | LiHMDS | ether | rt | 0 |
| 8 | LiHMDS | THF | rt | 60 ^[a] |

[a] Conversion determined by ¹H NMR spectroscopy

Using LiHMDS to deprotonate **71** in THF prior to addition of the electrophile, a variety of primary (**79-81**, **85**, **86**), allylic (**82**), and benzylic (**83**) electrophiles featuring bromide, iodide

and tosylates leaving groups were alkylated (Scheme 35). Products **85** and **86** were isolated without removing the triphenylsilyl group, verifying that the alkylation takes place on the silyl protected amines. Product **85** demonstrates that *ortho*-substitution does not prevent alkylation and product **86** illustrates that esters are well tolerated. Reaction of **71** with isopropyl iodide resulted in no alkylated product, likely because elimination occurred rather than the desired substitution. When (1-bromoethyl)benzene was used as the electrophile a large amount of styrene was formed which is the product of elimination.

Scheme 35. Alkylation of triphenylsilyl protected anilines with alkyl bromides, iodides and tosylates.



[a]. Product isolated without silyl group removal.

Removal of the triphenylsilyl group was accomplished by addition of 1M HCl to the THF

reaction mixture or addition of TBAF. Both are facile reactions at room temperature, although TBAF is noticeably slower taking up to 2 h to reach completion. These procedures for protecting group removal are milder than what is required for non-silyl ammonia equivalents.

Conclusions

Aminotriphenylsilane (**70**) is a convenient ammonia equivalent that can be coupled using *Pd-PEPPSI-Pent^{Cl}* and LiHMDS for non-base-sensitive substrates. For base-sensitive substrates addition of ZnCl₂ to form ZnHMDS *in situ* makes the conditions sufficiently mild to couple esters, nitriles, and nitro groups. The silyl protected products are useful intermediates for selective N-alkylation, yielding the secondary amine after a mild deprotection in acid or with fluoride.

Experimental Section

General Experimental

All experiments were conducted under an atmosphere of dry argon in oven-dried glassware using standard Schlenk techniques unless noted otherwise. Experiments performed in an oil bath were done using Fisher Scientific silicone oil in a Pyrex crystallizing dish on top of an IKA RCT basic model magnetic hotplate stirrer with an ETS-D5 electronic contact thermometer. Glovebox manipulations were performed in an MBraun Unilab glove-box under an atmosphere of dry argon. All reagents were purchased from Sigma-Aldrich or Alfa Aesar and were used without further purification unless noted otherwise. Pre-catalysts were acquired from Total Synthesis Ltd., Toronto, Canada. All reaction vials (screw-cap threaded, caps attached, 15x45 mm) were purchased from Fisher Scientific. Analytical thin layer chromatography (TLC) was performed on EMD 60 F254 pre-coated glass plates and spots were visualized with UV light (254 nm). Column chromatography purifications were carried out using the flash technique on ZEOprep 60 silica gel (40 - 63 μm). NMR spectra were recorded on a Bruker 400 AVANCE spectrometer. The chemical shifts for ^1H -NMR spectra are given in parts per million (ppm) referenced to the residual proton signal of the deuterated solvent; coupling constants are expressed in Hertz (Hz). ^{13}C -NMR spectra were referenced to the carbon signal(s) of the deuterated solvent. ^{19}F -NMR Spectra were referenced to (trifluoromethyl)benzene. The following abbreviations are used to describe peak multiplicities: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, tt = triplet of triplets, qt = quartet of triplets, qd = quartet of doublets, and m = multiplet. High Resolution Mass Spectrometry (HRMS) analysis

was performed by the Mass Spectrometry and Proteomics Unit at Queen's University in Kingston, Ontario.

Synthetic Procedures

General Amination Procedures A & B: An oven-dried argon filled vial (8 mL) containing a Teflon coated magnetic stir bar was charged with 4.9 mg of **47** (0.005 mmol, 2 mol%), 28.8 mg of NaO^tBu (0.30 mmol, 1.2 equiv. **Procedure A**) or 24.0 mg of NaO^tBu (0.25 mmol, 1.0 equiv. **Procedure B**) and, if solid, the aryl halide (0.25 mmol, 1 equiv.). The vial was sealed with a Teflon coated screw cap and backfilled with argon three times. The aryl halide, if liquid, (0.25 mmol, 1 equiv.) and 0.5 M NH₃ 1,4-dioxane solution (5 ml) were then added via syringe. The vial was then placed in a pre-heated oil bath at the given temperature and stirred for the indicated length of time. The reaction mixture was then cooled to rt, diluted with CH₂Cl₂, filtered through a plug of silica with ethyl acetate washing, and the filtrate concentrated *in vacuo*. The crude product was purified via flash chromatography on silica gel to yield the desired product.

General Amination Procedure C: An oven-dried argon filled vial (8 mL) containing a Teflon coated magnetic stir bar was charged with 2.2 mg of **27** (0.0025 mmol, 1 mol%), 28.8 mg of NaO^tBu (0.3 mmol, 1.2 equiv.), 1.7 mg of LiO^tPr (0.025 mmol, 0.1 equiv.) and, if solid, the aryl halide (0.25 mmol, 1 equiv.). The vial was sealed with a Teflon coated screw cap and backfilled with argon three times. The aryl halide, if liquid, (0.25 mmol, 1 equiv.) and 0.5 M NH₃ 1,4-dioxane solution (5 ml) were then added via syringe. The vial was then placed in a pre-heated oil bath at the given temperature and stirred for the indicated length of time. The reaction mixture was cooled to rt, diluted with CH₂Cl₂, filtered through a plug of silica with ethyl acetate washing, and the filtrate concentrated *in vacuo*. The crude product was purified via flash

chromatography on silica gel to yield the desired product.

