Late Transition Metal Catalyzed C–N and C–C Bond Forming Reactions

By John P. Wolfe

B. A. Chemistry, University of Colorado, 1994

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN
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Massachusetts Institute of Technology

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Abstract

New methods for the palladium-catalyzed amination of aryl halides are described. Key to these is the development of new catalysts and reaction conditions for these transformations.

Initially, P(*o*-tol)$_3$ ligated palladium catalysts were investigated but gave way to systems that used chelating phosphine ligands which substantially expanded the scope of the catalytic amination methodology. Palladium catalyst systems based on BINAP ((2,2'-diphenylphosphino)-1,1'-binaphthyl) allowed for the transformation of a much wider range of amines and aryl halide substrates, as well as aryl triflates. Of practical significance was that the use of cesium carbonate as a base at 100 °C substantially increased the functional group tolerance of the method.

Palladium catalysts supported by novel, bulky, electron-rich phosphine ligands are exceptionally effective in the C–N, C–O, and C–C coupling procedures. For some substrate combinations, these palladium catalysts are effective for the room-

temperature catalytic amination of aryl chlorides. These palladium catalysts are also highly effective for Suzuki coupling reactions of aryl bromides and chlorides at room temperature. Suzuki coupling reactions of aryl bromides and aryl chlorides are effective at very low catalyst loadings (0.000001–0.005 mol % Pd for ArBr, 0.02–0.05 mol % for ArCl) at 100 °C, and reactions of hindered aryl halides or boronic acids are effected at moderate catalyst loadings (1 mol % Pd). The high reactivity of these catalysts towards aryl chlorides challenges the conventional dogma that chloride substrates cannot be transformed under mild conditions with palladium catalysts, and significantly expands the pool of substrates available for cross-coupling chemistry.

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Preface

Portions of this work have been excerpted or adapted from the following articles which were co-written by the author:

"Palladium-Catalyzed Amination of Aryl Iodides" John P. Wolfe and Stephen L. Buchwald *J. Org. Chem.* **1996**, *61*, 1133-1135.

"Intramolecular Palladium-Catalyzed Aryl Amination and Aryl Amidation" John P. Wolfe, Roger A. Rennels, and Stephen L. Buchwald *Tetrahedron* **1996**, *21*, 7525-7546.

"An Improved Catalyst System for Aromatic Carbon-Nitrogen Bond Formation: The Possible Involvement of Bis(Phosphine) Palladium Complexes as Key Intermediates" John P. Wolfe, Seble Wagaw, and Stephen L. Buchwald *J. Am. Chem. Soc.* **1996**, *118*, 7215-7216.

"Synthesis of Oxygen Heterocycles via a Palladium-Catalyzed C-O Bond Forming Reaction" Michael Palucki, John P. Wolfe, and Stephen L. Buchwald *J. Am. Chem. Soc.* **1996**, *118*, 10333-10334.

"Palladium-Catalyzed Amination of Aryl Triflates" John P. Wolfe and Stephen L. Buchwald *J. Org. Chem.* **1997**, *62*, 1264-1267.

"Nickel-Catalyzed Amination of Aryl Chlorides" John P. Wolfe and Stephen L. Buchwald *J. Am. Chem. Soc.* **1997**, *119*, 6054-6058.

"Room-Temperature Catalytic Amination of Aryl Iodides" John P. Wolfe and Stephen L. Buchwald *J. Org. Chem.* **1997**, *62*, 6066-6068.

"Improved Functional Group Compatibility in the Palladium-Catalyzed Amination of Aryl Bromides" John P. Wolfe and Stephen L. Buchwald *Tetrahedron Lett.* **1997**, *38*, 6359-6362.

"An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates" John P. Wolfe, Jens Åhman, Joseph P. Sadighi, and Stephen L. Buchwald *Tetrahedron Lett.* **1997**, *38*, 6367-6370.

"The Rational Development of Practical Catalysts for Aromatic Carbon-Nitrogen Bond Formation" John P. Wolfe, Seble Wagaw, Jean-Francois Marcoux, and Stephen L. Buchwald. *Acc. Chem. Res.* **1998**, *31*, 805-818.

"A Highly Active Catalyst for Palladium-Catalyzed Cross-Coupling Reactions: Room-Temperature Suzuki Couplings and Amination of

Unactivated Aryl Chlorides" David W. Old, John P. Wolfe, and Stephen L. Buchwald *J. Am. Chem. Soc.* **1998**, *120*, 9722-9723.

"Novel Electron-Rich Bulky Phosphine Ligands Facilitate the Palladium-Catalyzed Preparation of Diaryl Ethers" Attila Aranyos, David W. Old, Ayumu Kiyomori, John P. Wolfe, Joseph P. Sadighi, and Stephen L. Buchwald *J. Am. Chem. Soc.* In Press.

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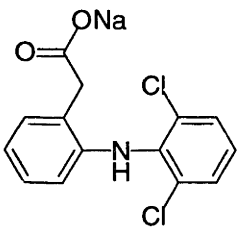
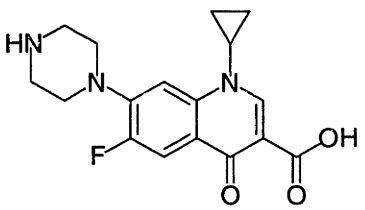
Introduction

Aryl C–N bonds are found in a wide variety of useful compounds. Aniline derivatives have numerous applications in pharmaceuticals,[1a] agrochemicals,[1b] materials,[1c] photography,[1d] xerography,[1e] and pigments.[1f] For example, Voltaren (an anti-inflammatory) and Ciproxin (an antibacterial) were both among the top twenty best selling pharmaceuticals in 1994,[2] and polyaniline is a conducting polymer with many potential applications (Figure 1).[1c]

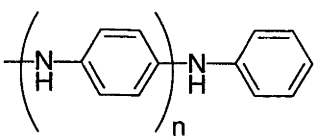
Figure 1: Examples of Important Arylamines



Voltaren



Ciproxin

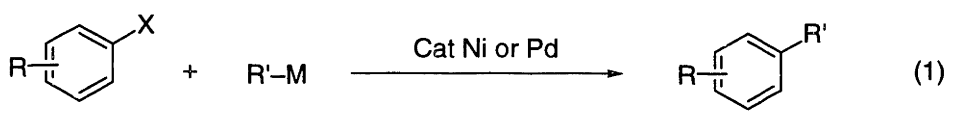


Polyaniline

Numerous methods for the formation of aryl C–N bonds have been developed.[3] The most common approaches typically involve electrophilic procedures, such as nitration followed by reduction;[3a] other electrophilic aminating reagents, such as electron-deficient azodicarboxylates have also been employed.[3b] Nucleophilic aromatic substitution reactions have been used for the synthesis of arylamines,[3c-e] as have reactions which proceed via benzyne intermediates.[3f] Barton has reported the N-arylation of amines using triarylbismuth reagents,[3g,h] and numerous copper mediated procedures for the amination of aryl halides have been developed.[3i-k] However, most of the above methods are limited in scope by the requirement for harsh reaction conditions and/or activated substrates. Furthermore, reactions which proceed through benzyne intermediates often afford mixtures of regioisomers. Due to the

limitations of these protocols, the development of new, mild, general, and selective methods for the synthesis of aryl C–N bonds is desirable.

The use of late transition metal catalysts for the synthesis of sp^2-sp^2 C–C bonds has been well developed and widely applied to the synthesis of complex molecules over the past 20 years.[4] These reactions typically involve the cross-coupling of an aryl (or vinyl) halide with an organometal species such as a Grignard reagent (Kumada coupling),[5a] an organostannane (Stille coupling),[5b] an organoboron reagent (Suzuki



(1)

X=halide, triflate

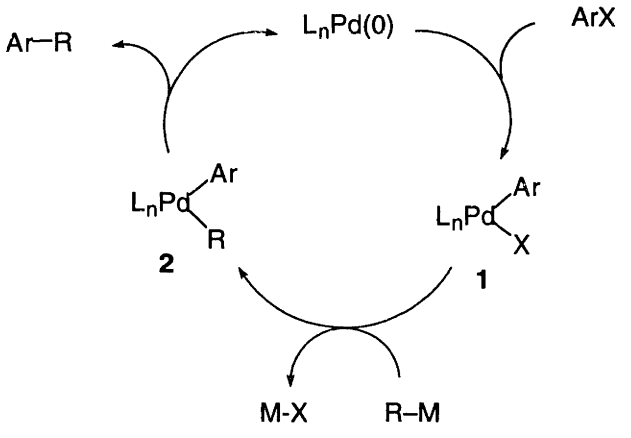
M= MgX (Kumada coupling)
=SnR_3 (Stille coupling)
=$B(OH)_2$ (Suzuki coupling)
=ZnX (Negishi coupling)

R'=aryl, vinyl

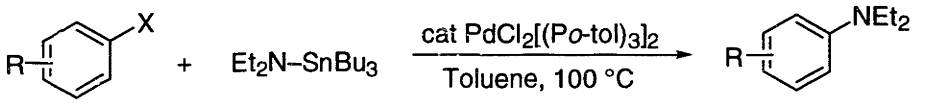
coupling),[5c] or an organozinc reagent (Negishi coupling)[5d] (eq 1). These methods allow for the regiospecific and stereospecific construction of C–C bonds which cannot easily be formed in the absence of metal catalysts.[4] With the exception of Kumada coupling, these methods employ relatively mild reaction conditions which are tolerant of most common functional groups.[4]

The mechanism of the reactions which utilize palladium catalysts is believed to proceed via a catalytic cycle similar to that depicted in Scheme 1.[4] Oxidative addition of an aryl halide to a Pd(0) species affords complex **1**. Transmetallation from a main-group metal to palladium affords **2**, which then undergoes reductive elimination to form the desired product and regenerate the Pd(0) catalyst.

Scheme 1



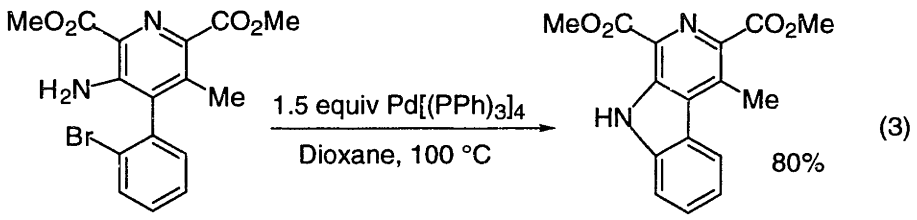
Despite the widespread use of these C–C bond forming reactions, prior to 1994 only a few examples of the analogous carbon-heteroatom bond forming processes had been described. In 1983 Migita reported the first palladium catalyzed C–N bond forming process in which *N,N*-diethylamino(tributyl)tin was used for the synthesis of



(2)

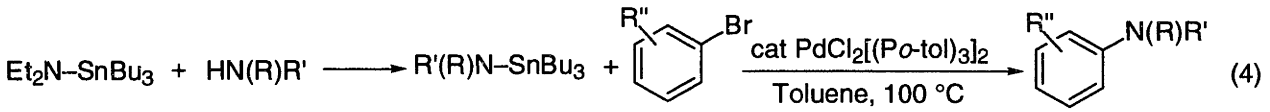
N,N-diethylaniline derivatives in a hetero-Stille type reaction (eq 2).[6] Although a number of *N,N*-diethylaniline derivatives were synthesized, the method was limited to aryl bromide substrates, and only examples of $-NEt_2$ transfer were demonstrated. Migita also reported related studies on the synthesis of aryl sulfides,[7] and in some cases use of a NaSR species eliminated the necessity for an organotin reagent.[7b]

In 1985 Boger reported the first tin-free amination of an aryl halide in the total synthesis of Lavendaymycin.[8] A stoichiometric amount of $Pd(PPh)_4$ (1.5 equiv) was required to effect this transformation at 100 °C, nonetheless an 80% isolated yield of the desired product was obtained (eq 3).



(3)

No further development of these reactions was reported until 1994, at which time Guram and Buchwald described an improved version of the Migita reaction.[9a] The synthesis of a wide variety of aniline derivatives was facilitated by an *in situ* aminostannane transamination protocol. The generation of various aminostannanes was accomplished by heating mixtures of *N,N*-diethylamino(tributyl)tin and nonvolatile amines under an argon purge. Reaction of the new aminostannanes with aryl halides in the presence of $PdCl_2[P(o\text{-tol})_3]_2$ provided the desired arylamine products in good yields (eq 4). Dr. Roger Rennels showed that this protocol was also effective for intramolecular reactions.[9b] The main side products observed in the amination reactions were arenes which presumably were formed via β-hydride elimination of intermediate **3** (Scheme 2, below) to form an arylpalladium hydride (with the release of an imine) that undergoes reductive elimination to generate the reduced side product. Despite the improved generality of the protocol for *in situ* generation of aminostannanes, the method still had several limitations. Only aryl bromides were effectively transformed, reactions of primary amines were often problematic, and



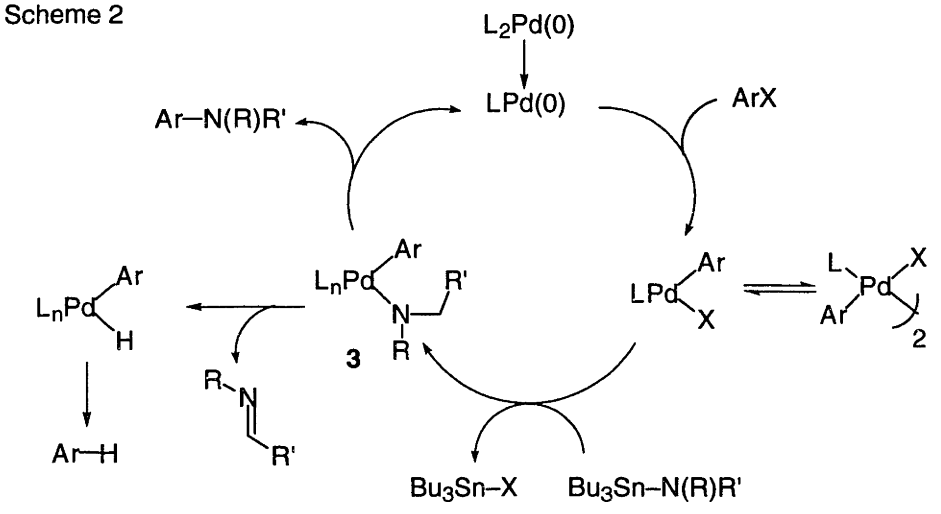
(4)

stoichiometric amounts of toxic tin reagents were required.

At roughly the same time, Hartwig reported studies on the mechanism of the Migita reaction;[10] the rate limiting step of the catalytic cycle was found to be

transmetallation of the amino group from tin to palladium. Hartwig also reported the synthesis of a new catalyst for this reaction, $Pd[P(o\text{-tol})_3]_2$, demonstrated that the oxidative addition complex was dimeric, and suggested that the reaction proceeded via (monophosphine)palladium intermediates (Scheme 2).[10] He later reported detailed studies which confirmed the importance of L_1Pd intermediates.[11]

Scheme 2



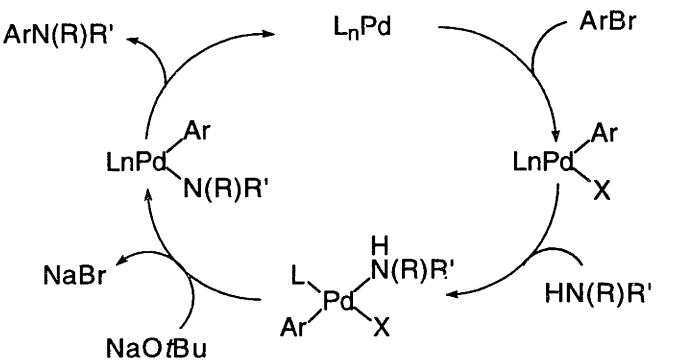
X=halide

Subsequent research in the Buchwald group[12] and Hartwig group[13] led to the development of tin-free conditions for the palladium-catalyzed amination of aryl halides. Guram, Rennels, and Buchwald demonstrated that amines could be coupled with aryl bromides in good yields in the presence of stoichiometric amounts of NaO*t*Bu using the $PdCl_2[P(o\text{-tol})_3]_2$ catalyst.[12] This protocol was applied to inter- and intramolecular amination reactions. Hartwig independently made similar discoveries using NaHMDS as the stoichiometric base.[13]

The catalytic cycle for this process was postulated to involve oxidative addition of the aryl bromide to Pd(0), followed by amine coordination, deprotonation, and reductive elimination to generate the aniline product with concomitant regeneration of

the Pd(0) catalyst (Scheme 3).[12] Detailed studies of the amine coordination were later conducted by Dr. Ross Widenhoefer (see chapters 1 and 3).[14] As in the aminostannane method, the main side products were arenes resulting from reduction of the aryl halide as shown above (Scheme 2).

Scheme 3: Proposed Tin-Free Catalytic Cycle



While the elimination of the need for a main group metal was a significant advance in this method, there remained many limitations. The reaction was only effective for the transformation of aryl bromide substrates, and amination reactions of primary amines were only effective with certain activated or ortho-substituted halides. Furthermore, the need for the strong base NaO*t*Bu limited the functional group tolerance of these reactions. Additionally, while amine nucleophiles provided good results, reactions of alcohols failed to provide the corresponding arylether products. Studies to overcome these limitations are described in this thesis.

Recent work in the area of catalytic amination reactions, including portions of the research described in this thesis, has been the subject of numerous reviews.[11e-f,15] Additional background information precedes the chapter(s) in this thesis to which it is relevant.

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Part One:

Amination Using Pd/P(*o*-tol)$_3$ Catalyst Systems

Chapter One:

Catalytic Amination of Aryl Iodides

Introduction

In most palladium-catalyzed cross-coupling, carbonylation, and Heck reactions, aryl iodide substrates can be transformed more easily than the corresponding aryl bromides.[1] Furthermore, the rate of oxidative addition to Pd(0) is substantially faster for aryl iodides than for the corresponding aryl bromides,[1] and some C–C bond forming reactions of iodide substrates proceed efficiently at room temperature.[2] In light of their high reactivity, it was curious to us that aryl iodides were unable to be successfully coupled with *N*,*N*-diethylamino(tributyl)tin under palladium catalysis.[3] Initial attempts by Dr. Anil Guram to utilize aryl iodides as substrates in intermolecular catalytic aminations with *in situ* generated aminostannanes were also unsuccessful,[4a] as were his efforts to aminate aryl iodides under conditions developed for the tin-free catalytic amination of aryl bromides,[4b] although only a few experiments were conducted.[5]

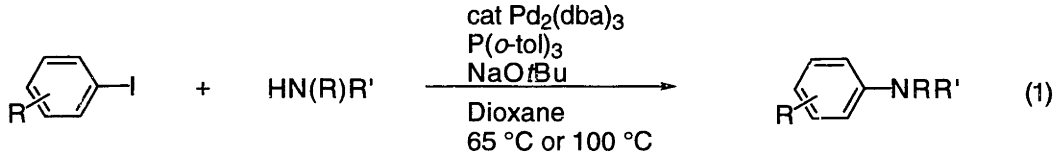
Interestingly, Dr. Roger Rennels demonstrated that aryl iodides were excellent substrates for intramolecular catalytic amination reactions; the cyclization reactions even functioned well at room-temperature provided that Et_3N was used as the solvent or base.[4b,c] The intramolecular catalytic amination of aryl iodides was applied to the formal total synthesis of the natural products dehydrobufotenine, mackaluvamine, and damirones A and B by Dr. Andy Peat.[6]

Results and Discussion

Reactions of aryl iodides with amines using a catalyst comprised of $Pd_2(dba)_3$ and P(*o*-tol)$_3$ at room temperature in the presence of NaO*t*Bu were largely unsuccessful; typically reactions proceeded to only 5–10% conversion with catalyst loadings of 2–4 mol % Pd. The use of various additives, such as tetrabutylammonium

chloride,[7] or solvents/bases such as Et_3N failed to improve these reactions. Heating the reactions to 65–100 °C led to complete consumption of the starting aryl iodide, but low yields of the desired products were obtained; homocoupling of the substrate led to the formation of substantial amounts of biaryl side products.

After a great deal of experimentation it was found that use of dioxane as solvent at 65–100 °C allowed for the reasonably efficient conversion of aryl iodides to aniline derivatives (eq 1); the formation of homocoupled side products was minimized under these conditions. Use of other solvents such as toluene, DMF, DME and THF resulted in decreased yields. Employment of excess amine (2.4 equiv) and excess NaO*t*Bu (2.8 equiv) further diminished the amount of biaryl which was formed. Reactions proceeded to completion using only 1 mol % of the palladium catalyst at 100 °C;



use of lower reaction temperatures (65 °C) required increased amounts of the palladium catalyst (4 mol %) but gave yields similar to those obtained at higher temperatures. A variety of triarylphosphines were examined as ligands for these reactions but were less effective than P(*o*-tol)$_3$.

As can be seen from the results presented in Table 1, the method works with both electron-rich and electron-deficient aryl iodides. Functional groups which are not sensitive to the strong base are well tolerated. The reaction conditions promoted catalytic amination in preference to the Heck reaction[8] in the coupling of an olefin-containing amine (entry 14); no side products resulting from Heck arylation of the olefin were detected in the reaction mixture.

Table 1: Catalytic Amination of Aryl Iodides

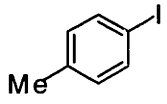
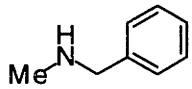
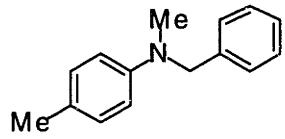
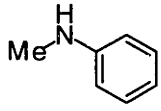
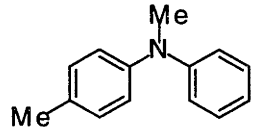
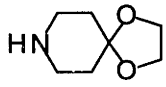
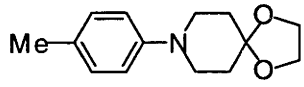
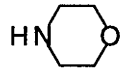
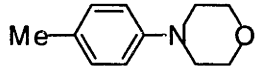
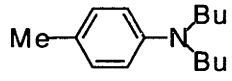
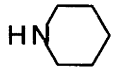
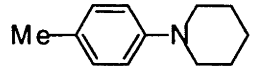
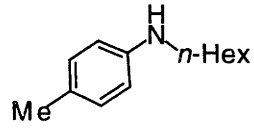
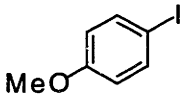
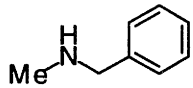
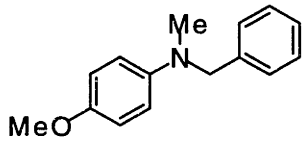
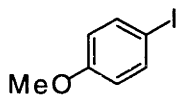
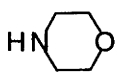
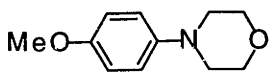
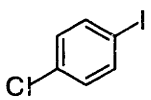
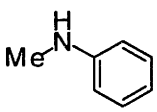
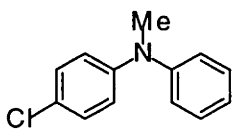
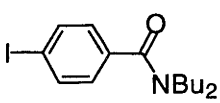
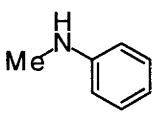
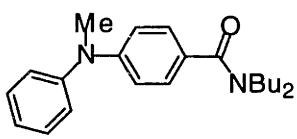
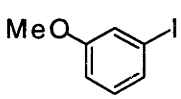
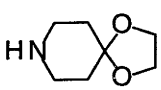
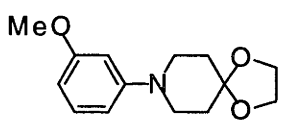
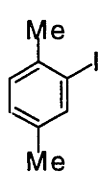
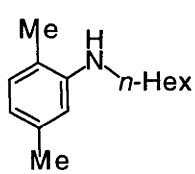
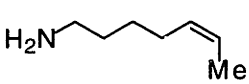
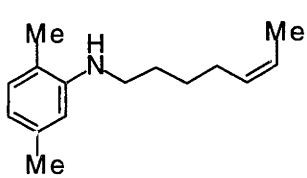
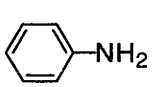
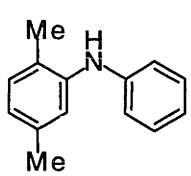
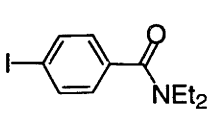
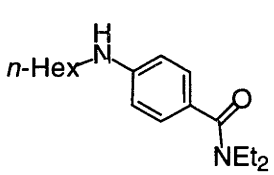
Entry	Halide	Amine	Product	Method[a]	Yield (%)
1				A B	78 79
2				A	74
3				A	66
4				A	73
5				A	68
6				A B	59 65
7		*n*HexNH$_2$		A	18
8				A B	63 63

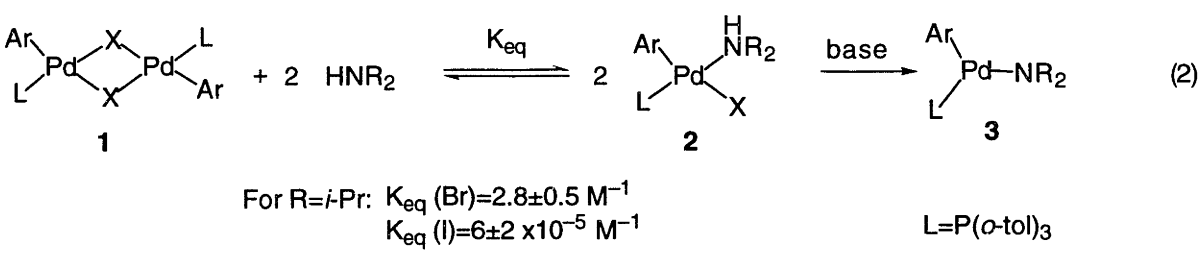
Table 1: Catalytic Amination of Aryl Iodides (cont.)

Entry	Halide	Amine	Product	Method[a]	Yield (%)
9				A	66
10				A	61
11				A	59
12				A	59
13		nHexNH$_2$		A	69
14				A	68
15				A	64
16		nHexNH$_2$		A[b]	19

(a) Reaction conditions: Method A: 1.0 equiv aryl iodide, 2.4 equiv amine (1.1 equiv for 1° amines), 2.8 equiv NaO*t*Bu, $Pd_2(dba)_3$ (0.005 equiv, 1.0 mol % Pd), P(*o*-tol)$_3$ (0.02 equiv, 2 mol %),dioxane (4 mL/mmol halide for 2° amines, 9 mL/mmol halide for 1° amines), 100 °C; Method B: 1.0 equiv aryl iodide, 2.4 equiv amine, 2.8 equiv NaO*t*Bu, $Pd_2(dba)_3$ (0.02 equiv, 4 mol % Pd), P(*o*-tol)$_3$ (0.08 equiv, 8 mol %), dioxane (4 mL/mmol halide), 65 °C; (b) 1.5 mol % $Pd_2(dba)_3$ (3.0 mol % Pd) was required for the reaction to proceed to completion.

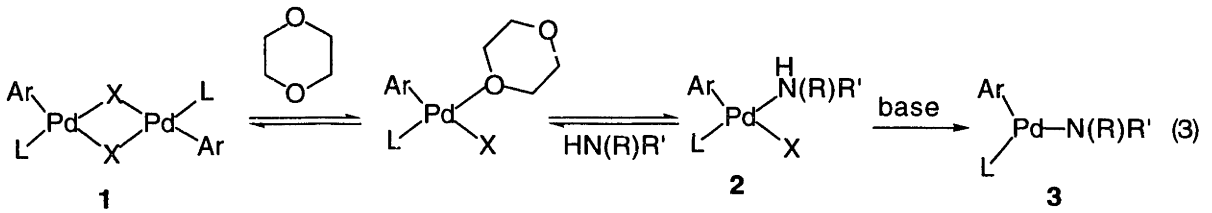
In general, secondary amines are better substrates than primary amines. In the case of primary amines, including aniline, acceptable yields are only realized when there is a substitutent ortho to the iodide.[9] Additionally, while a *p*-substituted electron-deficient bromide provided the corresponding aniline in ~70 % yield,[4b] attempts toeffect a similar transformation with an iodide were not efficient (entry 16).

Since oxidative addition of aryl iodides to Pd(0) is facile[1] and reductive elimination to form the arylamine presumably occurs through a common intermediate for both bromide and iodide substrates, the relatively low reactivity of aryl iodides in catalytic amination reactions is most likely due to difficulty in converting the oxidative addition complex **1** to the amido complex **3** (eq 2). The iodide ion has been shown to be a less labile leaving group in nucleophilic displacement reactions from Pd(II) than bromide or chloride ions,[10] and studies performed by Dr. Ross Widenhoefer demonstrated that the equilibrium for diisopropylamine coordination to the LPd(Ar)X dimer **1** is less favorable for iodides than for bromides (eq 2).[11] When smaller amines are used the equilibrium is shifted predominantly towards **2**; however, the small amounts of **1** present may undergo undesirable side reactions, such as the



(2)

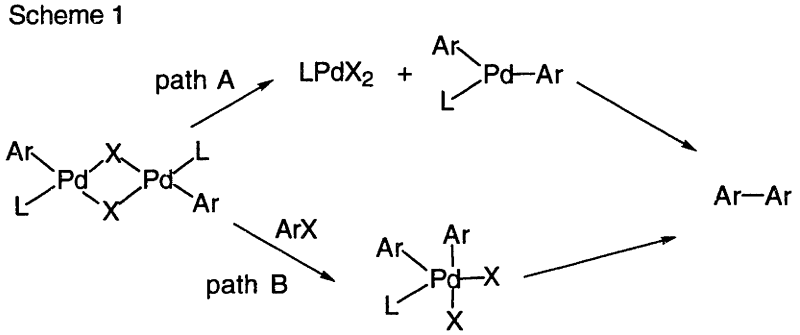
homocoupling of the aryl halide. Although these studies showed that the position of the equilibrium for amine coordination is actually less favorable in dioxane than in toluene,[11] it is possible that the coordinating solvent breaks up the dimer (eq 3), and disfavors homocoupling of the arene via disproportionation of **1** (see below). The fact that aryl iodides are excellent substrates for intramolecular palladium-catalyzed



amination reactions,[4b,c] but give relatively poor yields in intermolecular reactions further supports the notion that Pd-N bond formation is problematic in the intermolecular cases.

The homocoupling reaction presumably occurs via transmetallation of an aryl group from one palladium to another followed by reductive elimination (Scheme 1, path A),[12a-c] although a second oxidative addition reaction to form a Pd(IV) complex which undergoes reductive elimination (path B) to form the biaryl cannot be ruled out.[12d]

Scheme 1



In conclusion, the use of dioxane allows for the palladium-catalyzed amination of aryl iodides in moderate yields. An improved catalyst system for this transformation is discussed in chapter five, and Hartwig has reported related amination reactions of aryl iodides using a DPPF-ligated palladium catalyst.[13,14]

Experimental Section

General Considerations All reactions were carried out under an argon atmosphere in oven-dried glassware. Elemental analyses were performed by E&R Microanalytical Laboratory Inc., Corona N.Y. Anhydrous dioxane was purchased form Aldrich Chemical Co. and was used without further purification. Dichloromethane was dried by distillation from CaH_2 under nitrogen. All amines were obtained from commercial sources and were purified either by distillation from CaH_2, or by passing through a short column of alumina. Aryl iodides (except the substrates in entries 11 and 16) were obtained from commercial sources and were used without further purification. Sodium *t*-butoxide was purchased from Aldrich Chemical Company; the bulk of this material was stored under nitrogen in a Vacuum Atmospheres glovebox. Small portions (1-2 g) were removed from the glovebox in glass vials, stored in the air in desiccators filled with anhydrous calcium sulfate, and weighed in the air. Tris(dibenzylideneacetone)dipalladium(0) was obtained from Aldrich Chemical Co. or Strem Chemical Co. and used without further purification. Tri-*o*-tolyl phosphine was purchased from Strem Chemical Co. and was used without further purification. Preparative flash chromatography was performed on ICN Biomedicals Silitech 32-63d silica gel. Yields refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^1H NMR, and either capillary GC (known compounds) or combustion analysis (new compounds).

General Procedure for the catalytic amination of aryl iodides with secondary amines or secondary anilines.

To a solution of aryl iodide (1 mmol), amine (2.4 mmol), and sodium *t*-butoxide (2.8 mmol) in dioxane (4 mL) was added tris(dibenzylideneacetone)dipalladium(0)

(0.005 mmol, 1 mol % Pd), and tri-*o*-tolyl phosphine (0.02 mmol). The solution was heated to 100 °C with stirring until the aryl halide had been completely consumed as judged by GC analysis. The solution was then cooled to room temperature, taken up in ether (30 mL), and washed with brine (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel. Fractions containing product were concentrated to give the pure compound.

***N*-Benzyl-*N*-methyl-*p*-methylaniline** (Table 1, entry 1).[15] The general procedure gave 164 mg (78%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.22 (m, 5H), 7.03 (d, 2H, J = 8.73 Hz), 6.68 (d, 2H, J = 8.67 Hz), 4.49 (s, 2H), 2.97 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.7, 139.2, 129.6, 128.4, 126.8, 126.7, 125.6, 112.6, 56.9, 38.5, 20.2; IR (neat, cm^{-1}) 3084, 3062, 3026, 2918, 1619, 1569, 1523, 1494, 1475, 1453, 1369, 1354, 1325, 1295, 1250, 1210, 1192, 1115, 1028, 947, 803, 733, 696.

***N*-Methyl-*N*-phenyl-*p*-methylaniline** (Table 1, entry 2). The general procedure gave 146 mg (74%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–6.86 (m, 9H), 3.28 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.3, 146.5, 131.9, 129.9, 129.0, 122.5, 119.7, 118.1, 40.2, 20.7; IR (neat, cm^{-1}) 3025, 2919, 2874, 1596, 1572, 1510, 1498, 1451, 1342, 1296, 1268, 1253, 1131, 992, 868, 820, 751, 696; GC/MS (*m/z*) 197, 196, 180, 167, 152, 118, 104, 91, 77, 51. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 84.99; H, 7.63.

***N*-(*p*-Methylphenyl)-1,4-dioxa-8-azaspiro [4.5] decane** (Table 1, entry 3). The general procedure gave 154 mg (66%) of a white solid, mp 64.8–65.6 ° C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, 2H, J = 8.4 Hz), 6.86, (d, 2H, J = 8.7 Hz), 3.99 (s,

4H), 3.26 (t, 4H, J = 5.7 Hz), 2.26 (s, 3H), 1.85 (t, 4H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 129.5, 128.9, 117.0, 64.2, 48.3, 34.5, 20.3; IR (KBr, cm^{-1}) 2961, 2885, 2840, 1616, 1518, 1464, 1368, 1333, 1232, 1209, 1142, 1098, 1036, 962, 945, 925, 894, 823; GC/MS (*m/z*) 233, 188, 172, 146, 119, 91, 65. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.06; H, 8.21. Found: C, 72.26; H, 8.10.

4-(4-Methylphenyl)morpholine (Table 1, entry 4).[16] The general procedure gave 130 mg (73%) of a yellow solid, mp 49.8–50.4 °C (lit. mp 48 °C):[16] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (d, 2H, J = 8.7 Hz), 6.82 (d, 2H, J = 8.7 Hz), 3.85 (m, 4H), 3.10 (m, 4H), 2.27 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 129.7, 129.5, 116.0, 66.9, 49.9, 20.4; IR (KBr, cm^{-1}) 2957, 2853, 2830, 1517, 1452, 1380, 1298, 1260, 1235, 1118, 928, 819.

***N,N*-Dibutyl-*p*-methylaniline** (Table 1, entry 5).[17] The general procedure gave 149 mg (68%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (d, 2H, J = 8.1 Hz), 6.60–6.56 (m, 2H), 3.22 (t, 4H, J = 7.8 Hz), 2.23 (s, 3H), 1.53 (quint, 4H, J = 7.5 Hz), 1.33 (sext, 4H, J = 7.8 Hz), 0.94 (t, 6H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1, 129.6, 124.3, 112.2, 51.0, 29.4, 20.3, 20.1, 14.0; IR (neat, cm^{-1}) 2957, 2931, 2871, 1619, 1520, 1464, 1394, 1368, 1283, 1216, 1189, 800.

1-(4-Methylphenyl)piperidine (Table 1, entry 6).[16] The general procedure gave 107 mg of a yellow oil which was Kugelrohr distilled to give 103 mg (59%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, 2H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 3.09 (t, 4H, J = 5.4 Hz), 2.26 (s, 3H), 1.73–1.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.3, 129.5, 128.7, 116.9. 51.3, 25.9, 24.3, 20.4; IR (neat, cm^{-1}) 2933, 2854, 2803, 1619, 1514, 1464, 1452, 1443, 1383, 1333, 1237, 1131, 1027, 920, 810.

***N*-Benzyl-*N*-methyl-*p*-methoxyaniline** (Table 1, entry 8).[18] The general procedure gave 143 mg (63%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.23 (m, 5H), 6.83–6.72 (m, 4H), 4.42 (s, 2H), 3.74 (s, 3H), 2.91 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.7, 144.7, 139.2, 128.4, 127.0, 126.8, 114.6, 114.4, 57.9, 55.6, 38.9; IR (neat, cm^{-1}) 3061, 3027, 2992, 2933, 2903, 2830, 1514, 1494, 1453, 1355, 1295, 1244, 1213, 1181, 1117, 1040, 947, 814, 734, 697.

4-(4-Methoxyphenyl)morpholine (Table 1, entry 9).[16] The general procedure gave 128 mg (66%) of a tan solid, mp 73.3 °C (lit. mp 71 °C).[16] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91–6.84 (m, 4H), 3.86 (t, 4H, J = 4.8 Hz), 3.78 (s, 3H), 3.06 (t, 4H, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9, 145.5, 117.7, 114.4, 66.9, 55.4, 50.7; IR (KBr, cm^{-1}) 2971, 2854, 2816, 1514, 1452, 1294, 1266, 1247, 1229, 1185, 1121, 1030, 928, 818.

***N*-Methyl-*N*-phenyl-*p*-chloroaniline** (Table 1, entry 10). The general procedure gave 133 mg (61%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–6.88 (m, 9H), 3.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.6, 147.6, 129.3, 129.0, 125.5, 122.2, 121.4, 120.5, 40.3; IR (neat, cm^{-1}) 3061, 3037, 2943, 2880, 2815, 1601, 1588, 1568, 1494, 1452, 1342, 1304, 1253, 1184, 1156, 1133, 1098, 1085, 1066, 817, 744, 696; GC/MS (*m/z*) 219, 218, 217, 216, 201, 181, 167, 138, 125, 113, 104, 90, 77, 51. Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.87; H, 5.57. Found: C, 71.95; H, 5.81.

***N,N*-Dibutyl-*p*-(*N*-methylaniline)benzamide** (Table 1, entry 11). The general procedure gave 198 mg (59%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–6.87 (m, 9H), 3.50–3.33 (m, br, 4H), 1.60–0.80 (m, br, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.7, 149.5, 148.1, 129.3, 127.9, 127.7, 123.1, 116.6, 40.0, 30.1 (br), 19.1, 13.6; IR (neat, cm^{-1}) 3036, 2957, 2930, 2871, 1627, 1593, 1561, 1514, 1496, 1465,

1422, 1345, 1295, 1256, 1191, 1132, 1103, 830, 762, 700. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93. Found: C, 77.87; H, 9.16.

***N*-(3-Methoxyphenyl)-1,4-dioxa-8-azaspiro [4.5] decane** (Table 1, entry 12).[4b] The general procedure gave 147 mg (59%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (t, 1H, J = 8.1 Hz), 6.58–6.37 (m, 3H), 3.99 (s, 4H), 3.79 (s, 3H), 3.32 (t, 4H, J = 6 Hz), 1.83 (t, 4H, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.5, 152.1, 129.6, 109.2, 107.1, 104.0, 102.8, 64.2, 55.0, 47.5, 34.3; IR (neat, cm^{-1}) 2956, 2884, 2833, 1602, 1579, 1496, 1466, 1438, 1365, 1341, 1294, 1251, 1228, 1202, 1168, 1143, 1103, 1053, 965, 946, 912, 833, 761, 690.

General Procedure for the catalytic amination of aryl iodides with primary amines or anilines.

To a solution of aryl iodide (1 mmol), amine (1.1 mmol), and sodium *t*-butoxide (2.8 mmol) in dioxane (9 mL) was added tris(dibenzylideneacetone)dipalladium (0) (0.005 mmol, 1 mol % Pd), and tri-*o*-tolyl phosphine (0.02 mmol). The solution was heated to 100 °C with stirring until the aryl halide had been completely consumed as judged by GC analysis. The solution was then cooled to room temperature, taken up in ether (30 mL) and washed with brine (15 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel. Fractions containing product were concentrated to give the pure compound.