General procedure for amination of aryl halides with aminotriphenylsilane using LiHMDS

(Procedure D): In a glovebox, a vial (8 mL) containing a Teflon-coated magnetic stir bar was charged with LiHMDS (44.9 mg, 0.275 mmol), sealed, and removed from the glovebox. The vial was then charged with aminotriphenylsilane (75.7 mg, 0.275 mmol), *Pd-PEPPSI-Pent^{Cl}* (6.5 mg, 3 mol%), and if solid, the aryl halide (0.25 mmol, 1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3X). The aryl halide, if liquid, (0.25 mmol, 1 equiv.) and toluene (4 mL) were then added via syringe. The vial was then placed in a pre-heated oil bath at the given temperature and the reaction stirred for 24 h. The mixture was then cooled to rt, diluted with CH₂Cl₂, filtered through a plug of silica with ethyl acetate containing 1% triethylamine, and the filtrate concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel using an eluent containing 1% triethylamine to yield the desired product.

General procedure for amination of aryl halides with aminotriphenylsilane using LiHMDS

and ZnCl₂ (Procedure E): An oven-dried argon filled vial (A, 8 mL) containing a Teflon-coated magnetic stir bar was charged with 1.0 M LiHMDS in THF (0.275 mL, 0.275 mmol), 0.5 M ZnCl₂ in THF (0.275 mL, 0.138 mmol), and THF (1.45 mL) via syringe and the resultant solution stirred for 20 min. A separate oven-dried argon filled vial (B, 8 mL) containing a Teflon-coated magnetic stir bar was charged with *Pd-PEPPSI-Pent^{Cl}* (6.5 mg, 3 mol%). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3X). Toluene (2 mL) and 1.0 M *n*Bu₂Mg in heptanes (15 μL, 6 mol%) were added *via* syringe and the solution stirred for 10 min. An oven-dried argon-filled vial (C, 8 mL) containing a Teflon-coated magnetic stir bar

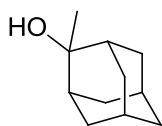
was charged with aminotriphenylsilane (75.7 mg, 0.275 mmol), and the aryl halide (0.25 mmol, 1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon (3X). The contents of vial B were transferred *via* syringe to vial C. The contents in vial A were then transferred to vial C *via* syringe. Vial C was then placed in a pre-heated oil bath at 65 °C and stirred for 24 h. The reaction mixture was then cooled to rt, diluted with CH₂Cl₂, filtered through a plug of silica with ethyl acetate containing 1% triethylamine, and the filtrate concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel using an eluent containing 1% triethylamine to yield the desired product.

Alkylation of silylated amines (Procedure F): An oven-dried argon filled vial (8 mL) containing a Teflon-coated magnetic stir bar was charged with the silylated amine (1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon three times. THF was then added *via* syringe to dilute the silylated amine to 1.0 M. LiHMDS (1.0 M, 1.1 equiv.) and the electrophile (1.2 equiv.) were then added *via* syringe and reaction progress was monitored by TLC. When the reaction was judged completed, either 1.0 M aqueous HCl (5 equiv.) or 1.0 M TBAF in THF (5 equiv.) were added and the resultant mixture was stirred until complete removal of the triphenylsilyl group was confirmed by TLC analysis. The reaction mixture was then diluted with ether, 0.1 M NaOH added and the layers separated. The pooled organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel to yield the desired product.

Alkylation of silylated amines (Procedure G): An oven-dried argon filled vial (8 mL) containing a Teflon-coated magnetic stir bar was charged with the silylated amine (1 equiv.). The vial was sealed with a Teflon-coated screw cap and backfilled with argon three times. THF was

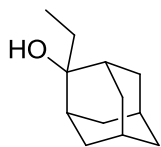
then added *via* syringe to dilute the silylated amine to 1.0 M. LiHMDS (1.0 M, 1.1 equiv.) and the electrophile (1.2 equiv.) were then added *via* syringe and reaction progress was monitored by TLC analysis. When the reaction was judged completed, it was diluted with CH₂Cl₂, filtered through a plug of silica with ethyl acetate containing 1% triethylamine, and the filtrate concentrated *in vacuo*. The crude product was purified *via* flash chromatography on silica gel using an eluent containing 1% triethylamine to yield the desired product.

Synthesis of 2-methyl-2-adamantanol (**38**).



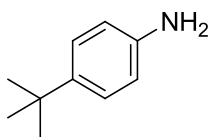
A 50 mL flame dried round bottom flask was charged with 3 M methylmagnesium bromide in ether (16.5 mmol, 5.5 mL) under argon and diluted with 15 mL of dry THF. A separate 50 mL flame dried round bottom flask was charged with 2-adamantone (15 mmol, 2.25 g) under a cone of argon and dissolved in 15 mL of dry THF. The flask containing methylmagnesium bromide was cooled to 0 °C and 2-adamantone was added dropwise *via* syringe with stirring over 30 minutes. The reaction mixture was then quenched with 15 mL of 1M NH₄Cl, extracted with ethyl acetate (3x15 mL), dried with MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by *via* flash column chromatography on silica gel (5% ethyl acetate/hexanes, R_f = 0.3) to give 2.33 g of **38** as a white solid (94% yield). MP = 212-214 °C (lit value 209-212 °C)¹¹⁶ ¹H NMR (400 MHz, CDCl₃) δ 2.19-2.16 (m, 2H), 1.85-1.68 (m, 9H), 1.57-1.55 (m, 2H), 1.43 (s, 1H), 1.34 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 73.8, 39.1, 38.3, 35.1, 32.9, 27.5, 27.4, 27.0. The spectral data are in accordance with those reported in the literature.¹¹⁶

Synthesis of 2-ethyl-2-adamantanol (**39**).

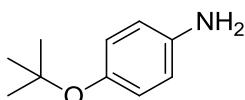


A 50 mL round bottom flask was charged with ZnCl₂ (1.5 mmol, 205 mg) and LiCl (16.5 mmol, 700 mg) and melt dried. Dry THF (15 mL) was added *via* syringe followed by 3 M ethylmagnesium bromide in ether (16.5 mmol, 5.5 mL) and 1 M (trimethylsilyl)methylmagnesium bromide in ether (3 mmol, 3 mL). A separate flame dried 50 mL flask was charged with 2-adamantone (15 mmol, 2.25g) under a cone of argon followed by 15 mL of dry THF added *via* syringe. The flask containing ethylmagnesium bromide was cooled to 0 °C and 2-adamantone was added dropwise *via* syringe with stirring over 30 minutes. The reaction mixture was then quenched with 15 mL of 1M NH₄Cl, extracted with ethyl acetate (3x15 mL), dried with MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by *via* flash column chromatography on silica gel (5% ethyl acetate/ hexanes, R_f = 0.3) to give 2.33 g of **39** as a white solid (59% yield). MP = 65-67 °C. ¹H NMR (400 MHz, CDCl₃) δ 2.18-2.15 (m, 2H), 1.85-1.81 (m, 4H), 1.7-1.76 (m, 8H), 1.57-1.54 (m, 2H), 1.32 (s, 1H), 0.88 (t, J = 7.6 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 74.8, 38.2, 36.4, 34.4, 32.9, 30.4, 27.4, 27.2, 6.3. The spectral data are in accordance with those reported in the literature.¹¹⁷

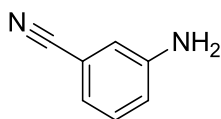
Compound Characterization Data for Pd-Catalyzed Amination Reactions with ammonia:



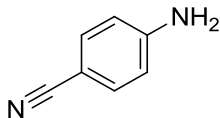
4-tert-Butylaniline (33) (Scheme 26). Following amination procedure A, 34.4 mg of **33** were isolated by flash chromatography (25% ether/pentane, $R_f = 0.2$) as a yellow oil (92% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.19 (d, $J = 8.8$ Hz, 2H), 6.65 (d, $J = 8.8$ Hz, 2H), 3.56 (br s, 2H), 1.29 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 143.9, 141.5, 126.1, 115.0, 34.0, 31.6. The spectral data are in accordance with those reported in the literature.¹⁰



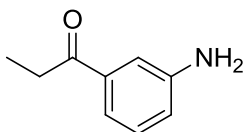
4-tert-Butoxyaniline (48) (Scheme 26). Following amination procedure A, 37.6 mg of **48** were isolated by flash chromatography (50% ether/pentane, $R_f = 0.4$) as a yellow oil (91% yield). ^1H NMR (400 MHz, CDCl_3) δ 6.60 (d, $J = 6.4$ Hz, 2H), 6.58 (d, $J = 6.4$ Hz, 2H), 3.50 (br s, 2H), 1.28 (s, 9H); ^{13}C -NMR (100 MHz, CDCl_3) δ 147.3, 142.4, 125.4, 115.5, 77.8, 28.8. The spectral data are in accordance with those reported in the literature.⁷⁷



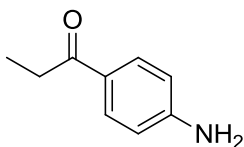
3-Aminobenzonitrile (49) (Scheme 26). Following amination procedure B, 25.0 mg of **49** were isolated by flash chromatography (33% ethyl acetate/hexanes, $R_f = 0.4$) as a yellow solid (85% yield). MP = 48 °C (lit value 46 °C);¹¹⁸ ^1H NMR (400 MHz, CDCl_3) δ = 7.22 (dd, $J = 8.4, 7.6$ Hz, 1H), 7.01 (d, $J = 7.6$ Hz, 1H), 6.90 (s, 1H), 6.86 (d, $J = 8.4$ Hz, 1H), 3.87 (br s, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ = 146.9, 130.0, 121.9, 119.2 (2 signals), 117.4, 112.9. The spectral data are in accordance with those reported in the literature.¹¹⁸



4-Aminobenzonitrile (50) (Scheme 26). Following amination procedure B, 27.1 mg of **50** were isolated by flash chromatography (66% ether/hexanes, $R_f = 0.3$) as a beige solid (92% yield). MP = 81 °C (lit value 82-84 °C); ^1H NMR (400 MHz, CDCl_3) δ 7.4 (d, $J = 7.2$ Hz, 2H), 6.64 (d, $J = 7.2$ Hz, 2H), 4.18 (br s, 2H); ^{13}C -NMR (100 MHz, CDCl_3) δ 150.4, 133.8, 120.1, 114.4, 100.2. The spectral data are in accordance with those reported in the literature.⁸²

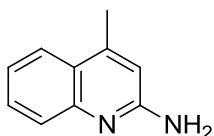


3'-Aminopropiophenone (51) (Scheme 26). Following amination procedure B, 32.7 mg of **51** were isolated by flash chromatography (33% ethyl acetate/hexanes $R_f = 0.3$) as a dark orange solid (88% yield). MP = 40 °C. ^1H NMR (400 MHz, CDCl_3) δ = 7.32 (d, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 1.6$ Hz, 1H), 7.22 (dd, $J = 8.0, 7.6$ Hz, 1H) 6.85 (dd, $J = 8.0, 1.6$ Hz, 1H), 3.79 (br s, 2H), 2.94 (q, $J = 7.2$ Hz, 2H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ = 201.1, 146.7, 140.0, 129.4, 119.4, 118.3, 113.8, 31.8, 8.3; HRMS (ESI) $[M]^+$ calcd. for $\text{C}_9\text{H}_{11}\text{NO}$ 149.0841; found: 149.0845.