***N*-(4-Methylphenyl) hexylamine** (Table 1, entry 7). The general procedure gave 75 mg (39%) of a yellow oil which was Kugelrohr distilled to give 35 mg (18%) of a white solid, mp 37.1–37.3 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (d, 2H, J = 8.89 Hz), 6.54 (d, 2H, J = 8.7 Hz), 3.45 (s, br, 1H), 3.07 (t, 2H, J = 7.5 Hz), 1.64–1.26 (m, 8H),

0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.3, 129.7, 126.3, 112.9, 44.4, 31.6, 29.6, 26.8, 22.6, 20.3, 14.0; IR (KBr, cm^{-1}) 3413, 2927, 2858, 1618, 1522, 1458, 806; GC/MS (*m/z*) 191, 120. Anal. Calcd for $C_{13}H_{21}N$: C, 81.61; H, 11.06. Found: C, 81.82; H, 10.83.

***N*-(2,5-Xylyl)-hexylamine** (Table 1, entry 13). The general procedure gave 141 mg (69%) of a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H, J = 7.5 Hz), 6.47–6.43 (m, 2H), 3.38 (s, 1H, br), 3.13 (t, 2H, J = 7.2 Hz), 2.29 (s, 3H), 2.09 (s, 3H), 1.66 (quint, 2H, J = 7.8 Hz), 1.45–1.30 (m,6H), 0.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 136.6, 129.8, 118.6, 117.2, 110.5, 43.9, 31.6, 29.6, 26.9, 22.6, 21.5, 16.9, 14.0; IR (neat, cm^{-1}) 3428, 3014, 2956, 2926, 2856, 1615, 1584, 1523, 1466, 1426, 1376, 1312, 1298, 1266, 792; GC/MS (*m/z*) 205, 134. Anal. Calcd for $C_{14}H_{23}N$: C, 81.88; H, 11.30. Found: C, 82.07; H, 11.22.

(*Z*)-*N*-(5-Hexenyl)-2,5-xylidine (Table 1, entry 14). The general procedure gave 155 mg of a yellow oil which was Kugelrohr distilled to give 147 mg (68%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H, J = 7.5 Hz), 6.47–6.42 (m, 2H), 5.51–5.35 (m, 2H), 3.38 (s, 1H, br), 3.14 (t, 2H, J = 6.9 Hz), 2.29 (s, 3H), 2.29–2.07 (m, 5H), 1.72–1.6 (m, 5H), 1.49 (quint, 2H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 136.7, 130.2, 129.8, 124.2, 118.7, 117.2, 110.5, 43.8, 29.2, 27.1, 26.5, 21.5, 17.0, 12.8; IR (neat, cm^{-1}) 3426, 3012, 2927, 2856, 1615, 1583, 1523, 1444, 1298, 1267, 793, 701; GC/MS (*m/z*) 217, 160, 134, 105, 91, 77. Anal. Calcd for $C_{15}H_{23}N$: C, 82.88; H, 10.67. Found: C, 83.10, H, 10.45.

***N*-Phenyl-2,5-xylidine** (Table 1, entry 15).[19] The general procedure gave 137 mg of a yellow oil which was Kugelrohr distilled to give 128 mg (64%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26–6.73 (m, 8H), 5.31 (s, br, 1H), 2.26 (s,

3H), 2.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 140.9, 136.4, 130.7, 129.2, 125.3, 122.8, 120.2, 119.5, 117.3, 21.1, 17.4; IR (neat, cm^{-1}) 3386, 3048, 3018, 2920, 2858, 1600, 1578, 1518, 1497, 1464, 1412, 1377, 1311, 1000, 805, 747, 694.

***N,N*-Diethyl-*p*-(hexylamino)benzamide** (Table 1, entry 16). To a solution of *N,N*-diethyl-*p*-iodobenzamide (303 mg, 1.0 mmol), *n*-hexylamine (0.15 mL, 1.1 mmol), sodium *t*-butoxide (270 mg, 2.78 mmol) in dioxane (9 mL) was added tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.005 mmol), and tri *o*- tolyl phosphine (6 mg, 0.02 mmol). The solution was heated to 100 °C with stirring. Additional portions of the palladium complex (5 mg, 0.005 mmol) and phosphine (6 mg, 0.02 mmol) were added after 16 h, and after 22 h. Complete consumption of starting material occurred after 40 h (as judged by GC analysis). The solution was then cooled to room temperature, taken up in ether (30 mL), filtered, and concentrated. The crude product was then purified by flash chromatography on silica gel using 4/1 hexane/ethyl acetate as the eluant. Fractions containing product were concentrated to give 52 mg (19%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.23 (m, 2H), 6.56–6.53 (m, 2H), 3.87 (s, br, 1H), 3.43 (q, 4H, J = 6.9 Hz), 3.11 (t, 2H, J = 7.2 Hz), 1.61 (quint, 2H, J = 6.9 Hz), 1.42–1.29 (m, 6H), 1.18 (t, 6H, J = 6.9 Hz), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 149.4, 128.4, 125.1, 111.6, 43.6, 31.5, 29.3, 26.7, 22.5, 14.0; IR (neat, cm^{-1}) 3333, 2958, 2930, 2858, 1614, 1531, 1470, 1456, 1425, 1380, 1335, 1314, 1285, 1176, 1098, 831, 764. Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21. Found: C, 74.12; H, 10.26.

***N,N*-Dibutyl-*p*-iodobenzamide** (Substrate). To a solution of di *n*-butylamine (1.7 mL, 10.0 mmol) in dichloromethane (2 mL) in an oven-dried Schlenk flask at 0 °C was added 4-iodobenzoyl chloride (1.066 g, 4.0 mmol) in dichloromethane (2 mL) slowly. The solution was stirred at 0 °C for 10 min, then

warmed to rt and stirred for 5 h. The reaction mix was then diluted with ether (30 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), and washed with brine (10 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated to give 1.29 g (90%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.75 (m, 2H), 7.1 (m, 2H), 3.60–3.10 (m, br, 4H), 1.70–0.70 (m, 14 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 137.2, 136.5, 128.0, 94.8, 48.5, 44.3, 30.6, 29.3, 20.0, 19.5, 13.6, 13.4; IR (neat, cm^{-1}) 2957, 2930, 2871, 1632, 1586, 1558, 1487, 1465, 1425, 1379, 1296, 1265, 1234, 1182, 1101, 1007, 830, 754; GC/MS (*m/z*) 359, 358, 316, 231, 203, 104, 76. Anal. Calcd for $C_{15}H_{22}INO$: C, 50.15; H, 6.17. Found: C, 50.38, H, 6.07.

***N,N*-Diethyl-*p*-iodobenzamide** (Substrate).[20] To a solution of diethylamine (1.05 mL, 10.0 mmol) in dichloromethane (2 mL) in an oven-dried flask at 0 °C was added 4-iodobenzoyl chloride (1.066 g, 4.0 mmol) in dichloromethane (2 mL) slowly. The solution was stirred at 0 °C for 10 min, then warmed to rt and stirred for 15 h. The reaction mix was then diluted with ether (30 mL), washed with saturated aqueous $NaHCO_3$ (10 mL), and washed with brine (10 mL). The organic layer was then dried over anhydrous $MgSO_4$, filtered, and concentrated to give 1.190 g (98%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.8–7.7 (m, 2H), 7.15–7.08 (m, 2H), 3.6–3.1 (m, br, 4H), 1.35–1.0 (m, br, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 137.5, 136.6, 128.0; IR (neat, cm^{-1}) 2972, 2933, 1632, 1586, 1488, 1470, 1458, 1427, 1383, 1363, 1347, 1315, 1288, 1095, 1008.

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Chapter Two:

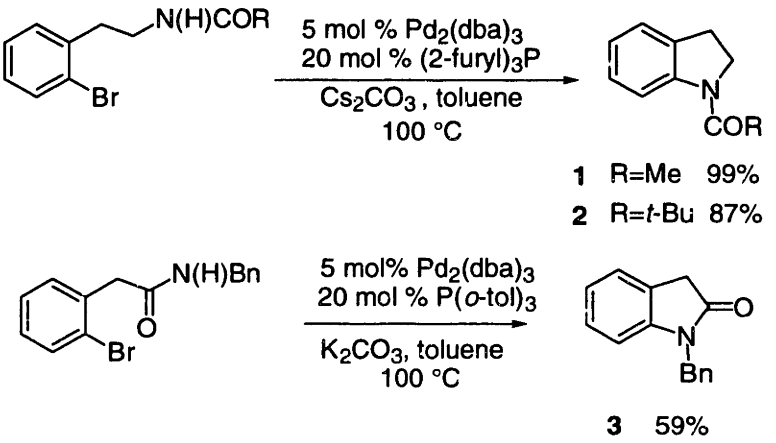
Intramolecular Amidation Reactions

Introduction

Nitrogen heterocycles are common structural elements found in many biologically active natural products and pharmaceuticals.[1] Numerous procedures have been developed for intramolecular C–N bond formation,[2] including methods which employ stoichiomteric amounts of palladium[2a] or copper.[2b-c] Formation of nitrogen heterocycles has also been accomplished using nucleophilic aromatic substitution reactions,[2d] the Chichibabin reaction,[2e] and reactions which proceed via benzyne intermediates.[2f-h] Other methods proceed through radical intermediates,[2i] employ organocerium reagents,[2j] or involve nucleophilic substitution of hydroxylamine derivatives.[2k] However, frequently these methods suffer from the same limitations of protocols for the intermolecular construction of aryl C–N bonds; harsh reaction conditions and/or activated substrates are often required.[2]

Dr. Roger Rennels had previously demonstrated the intramolecular palladium-catalyzed amination of aryl halides to form various nitrogen heterocycles.[3a,c] These reactions were effected using the previously described protocol for *in situ* generation of aminostannanes,[3b,c] or by employing the tin-free amination method using either K_2CO_3, Et_3N, or mixtures of NaO*t*Bu and K_2CO_3 as the base.[3a,c] In contrast to the intermolecular reactions, use of PPh_3 or P(2-furyl)$_3$ as ligands often gave results which were equal or superior to those obtained with P(*o*-tol)$_3$.[3a,c] Dr. Andy Peat applied the intramolecular catalytic amination to the formal total syntheses of the natural products dehydrobufotenine, mackaluvamine C, and damirones A and B.[4] Dr. Rennels also demonstrated the intramolecular cyclization of amide substrates to form five-membered rings as depicted below in Scheme 1.[3c]

Scheme 1



Results and Discussion

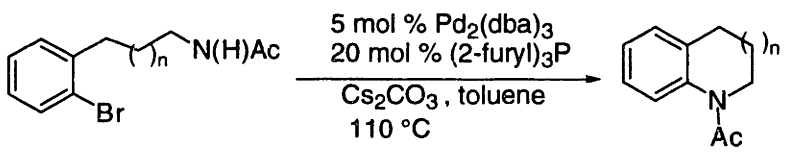
Substrates for the cyclization reactions were synthesized in 4–6 steps using standard synthetic manipulations which will not be discussed. These syntheses were published in the experimental section of a full paper describing the intramolecular palladium-catalyzed amination and amidation reactions.[3b]

The cyclization of amide substrates to form six-membered rings was achieved using a protocol similar to that employed for the formation of five-membered rings. Formation of six-membered rings bearing exocyclic amides was less facile than the formation of the analogous five membered ring products; the yield obtained of the *N*-acyl tetrahydroquinoline **4** was considerably lower (44%) than that obtained of the *N*-acyl indoline **1** shown above (99%) (Scheme 2). In contrast, the trend was reversed for the formation of endocyclic amides; the yield of the tetrahydroisoquinolone **6** (82%) was higher than that of the oxindole **3** (59%). Attempts to form 7-membered rings using these conditions gave little or no desired products; reduction of the starting aryl bromide was the predominant reaction observed.

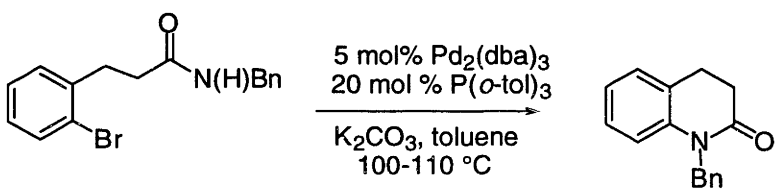
The best results were obtained with either Cs_2CO_3 or K_2CO_3 as base; reactions employing other alkali metal carbonates were slow and/or gave low yields. Protocols

which used NaO*t*Bu, or alkali metal acetates as bases were also unsuccessful. Ligands such as PPh_3, $AsPh_3$, or $(C_6F_5)_3P$ were not effective in these reactions; (2-furyl)$_3$P was most effective for the acetamide cyclizations, while P(*o*-tol)$_3$ worked well for the formation of endocyclic amides.

Scheme 2



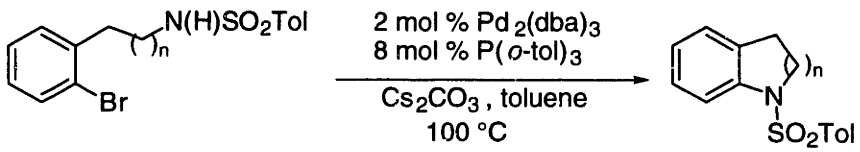
4 n=1 44%
5 n=2 0%



6 n=1 82%
7 n=2 ~5% (2-furyl)$_3$ P used as ligand

Conditions similar to those used for the amide cyclizations promoted intramolecular C–N bond forming reactions of sulfonamides in good yields (Table 1); these are the first examples of Pd-catalyzed aryl C–N bond formation which involve sulfonamide substrates. The sulfonamide cyclizations were much faster and required lower catalyst loading than those for corresponding amides. We attribute this to the enhanced acidity of the sulfonamide N-H proton.[5] Reaction times were dependent on ring size, and formation of smaller rings was fastest. As with amide substrates, attempts to form seven-membered heterocycles failed, and intermolecular reactions of aryl halides with sulfonamides usually gave little or no coupled products.

Table 1: Cyclization of Bromo-Sulfonamides



Product	n	ReactionTime	Yield
8	1	5h	88%
9	2	14h	87%
10	3	–	0%

The fact that sulfonamides and amides give satisfactory results for the formation of five and six membered rings, but the process fails for larger rings and in intermolecular cases suggests that nitrogen coordination of the sulfonamide or amide to the metal may be less facile than amine coordination. The nitrogen in amides and sulfonamides is considerably less basic than the amine nitrogen,[6] and known complexes of the type MCl_2L_2 (where M=Pt or Pd, and L=DMF, NMA or DMA) have been shown to be O-bonded.[7] NMR experiments showed no detectable coordination of *N*-methyl acetamide to the (*o*-tol)$_3$PPd(4-*t*-BuPh)Br dimer in C_6D_6. Labile ligands such as P(2-furyl)$_3$ and P(*o*-tol)$_3$ are presumably required to help facilitate amide/sulfonamide coordination and may promote reactivity via monophosphine palladium complexes.[8]

Recent studies have demonstrated that the coordination of the amide to the metal is dependent on ring size, and that C–N bond forming reductive elimination of the amide substrates appears to be slower than that of aliphatic amines.[9] In many carbon-heteroatom bond forming reactions the rate of reductive elimination is proportional to the nucleophilicity of the substrate.[10] However, the fact that the less nucleophilic sulfonamides react considerably faster than amides suggests that reductive elimination may not be rate limiting. Reductive elimination in the intramolecular reactions may be facilitated by the large steric bulk of the substrates (all

substrates contain a substituent, the pendant amide, ortho to the bromide).[11] Furthermore, the chelating group on the substrate forces the amide and aryl groups into the cis orientation in the intermediate palladium amido complex.[12] The factors which enhance reductive elimination in the intramolecular reactions presumably allow for the use of relatively small ligands (e.g. (2-furyl)$_3$P) in these reactions; use of triarylphosphine ligands smaller than P(*o*-tol)$_3$ in intermolecular amination reactions leads to increased formation of arene side products.[11b]

Weak bases presumably are effective for these reactions due to the increased acidity of the amide or sufonamide N-H proton relative to the amine N-H proton;[5] use of K_2CO_3 for intramolecular reactions of amines requires reaction times in excess of 36 h and/or extremely high reaction temperatures (200 °C).[4] The poor results obtained with stronger bases (e.g. NaO*t*Bu) may be due to the insolubility of the fully deprotonated amides. Recent studies by Dr. Bryant Yang have led to improved catalyst systems and reaction conditions for intramolecular amidation reactions.[13]

Experimental Section

General Considerations The general considerations are the same as for chapter one with the following exceptions. Toluene, THF, and ether were continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen or argon. Dichloromethane was dried by continuous reflux and distillation from CaH_2 under nitrogen. Triethylamine was purchased from Fischer and distilled from CaH_2 before use. Tosyl chloride, and tri(2-furyl) phosphine were obtained from Aldrich Chemical Co. and used without further purification. Acetyl Chloride was purchased from Mallinckrodt Chemical Co. and used as received. Anhydrous potassium carbonate was purchased from Mallinckrodt Chemical Co. and was finely ground with a mortar and pestle before use. Cesium carbonate was purchased from Strem

Chemical Co. and were used as received All other reagents were purchased from commercial sources and used without further purification. Cyclization substrates were prepared according to literature procedures, or using standard synthetic methods. See reference 3c for full experimental details concerning the synthesis of substrates.

General procedure for the preparation of acetamides. To a solution of amine (4.0 mmol) and triethylamine (4.4 mmol) in dichloromethane (4 mL) at 0° C was slowly added acetyl chloride (4.4 mmol); a white precipitate formed. The reaction mixture was stirred at 0° C for 15 min, then warmed to ambient temperature and stirred for 2 h. The mixture was then diluted with ether (10 mL) and washed with brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-Acetyl-3-(*o*-bromophenyl)propylamine.** Acylation of 3-(*o*-bromophenyl)propylamine[3c,14a] was accomplished using the general procedure (on a 5 mmol scale) to afford 0.625 g (49%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54–7.03 (m, 4H), 5.55 (br, 1H), 3.31 (q, 2H, J = 6.6 Hz), 2.77 (t, 2H, J = 7.5 Hz), 1.97 (s, 3H), 1.84 (quint, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 140.5, 132.6, 130.2, 127.6, 127.4, 124.1, 38.9, 33.3, 29.4, 23.1; IR (neat, cm^{-1}) 3284, 3083, 2933, 1654, 1560, 1471, 1438, 1368, 1021, 749. Anal. Calcd for $C_{11}H_{14}NOBr$: C, 51.58; H, 5.51. Found: C, 51.38; H, 5.31.

***N*-Acetyl-4-(*o*-bromophenyl)butylamine.** Acylation of 4-(*o*-bromophenyl)butylamine[3c] was accomplished using the general procedure to afford 0.875 g (81%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.02 (m, 4H), 5.47 (br, 1H), 3.29 (q, 2H, J = 6.3 Hz), 2.75 (t, 2H, J = 7.5 Hz), 1.97 (s, 3H), 1.70–1.53 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 141.1, 132.5, 130.1, 127.4, 127.2, 124.1,

39.1, 25.5, 28.9, 27.0, 23.0; IR (neat, cm^{-1}) 3283, 3083, 2933, 2861, 1647, 1558, 1471, 1438, 1368, 1292, 1022, 750. Anal. Calcd for $C_{12}H_{16}NOBr$: C, 53.35; H, 5.97. Found: C, 53.23; H, 6.15.

General procedure for cyclization of acetamides. A Schlenk flask was charged with the acetamide (1 mmol), Cesium carbonate (2 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.05 mmol, 10 mol % Pd), and tri-(2-furyl) phosphine (0.2 mmol). The flask was purged with argon for 1 min, then toluene (2 mL) was added and the reaction mixture was heated to 100–110 °C with stirring until the starting material had been completely consumed as judged by GC analysis. The solution was then allowed to cool to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-Acetyl-1,2,3,4-tetrahydroquinoline (4).**[2k] Cyclization of *N*-Acetyl-3-(*o*-bromophenyl)propylamine using the general procedure gave 75 mg (43%) of a pale yellow oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.13 (m, 4H), 3.79 (t, 2H, *J*= 6.3 Hz), 2.72 (t, 2H, *J*= 6.6 Hz), 2.23 (s, 3H), 1.96 (quint, 2H, *J*= 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 128.4, 126.0, 125.1, 124.5, 26.8, 24.0, 23.1; IR (neat, cm^{-1}) 3064, 2947, 1652, 1494, 1260, 732, 617. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.4; H,7.48. Found C, 75.24; H, 7.66.