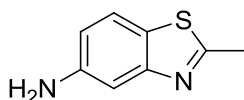


4'-Aminopropiophenone (52) (Scheme 26). Following amination procedure B, 34.6 mg of **52** were isolated by flash chromatography (33% ethyl acetate/hexanes $R_f = 0.3$) as a beige solid

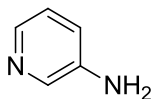
(93% yield). MP = 139 °C (lit value 136-137 °C);¹¹⁹ ¹H NMR (400 MHz, CDCl₃) δ 7.81 (d *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 4.15 (br s, 2H), 2.89 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 199.2, 150.9, 130.4, 127.4, 113.7, 31.0, 8.6. The spectral data are in accordance with those reported in the literature.¹⁰



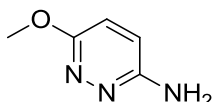
2-Amino-4-methylquinoline (53) (Scheme 26). Following amination procedure A, 34.7 mg of **53** were isolated by flash chromatography (5% methanol/ethyl acetate, *R_f* = 0.1) as a colourless solid (88% yield). MP = 131 °C (lit value 131-133 °C);¹²⁰ ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 6.56 (s, 1H), 4.86 (br s, 2H), 2.55 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 156.9, 147.7, 146.0, 129.5, 126.4, 124.0, 123.7, 122.4, 111.9, 18.8. The spectral data are in accordance with those reported in the literature.⁷⁴



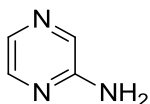
5-Amino-2-methylbenzo[d]thiazole (54) (Scheme 26). Following amination procedure A, 36.5 mg of **54** were isolated by flash chromatography (ethyl acetate, *R_f* = 0.4) as a beige solid (89% yield). ¹MP = 101 °C (lit value 100-101 °C);⁸² ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 8.6 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.0 Hz, 1H), 3.80 (br s, 2H), 2.78 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 167.8, 154.9, 145.3, 125.5, 121.7, 114.5, 107.5, 20.2. The spectral data are in accordance with those reported in the literature.⁸²



3-Aminopyridine (55) (Scheme 26). Following amination procedure A, 20.6 mg of **55** were isolated by flash chromatography (ethyl acetate, $R_f = 0.1$) as a beige solid (88% yield). MP = 61 °C (lit value 63-65 °C);¹⁰ $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.09 (d, $J = 2.4$ Hz, 1H), 8.01 (d, $J = 4.6$ Hz, 1H), 7.05 (dd, $J = 8.0, 4.6$ Hz, 1H), 6.95 (d, $J = 8.0$ Hz, 1H), 3.71 (br s, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 142.5, 140.1, 137.6, 123.8, 121.5. The spectral data are in accordance with those reported in the literature.¹⁰

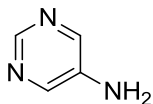


3-Amino-6-methoxypyridazine (56) (Scheme 26). Following amination procedure A, 23.8 mg of **56** were isolated by flash chromatography (5% methanol/ethyl acetate, $R_f = 0.6$) as a beige solid (76% yield). MP = 104 °C (lit value 104 °C);¹²¹ $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.81 (d, $J = 9.2$ Hz, 1H), 6.77 (d, $J = 9.2$ Hz, 1H), 4.48 (br s, 2H), 4.00 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.6, 156.2, 120.1, 119.7, 54.4. The spectral data are in accordance with those reported in the literature.¹²¹

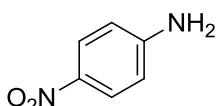


2-Aminopyrazine (57) (Scheme 26). Following amination procedure A, 18.8 mg of **57** were isolated by flash chromatography (5% methanol/ethyl acetate, $R_f = 0.3$) as a white solid (79% yield). MP = 116 °C (lit value 117-118 °C);¹²² $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.98-7.97 (m, 2H),

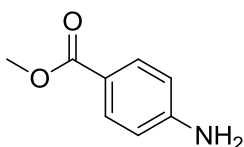
7.88 (d, $J = 2.0$ Hz, 1H) 4.65 (br s, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 154.6, 142.1, 134.3, 132.7. The spectral data are in accordance with those reported in the literature.¹²³



5-Aminopyrimidine (58) (Scheme 26). Following amination procedure A, 19.2 mg of **58** were isolated by flash chromatography (5% methanol/ethyl acetate, $R_f = 0.2$) as a white solid (81% yield). MP = 171 °C (lit value 170-171 °C);¹²² $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 8.65 (s, 1H), 8.20 (s, 2H), 3.75 (br s, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 149.8, 143.0, 140.5. The spectral data are in accordance with those reported in the literature.¹²⁴

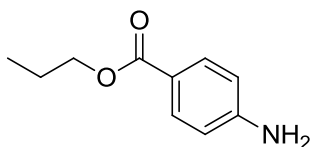


4-Nitroaniline (59) (Scheme 26). Following amination procedure B, 30.6 mg of **59** were isolated by flash chromatography (50% ethyl acetate/hexanes, $R_f = 0.4$) as an orange solid (89% yield). MP = 143 °C (lit value 145-146 °C);¹²⁵ $^1\text{H NMR}$ (400 MHz, DMSO-d_6) δ 7.94 (d, $J = 9.0$ Hz, 2H), 6.71 (s, 2H), 6.59 (d, $J = 9.0$ Hz, 2H); $^{13}\text{C-NMR}$ (100 MHz, DMSO-d_6) δ 155.7, 135.6, 126.4, 112.4. The spectral data are in accordance with those reported in the literature.¹²⁵

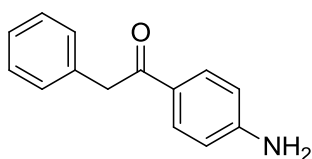


Methyl 4-aminobenzoate (60) (Scheme 26). Following amination procedure B, 23.4 mg of **60** were isolated by flash chromatography (33% ethyl acetate/hexanes, $R_f = 0.1$) as a white solid

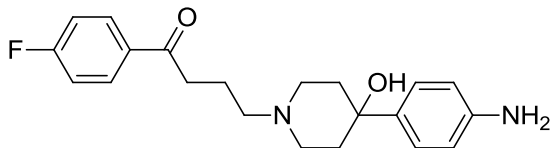
(51% yield). MP = 110 °C (lit value 109 °C);⁸² ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.07, (br s, 2H), 3.85 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 167.2, 150.9, 131.7, 119.8, 113.9 51.7. The spectral data are in accordance with those reported in the literature.⁸²



Propyl 4-aminobenzoate (61) (Scheme 26). Following amination procedure B, 30.8 mg of **61** were isolated by flash chromatography (25% ethyl acetate/hexanes, *R_f* = 0.3) as a beige solid (69% yield). MP. 73 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.8 Hz, 2H), 6.63 (d, *J* = 8.8 Hz, 2H), 4.22 (t, *J* = 6.8 Hz, 2H) 4.06, (br s, 2H), 1.75 (qt, *J* = 7.2, 6.8 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ¹³C-NMR (100 MHz, CDCl₃) δ 166.8, 150.8, 131.6, 120.2, 113.9, 66.0, 22.3, 10.6; HRMS (ESI) [M]⁺ calcd. for C₁₀H₁₃NO₂ 179.0946; found: 179.0950.

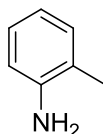


1-(4-Aminophenyl)-2-phenylethan-1-one (62) (Scheme 26). Following amination procedure B, 44.2 mg of **62** were isolated by flash chromatography (50% ethyl acetate/hexanes, *R_f* = 0.3) as a pale yellow solid (84% yield). MP = 140 °C (lit value 143 °C);¹²⁶ ¹H NMR (400 MHz, CDCl₃) δ 7.87 (d, *J* = 8.0 Hz, 2H), 7.33-7.23 (m, 5H), 6.61 (d, *J* = 8.0 Hz, 2H) 4.19 (s, 2H), 4.15 (br s, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 195.8, 151.2, 135.4, 131.1, 129.4, 128.5, 127.0, 126.6, 113.8, 44.9. The spectral data are in accordance with those reported in the literature.¹²⁶



4-(4-(4-Aminophenyl)-4-hydroxypiperidin-1-yl)-1-(4-fluorophenyl)butan-1-one (63)

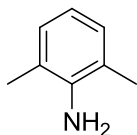
(Scheme 26). Following amination procedure B, 74.8 mg of **63** was isolated by flash chromatography (5% methanol/methylene chloride $R_f = 0.2$) as a colourless solid (84% yield). MP 170 °C. ^1H NMR (400 MHz, DMSO- d_6) δ = 8.06 (dd, $J = 8.0, 6.0$ Hz, 2H), 7.34 (t, $J = 8.4$ Hz, 2H), 6.99 (d, $J = 8.0$ Hz, 2H), 6.47 (d, $J = 8.0$ Hz, 2H), 4.87 (br s, 2H), 4.41 (bs, 1H), 2.97 (t, $J = 6.8$ Hz, 2H), 2.65-2.45 (m s, 2H), 2.45-2.25 (m, 4H), 1.90-1.75 (m, 2H), 1.70-1.55 (m, 2H), 1.48-1.38 (m, 2H); ^{13}C -NMR (100 MHz, DMSO- d_6) δ : 198.3, 164.8 (d, $J = 249$ Hz), 146.8, 137.4, 133.9 (d, $J = 2$ Hz), 130.9 (d, $J = 10$ Hz), 125.2, 115.6 (d, $J = 21$ Hz), 113.3, 69.0, 57.2, 49.2, 37.9, 35.7, 21.9. ^{19}F -NMR (376 MHz, DMSO- d_6) δ = -109.4. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{21}\text{H}_{25}\text{FN}_2\text{O}_2$ 356.1900; found: 356.1911.



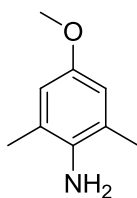
2-Methylaniline (64) (Scheme 27). Following amination procedure C, 23.6 mg of **64** were isolated by flash chromatography (25% ethyl acetate/hexanes, $R_f = 0.3$) as a yellow oil (87% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.09-7.04 (m, 2H), 6.76-6.68 (m, 2H), 3.61 (br s, 2H), 2.19 (s, 3H); ^{13}C -NMR (100 MHz, CDCl_3) δ 144.6, 130.5, 127.0, 122.4, 118.7, 150.0, 17.4. The spectral data are in accordance with those reported in the literature.¹⁰

Following amination procedure A, 20.0 mg of **64** was isolated by flash chromatography (25%

ethyl acetate/hexanes $R_f = 0.3$) as a yellow oil (75% yield).

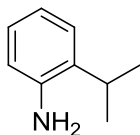


2,6-Dimethylaniline (65) (Scheme 27). Following amination procedure A, 27.5 mg of **65** were isolated by flash chromatography (10% ethyl acetate/hexanes, $R_f = 0.2$) as a yellow oil (91% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 6.98 (d, $J = 7.6$ Hz, 2H), 6.69 (t, $J = 7.6$ Hz, 1H), 3.60 (br s, 2H), 2.22 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 142.7, 128.2, 121.6, 117.9, 17.6. The spectral data are in accordance with those reported in the literature.¹⁰

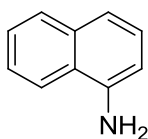


4-Methoxy-2,6-dimethylaniline (66) (Scheme 27). Following amination procedure C, 37.2 mg of **66** was isolated by flash chromatography (25% ethyl acetate/hexanes $R_f = 0.3$) as a purple oil (98% yield). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 6.57 (s, 2H), 3.74 (s, 3H), 3.32 (br s, 2H), 2.19 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ = 152.1, 136.5, 123.2, 114.0, 55.8, 18.0. The spectral data are in accordance with those reported in the literature.¹²⁷

Following amination procedure A, 31.9 mg of **66** was isolated by flash chromatography (25% ethyl acetate/hexanes $R_f = 0.3$) as a purple oil (70% yield).