General procedure for preparation of N-benzyl amides. To the neat carboxylic acid (5 mmol) in a round bottom flask was added thionyl chloride (4 mL). The solution was stirred at room temperature for 2.5 h. Excess thionyl chloride was removed *in vacuo* and dichloromethane (2.5 mL) was added. This solution was slowly added to a solution of benzylamine (12.5 mmol) in dichloromethane (2.5 mL) at

0° C; a white solid precipitated. The reaction mixture was stirred at 0 °C for 15 min, then warmed to ambient temperature and stirred for 2 h. The reaction mixture was then diluted with ether (10 mL), washed with saturated aqueous sodium bicarbonate (5 mL), and washed with brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-Benzyl-3-(*o*-bromophenyl)propionamide.**[14b] 3-(*o*-bromophenyl)propionic acid[14b] was converted using the general procedure to afford 1.271 g (80%) of a white solid, mp 90.4–91.6 °C (lit. mp 70–73 °C):[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.05 (m, 9H), 5.66 (br, 1H), 4.42 (d, 2H, *J*= 5.7 Hz), 3.12 (t, 2H, *J*= 7.2 Hz), 2.53 (t, 2H, *J*= 8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6, 139.9, 132.6, 130.5, 128.4, 127.8, 127.43, 127.39, 127.1, 124.1, 43.3, 36.1, 31.9; IR (KBr, cm^{-1}) 3296, 3030, 2940, 1641, 1542, 1469, 1553, 1024, 752, 697.

***N*-Benzyl-4-(*o*-bromophenyl)butyramide.** 4-(*o*-bromophenyl)butyric acid[3c,15] was converted using the general procedure (on a 6 mmol scale) to afford 1.328 g (67%) of a white solid, mp 110.6–112.0 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53–7.02 (m, 9H), 5.70 (br, 1H), 4.45 (d, 2H, *J*= 5.4 Hz), 2.80 (t, 2H, *J*= 7.2 Hz), 2.28 (t, 2H, *J*= 7.5 Hz), 2.00 (p, 2H, *J*= 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.3, 140.7, 138.3, 132.7, 130.4, 128.7, 127.8, 127.7, 127.5, 127.4, 124.4, 43.6, 35.8, 35.3, 25.7; IR (KBr, cm^{-1}) 3293, 3052, 2951, 1636, 1559, 1545, 1458, 745, 698. Anal. Calcd for $C_{17}H_{18}NOBr$: C, 61.46; H, 5.46. Found: C, 61.66; H, 5.46.

***N*-Benzyl-1,2,3,4-tetrahydroisoquinoline-2-one (6).**[16] A Schlenk flask was charged with *N*-Benzyl-3-(*o*-bromophenyl)propionamide (159 mg, 0.5 mmol), potassium carbonate (97 mg, 0.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (18

mg, 0.02 mmol, 8 mol % Pd), and tri-*o*-tolyl phosphine (24 mg, 0.08 mmol). The flask was purged with argon for 1 min, then toluene (4 mL) was added and the mixture was heated to 100 °C with stirring. GC analysis after 68 h showed incomplete consumption of starting material. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.005 mmol, 2 mol % Pd), and tri-*o*-tolyl phosphine (6 mg, 0.02 mmol) was added and the mixture was heated for an additional 24 h, when GC analysis showed complete consumption of starting material. The reaction mixture was cooled to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was purified further by flash chromatography on silica gel using 5/1 hexane/ethyl acetate as the eluant to give 91 mg (76%) of a colorless oil which solidified upon standing to give a white solid, mp 49.8–51.2 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–6.86 (m, 9H), 5.18 (s, 2H), 3.01–2.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 139.8, 136.9, 128.7, 127.8, 127.4, 127.0, 126.3, 122.8, 115.5, 46.1, 31.8, 25.5; IR (KBr, cm^{-1}) 3087, 3060, 3026, 2961, 2943, 1674, 1599, 1588, 1496, 1469, 1454, 1427, 1381, 1191, 755, 728, 708. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37. Found: C, 80.88; H, 6.45.

General Procedure for the preparation of *p*-toluenesulfonamides. To a solution of the amine (5 mmol), and triethylamine (5.5 mmol) in dichloromethane (2.5 mL) at 0°C was slowly added a solution of *p*-toluenesulfonyl chloride (5.5 mmol) in dichloromethane (2.5 mL); a white precipitate formed. The reaction mixture was stirred at 0°C for 15 min, then warmed to ambient temperature and stirred for 2 h. The reaction mixture was then diluted with ether (10 mL), washed with aqueous saturated sodium bicarbonate (5 mL), and washed with brine (5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-(*p*-Toluensulfonyl)-*o*-bromophenylethylamine.** *o*-bromophenylethylamine[3c,14a] was tosylated using the general procedure to afford 1.21 g (68%) of a white solid, mp 71.2–72.0 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, 2H, *J*= 8.4 Hz), 7.50 (d, 1H, *J*= 8.1 Hz), 7.30–7.08 (m, 5H), 4.06 (br, 1H), 3.24 (q, 2H, *J*= 6.9 Hz), 2.92 (t, 2H, *J*= 6.9 Hz), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 137.1, 136.8, 132.9, 131.1, 129.7, 128.5, 127.6, 127.0, 124.4, 42.5, 36.3, 21.5; IR (KBr, cm^{-1}) 3249, 2946, 1599, 1567, 1469, 1437, 1323, 1163, 1092, 1068, 1021, 889, 813, 762, 748, 653. Anal. Calcd for $C_{15}H_{16}NSO_2Br$: C, 50.86; H, 4.55. Found: C, 50.90, H, 4.64.

***N*-(*p*-Toluenesulfonyl)-3-(*o*-bromophenyl)propylamine.** 3-(*o*-bromophenyl)propylamine[3c,14a] was tosylated using the general procedure to afford 1.187 g (65%) of a colorless oil which solidified upon the addition of hexane. The hexane was removed *in vacuo* to give a white solid, mp 58.2–59.3 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 2H, *J* = 8.4 Hz), 7.49 (d, 1H, *J* = 9.0 Hz), 7.32–7.05 (m, 5H), 4.51 (br, 1H), 3.00 (q, 2H, *J* = 6.6 Hz), 2.72 (t, 2H, *J* = 7.5 Hz), 2.43 (s, 3H), 1.78 (quint, 2H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.2, 140.2, 137.0, 132.7, 130.3, 129.6, 127.7, 127.4, 127.0, 124.2, 42.5, 32.9, 29.5, 21.4; IR (KBr, cm^{-1}) 3283, 3063, 2929, 2867, 1598, 1495, 1471, 1439, 1325, 1159, 1094, 1020, 814, 752, 661. Anal. Calcd for $C_{16}H_{18}NSO_2Br$: C, 52.18; H, 4.93. Found: C, 52.28; H, 4.95.

***N*-(*p*-Toluenesulfonyl)-4-(*o*-bromophenyl)butylamine.** To a suspension of sodium cyanide (1.11 g, 22.7 mmol) in THF (25 mL)/DMSO (36 mL) was added 3-(*o*-bromophenyl)propylmethanesulfonate[3c] in THF (11 mL). The reaction mixture was heated to 65 °C with stirring until all starting material had been consumed (6 h) as judged by TLC. The reaction mixture was cooled to room temperature, diluted with ether (75 mL), filtered, and concentrated. The crude product was purified further by

flash chromatography on silica gel using 9/1 hexane/ethyl acetate as the eluant to afford 4-(*o*-bromophenyl)butyronitrile as a colorless oil (2.534 g, 62%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, 1H, J = 8.4 Hz), 7.27–7.24 (m, 2H), 7.13–7.10 (m, 1H), 2.91 (t, 2H, J = 7.5 Hz), 2.37 (t, 2H, J = 6.9 Hz), 2.01 (quint, 2H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 133.0, 130.5, 128.2, 127.6, 124.2, 119.3, 34.7, 25.3, 16.5; IR (neat, cm^{-1}) 3056, 3011, 2935, 2246, 1471, 1456, 1440, 1019, 755.

A Schlenk flask was charged with solid aluminum chloride (1.51 g, 11.3 mmol) and cooled to 0 °C. Ether (25 mL) was added, followed by 1M Lithium Aluminum Hydride in ether (14.7 mL, 14.7 mmol). To this suspension was added 4-(*o*-bromophenyl)butyronitrile (2.53 g, 11.3 mmol) in ether (5 mL). The reaction mixture was warmed to ambient temperature with stirring for 11 h. The mixture was then cooled to 0 °C and slowly quenched with ice water. Sulfuric acid (2M, ~20 mL) was added until all solids dissolved. The layers were separated, and the aqueous layer was extracted with ether (40 mL). The aqueous layer was then brought to pH 11 with 1M NaOH, and extracted with ether (3 x 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated to afford 4-(*o*-bromophenyl)butylamine as a colorless oil (1.93 g, 75%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.50 (m, 1H); 7.29–7.15 (m, 2H), 7.10–7.00 (m, 1H), 2.80–2.70 (m, 4H), 1.71–1.45 (m, 4H), 1.52 (br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.5, 132.6, 130.1, 127.3, 127.2, 124.2, 41.6, 35.7, 32.8, 27.0; IR (neat, cm^{-1}) 3287, 3055, 3011, 2929, 1566, 1471, 1438, 1022, 749.

4-(*o*-bromophenyl)butylamine was tosylated using the general procedure (on a 3 mmol scale) to afford 1.026 g (90%) of a colorless oil which solidified upon the addition of hexane. The hexane was removed *in vacuo* to give *N*-(*p*-toluenesulfonyl)-4-(*o*-bromophenyl)butylamine as a white solid, mp 91.0–92.5 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, 2H, J = 8.3 Hz), 7.50 (d, 1H, J = 8.1 Hz), 7.31–7.05 (m, 5H), 4.45 (br, 1H), 2.99 (q, 2H, J = 6.7 Hz), 2.66 (t, 2H, J = 6.7 Hz), 2.42 (s, 3H), 1.60–1.53 (m,

4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.2, 141.0, 136.8, 132.6, 130.2, 129.6, 127.5, 127.3, 127.0, 124.2, 42.9, 35.3, 29.0, 26.6, 21.4; IR (KBr, cm^{-1}) 3262, 3062, 2952, 1598, 1566, 1493, 1482, 1468, 1458, 1425, 1333, 1304, 1156, 1117, 1094, 1077, 1066, 1046, 1020, 810, 753. Anal. Calcd for $C_{17}H_{20}NSO_2Br$: C, 53.41, H, 5.27. Found: C, 53.57; H, 5.27.

General procedure for Pd-catalyzed cyclization of sulfonamides. A Schlenk flask was charged with the sulfonamide (0.5 mmol), potassium carbonate (0.7 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.01 mmol, 4 mol % Pd), and tri-*o*-tolyl phosphine (0.04 mmol). The flask was purged with argon for 1 min, then toluene (4 mL) was added. The solution was heated to 100 °C with stirring until the starting material had been completely consumed as judged by TLC analysis. The solution was then cooled to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-(*p*-Toluenesulfonyl)indoline (8).**[17] Cyclization of N-(*p*-toluensulfonyl)-*o*-bromophenylethylamine using the general procedure gave 120 mg (88%) of a white solid, mp 101.5–102.3 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.66 (t, 3H, J = 8.4 Hz), 7.26–6.96 (m, 5H), 3.91 (t, 2H, J = 8.1 Hz), 2.88 (t, 2H, J = 8.1 Hz), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.0, 141.9, 133.9, 131.7, 129.6, 127.6, 127.2, 125.0, 123.6, 114.9, 49.9, 27.8, 21.5; IR (KBr, cm^{-1}) 3029, 2874, 2853, 1597, 1480, 1460, 1348, 1307, 1239, 1168, 1104, 1090, 1044, 975, 754. Anal. Calcd for $C_{15}H_{15}NSO_2$: C, 65.91; H, 5.53. Found: C, 65.99; H, 5.50.

***N*-(*p*-Toulenesulfonyl)-1,2,3,4-tetrahydroquinoline (9).**[18] Cyclization of N-(*p*-toluenesulfonyl)-3-(*o*-bromophenyl)propylamine using the general procedure gave

121 mg (84%) of a white solid; mp 94.6– 95.4 °C (lit. mp 95–96 °C):[18] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80–7.01 (m, 8H), 3.80 (t, 2H, J = 6.9 Hz), 2.44 (t, 2H, J = 6.9 Hz), 2.38 (s, 3H),1.63 (quint, 2H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.4, 137.8, 136.9, 130.6, 129.5, 129.0, 127.1, 126.5, 124.9, 46.5, 26.6, 21.7, 21.5; IR (KBr, cm^{-1}) 3057, 2950, 1598, 1488, 1453, 1356, 1340, 1309, 1163, 1092, 1071, 1019, 840, 762, 687, 579. Anal. Calcd for $C_{16}H_{17}NSO_2$: C, 66.87; H, 5.96. Found: C, 66.87; H, 6.08.

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Chapter Three:

The Coupling of Primary Amines with Ortho-Substituted Aryl Halides

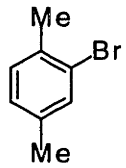
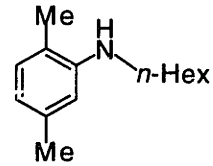
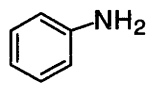
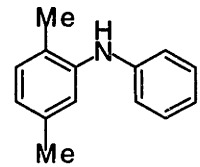
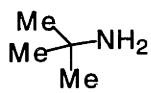
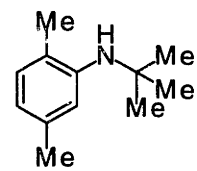
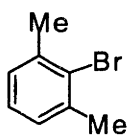
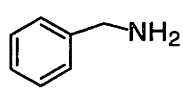
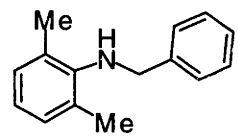
Introduction

Although Dr. Anil Guram had shown the palladium-catalyzed amination of bromides to be effective for several substrate combinations in the absence of tin reagents,[1] reactions of ortho-substituted aryl bromides were not examined. Additionally, the only successful arylation of a primary amine substrate was the coupling of *n*-hexylamine with 4-bromobenzophenone,[1] an activated aryl bromide; reactions of primary amines with unhindered halides usually resulted in low conversions and/or large amounts of reduced arene side products,[2] and reactions of primary anilines had not been examined under the tin-free conditions.

Results and Discussion

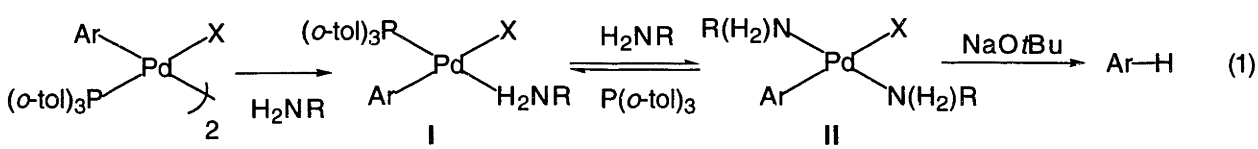
The reactions of secondary amines with ortho-substituted halides were typically inefficient with the Pd/P(*o*-tol)$_3$ catalyst system. However, the combination of primary amines with aryl bromides bearing one or two ortho substituents proceeded in moderate to good yields (Table 1). The reaction of *n*-hexylamine with 2-bromo-*p*-xylene afforded *N*-(2,5-xylyl)hexylamine in 66% isolated yield using 2 mol % $Pd_2(dba)_3$ and 8 mol % P(*o*-tol)$_3$ at 80°C (entry 1). Aniline and *t*-butylamine were also successfully arylated with this substrate (entries 2 and 3), and 2-bromo-*m*-xylene reacted efficiently with benzylamine.

Table 1: Arylation of Primary Amines[a]

Entry	Halide	Amine	Product	Yield (%)
1		*n*-HexylNH$_2$		66
2				90
3				70
4				73

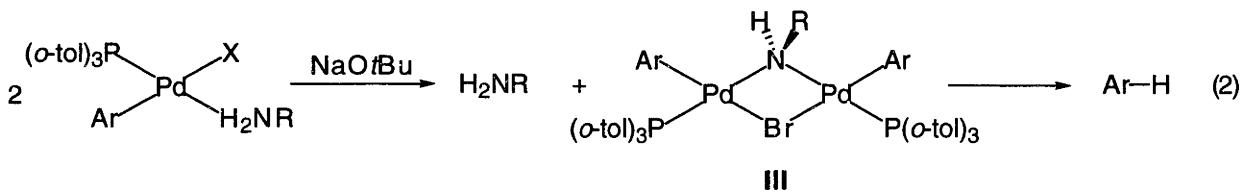
(a) Reaction conditions: 1.0 equiv aryl bromide, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 2 mol % $Pd_2(dba)_3$, 8 mol % P(*o*-tol)$_3$, toluene (9 mL/mmol halide), 80-100 °C.

Mechanistic studies performed by Dr. Ross Widenhoefer have indicated that primary amines are capable of displacing the P(*o*-tol)$_3$ ligand from palladium mono(amine) complexes (**I**) leading to the formation of bis(amine) palladium complexes such as **II**.[3] Reaction of these complexes with NaO*t*Bu does not lead to the formation of the desired product, but instead releases the reduced arene side product (eq 1).[3] Furthermore, Widenhoefer demonstrated that palladium complexes of primary amines undergo dimerization upon treatment with NaO*t*Bu to form bridging amido



(1)

complexes (**III**) which appear to be catalytically inactive.[4] Prolonged heating of these compounds leads to arene formation (eq 2).[4] Presumably these undesired side reactions contribute to the low reactivity and low yields which are observed in arylations of primary amines with unhindered aryl halides.



III

The coupling reactions of primary amines with ortho-substituted aryl halides are presumably successful because the increased steric bulk of the aryl group decreases the facility of these side reactions. Hindered aryl groups should disfavor the formation of bridging amido complexes, and either inhibit the formation of bis(amine) complexes, or favor the dissociation of one equivalent of amine from the bis(amine)complex to afford the desired (monoamine)Pd(monophosphine) complex.

These studies highlighted some of the limitations of the P(*o*-tol)$_3$ catalyst system. Reactions of ortho-substituted halides, particularly those bearing electron-donating groups, were usually inefficient, as were arylation reactions of primary amines. However, reaction of primary amines with hindered halides resulted in good yields of the desired products. This illustrates the need to examine a wide variety of substrate combinations, and to use caution when making generalizations about the process without sufficient data. An improved catalyst system which permits the coupling of a wide variety of aryl halides with primary amines is described in part two of this thesis.

Experimental Section

General Considerations The general considerations are the same as for the previous chapters

General Procedure for the coupling of ortho-substituted aryl bromides with primary amines.

An oven-dried Schlenk flask was cooled to room temperature under an argon purge and charged with $Pd_2(dba)_3$ (19.0 mg, 0.02 mmol, 4 mol % Pd), P(*o*-tol)$_3$ (25.0 mg, 0.08 mmol, 8 mol %), and NaO*t*Bu (136 mg, 1.4 mmol). The flask was purged with argon and toluene (9 mL), the aryl bromide (1.0 mmol), and the amine (1.2 mmol) were added. The flask was heated to 100 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (30 mL), washed with brine (15 mL) and the layers were separated. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

***N*-(2,5-Xylyl)hexylamine** (Table 3, entry 1). The general procedure using a reaction temperature of 80 °C gave 138 mg (66%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H, J = 7.5 Hz), 6.47–6.43 (m, 2H), 3.38 (s, 1H, br), 3.13 (t, 2H, J = 7.2 Hz), 2.29 (s, 3H), 2.09 (s, 3H), 1.66 (p, 2H, J = 7.8 Hz), 1.45–1.30 (m, 6H), 0.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 136.6, 129.8, 118.6, 117.2, 110.5, 43.9, 31.6, 29.6, 26.9, 22.6, 21.5, 16.9, 14.0; IR (neat, cm^{-1}) 3428, 3014, 2956, 2926, 2856, 1615, 1584, 1523, 1466, 1426, 1376, 1312, 1298, 1266, 792; Anal. calcd for $C_{14}H_{23}N$: C, 81.88; H, 11.30. Found: C, 81.74; H, 11.19.

***N*-Phenyl-2,5-xylidene**[5] (Table 3, entry 2). The general procedure gave 180 mg (90%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–6.73 (m, 8H), 5.31 (s, br, 1H), 2.26 (s, 3H), 2.19 (s, 3H);^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.1, 140.9, 136.4, 130.7, 129.2, 125.3, 122.8, 120.2, 119.5, 117.3, 21.1, 17.4; IR (neat, cm^{-1}) 3386, 3048, 3018, 2920, 2858, 1600, 1578, 1518, 1497, 1464, 1412, 1377, 1311, 1000, 805, 747, 694. Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 85.34; H, 7.80.

***N*-(2,5-Xylyl)-*t*-butylamine** (Table 3, entry 3)[6] The general procedure gave 117 mg (66%) of a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.93 (d, 1H, J = 7.2 Hz), 6.73 (s, 1H), 6.46 (d, 1H, J = 7.2 Hz), 2.28 (s, 3H), 2.10 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 136.0, 130.2, 120.7, 117.8, 115.2, 51.2, 30.2, 21.7, 17.7; IR (neat, cm^{-1}) 3442, 2970, 1615, 1227, 791.