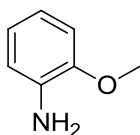


2-Isopropylaniline (67) (Scheme 27). Following amination procedure C, 26.5 mg of **67** was isolated by flash chromatography (12% ethyl acetate/hexanes $R_f = 0.4$) as a yellow oil (78% yield). ^1H NMR (400 MHz, CDCl_3) $\delta = 7.16$ (d, $J = 7.2$ Hz, 1H), 7.03 (t, $J = 7.2$ Hz, 1H), 6.80 (t, $J = 7.6$ Hz, 1H), 6.69 (d, $J = 8.0$ Hz, 1H), 3.66 (br s, 2H), 2.92 (m, 1H), 1.28 (d, $J = 6.8$ Hz, 6H); ^{13}C -NMR (100 MHz, CDCl_3) $\delta = 143.4, 132.7, 126.6, 125.5, 119.1, 115.9, 27.7, 22.3$. The spectral data are in accordance with those reported in the literature.¹⁰



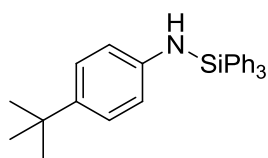
1-Naphthylamine (68) (Scheme 27). Following amination procedure A, 29.4 mg of **68** was isolated by flash chromatography (25% ethyl acetate/hexanes $R_f = 0.5$) as a purple solid (82% yield). MP = 49 °C (lit value 48-49 °C);¹²⁸ ^1H NMR (400 MHz, CDCl_3) $\delta = 7.86$ -7.82 (m, 2H), 7.51-7.47 (m, 2H), 7.36-7.32 (m, 2H), 6.81-6.78 (m, 1H) 4.14 (br s, 2H); ^{13}C -NMR (100 MHz, CDCl_3) $\delta = 142.0, 134.3, 128.5, 126.2, 125.8, 124.8, 123.5, 120.7, 118.9, 109.6$. The spectral data are in accordance with those reported in the literature.¹⁰

Following amination procedure A, 28.3 mg of **68** was isolated by flash chromatography (25% ethyl acetate/hexanes $R_f = 0.5$) as a purple solid (79% yield).

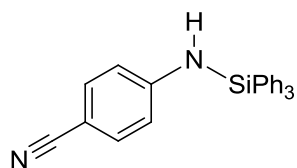


2-Methoxyaniline (69) (Scheme 27). Following amination procedure C, 20.8 mg of **69** was isolated by flash chromatography (15% ethyl acetate/hexanes $R_f = 0.3$) as a dark oil (68% yield). ^1H NMR (400 MHz, CDCl_3) $\delta = 6.82\text{-}6.78$ (m, 2H), 6.76-6.71 (m, 2H), 3.86 (s, 3H), 3.78 (br s, 2H); ^{13}C -NMR (100 MHz, CDCl_3) $\delta = 147.4, 136.2, 121.1, 118.6, 115.1, 110.5, 55.5$. The spectral data are in accordance with those reported in the literature.¹⁰

Compound Characterization Data for Pd-Catalyzed Amination Reactions with Aminotriphenylsilane:

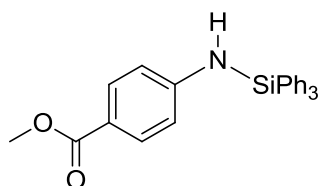


N-(4-(tert-butyl)phenyl)-1,1,1-triphenylsilanamine (71) (Scheme 34). Following amination procedure D, 99.8 mg of **71** were isolated by flash chromatography (1% triethylamine, 94% hexanes, 5% ethyl acetate, $R_f = 0.5$) as a white solid (98% yield). MP = 168 °C. ^1H -NMR (400 MHz, CDCl_3) $\delta 7.74\text{-}7.72$ (m, 6H), 7.48-7.40 (m, 9H), 7.09 (d, $J = 8.0$ Hz, 2H), 6.65 (d, $J = 8.0$ Hz, 2H), 4.05 (bs, 1H), 1.27 (s, 9H); ^{13}C -NMR (100 MHz) $\delta 143.8, 140.8, 135.6, 134.2, 130.0, 128.0, 125.8, 116.6, 33.8, 31.5$. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{28}\text{H}_{29}\text{NSi}$ 407.2069; found: 407.2060.

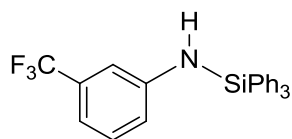


4-((triphenylsilyl)amino)benzonitrile (72) (Scheme 34). Following amination procedure E, 69.6 mg of **72** were isolated by flash chromatography (1% triethylamine, 84% hexanes, 15%

methylene chloride, $R_f = 0.3$) as a light-brown solid (74% yield). MP = 233-236. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.68 (d, $J = 7.6$ Hz, 6H), 7.50-7.41 (m, 9H), 7.30 (d, $J = 8.6$ Hz, 2H), 6.68 (d, $J = 8.6$ Hz, 2H), 4.52 (bs, 1H); $^{13}\text{C-NMR}$ (100 MHz) δ 151.0, 135.4, 133.4, 132.5, 130.5, 128.3, 119.9, 117.3, 100.7. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{N}_2\text{Si}$ 376.1396; found: 376.1389.

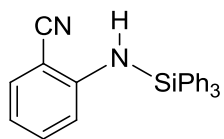


methyl 4-((triphenylsilyl)amino)benzoate (73) (Scheme 34). Following amination procedure E, 65.5 mg of **73** were isolated by flash chromatography (1% triethylamine, 89% hexanes, 10% ethyl acetate, $R_f = 0.3$) as an off-white solid (64% yield). MP = 132-135 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.75 (d, $J = 8.4$ Hz, 2H), 7.69 (d, $J = 7.2$ Hz, 6H), 7.48 (dd, $J = 7.2, 7.2$ Hz, 3H), 7.41 (dd, $J = 7.2, 7.2$ Hz, 6H), 6.68 (d, $J = 8.4$ Hz, 2H) 4.47 (bs, 1H) 3.82 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz) δ 167.2, 151.5, 135.5, 133.1, 131.2, 130.4, 128.3, 120.0, 116.7, 51.6. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{26}\text{H}_{23}\text{NO}_2\text{Si}$ 409.1498; found: 409.1491.

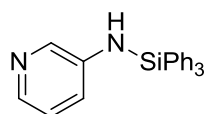


1,1,1-triphenyl-N-(3-(trifluoromethyl)phenyl)silanamine (74) (Scheme 34). Following amination procedure E, 78.7 mg of **74** were isolated by flash chromatography (1% triethylamine, 89% hexanes, 10% ethyl acetate, $R_f = 0.7$) as a pale-yellow solid (75% yield). MP = 103-107 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.74 (d, $J = 7.6$ Hz, 6H), 7.53-7.43 (m, 9H), 7.12 (dd, $J = 8.0, 7.6$ Hz, 1H), 6.98-6.84 (m, 2H), 6.82 (d, $J = 7.6$ Hz, 1H) 4.31 (bs, 1H); $^{13}\text{C-NMR}$ (100 MHz) δ

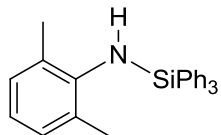
147.0, 135.5, 133.2, 131.3 (q, $^2J_{FC} = 32$ Hz), 130.3, 129.4, 128.2, 124.1 (q, $^1J_{FC} = 270$ Hz), 119.9, 114.8 (q, $^3J_{FC} = 4.0$ Hz), 113.8 (q, $^3J_{FC} = 4.0$ Hz). ^{19}F -NMR (376 MHz, CDCl_3) δ -63.4. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{F}_3\text{NSi}$ 419.1317; found: 419.1310.



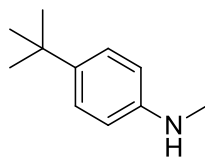
2-((triphenylsilyl)amino)benzonitrile (75) (Scheme 34). Following amination procedure E, 46.1 mg of **75** were isolated by flash chromatography (1% triethylamine, 89% hexanes, 10% ethyl acetate, $R_f = 0.3$) as a pale-yellow solid (49% yield). MP = 191-192°C. ^1H -NMR (400 MHz, CDCl_3) δ 7.73-7.70 (m, 6H), 7.51-7.41 (m, 10H), 7.12 (dd, $J = 8.0, 8.4$ Hz, 1H), 6.75-6.71 (m, 2H), 4.99 (bs, 1H); ^{13}C -NMR (100 MHz) δ 150.0, 135.4, 133.5, 132.6, 132.4, 130.5, 128.3, 118.3, 118.0, 117.2, 99.7. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{25}\text{H}_{20}\text{N}_2\text{Si}$ 376.1396; found: 376.1389.



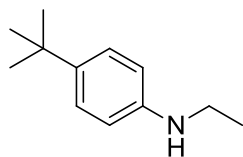
N-(triphenylsilyl)pyridin-3-amine (76) (Scheme 34). Following amination procedure D, 39.5 mg of **76** were isolated by flash chromatography (2% triethylamine, 78% hexanes, 20% ethyl acetate, $R_f = 0.3$) as a gummy purple solid (45% yield). ^1H -NMR (400 MHz, CDCl_3) δ 7.83 (d, $J = 4.8$ Hz, 1H) 7.78 (d, $J = 1.6$ Hz, 1H), 7.71 (d, $J = 7.6$ Hz, 6H), 7.48-7.38 (m, 9H), 7.01 (dd, $J = 8.0, 4.8$ Hz, 1H) 6.90 (d, $J = 8.0$ Hz, 1H); ^{13}C -NMR (100 MHz) δ 142.71, 138.9, 136.5, 136.1, 135.1, 129.8, 127.8, 123.9, 122.0. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{Si}$ 352.1396; found: 352.1389.



***N*-(2,6-dimethylphenyl)-1,1,1-triphenylsilanamine (77)** (Scheme 34). Following amination procedure D, 75.9 mg of **77** were isolated by flash chromatography (1% triethylamine, 94% hexanes, 5% ethyl acetate, $R_f = 0.7$) as a pale-yellow solid (80% yield). MP = 143-144 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.59 (d, $J = 7.2$ Hz, 6H), 7.39 (dd, $J = 7.2, 7.2$ Hz, 3H), 7.34 (dd, $J = 7.2, 7.2$ Hz, 6H), 6.90 (d, $J = 7.6$ Hz, 2H), 6.76 (dd, $J = 7.6, 7.6$ Hz, 1H) 3.43 (bs, 1H) 2.07 (s, 6H); $^{13}\text{C-NMR}$ (100 MHz) δ 142.9, 135.7, 135.4, 130.5, 129.7, 128.5, 127.7, 121.3, 20.5. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{26}\text{H}_{25}\text{NSi}$ 379.1756; found: 379.1759.

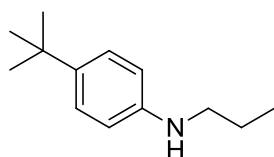


4-(*tert*-butyl)-*N*-methylaniline (79) (Scheme 35). Following procedure F, 35.1 mg of **79** were isolated by flash chromatography (17% ethyl acetate/hexanes $R_f = 0.4$) as a yellow oil (86% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.4$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 2H), 3.41 (bs, 1H), 2.84 (s, 3H) 1.31 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz) δ 147.1, 140.1, 126.0, 112.3, 33.9, 31.6, 31.1. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{11}\text{H}_{17}\text{N}$ 163.1361; found: 163.1365

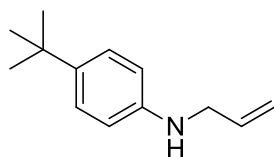


4-(*tert*-butyl)-*N*-ethylaniline (80) (Scheme 35). Following procedure F, 35.9 mg of **80** were

isolated by flash chromatography (10% ethyl acetate/hexanes, $R_f = 0.3$) as a yellow oil (81% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21 (d, $J = 8.6$ Hz, 2H), 6.57 (d, $J = 8.6$ Hz, 2H), 3.46 (bs, 1H), 3.15 (q, $J = 7.2$ Hz, 2H) 1.28 (s, 9H) 1.25 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz) δ 146.2, 140.1, 126.1, 112.6, 38.8, 33.9, 31.6, 15.1. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{12}\text{H}_{19}\text{N}$ 177.1517; found: 177.1522.