***N*-Benzyl-2,6-dimethylaniline** (Table 3, entry 4) The general procedure using a reaction temperature of 80 °C gave 163 mg (73%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 7.0 (d, 2H, J = 7.5 Hz), 6.87–6.82 (m, 1H), 4.11 (s, 2H), 3.20 (s, br, 1H), 2.27 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 140.4, 129.8, 128.8, 128.5, 127.9, 127.3, 122.2, 52.8, 18.5; IR (neat, cm^{-1}) 3364, 2943, 1594, 1217. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.24; H, 8.21.

References and Notes

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(3) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534–3542.

(4) Widenhoefer, R. A.; Buchwald, S. L. Unpublished results.

(5) Kricka, L. J.; Vernon, J. M. *Can. J. Chem.* **1974**, *52*, 299–302.

(6) Xin, H. Y.; Biehl, E. R. *J. Org. Chem.* **1983**, *48*, 4397–4399.

Part Two:

Pd-Catalyzed C–N and C–O Bond Formation Using Palladium Catalysts Bearing Chelating Phosphine Ligands

Chapter Four:

Pd/BINAP Catalyzed Amination of Aryl Bromides and Triflates

Introduction

The scope of catalytic amination reactions that employed the Pd/P(*o*-tol)$_3$ catalyst system was fairly limited. Although some aryl iodides and bromides were efficiently coupled, many substrate combinations gave unsatisfactory results due to the competing reduction of the aryl halide, presumably via a pathway involving β-hydride elimination followed by reductive elimination.[1] In most cases reactions of ortho-substituted halides with secondary amines gave large amounts of arene side products, and as previously stated in chapter 3, arylations of primary amines were usually inefficient unless certain ortho-substituted, or activated aryl halides were used as coupling partners.

Aryl triflates are desirable coupling partners due to their ease of preparation from phenols.[2a] However, aminations of aryl triflates were not effective when catalysts based on P(*o*-tol)$_3$ were employed; only phenol products were formed resulting from attack at the electrophilic sulfur center by NaO*t*Bu. Some cross-coupling reactions of aryl triflate substrates require the use of additives[2a] such as LiCl or Bu_4NCl, or coordinating solvents[2b] such as THF or DMF, however these modifications of our amination protocol failed to improve the reactions of aryl triflates. Procedures which utilized weaker bases such as K_2CO_3 prevented cleavage of the triflate moiety, but failed to generate the desired cross-coupled products.

Occasionally β-hydride elimination is problematic in Kumada couplings or Suzuki coupling reactions of alkylboron derivatives, and chelating phosphine ligands such as DPPF are employed to minimize this undesirable side reaction.[3] Palladium-catalyzed carbonylation,[4a] reduction,[4b] and cyanation[4c] reactions of aryl triflate substrates are often improved with the use of chelating ligands; these reactions frequently fail when monodentate phosphines are employed. Furthermore, Heck arylations of aryl triflates have been shown to proceed in nonpolar solvents such as

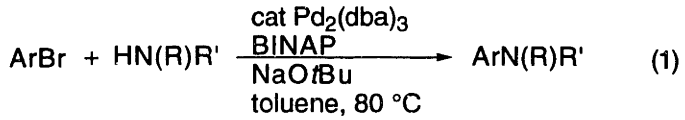
toluene when chelating ligands are used.[5] However, Hartwig's mechanistic studies of the aminostannane amination protocol suggested that this solution would be ineffective for catalytic amination reactions; chelating ligands would decrease the accessibility of the three-coordinate, monophosphine complexes which appeared to be required for the oxidative addition, transmetallation, and reductive elimination steps in the catalytic cycle.[6] Additionally, preliminary experiments conducted by Dr. Anil Guram suggested that chelating phosphines were inefficient ligands for palladium-catalyzed amination reactions.[7a]

During the course of studies to effect the kinetic resolution of chiral amines, Seble Wagaw examined the use of (S)-BINAP[8] as a ligand for the coupling of racemic *sec*-phenethylamine with 4-bromobiphenyl. Although the desired product was obtained in low optical purity, the coupling reaction was considerably more efficient than other reactions of primary amines with unhindered aryl bromides.[7b] This finding indicated that bis(phosphine) palladium complexes are not only viable as catalysts (and as intermediates) but may manifest superior efficiency in aryl C–N bond forming procedures, and led us to undertake a study of the scope of the Pd/BINAP catalyst system in catalytic amination reactions.

Although most of the reactions described in this chapter employed optically active BINAP (the R and S enantiomers were used interchangeably), commercially available racemic BINAP may also be used for these reactions.

Results and Discussion

The Pd/BINAP catalyst system gave much better results for the arylation of primary amines (eq 1) than were obtained when P(*o*-tol)$_3$ was employed as a ligand. For example, the coupling of *n*-hexylamine and 5-bromo-*m*-xylene with the P(*o*-tol)$_3$



(1)

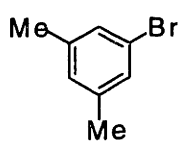
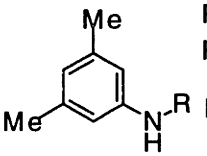
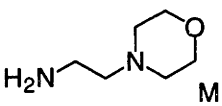
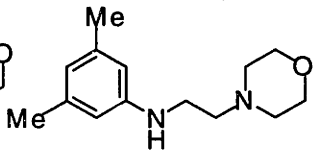
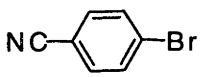
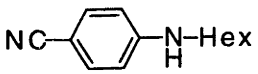
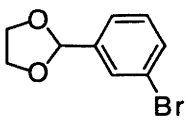
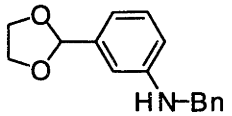
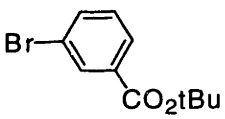
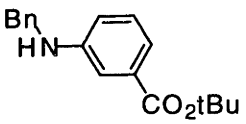
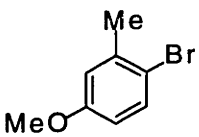
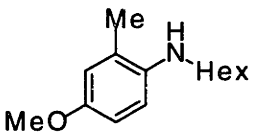
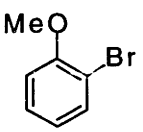
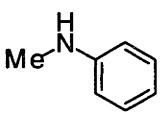
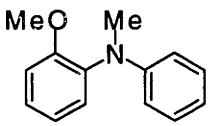
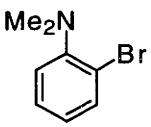
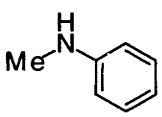
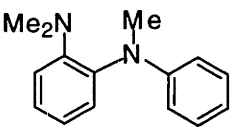
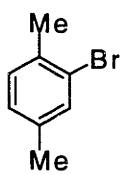
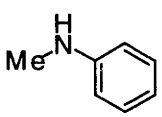
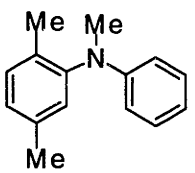
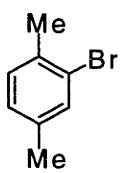
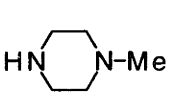
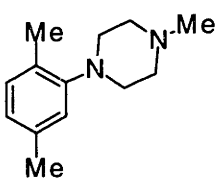
catalyst system (2 % Pd) resulted in only a partial conversion to products after 22 h at 80 °C and gave 35% (isolated yield) of the desired product. In contrast, an 88% yield was realized when the $Pd_2(dba)_3$/BINAP (0.5 % Pd, 80° C, 2h) combination was employed (Table 1, entry 1).

Both electron-rich and electron-poor aryl bromides are efficiently aminated at catalyst loadings as low as 0.05 mol % (~2000 turnovers) as detailed in Table 1. The high activity of this catalyst also allows for the reactions to be conducted at 80° C, approximately 20° C lower than before. Many functional groups, including acetals, nitriles, and *t*-butyl esters are tolerated, although the use of substrates which are sensitive to the strong base is precluded. The principal side products formed in the arylation of primary amines are small amounts of diaryl(alkyl)amines which result from double arylation of the amine substrate (see below).

The use of BINAP as a ligand for coupling 2° amines with *o*-substituted halides also resulted in much higher yields than were obtained when P(*o*-tol)$_3$ was employed (Table 1, entries 1, 9–12). For example, arylation of *N*-methyl piperazine with 2-bromo-*p*-xylene resulted in only 47% yield of the cross-coupled product when the $Pd_2(dba)_3$/P(*o*-tol)$_3$ catalyst system was used, but when BINAP was substituted for P(*o*-tol)$_3$, the yield improved to 98%. These reactions were most efficient when conducted in the absence of solvent, and in some cases proceeded to completion with only 0.05 mol % Pd (entry 12).

Despite the improved results obtained with this catalyst system, some substrates were not effectively handled. Reactions of acyclic secondary amines (with the exception of *N*-methyl aniline), and very hindered primary amines, such as

Table 1: BINAP/Pd-Catalyzed Arylamination

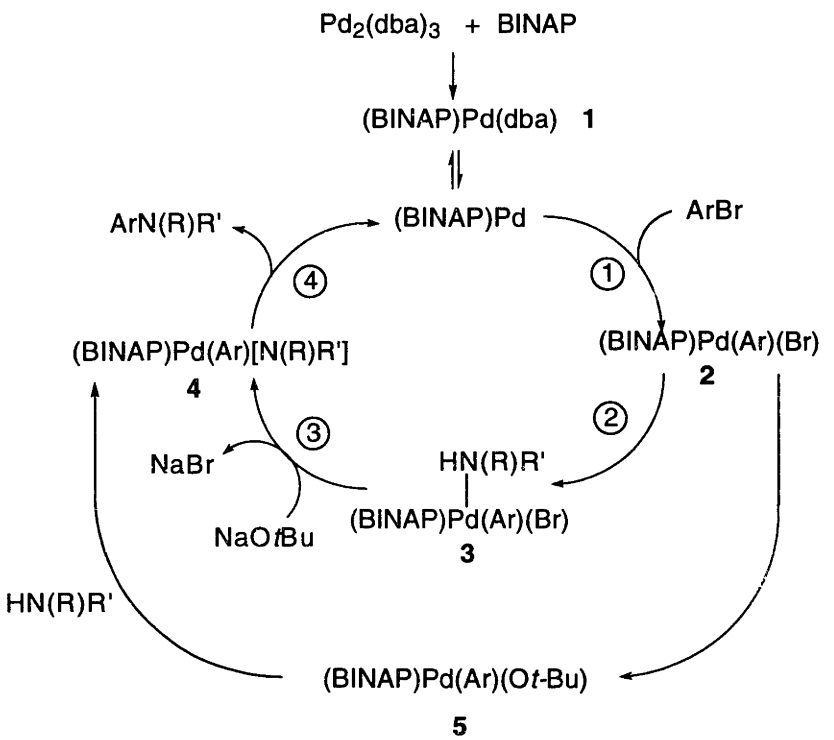
Entry	Halide	Amine	Product	Catalyst Loading (mol % Pd)	Rxn Time (h)	Isolated Yield (%)
1		RNH_2		R= *n*-Hexyl 0.5	2	88 (35)[a]
2				R=Bn 0.5	4	79
3				R= Cy 0.05	7	79
				0.5	18	83
4				0.5	20	84
5		$nHexNH_2$		0.5	<1	98[b]
				0.05	1.5	97
6		H_2NBn		0.5	2	81
7		H_2NBn		0.5	3.5	71
8		$nHexNH_2$		0.5	6	95
9				0.5[c]	29	75
				2.0	14	61 (0)[a]
10				1.0[c]	39	66
				2.0	36	65 (0)[a]
11				0.5[c]	36	94
				2.0	4	79 (5)[a]
12				0.5[c]	4	98
				2.0	15	98 (47)[a]
				0.05[c]	6	94

(a) Yields in parentheses refer to yields obtained when P(*o*-tol)$_3$ was used as the phosphine ligand. (b) Control experiments showed no formation of the desired product after 17 h at 100 °C in the absence of palladium. (c) Reaction run neat.

t-butylamine, usually gave poor results. Electron-rich substrates were also problematic unless they contained an ortho-substituent. Piperidine proved to be difficult to arylate with electron-rich or -neutral bromides substrates, although it reacted well in amination reactions of aryl triflates (see below).

In analogy to what has previously been reported,[1] we surmise that the catalytic cycle is as shown in Scheme 1. We have isolated two of the presumed intermediates in this sequence. Dr. Ross Widenhoefer found that stirring a purple solution of $Pd_2(DBA)_3$ and BINAP in benzene at room temperature for 2 h gave an orange solution from which (BINAP)Pd(dba) (**1**) was isolated in 71 % yield as an orange powder.[9] The oxidative addition complex (BINAP)Pd(*p*-$C_6H_4CMe_3$)(Br) (**2**) was prepared by the reaction of BINAP with {Pd[P(*o*-tol)$_3$](*p*-$C_6H_4CMe_3$)(μ-Br)}$_2$[10a] in benzene at room temperature and was isolated in 50 % yield as a cream-colored solid. No evidence (^{1}H NMR) for the formation of an amine adduct was detected when

Scheme 1: Proposed Catalytic Cycle



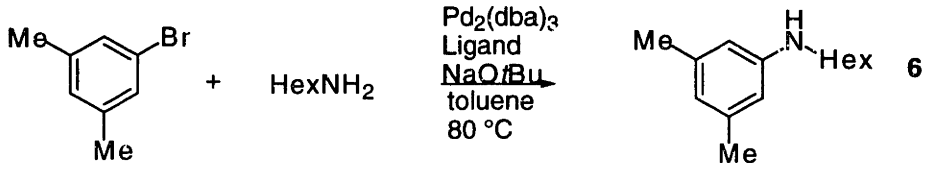
a large excess (5 equiv) of benzylamine was added to a C_6D_6 solution of **2**. However, addition of sodium *tert*-butoxide to the solution caused the rapid formation of *N*-benzyl-4-*t*-butylaniline as the only *tert*-butylphenyl containing product detected (^{1}H NMR analysis). Both **1** and **2** were shown to catalyze the coupling of amines with aryl bromides with reaction rates and product distributions similar to those observed when mixtures of $Pd_2(dba)_3$ and BINAP were employed.

In contrast to Hartwig's early mechanistic studies,[6] the effectiveness of $Pd_2(dba)_3$/BINAP suggests that any or all of steps 1-4 (Scheme 1) may occur from intermediates without prior phosphine dissociation. In particular, coordination of the amine to **2** would form pentacoordinate **3**.[11] Deprotonation of the coordinated amine by NaO*t*Bu would give **4** which undergoes reductive elimination to give (BINAP)Pd and the aniline product. Alternatively, Hartwig has recently demonstrated that treatment of (DPPF)Pd(Ar)(O*t*Bu) with amine leads to the formation of arylamine products,[12] thus it is also possible that the reaction proceeds via *t*-butoxide complex **5**. This complex may also form and react without the dissociation of a phosphine.

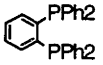
A variety of different chelating ligands were examined for the arylation of *n*-hexylamine with 5-bromo-m-xylene (Table 2). All ligands examined were inferior to BINAP for this reaction, although Hartwig has demonstrated that under some conditions, DPPF is effective for certain classes of substrates (see below)[13]

We believe that structural features specific to BINAP are key to the success of this catalyst system. The efficiency of BINAP in the palladium-catalyzed arylation of primary amines may result from its ability to inhibit the formation of catalytically inactive palladium bis(amine) aryl halide complexes[10b] and bridging amido complexes[10c] (see chapter 3). β-Hydride elimination of **4** may be inhibited due to the inaccessibility of a 3-coordinate mono(phosphine) intermediate.[14,15] Dissociation of one arm of a chelating ligand (de-chelation) could lead to increased amounts of β-hydride

Table 2: Ligand Effects on Arylation of *n*-hexylamine



6

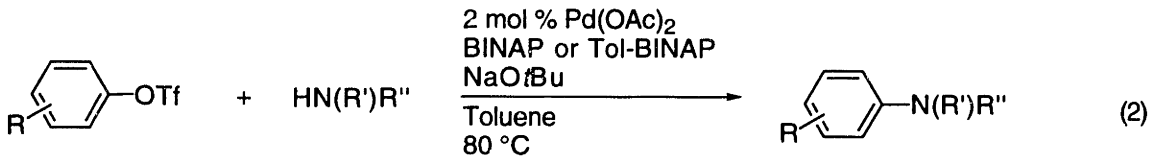
Ligand	% Conversion (Time)	Ratio of Product/ Reduced S.M.	Ratio of Product/ Doubly Arylated Amine	Isolated Yield 6
BINAP	100% (2 h)	40/1	39/1	88%
$P(o\text{-tol})_3$	88% (22 h)	1.5/1	7.6/1	35%
DPPE	7% (6 h)	1/5.4	—	—
DPPP	>2% (6 h)	—	—	—
DPPB	18% (3 h)	1/1.6	—	—
DPPF	100% (3 h)	13.2/1	2.2/1	—
	22% (12 h)	2.5/1	10/1	—

elimination; the rigidity of the binaphthyl backbone and the small bite angle[16a] of BINAP (92.7 °)[16b] relative to DPPF (99.1 °)[3a] presumably lead to the formation of a tight chelate. The increased size of BINAP relative to other chelating ligands disfavors double arylation of the primary amine substrate. BINAP also appears to be an exceptional ligand for palladium; usually a ratio of ≤1.5/1 L/Pd is sufficient for high catalyst activity.

Hartwig has reported related studies involving the use of DPPF in catalytic amination reactions.[13] The DPPF catalyst system was found to be effective for the arylation of primary amines and anilines with electron-deficient aryl bromides, and for the coupling of primary anilines with aryl iodides. Reactions typically required 5 mol % $(DPPF)PdCl_2$ and 15 mol % added DPPF, and were conducted at 100 °C in THF. Many of the products were isolated by sublimation, presumably due to the difficulty in separating the products from DPPF.

Although we were unable to transform aryl triflates using catalysts based on $P(o\text{-tol})_3$, the greatly improved reactivity we observed in aminations of aryl bromides

which employed BINAP as the ligand for palladium prompted us to reexamine aminations of triflate substrates. The Pd/BINAP catalyst proved to be useful for reactions of unactivated aryl triflates (eq 2). For example, reaction of



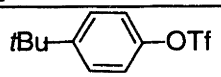
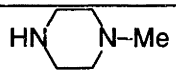
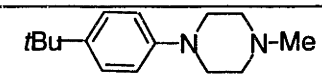
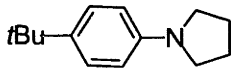
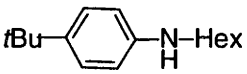
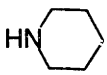
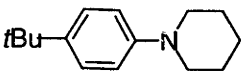
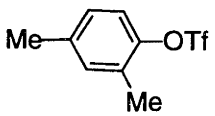
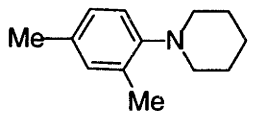
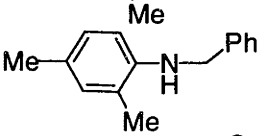
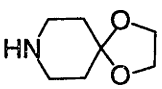
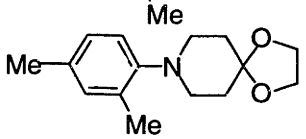
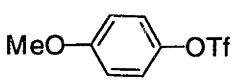
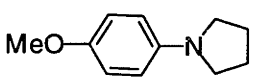
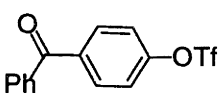
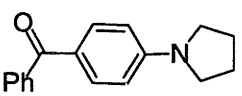
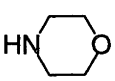
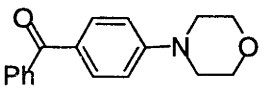
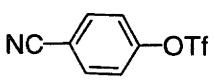
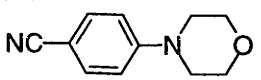
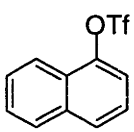
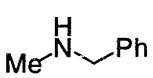
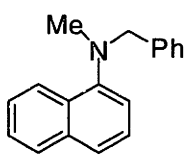
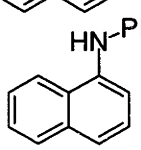
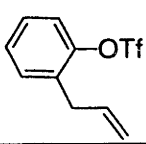
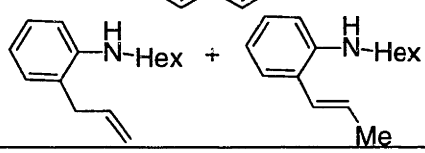
(2)

4-*t*-butylphenyl triflate with *N*-methyl piperazine employing a mixture of $Pd(OAc)_2$/BINAP (2 mol % Pd) and NaO*t*Bu (1.4 eq) in toluene at 80 °C for 3 h gave the *N*-arylpiperazine in 73% yield. The main side product of the reaction was 4-*t*-butylphenol resulting from nucleophilic cleavage of the triflate by NaO*t*Bu,[17] although a small amount of 4-*t*-butylbenzene resulting from the reduction of the aryl triflate was also detected.

As is evident (Table 3), the best yields of coupled products were obtained with electronically neutral or electron rich aryl triflates such as 2,4-dimethylphenyl triflate, 4-*t*-butylphenyl triflate, and 4-methoxyphenyl triflate as substrates. A substrate containing an *o*-allyl group was partially isomerized to afford a mixture of *o*-allyl and *o*-(2-methyl)vinyl arylamine products (entry 14).

In contrast to results obtained in the amination of aryl bromides, aminations of electron poor aryl triflates such as 4-cyanophenyl triflate gave significantly lower yields. The moderate yields obtained with electron-poor aryl triflates may be due to the enhanced leaving group ability of the electron deficient phenoxide which leads to an increased rate of triflate cleavage. Addition of various halides (LiCl, LiBr, Bu_4NBr) failed to increase the yields of these reactions and, in fact, resulted in lower yields of coupled products when electronically neutral triflates were employed. However, employment of $Pd_2(dba)_3$ at high catalyst loading (5 mol % Pd) under high-dilution

Table 3: Catalytic Amination of Aryl Triflates

Entry	Triflate	Amine	Product	Method[a]	Yield(%)[b]
1				A B	73 75
2				A	67
3		$HexNH_2$		A B C	55 47 65[c]
4				A C	69 35[c]
5				A B	76 73
6		$BnNH_2$		A B	72 73
7				A	77
8				A B	64 61
9				A	49
10				A D	47 53[c]
11				A B C D	28 31[c] 53[c] 60
12				A B C	61 47 56[c]
13		$PhNH_2$		A D	61 68[c]
14		$HexNH_2$		A C	54 (3/1)[d] 48[c] (15/1)[d]

a) Method A: 2 mol % $Pd(OAc)_2$, BINAP/$Pd(OAc)_2$ (1.1/1), 0.25 M in aryl halide; Method B: 2 mol % $Pd(OAc)_2$, Tol-BINAP/$Pd(OAc)_2$ (1.1/1), 0.25 M in aryl halide; Method C: 2.5 mol % $Pd_2(dba)_3$ (5 mol % Pd), BINAP/$Pd_2(dba)_3$ (2.2/1), 0.02 M in aryl halide. Method D: Same as method A, but triflate added over 30 min. See experimental section for further details b) All yields represent isolated yields (average of two runs) unless otherwise noted. c) Isolated yield obtained from a single experiment. d) Ratio (GC, ^1H NMR) of 2-propenyl/1-propenyl.

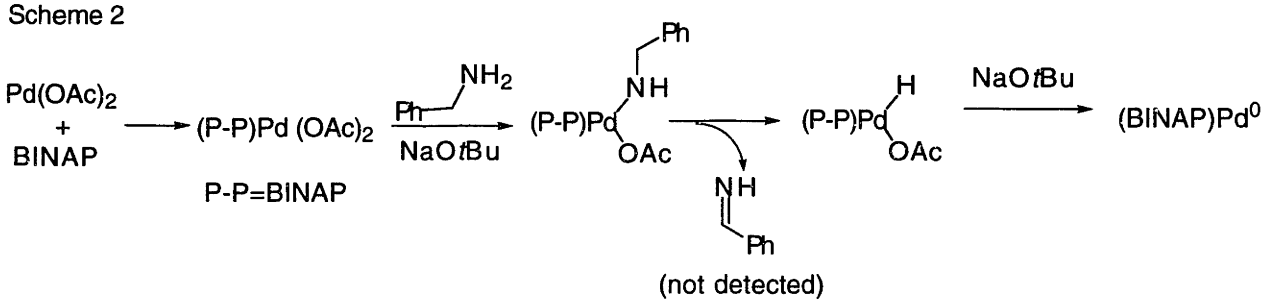
conditions gave higher yields in some cases.[18] In most cases, use of DPPF as a ligand afforded lower yields of coupled products when $Pd(OAc)_2$ was employed as a precatalyst (2 mol % Pd catalyst loading). However, Hartwig has found that DPPF affords the coupled products in good yields when a higher catalyst loading (5 mol %) of $Pd(dba)_2$ was employed at 100 °C under more dilute conditions.[18] Additionally, Hartwig has shown that yields for some coupling reactions may be improved by slow addition of the triflate to the reaction mixture.[18] We have found that in some cases this works well, and yields are significantly improved (Table 1, entry 11); however, for others there is only slight improvement (Table 1, entry 10).

The related ligand Tol-BINAP[19] provided results similar to those obtained with BINAP. However, procedures employing other chelating ligands such as DPPE, DPPP, and DPPBenzene or 1,10-phenanthroline derivatives resulted in little or no product formation.[19] In some cases, $Pd_2(dba)_3$ gave lower yields than $Pd(OAc)_2$, presumably due to inhibition of the catalytic reaction by the dba ligand.[20] Solvents such as DMF, THF, and dioxane also afforded lower yields of aminated products, presumably due to increased solvation of Na^+ resulting in enhanced nucleophilicity of the alkoxide base. Bases weaker than NaO*t*Bu such as K_2CO_3, Na_2CO_3, DABCO, DBU, Proton Sponge, Et_3N, Na_3PO_4, and NaOH failed to promote coupling.[21]

The catalytic cycle for the BINAP/Pd-catalyzed amination of aryl triflates is thought to be similar to that described above for the catalytic amination of aryl bromides. For triflate substrates cationic intermediates (ion pairs) may be involved due to the weak coordination of the triflate counterion,[22] although reaction of the cationic oxidative addition complex with NaO*t*Bu may occur to provide neutral alkoxide intermediates.[12] The effectiveness of aryl triflate substrates with the BINAP catalyst system may arise from the ability of BINAP to prevent decomposition of the cationic oxidative addition complex prior to amine or base coordination.

As the protocol for the palladium-catalyzed amination of aryl triflates employs $Pd(OAc)_2$ as a precatalyst, but presumably proceeds through a Pd(0)–Pd(II) catalytic cycle, NMR studies were undertaken to determine what was responsible for the initial reduction of $Pd(OAc)_2$ to the active catalyst.[23] Mixing $Pd(OAc)_2$/(S)-BINAP in an 1/1.5 ratio in C_6D_6 resulted in the formation of a complex identified as [(S)-BINAP]$Pd(OAc)_2$[23] which was characterized as a singlet at +26 ppm in the ^{31}P NMR spectrum;[24] free BINAP was also observed. Treatment of this complex with excess benzylamine did not provide a new complex. Upon addition of NaO*t*Bu (in the presence of excess benzylamine) the color of the solution changed from yellow to red, and a new ^{31}P NMR signal was observed at +27.3 ppm; at the same time the signal for free (S)-BINAP disappeared. This new complex possesses the same chemical shift reported by Hayashi for $(BINAP)_2Pd$,[23,24] although it is possible that this complex is actually $(BINAP)PdL_n$ (L=amine, solvent), as use of a 1/1 ratio of BINAP/Pd provided similar results.[25] None of the monophosphineoxide of BINAP was detected in the reaction mixture, thus the phosphine ligand is not responsible for reduction of the Pd(II) precatalyst to the active Pd(0) catalyst.[23] It appears that the mixture of amine and base reduces the precatalyst, presumably by a mechanism involving formation of a Pd(amido)complex which then undergoes β-hydride followed by reductive elimination (Scheme 2).

Scheme 2

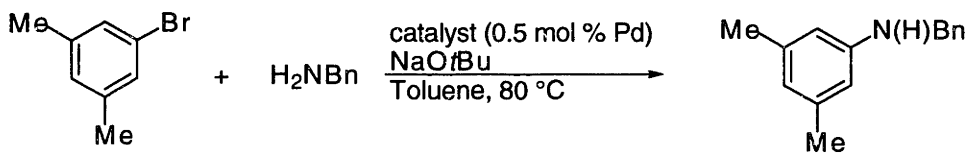


Addition of excess 5-bromo-*m*-xylene[26a] (10 equiv) to the [(S)-BINAP]Pd^0 reaction mixture did not produce any new ^{31}P NMR signals, and after heating to 40 °C for 20 minutes, proton NMR analysis did not show formation of the arylamine product. Heating of this mixture to 80 °C also did not produce new ^{31}P NMR signals; however after heating for 10-15 min, the arylamine product was detected in the proton NMR, suggesting that the resting state of the catalyst during the amination of aryl bromides is a (BINAP)Pd^0 species. This result implies that the rate limiting step in the catalytic cycle is either oxidative addition of the aryl halide, or dissociation of a ligand (amine, solvent, or BINAP) to form (BINAP)Pd which then undergoes rapid oxidative addition of the aryl halide.

In order to more closely simulate the conditions of the catalytic reactions, a mixture of $Pd(OAc)_2$, (S)-BINAP (2 BINAP/Pd),[26b] and excess NaO*t*Bu was dissolved in C_6D_6. Analysis of this mixture by ^{31}P NMR provided a surprising result, only a small amount of the (BINAP)$Pd(OAc)_2$ complex had formed. Treatment of this mixture with benzylamine led to the formation of a small peak at +27.3 ppm characteristic of the Pd(0) complex, however, the majority of the BINAP remained uncomplexed to Pd suggesting that little active catalyst was being formed under these conditions. These experiments led to the discovery that much faster reactions occurred if the BINAP was premixed with $Pd(OAc)_2$ before the addition of base to the reaction mixture. For example, the reaction of 5-bromo-*m*-xylene with benzylamine using the $Pd(OAc)_2$/(S)-BINAP catalyst system (1 mol % Pd) was complete in less than ten minutes when the palladium and ligand were mixed in toluene prior to the addition of the other reagents. In comparison, when $Pd(OAc)_2$ was not mixed with the ligand in toluene before the amine and base were added, the reaction proceeded to only 21% conversion in the same amount of time, and required over 2 h for all of the starting aryl halide to be consumed. Both reactions gave similar ratios (>100/1) of product/reduced arene side product, suggesting that the same active catalyst was formed in both reactions, albeit

in different amounts. This reaction of 5-bromo-*m*-xylene with benzylamine was examined for several different precatalyst mixtures; the results are shown below in Table 4. Reactions were fastest when $Pd(OAc)_2$ was premixed with BINAP. Both (S)-BINAP and (±)-BINAP gave similar results, although it was necessary to heat the

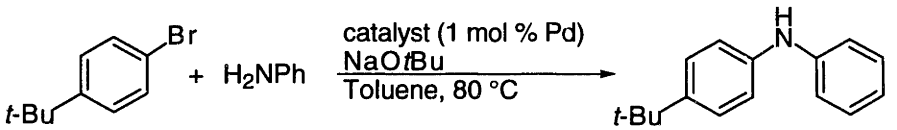
Table 4



catalyst	catalyst and ligand mixed before addition of other reagents	k_{obs} (min^{-1})	relative rate
$Pd_2(dba)_3$/(±)-BINAP	No	0.017±0.001	1.0±0.1
$Pd_2(dba)_3$/(S)-BINAP	No	0.019±0.001	1.1±0.1
$Pd(OAc)_2$/(±)-BINAP	No	0.044±0.003	2.6±0.2
$Pd(OAc)_2$/(S)-BINAP	No	0.044±0.005	2.6±0.3
$Pd_2(dba)_3$/(±)-BINAP	Yes	0.021±0.002	1.2±0.1
$Pd(OAc)_2$/(±)-BINAP	Yes	0.175±0.025	10.3±1.5
$Pd(OAc)_2$/(S)-BINAP	Yes	0.159±0.014	9.4±0.8

precatalyst mixture when (±)-BINAP was employed, due to the low solubility of the racemate. Reactions which used $Pd_2(dba)_3$ as a precatalyst were much slower, and premixing the catalyst did not affect reaction rates; (±)-BINAP provided similar reaction rates to those obtained with (S)-BINAP.

Premixing the $Pd(OAc)_2$/BINAP catalyst precursors was particularly important for the reaction of aniline with 1-bromo-4-*t*-butylbenzene. This reaction proceeded to completion in high yield in <20 h if the BINAP and $Pd(OAc)_2$ were premixed (eq 3).



(3)

Catalyst premixed: 94% isolated yield
Catalyst not premixed: 50-85% conversion

However, if the catalyst precursors were not mixed prior to the addition of the other reagents, the reaction did not proceeded to completion. This effect was also observed by Joseph Sadighi for the arylation of aniline derivatives using a catalyst comprised of $Pd(OAc)_2$/DPE-Phos.[27] It is worth noting that the arylation of primary anilines can also be accomplished if $Pd_2(dba)_3$ is substituted for palladium acetate; premixing the catalyst does not affect the efficiency or rate of these reactions.

One possible explanation for the differences observed in the relative rates of reactions catalyzed by BINAP and palladium acetate is that the formation of $Pd(OtBu)_n$ complexes may inhibit the coordination of the BINAP ligand to the metal due to the large size of the -O*t*Bu moiety. NMR studies showed that a new complex forms upon reaction of $Pd(OAc)_2$ with NaO*t*Bu, and this complex does not react at an appreciable rate with BINAP. Treatment of this mixture with benzylamine led to the formation of a small amount of "(BINAP)Pd^0"; the signal for the catalytically active species slowly increased upon heating (in the absence of an aryl halide).

Presumably these *t*-butoxide complexes may undergo decomposition to catalytically inactive species under the conditions of the catalytic reactions, thus faster reactions rates are observed (due to the presence of larger amounts of the active catalyst) when the $Pd(OAc)_2$ and BINAP are mixed before the amine and base are added. The rates of reactions which did not employ preformed catalysts did not increase with time, suggesting that the *t*-butoxide complexes are not slowly converted to catalytically active species during the course of the reaction. The low reactivity of primary anilines observed when the catalyst precursors (palladium acetate, BINAP) are not premixed may be due to a problematic reduction of the Pd(II) precatalyst. The

pathway by which Pd(II) is reduced to Pd(0) when primary anilines are employed is not clear, and this reduction may require prior coordination of the ligand to the metal.

In conclusion, we have demonstrated that the combination of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and BINAP serves as an efficient catalyst for the amination of aryl bromides and triflates, even at catalyst loadings as low as 0.05 mol % Pd. Primary amine substrates are efficiently arylated using this catalyst system, and several substrate combinations which could not be effectively coupled with P(*o*-tol)$_3$ as the supporting ligand for palladium provide products in high yields with BINAP. Mechanistic studies have shown that the combination of amine and base is most likely responsible for reducing the Pd(II) precatalyst to Pd(0), and that faster reaction rates are obtained in reactions employing $Pd(OAc)_2$ if BINAP and the precatalyst are mixed prior to the addition of the other reactants. Subsequent to this work, a catalyst system based on PPF-OMe[28] which was capable of transforming problematic substrates such as acyclic secondary amines was examined by Dr. Jeff Marcoux and Seble Wagaw,[29] and improved reaction conditions for aminations of aryl triflate substrates were developed by Dr. Jens Åhman.[21] Wagaw also found the BINAP catalyst system to be useful for aminations of bromopyridine substrates[30a] and for arylations of α-chiral amines.[30b] New catalysts based on bulky, electron-rich phosphine ligands have recently been found to be very effective for palladium-catalyzed C–N and C–C bond forming reactions; these catalysts will be discussed in chapters 9–10.

Experimental Section

General Considerations The general considerations are the same as for the previous chapters with the following exceptions. *Tert*-butyl alcohol was purchased from Mallinckrodt Chemical Co. and dried over 3 Å molecular sieves. Lithium *t*-butoxide was purchased from Aldrich Chemical Co. and stored under nitrogen in a

vacuum atmospheres glovebox. (S)--BINAP, (R)–BINAP, and (±)–BINAP, (R)–Tol-BINAP, and (S)–Tol-BINAP were purchased from Strem Chemical Co. or were gifts from Pfizer and were used without further purification. Triflic anhydride, 1-naphthyl triflate, and 1,1'-bis-(diphenylphosphino)ferrocene were purchased from Aldrich Chemical Company and were used without further purification. Pyridine was distilled from calcium hydride and stored over molecular sieves. Palladium acetate was purchased from Alfa Chemical Company or Strem Chemical Co. and was used without further purification. Aryl triflates were prepared according to the procedure of Stille.[1a] 4-*t*-butylphenyl triflate,[31] 4-cyanophenyl triflate,[32] 4-methoxyphenyl triflate,[1a] and 2-(2-propenyl)phenyl triflate[1a] have been previously reported and adequately characterized in the literature.

Pd[(R)-BINAP](dba) (1). A purple solution of $Pd_2(dba)_3$ (72 mg, 0.08 mmol), and (R)–BINAP (100 mg, 0.16 mmol) in benzene (5 mL) was stirred at room temperature for 2 h. The resulting orange solution was filtered through Celite and concentrated under vacuum to give an oily residue which was dissolved in ether (5 mL). The precipitate which formed over 4 h was collected, washed with ether and dried under vacuum to give **1** (110 mg, 70 %) as an orange solid: ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C): δ 7.82 (t, J = 8.2 Hz), 7.69 (br), 7.55 (br), 7.48 (m), 7.37 (t, J = 8.8 Hz), 7.21 (q, J = 7.6 Hz), 7.11 (m), 7.0–6.7 (br, m), 6.60 (t, J = 7.4 Hz), 6.46 (t, J = 6.5 Hz), 6.31 (t, J = 6.9 Hz); ^{31}P {^{1}H} NMR (121 MHz, $CDCl_3$, 25 °C) δ 25.8 (br, s), 24.6 (br, s). IR (KBr, cm^{-1}) 3051, 1641, 1587, 1498, 1474, 1436, 1332, 1207, 1092, 743, 695. Anal. Calcd for $C_{61}H_{46}OP_2Pd$: C, 76.05; H, 4.81; P, 6.43. Found: C, 75.82; H, 4.62; P, 6.50.

[(R)-BINAP]Pd(4-t-butylphenyl)(Br) (2). A solution of BINAP (100 mg, 0.16 mmol), and {Pd[P(*o*-tolyl)$_3$](*p*-$C_6H_4CMe_3$)(μ-Br)}$_2$[10a] (100 mg, 0.16 mmol) in

benzene (16 mL) was stirred at room temperature under argon for 1.5 h. The solvent was evaporated under vacuum to afford an oily solid which was dissolved in ether (20 mL). A white precipitate formed quickly and was collected, washed with ether, and dried under vacuum to give **2** (76 mg, 50 %) as a yellow-white solid, mp 178 °C (dec): ^{1}H NMR (C_6DC_6, 300 MHz, 25 °C) δ 8.15–8.05 (m, 3H), 7.92–7.78 (m, 4H), 7.76–7.55 (br, 2H), 7.42–7.39 (m, 1H), 7.27–7.15 (m, 8H), 7.12–6.91 (m, 6H), 6.81–6.75 (m, 4H), 6.66–6.53 (m, 2H), 6.50–6.42 (m, 1H), 6.40–6.30 (m, 3H), 6.30–6.20 (m, 2H), 1.24 (s, 9H); ^{31}P {^{1}H} NMR (C_6DC_6, 121 MHz, 25 °C) δ 27.9 (d, J = 38.1 Hz), 12.1 (d, J = 38.0 Hz); IR (KBr, cm^{-1}) 3053, 2956, 1560, 1500, 1479, 1436, 808, 696. Anal. Calcd for $C_{54}H_{45}P_2PdBr$: C, 68.84; H, 4.81. Found: C, 68.78; H, 5.00.

***t*-Butyl-(3-bromo)-benzoate**[33] To a solution of lithium *t*-butoxide (401 mg, 5.0 mmol) in *t*-butanol (7 mL) was slowly added 3-bromobenzoyl chloride (0.66 mL, 5.0 mmol) in ether (4 mL). The solution was allowed to stir at room temperature for 18h, then diluted with ether (20 mL) and poured into a separatory funnel. The solution was washed with brine (3 X 5 mL), and the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was purified further by flash chromatography on silica gel using 2% ethyl acetate/hexane as the eluant to afford 760 mg (59%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11 (t, 1H, J = 1.1 Hz), 7.94–7.89 (m, 1H), 7.67–7.62 (m, 1H),7.29 (t, 1H, J = 7.7 Hz), 1.59 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3, 135.3, 133.9, 132.4, 129.7, 128.0, 122.2, 81.6, 28.1; IR (neat, cm^{-1}) 2978, 1715, 1368, 1160; GC/MS (*m/z*) 258, 256, 185, 183.