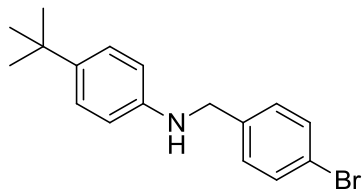


4-(tert-butyl)-N-propylaniline (81) (Scheme 35). Following procedure F, 34.0 mg of **81** were isolated by flash chromatography (10% ethyl acetate, $R_f = 0.3$) as a yellow oil (71% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.21 (d, $J = 8.6$ Hz, 2H), 6.57 (d, $J = 8.6$ Hz, 2H), 3.07 (q, $J = 7.0$ Hz, 2H) 1.63 (qt, $J = 7.2, 7.0$ Hz, 2H) 1.28 (s, 9H) 1.25 (t, $J = 7.2$ Hz, 3H); $^{13}\text{C-NMR}$ (100 MHz) δ 146.3, 140.0, 126.1, 112.5, 46.2, 33.9, 31.6, 22.9, 11.8. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{13}\text{H}_{21}\text{N}$ 191.1674; found: 191.1679.

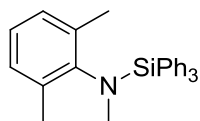


N-allyl-4-(tert-butyl)aniline (82) (Scheme 35). Following procedure F, 39.3 mg of **82** were isolated by flash chromatography (10% ether/hexanes $R_f = 0.3$) as a yellow oil (83% yield). $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.23 (d, $J = 8.6$ Hz, 2H), 6.61 (d, $J = 8.6$ Hz, 2H) 5.99 (m, 1H), 5.31 (d, $J = 17.2$ Hz, 1H) 5.18 (d, $J = 10.4$ Hz, 1H) 3.78 (d, $J = 5.2$ Hz, 2H) 3.69 (bs, 1H), 1.31 (s, 9H); $^{13}\text{C-NMR}$ (100 MHz) δ 145.8, 140.4, 135.9, 126.0, 116.2, 112.8, 47.0, 33.9, 31.6. HRMS

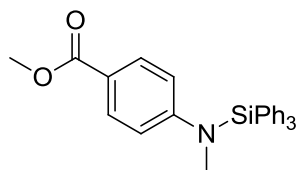
(ESI) [M]⁺ calcd. for C₁₃H₁₉N 189.1517; found: 189.1514. HRMS (ESI) [M]⁺ calcd. for C₁₃H₁₉N 189.1517; found: 189.1514.



***N*-(4-bromobenzyl)-4-(*tert*-butyl)aniline (83)** (Scheme 35). Following procedure F, 62.8 mg of **83** were isolated by flash chromatography (17% ether/hexanes, R_f = 0.3) as a pale-yellow solid (79% yield). MP = 89-90 °C. ¹H-NMR (400 MHz, CDCl₃) δ 7.46 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.58 (d, *J* = 8.8 Hz, 2H), 4.28 (s, 2H), 3.97 (bs, 1H), 1.29 (s, 9H); ¹³C-NMR (100 MHz) δ 145.5, 140.6, 138.8, 131.6, 129.1, 126.0, 120.8, 112.6, 47.9, 33.8, 31.5. HRMS (ESI) [M]⁺ calcd. for C₁₇H₂₀BrN 317.0779; found: 317.0787.



***N*-(2,6-dimethylphenyl)-*N*-methyl-1,1,1-triphenylsilanamine (85)** (Scheme 35). Following procedure G, 96.4 mg of **85** were isolated by flash chromatography (1% triethylamine/hexanes, R_f = 0.7) as a light-brown solid (98% yield). MP = 154-156 °C. ¹H-NMR (400 MHz, CDCl₃) δ 7.47-7.39 (m, 9H) 7.34-7.30 (m, 6H) 6.96-6.94 (m, 3H) 3.12 (s, 3H) 2.15 (s, 6H); ¹³C-NMR (100 MHz) δ 146.5, 138.2, 136.0, 135.5, 129.3, 128.5, 127.5, 125.4, 37.9, 19.4. HRMS (ESI) [M]⁺ calcd. for C₂₇H₂₇NSi 393.1913; found: 393.1908.



methyl 4-(methyl(triphenylsilyl)amino)benzoate (86) (Scheme 35). Following procedure G, 96.3 mg of **86** were isolated by flash chromatography (1% triethylamine, 90% hexanes, 9% ethyl acetate, $R_f = 0.5$) as an off-white solid (91% yield). MP = 122-125 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.72 (d, $J = 9.0$ Hz, 2H), 7.62 (d, $J = 7.4$ Hz, 6H), 7.44 (dd, $J = 7.2, 7.2$ Hz, 3H), 7.38 (dd, $J = 7.2, 7.4$ Hz, 6H), 6.88 (d, $J = 9.0$ Hz, 2H) 3.81 (s, 3H) 3.02 (s, 3H); $^{13}\text{C-NMR}$ (100 MHz) δ 167.3, 154.6, 135.8, 133.3, 130.1, 130.0, 128.1, 119.6, 117.0, 51.5, 36.8. HRMS (ESI) $[\text{M}]^+$ calcd. for $\text{C}_{27}\text{H}_{25}\text{NSi}$ 393.1913; found: 393.1908.

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