General Procedure for Arylation of 1° Amines A Schlenk flask was charged with aryl halide (1.0 mmol), amine (1.1 mmol), sodium *t*-butoxide (1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0025 mmol, 0.5 mol % Pd), BINAP (0.0075 mmol), and toluene (2 mL) under argon. The flask was immersed in an 80 °C

oil bath with stirring until the starting material had been completely consumed as judged by GC analysis. The solution was then allowed to cool to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

***N*-Hexyl-3,5-xylidene** (Table 1, entry 1). The general procedure gave 176 mg (86%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.35 (s, 1H), 6.24 (s, 2H), 3.48 (s, br, 1H), 3.08 (t, 2H, J = 7.2 Hz), 2.23 (s, 6H), 1.62–1.29 (m, 8H), 0.90 (t, 3H, J = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.6, 138.7, 119.0, 110.6, 44.0, 31.6, 29.6, 26.8, 22.6, 21.4, 14.0; IR (neat, cm^{-1}) 3409, 2955, 2926, 1601, 1188, 820. Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29. Found C, 81.78; H, 11.20.

***N*-Benzyl-3,5-xylidene** (Table 1, entry 2) The general procedure gave 177 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.25 (m, 5H), 6.39 (s, 1H), 6.29 (s, 2H), 4.30 (s, 2H), 3.89 (s, br, 1H), 2.23 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.3, 139.6, 138.8, 128.5, 127.5, 127.1, 119.5, 110.7, 48.3, 21.4; IR (neat, cm^{-1}) 3411, 3061, 3028, 2915, 1605, 1513, 1494, 1337, 1182, 821. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.04; H, 8.25.

***N*-Cyclohexyl-3,5-xylidene** (Table 1, entry 3).[34] The general procedure gave 172 mg (85%) of a white solid, mp 49.7–51.6 °C (lit mp 50–52 °C):[34] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.32 (s, 1H), 6.22 (s, 2H), 3.42 (s, br, 1H), 3.19–3.29 (m, 1H), 2.22 (s, 6H), 2.08–2.00 (m, 2H), 1.78–1.60 (m, 3H), 1.42–1.08 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.4, 138.7, 118.8, 111.0, 51.5, 33.5, 25.9, 25.0, 21.4; IR (KBr, cm^{-1}) 3396, 2928, 2853, 1603, 1338, 819.

***N*-(2-Ethylmorpholino)-3,5-xylidene** (Table 1, entry 4). The general procedure gave 193 mg (82%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (s, 1H), 6.29 (s, 2H), 4.20 (s, br, 1H), 3.72 (t, 4H, J = 5.0 Hz), 3.15 (t, 2H, J = 6.0 Hz), 2.62 (t, 2H, J = 6.0 Hz), 2.46 (m, 4H), 2.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4, 138.7, 119.2, 110.7, 66.8, 57.0, 53.2, 39.8, 21.4; IR (neat, cm^{-1}) 3382, 2955, 2914, 1602, 1474, 1120, 821. Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46. Found: C, 71.91; H, 9.44.

***N*-(4-Cyanophenyl)-hexylamine** (Table 1, entry 5). The general procedure gave 196 mg (97%) of a white solid, mp 35.1–35.7 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43–7.39 (m, 2H), 6.56–6.51 (m, 2H), 4.16 (s, br, 1H), 3.14 (m, 2H), 1.65–1.29 (m, 8H), 0.90 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 133.4, 120.6, 111.8, 97.6, 43.0, 31.3, 28.8, 26.5, 22.4, 13.8; IR (KBr, cm^{-1}) 3382, 2930, 2212, 1612, 1530, 1173. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 77.35; H, 9.02.

2-(3-*N*-Benzylanilino)-1,4 dioxolane (Table 1, entry 6). The general procedure gave 213 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35–7.25 (m, 5H), 7.18 (t, 1H, J = 7.2 Hz), 6.84 (d, 1H, J = 7.8 Hz), 6.78 (s, 1H), 6.63 (d, 1H, J = 6.9 Hz), 5.75 (s, 1H), 4.34 (br, 3H), 4.12–3.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.1, 139.2, 138.8, 129.0, 128.3, 127.2, 126.9, 115.2, 113.2, 110.5, 103.6, 64.9, 47.9; IR (neat, cm^{-1}) 3404, 3060, 1611, 1494, 1094, 697. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.54; H, 6.67.

***t*-Butyl-3(*N*-benzylamino)-benzoate** (Table 1, entry 7). The general procedure gave 201 mg (71 %) of a white solid, mp 73.6–75.4 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38–7.26 (m, 7H), 7.19 (t, 1H, J = 7.7 Hz), 6.76 (dd, 1H, J = 2.4 Hz, 7.6 Hz), 4.36 (s, 2H), 4.15 (s, br, 1H), 1.57 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0,

147.9, 139.0, 132.8, 128.9, 128.5, 127.4, 127.2, 118.4, 116.5, 113.4, 80.5, 48.0, 28.0; IR (KBr, cm^{-1}) 3359, 3030, 1694, 1603, 1522, 1491, 1368, 1298, 1116, 756. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.47. Found: C, 76.59; H, 7.32.

***N*-Hexyl-2-methyl-4-methoxyaniline** (Table 1, entry 8). The general procedure gave 207 mg (94%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.71–6.69 (m, 2H), 6.57–6.53 (m, 1H), 3.74 (s, 3H), 3.12 (s, Br, 1H), 3.09 (t, 2H, J = 7.2 Hz), 2.13 (s, 3H), 1.67–1.30 (m, 8H), 0.90 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.4, 140.7, 123.5, 116.8, 111.5, 110.7, 55.6, 44.7, 31.6, 29.6, 26.9, 22.6, 17.6, 14.0; IR (neat, cm^{-1}) 3414, 2928, 1514, 1225, 1051. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47. Found: C, 75.93; H, 10.45.

General Procedures for Arylation of 2° Amines:

Method A-No Solvent An oven-dried glass vial was charged with Aryl halide (1.0 mmol), amine (1.2 mmol), sodium *t*-butoxide (1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0025 mmol, 0.5 mol %), and BINAP (0.0075 mmol). The vial was flushed with a stream of argon and tightly capped. The mixture was immersed in an oil bath and heated to 80 °C with stirring until the starting material had been completely consumed as judged by GC analysis. The mixture was allowed to cool to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

Method B-With Solvent: A Schlenk flask was charged with aryl halide (1.0 mmol), amine (1.2 mmol), sodium *t*-butoxide (1.4 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.0025–0.01 mmol, 0.5–2 mol %), BINAP (0.0075–0.03 mmol), and toluene (2–9 mL) under argon. The flask was immersed in an oil bath and heated to 80 °C with stirring until the starting material had been

completely consumed as judged by GC analysis. The mixture was allowed to cool to room temperature, taken up in ether (15 mL), filtered, and concentrated. The crude product was then purified further by flash chromatography on silica gel.

2-Methoxy-*N*-methyl-diphenylamine (Table 1, entry 9). The general procedure gave 172 mg (77%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23–7.14 (m, 4H), 7.00–6.94 (m, 2H), 6.74–6.63 (m, 3H), 3.78 (s, 3H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9, 149.3, 136.7, 129.1, 128.7, 126.9, 121.2, 117.1, 113.3, 112.6, 55.5, 39.0; IR (neat, cm^{-1}) 3060, 1602, 1589, 1497, 1260, 1027, 747. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.96; H, 7.22.

2-(Dimethylamino)-*N*-methyl-diphenylamine (Table 1, entry 10).[35] The general procedure (using 1.0 mol % Pd) gave 143 mg (63%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21–7.09 (m, 4H), 6.98 (dd, 1H, J = 1.5, 8.1 Hz), 6.87 (dt, 1H, J = 1.5, 7.8 Hz), 6.75–6.70 (m, 3H), 3.17 (s, 3H), 2.73 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 148.5, 139.0, 129.2, 128.7, 126.1, 121.1, 118.2, 117.0, 113.5, 42.1, 37.1; IR (neat, cm^{-1}) 2941, 1602, 1497, 1344, 1138, 746.

***N*-Methyl-*N*-phenyl-2,5-xylidene** (Table 1, entry 11). The general procedure gave 201 mg (95%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.14 (m, 3H), 7.01–6.95 (m, 2H), 6.72–6.67 (m, 1H), 6.54–6.51 (m, 2H), 3.20 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.1, 146.6, 137.1, 133.4, 131.1, 128.9, 128.7, 127.1, 116.6, 112.7, 38.9, 20.8, 17.3; IR (neat, cm^{-1}) 2920, 1597, 1500, 1340, 748. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.37; H, 8.03.

***N*-Methyl-*N'*-(2,5-xyiyl)-piperazine** (Table 1, entry 12). The general procedure gave 197 mg (97%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, 1H, J = 7.5 Hz), 6.83–6.78 (m, 2H), 2.94 (t, 4H, J = 4.8 Hz), 2.58 (s, br, 4H), 2.30 (s, 3H), 2.36 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.2, 135.9, 130.7, 129.1, 123.6, 119.6, 55.6, 51.5, 46.1, 21.1, 17.3; IR (neat, cm^{-1}) 2937, 2791, 1505, 1454, 1370, 1291, 1150. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87. Found: C, 76.31; H, 9.71.

2,4-Dimethylphenyl triflate[36] The procedure of Stille[1a] gave 3.34g (88%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15–7.00 (m, 3H), 2.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.5, 138.2, 132.7, 130.4, 128.1, 120.9, 118.7 (q, J = 318 Hz), 20.7, 16.2; IR (neat, cm^{-1}) 2930, 1493, 1421, 1248, 1143, 1089, 876. Anal. Calcd for $C_9H_9SO_3F_3$: C, 42.52; H, 3.57. Found: C, 42.48; H, 3.62.

4-Benzoylphenyl triflate[37] The procedure of Stille[1a] gave 4.24g (86%) of a colorless oil which solidified upon standing to give a white solid, mp 41–42 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.91 (d, 2H, J = 8.8 Hz), 7.80 (d, 2H, J = 7.1 Hz), 7.64 (t, 1H, J = 7.5 Hz), 7.52 (t, 2H, J = 7.3 Hz), 7.41 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.7, 151.9, 137.5, 136.7, 133.0, 132.1, 129.9, 128.5, 121.3, 118.7 (q, J = 319 Hz); IR (KBr, cm^{-1}) 3068, 1665, 1597, 1497, 1427, 1278, 1251, 1218, 1141, 888. Anal. Calcd for $C_{14}H_9SO_4F_3$: C, 50.91; H, 2.75. Found: C, 50.86; H, 2.91.

General Procedures for the Catalytic Amination of Aryl Triflates. Methods A and B: A Schlenk flask was charged with palladium acetate (0.01 mmol, 2 mol % Pd), BINAP (0.011 mmol, 2.2 mol %) (method A) or Tol-BINAP (0.011 mmol, 2.2 mol %) (method B), and sodium *t*-butoxide (0.7 mmol). To this mixture was added a solution of aryl triflate (0.5 mmol) and amine (0.6 mmol) in toluene (2 mL, 0.25 M in aryl halide) via syringe. The mixture was heated to 80 °C with stirring until the triflate

had been consumed as judged by GC analysis. The mixture was cooled to room temperature, taken up in ether, filtered, and concentrated. The crude material was purified by flash chromatography on silica gel.

Method C: A Schlenk flask was charged with tris(dibenzylideneacetone)dipalladium(0) (0.0125 mmol, 5 mol % Pd), BINAP (0.0275 mmol, 5.5 mol %), sodium *t*-butoxide (0.7 mmol), and toluene (20 mL). To this mixture was added a solution of aryl triflate (0.5 mmol), and amine (0.6 mmol) in toluene (5 mL, 0.02 M in aryl halide after addition) via syringe. The mixture was heated to 80 °C with stirring until the triflate had been consumed as judged by GC analysis (2–8 h). The mixture was cooled to room temperature, taken up in ether, filtered and concentrated. The crude material was purified by flash chromatography on silica gel.

Method D: A Schlenk flask was charged with palladium acetate (0.01 mmol, 2 mol % Pd), BINAP (0.011 mmol, 2.2 mol %), sodium *t*-butoxide (0.7 mmol), toluene (1.5 mL), and amine (0.6 mmol). The mixture was heated to 80 °C with stirring, and a solution of the triflate (0.5 mmol) in toluene (0.5 mL) was added dropwise to the reaction mixture over 30 min. via syringe. After the addition was complete, the mixture was heated at 80 °C with stirring until the triflate had been consumed as judged by GC analysis. The mixture was cooled to room temperature, taken up in ether, filtered, and concentrated. The crude material was purified by flash chromatography on silica gel.

***N*-(*p*-*t*-Butylphenyl)-*N'*-methylpiperazine** (Table 2, entry 1). General procedure A gave 86 mg (74%) of a tan solid, mp 82–83 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.9 Hz), 3.19 (t, 4H, J = 4.8 Hz), 2.57 (t, 4H, J = 5.0 Hz), 2.35 (s, 3H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 142.3, 125.8, 115.7, 55.2, 49.2, 46.1, 33.9, 31.4; IR (KBr, cm^{-1}) 2961, 1521, 1458, 1295, 1244, 1150, 820. Anal. Calcd for $C_{15}H_{24}N_2$: C, 77.53; H, 10.41. Found: C, 77.69; H, 10.29.

***N*-(*p*-*t*-Butylphenyl)pyrrolidine** (Table 2, entry 2). General procedure A gave 68 mg (67%) of a white solid, mp 38–39 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.7 Hz), 3.30–3.22 (m, 4H), 2.01–1.95 (m, 4H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9, 137.9, 125.9, 111.3, 47.6, 33.7, 31.6, 25.4; IR (KBr, cm^{-1}) 2962, 1522, 1364, 811. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.95; H, 10.60.

***N*-(*p*-*t*-Butylphenyl)hexylamine** (Table 2, entry 3). General procedure A gave 62 mg (53%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, 2H, J = 8.9 Hz), 6.56 (d, 2H, J = 8.9 Hz), 3.51 (s, br, 1H), 3.08 (t, 2H, J = 6.6 Hz), 1.66–1.55 (m, 2H), 1.45–1.28 (m, 6H), 1.27 (s, 9H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 139.8, 125.9, 112.4, 44.2, 33.8, 31.6, 31.5, 29.6, 26.9, 22.6, 14.0; IR (neat, cm^{-1}) 3412, 1616, 1520. Anal. Calcd for $C_{15}H_{23}N$: C, 82.34; H, 11.66. Found: C, 82.30, H, 11.66.

***N*-(*p*-*t*-Butylphenyl)piperidine** (Table 2, entry 4). General procedure A gave 70 mg (64%) of a white solid, mp 37–38 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, 2H, J = 9.8 Hz), 6.89 (d, 2H, J = 9.7 Hz), 3.11 (t, 4H, J = 5.5 Hz), 1.75–1.67 (m, 4H), 1.60–1.50 (m, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.0, 141.9, 125.7, 116.2, 50.9, 33.9, 31.4, 26.0, 24.3; IR (KBr, cm^{-1}) 2930, 1609, 1518, 1237, 820. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 82.78; H, 10.91.

***N*-(2,4-Dimethylphenyl)piperidine** (Table 2, entry 5).[38] General procedure A gave 71 mg (75%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00–6.88 (m, 3H), 2.80 (t, 4H, J = 5.1 Hz), 2.26 (s, 6H), 1.75–1.62 (m, 4H), 1.60–1.49 (m,

2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.5, 132.6, 131.9, 131.6, 126.8, 118.9, 53.5, 26.7, 24.4, 20.7, 17.6; IR (neat, cm^{-1}) 2933, 1503, 1226.

***N*-(2,4-Dimethylphenyl)benzylamine** (Table 2, entry 6). General procedure A gave 79 mg (75%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.26 (m, 5H), 6.91–6.89 (m, 2H), 6.52 (d, 1H, J = 7.2 Hz), 4.35 (s, 2H), 3.73 (s, br, 1H), 2.23 (s, 3H), 2.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.8, 139.7, 130.9, 128.6, 127.5, 127.3, 127.1, 126.3, 122.0, 110.2, 48.5, 20.3, 17.5; IR (neat, cm^{-1}) 3438, 2916, 1515. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.34; H, 8.25.

***N*-(2,4-Dimethylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane** (Table 2, entry 7). General procedure A gave 93 mg (75%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.00 (s, 1H), 6.95 (d, 2H, J = 1.7 Hz), 4.00 (s, 4H), 2.95 (t, 4H, J = 6.0 Hz), 2.274 (s, 3H), 2.266 (s, 3H), 1.87 (t, 4H, J=6.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 132.5, 132.4, 131.6, 126.9, 119.1, 107.2, 64.2, 50.3, 35.6, 20.6, 17.5; IR (neat, cm^{-1}) 2954, 1499, 1103, 1038. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56. Found: C, 72.61; H, 8.48.

***N*-(*p*-Anisidyl)pyrrolidine** (Table 2, entry 8).[39] General procedure A gave 56 mg (63%) of a white solid, mp 40–41 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 2H, J=9.1 Hz), 6.53 (d, 2H, J=9.0 Hz), 3.76 (s, 3H), 3.28–3.20 (m, 4H), 2.02–1.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.7, 143.2, 115.0, 112.5, 55.9, 48.2, 25.3; IR (KBr, cm^{-1}); IR (KBr, cm^{-1}) 2962, 1516, 1371, 1283, 1238, 1044, 814.

***N*-(*p*-Benzoylphenyl)pyrrolidine** (Table 2, entry 9). General procedure A gave 62 mg (49%) of a yellow solid, mp 138 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.80 (d, 2H, J = 9.5 Hz), 7.71 (d, 2H, J = 8.1 Hz), 7.55–7.40 (m, 3H), 6.54 (d, 2H, J = 9.6 Hz),

3.42–3.35 (m, 4H), 2.09–2.01 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.0, 150.8, 139.4, 132.9, 130.9, 129.3, 127.9, 124.1, 110.5, 47.5, 25.4; IR (KBr, cm^{-1}) 2852, 1654, 1601, 1574, 1540, 1400, 1320, 1285, 1150. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82. Found: C, 81.39; H, 6.92.

***N*-(*p*-Benzoylphenyl)morpholine** (Table 2, entry 10).[37,40] General procedure A gave 67 mg (50%) of a yellow solid, mp 137–138 °C (lit. mp 140 °C):[37] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 2H, J = 8.7 Hz), 7.71–7.68 (m, 2H), 7.55–7.38 (m, 3H), 6.85 (d, 2H, J = 9.6 Hz), 3.83 (t, 4H, J = 4.9 Hz), 3.29 (t, 4H, J = 4.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.2, 154.0, 138.6, 132.4, 131.5, 129.5, 128.0, 127.7, 113.1, 66.5, 47.5; IR (KBr, cm^{-1}) 2966, 1639, 1597, 1236, 924.

***N*-(*p*-Cyanophenyl)morpholine** (Table 2, entry 11).[37] General procedure A gave 31 mg (33%) of a yellow solid, mp 65–66 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, 2H, J = 9.5 Hz), 6.81 (d, 2H, J = 9.6 Hz), 3.82 (t, 4H, J = 4.8 Hz), 3.23 (t, 4H, J = 4.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.5, 133.5, 119.8, 114.0, 100.8, 66.4, 47.2; IR (KBr, cm^{-1}) 2981, 2218, 1606, 1518, 1246, 1182, 1116. Anal. Calcd for $C_{11}H_{12}NO$: C, 70.19; H, 6.43. Found: C, 69.97; H, 6.50.

***N*-Methyl-*N*-benzyl-1-naphthylamine** (Table 2, entry 12).[41] General procedure A gave 76 mg (61%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 8.40–8.32 (m, 1H), 7.88–7.80 (m, 1H), 7.55 (d, 1H, J = 8.4 Hz), 7.50–7.25 (m, 8H), 7.10 (d, 1H, J=7.3 Hz), 4.28 (s, 2H), 2.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.2, 138.8, 134.9, 128.35, 128.26 127.0, 125.7, 125.3, 123.8, 123.2, 115.6, 61.5, 41.7; IR (neat, cm^{-1}) 3048, 1575, 1396, 724.

***N*-Phenyl-1-naphthylamine** (Table 2, entry 13).[42] General procedure A gave 68 mg (62%) of a yellow solid, mp 56–57 °C (lit. mp 62 °C):[42] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05–7.80 (m, 2H), 7.60–7.22 (m, 5H), 7.20–7.02 (m, 2H), 7.00–6.80 (m, 3H), 5.90 (s, br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.7, 138.7, 134.7, 129.3, 128.5, 127.7, 126.1, 126.0, 125.6, 122.9, 121.8, 120.4, 117.3, 115.9; IR (KBr, cm^{-1}) 3408, 3051, 1576, 1307, 742.

***N*-2-(2-Propenylphenyl)hexylamine** (Table 2, entry 14). General procedure A gave 60 mg (55%) of a colorless oil which was a 3/1 mixture (determined by GC, NMR) of the title compound and its olefin regioisomer *trans N*,-2-(1-propenylphenyl)hexylamine (olefin stereochemistry assigned based on coupling constant of olefinic protons): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.00 (m, 3H), 6.70–6.55 (m, 3H), 6.38 (d, 1H, J = 15.6 Hz), 6.10–5.85 (m, 2 H), 5.15–5.05 (m, 2H), 3.68 (s, br, 1H), 3.28 (d, 2H, J = 6.5 Hz), 3.15–3.05 (m, 3H), 1.90 (dd, 1H, J = 1.3, 6.1 Hz), 1.70–1.55 (m, 11H), 1.47–1.25 (m, 4H), 0.92–0.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 145.2, 136.3, 129.7, 128.2, 128.1, 127.7, 127.4, 126.7, 123.3, 116.9, 116.8, 116.1, 110.3, 44.1, 43.8, 36.6, 31.6, 29.5, 29.4, 26.9, 22.6, 18.9, 14.0; IR (neat, cm^{-1}) 3421, 1604, 1512, 745. Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 83.15; H, 10.53.

General Procedure for Palladium-Catalyzed Amination Using $Pd(OAc)_2$/(±)-BINAP (Premixed Catalyst) An oven-dried Schlenk flask was purged with argon and charged with (±)–BINAP (9.3 mg, 0.0075 mmol, 1.5 mol %), and capped with a rubber septum. The flask was purged with argon and toluene (1 mL) was added. The mixture was heated to 80 °C with stirring until the BINAP dissolved (~1 min). The solution was cooled to room-temperature, the septum was removed, and $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol %) was added. The flask was

recapped with the septum, then purged with argon (for ~30 s), and toluene (0.2 mL) was added to rinse the Pd from the sides of the flask. The mixture was stirred at rt for ~1 min, then the aryl halide (1.0 mmol) and the amine (1.2 mmol) were added, the septum was removed, and NaO*t*Bu was added. The flask was recapped with the septum, then purged with argon, and additional toluene (0.8 mL) was added. The mixture was heated to 80 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis. The mixture was cooled to room-temperature, diluted with ether, filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

***N*-(4-*t*-butylphenyl)aniline**[43] (the product depicted in eq 3) The general procedure was conducted in a resealable Schlenk flask and gave the 211 mg (94 %) of the title compound as a white solid, mp 64–67 °C (lit. mp 66-67 °C):[43] ^{1}H (250 MHz, $CDCl_3$) δ 7.31–7.21 (m, 4H), 7.03 (d, 4H, J = 8.4 Hz), 6.89 (t, 1H, J = 7.3 Hz); 5.62 (s, br, 1H), 1.31 (s, 9H); ^{13}C δ 1441., 143.6, 129.2, 126.1, 120.3, 118.1, 117.0, 34.1, 31.4; IR (neat, cm^{-1}) 3388, 2962, 1594, 1497, 1304, 743. Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found: C, 84.98; H, 8.52.

Procedures for the Relative Rate Experiments Shown in Table 4

General procedure for Reactions Without Premixing the Catalyst An oven-dried Schlenk flask equipped with a stirbar and a rubber septum was attached to a ReactIR *in situ* IR instrument and purged with argon. The flask was charged with $Pd_2(dba)_3$ or $Pd(OAc)_2$ (0.5 mol % Pd), (S)– or (±)–BINAP (11.7 mg, 0.0188 mmol, 0.75 mol %), and NaO*t*Bu (336 mg, 3.5 mmol). The flask was purged with argon and Toluene (5 mL), dodecane (0.075 mL), 5-bromo-*m*-xylene (0.34 mL, 2.5 mmol), and benzylamine (3.0 mmol). A thermocouple was inserted into the flask through the

septum. The mixture was stirred at rt and the IR acquisition was begun. After 5 scans (2.5 min) the flask was immersed in an 85 °C oil bath; typically the internal temperature of the reactions were ~78 °C. An aliquot (~30 µL) was removed *via* syringe after 10 scans and the conversion was analyzed by GC in order to accurately correlate absorbance with concentration. The IR acquisition was continued until the starting aryl halide had been completely consumed.

General procedure for Reactions Employing (S)-BINAP in which the Catalyst was Premixed An oven-dried Schlenk flask equipped with a stirbar and a rubber septum was attached to a ReactIR *in situ* IR instrument and purged with argon. The flask was charged with $Pd_2(dba)_3$ or $Pd(OAc)_2$ (0.5 mol % Pd), (S)– or (±)–BINAP (11.7 mg, 0.0188 mmol, 0.75 mol %), and toluene (2.5 mL). The mixture was stirred at rt for ~1 min, then 5-bromo-*m*-xylene (0.34 mL, 2.5 mmol), and benzylamine (3.0 mmol) were added through the septum. The septum was removed and NaO*t*Bu (336 mg, 3.5 mmol) was added, the flask was capped with the septum, and then was purged with argon. Additional toluene (2.5 mL) and dodecane (0.575 mL) were added, and a thermocouple was inserted into the flask through the septum. The mixture was stirred at rt and the IR acquisition was begun. After 5 scans (2.5 min) the flask was immersed in an 85 °C oil bath; typically the internal temperature of the reactions were ~78 °C. An aliquot (~30 µL) was removed *via* syringe after 10 scans and the conversion was analyzed by GC in order to accurately correlate absorbance with concentration. The IR acquisition was continued until the starting aryl halide had been completely consumed.

General Procedure for Reactions Employing (±)-BINAP in which the Catalyst was Premixed An oven-dried Schlenk flask equipped with a stirbar and a rubber septum was attached to a ReactIR *in situ* IR instrument. It was purged with

argon and charged with (±)–BINAP (11.7 mg, 0.0188 mmol, 1.5 mol %), and capped with a rubber septum. The flask was purged with argon and toluene (2.5 mL) was added. The mixture was heated to 80 °C with stirring until the BINAP dissolved (~1 min). The mixture was cooled to rt, the septum was removed, and the $Pd_2(dba)_3$ or $Pd(OAc)_2$ was added. The flask was capped with the septum and stirred at rt for ~1 min, then 5-bromo-*m*-xylene (0.34 mL, 2.5 mmol), and benzylamine (3.0 mmol) were added through the septum. The septum was removed and NaO*t*Bu (336 mg, 3.5 mmol) was added, the flask was capped with the septum, and then was purged with argon. Additional toluene (2.5 mL) and dodecane (0.575 mL) were added, and a thermocouple was inserted into the flask through the septum. The mixture was stirred at rt and the IR acquisition was begun. After 5 scans (2.5 min) the flask was immersed in an 85 °C oil bath; typically the internal temperature of the reactions were ~78 °C. An aliquot (~30 µL) was removed *via* syringe after 10 scans and the conversion was analyzed by GC in order to accurately correlate absorbance with concentration. The IR acquisition was continued until the starting aryl halide had been completely consumed.

Analysis of Data For Relative Rate Experiments

The IR data was obtained in the form of absorbance vs time. The following formula was used to transform the absorbance data into a measure of aryl bromide concentration:

$$[ArBr] = \frac{Absorbance - Absorbance(T_{inf})}{Absorbance(T_0) - Absorbance(T_{inf})} \times [ArBr](T_0)$$

$Absorbance(T_{inf})$=absorbance at complete conversion
$Absorbance(T_0)$=absorbance at time=0
$[ArBr](T_0)$=initial concentration of Aryl Bromide (0.5 M)

Time was measured starting from the point at which the flask was immersed in the oil bath. Plots of [ArBr] vs Time gave exponential graphs. Plots of ln[ArBr] vs Time gave straight lines; the slopes of these lines are reported as the observed rates (k) for the reactions. All experiments were conducted at least two times; the results were averaged. The errors were estimated by taking the average of the differences of the individual runs from the median. The relative rates were determined by setting the rate of the slowest reaction to 1 and scaling the other results accordingly. One representative plot of [ArBr] vs Time and ln[ArBr] vs Time is shown for each set of experiments; since the plots are representative, the k values are different from the average k values shown in table 4. These representative plots can be found in appendix 1 of this thesis.

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(15) Recent results with bulky, electron-rich, monodentate phosphines such as *o*-(di-*t*-butylphosphino)biphenyl suggest that β-hydride elimination of 3-coordinate intermediates is less facile when ligands which possess the correct combination of steric and electronic properties are employed; see chapter 9.

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(23) Hayashi has found that in asymmetric Heck arylations catalyzed by $Pd(OAc)_2$/BINAP the Pd(II) precatalyst is reduced to Pd(0) by BINAP with concomitant oxidation of one of the phosphines. See: Ozawa, F ; Kubo, A.; Hayashi, T. *Chem. Lett.* **1992**, 2177–2180.

(24) Our observed chemical shifts for these complexes differed from those reported by Hayashi by ~1 ppm, however the chemical shift we observed for BINAP also differed by ~1 ppm from his value, suggesting that our values agree with those reported by Hayashi but there is a discrepancy in the referencing of the spectra to external standards.

(25) This is supported by the fact that the same species is formed regardless of the ratio of BINAP/Pd (ratios from 3/1 to 1/1 were examined), although we cannot rule out the possibility that when a ratio of <2/1 is employed not all of the palladium bears a phosphine ligand.

(26) (a) This reaction was conducted using an aryl bromide rather than an aryl triflate to avoid complications arising from NaO*t*Bu-promoted triflate cleavage. (b) (S)–BINAP was used rather than (±)–BINAP due to the relatively low solubility of the racemate.

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Chapter Five:

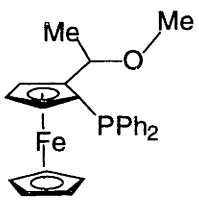
Development of Milder Reaction Conditions For Pd-Catalyzed Amination of Aryl Halides and Triflates

Introduction

Although the development of the BINAP catalyst system substantially improved the scope of the catalytic amination reactions, the conditions required for these transformations were still somewhat harsh; efficient reactions required temperatures of 80 °C and the use of the strong base NaO*t*Bu. With a new, active catalyst now in hand, we sought to find mild reaction conditions for the palladium-catalyzed amination of aryl halides which would proceed at room-temperature and/or in the presence of a weak base.

Development of conditions for room-temperature reactions is of importance to permit the use of substrates which may be thermally sensitive, and may be useful in cases where it is inconvenient to heat reactions (e.g., combinatorial chemistry applications). Although most C–C bond forming cross-coupling reactions of aryl bromide substrates require heating, there are several examples of the use of aryl iodide substrates at ambient temperature,[1] and some instances where aryl bromides may be employed at room temperature.[2] We reasoned that with the correct reaction conditions, catalytic amination of aryl iodide substrates could be effected without heating the reactions. The use of tetraalkylammonium salts as additives, which are commonly employed in room-temperature Heck arylations,[1a,b] failed to promote the catalytic amination of aryl iodides at ambient temperature. However, an observation made by Dr. Ross Widenhoefer during kinetics studies of the Pd/P(*o*-tol)$_3$ catalyzed amination of aryl bromides provided us with a solution to the problem of low reactivity at room-temperature. Dr. Widenhoefer noted that when a stoichiometric amount of 18-Crown-6 was added to the aminations of aryl bromides, a substantial increase in reaction rate occurred.[3] This led us to employ 18-Crown-6 as an additive in aryl iodide amination reactions.

We also sought to resolve issues of functional group tolerance in palladium catalyzed amination reactions. Substrates containing methyl or ethyl esters, enolizable ketones, or nitro groups were not efficiently transformed, and it was clear that the strong base, NaO*t*Bu, was the source of these problems. However, initial experiments with weaker bases were largely ineffective. We reasoned that catalytic amination reactions might occur in the presence of bases weaker than NaO*t*Bu if the palladium catalyst could be made more Lewis acidic. One approach to this idea was to employ the PPF-OMe ligand (**1**)[4] which had been examined by Dr. Jeff Marcoux and Ms. Seble Wagaw for amination reactions of bulky amine substrates.[5] We



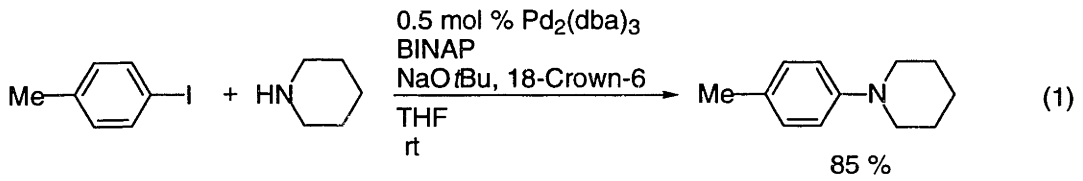
1

reasoned that because PPF-OMe is less strongly electron donating than the BINAP ligand, the Lewis acidity of the metal should be increased when the PPF-OMe ligand is employed. A second approach was simply to employ electron-deficient aryl bromide substrates which could be expected to increase the Lewis acidity of the metal center through an inductive effect. These ideas were used to develop conditions for the catalytic amination of aryl halides bearing base-sensitive functional groups.

Results and Discussion

Our first efforts to develop mild reaction conditions for the palladium catalyzed amination of aryl halides involved the use of 18-Crown-6 as an additive to promote the room-temperature catalytic amination of aryl iodides. For example, the reaction of *p*-

iodotoluene with piperidine in the presence of stoichiometric quantities of NaO*t*Bu and 18-Crown-6 and a catalytic amount of $Pd_2(dba)_3$/BINAP proceeds to completion in ~6 h at room temperature; the product *N*-(4-methylphenyl)piperidine was isolated in 85% yield (eq 1).



(1)

Studies to optimize this process were undertaken and the coupling of *p*-iodotoluene and piperidine catalyzed by $Pd_2(dba)_3$/BINAP (1 mol % Pd) at room temperature was examined using a variety of solvent/additive combinations. As shown in Table 1, the use of THF with added 18-Crown-6 was found to be the most effective system. Reactions with THF, triethylamine, toluene, TMEDA, NMP, DMSO, or DME as solvent without additives proceeded to low conversion. Reactions employing 18-Crown-6 as an additive in toluene, dioxane, or triethylamine were slower than those conducted in THF with added 18-Crown-6. Tetraglyme (tetraethyleneglycol dimethyl ether) was the most effective solvent in the absence of 18-Crown-6, although these reactions failed to proceed to completion (up to 85% conversion was obtained for the coupling of iodotoluene with piperidine). Addition of catalytic amounts (10 mol %) of 18-Crown-6 to reactions run in tetraglyme gave improved results, but these conditions did not prove to be effective with a wide range of substrates.

Although not shown in Table 1, use of the smaller crown ether 15-Crown-5 provided similar results to those obtained with 18-Crown-6. It is commonly believed that 18-crown-6 coordinates potassium ions, while 15-Crown-5 provides a better fit for the sodium cation. However, the binding constant for the coordination of Na^+ in

methanol is substantially higher for 18-Crown-6 (log K_S=4.35) than for 15-Crown-5 (log K_S=3.24),[6] and 15-Crown-5 actually binds K^+ almost twice as strongly as Na^+.[7]

Table 1: Solvent/Additive Effects on the Reaction Shown in Equation 1

Solvent/Additive	% Conversion
THF	13
DMF	55[a,b]
THF/18-Crown-6[d]	100 (85% isolated yield)
THF/TMEDA	13
THF/Bu_4NCl (1.0 eq)	18
THF/Poly(ethylene glycol), M_n=200	0
THF/Poly(ethylene glycol), M_n=3400	46
THF/Poly(ethylene oxide), M_n=200,000	44
THF/Tetraglyme	24
Tetraglyme[c]	85 (57% isolated yield)
Tetraglyme/cat.18-C-6[c]	96 (77% isolated yield)

(a) This reaction gave a mixture of *N*-(4-methylphenyl)piperidine and *N,N*-dimethyl-*p*-toluidine. An amide product resulting from amine exchange with DMF was also observed. (b) A control reaction run in DMF in the presence of 18-Crown-6 without a palladium catalyst afforded a mixture of the two products mentioned above, as well as their meta regioisomers. (c) Tol-BINAP was used in place of BINAP. Analogous reactions run with BINAP as the supporting ligand resulted in similar conversions. (d) A control reaction run in THF in the presence of 18-Crown-6 without a palladium catalyst gave no reaction after 24h at room temp.

As shown in Table 2, the THF/18-Crown-6 conditions are effective for the reactions of both electron-rich and electron-deficient aryl iodides with primary and secondary aliphatic amines at room temperature using moderate catalyst loadings (1 mol % Pd). This procedure is most effective for cyclic secondary amines, while attempted arylation of acyclic secondary amines often resulted in low conversion to and/or poor ratios of the desired products:reduced arene side products. This is consistent with our previous studies of the BINAP/Pd catalyzed amination of aryl bromides.[8]

Reactions which used anilines as substrates required slightly higher temperatures (40 °C) and catalyst levels (4-5 mol % Pd) to proceed to completion. The

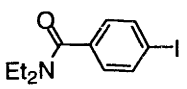
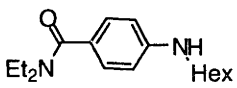
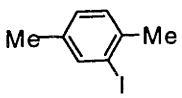
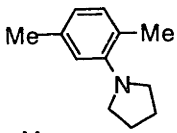
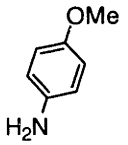
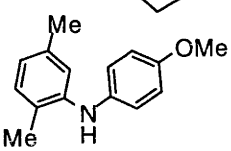
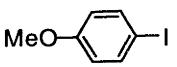
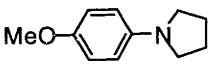
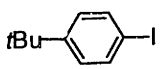
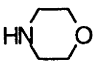
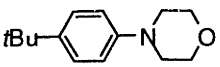
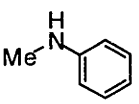
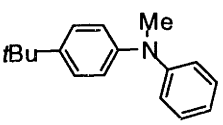
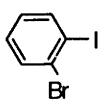
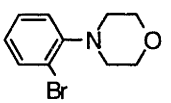
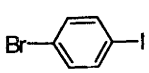
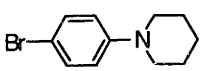
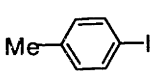
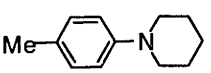
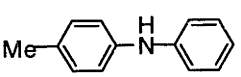
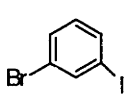
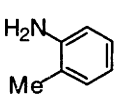
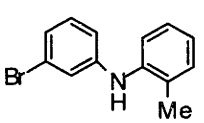
low reactivity of anilines is presumably related to their low nucleophilicity. Coordination of the amine to the (L-L)Pd(Ar)X complex should be more favorable for highly nucleophilic amines, and studies have shown that carbon-heteroatom bond forming reductive elimination becomes more facile with the increased nucleophilicity of the coupling partner.[9]

The reaction of 4-*t*-butyliodobenzene with *N*-methyl aniline afforded a 6.6:1 mixture of the desired product and a side product, *N*-methyl diphenylamine (Table 2, entry 6), although no products resulting from a similar process were detected in the reaction of 4-*t*-butyliodobenzene with morpholine (Table 2, entry 5). This side product may arise from aryl exchange between the BINAP ligand and the substrate;[10] formation of these types of phenylated side products has also been observed in the Pd/BINAP-catalyzed asymmetric arylation of ketone enolates.[11]

By employing our optimized reaction conditions, the selective substitution of the iodide in *o*-,*m*-, or *p*-bromo(iodo)benzene (Table 2, entries 7,8,11) can be achieved. Attempts to carry out this selective substitution using the Pd/P(*o*-tol)$_3$ catalyst system[12] resulted in the formation of a mixture of products. This is the first selective substitution of iodide over bromide observed in a palladium-catalyzed carbon-heteroatom bond forming reaction, although selective substitutions of this type have been reported in C–C bond forming processes.[13]

These reaction conditions represent a substantial improvement over our previous procedure for the palladium-catalyzed amination of aryl iodides.[12] Not only do these reactions function well at room temperature (previously temperatures of 65-100 °C were required; see chapter 1), but in many cases substantially improved yields are obtained. For example, the reaction of *N,N*-diethyl-(4-iodo)benzamide with *n*-hexylamine provided the desired product in 88 % isolated yield when the room-

Table 2: Room-Temperature Catalytic Amination of Aryl Iodides

Entry	Aryl Iodide	Amine	Product	Time	Temp.	Ligand[a]	Mol% Pd	Yield(%)[b]
1		$HexNH_2$		20 h 17 h	rt rt	BINAP Tol-BINAP	1 1	88 (19) 78
2				9 h 22 h 20 h	rt rt rt	BINAP Tol-BINAP DPPF	1 1 1	82 73 78[c]
3				22 h	40 °C	BINAP	4	85
4				3 h 12 h	rt rt	BINAP Tol-BINAP	1 1	83 91
5				17 h 18 h	rt rt	BINAP Tol-BINAP	1 1	90 91
6				25 h	40 °C	BINAP	5	71[d]
7				25 h 19 h	rt rt	BINAP Tol-BINAP	1 1	78 77
8				14 h 13 h	rt rt	BINAP Tol-BINAP	1 1	84 90
9				6 h 9 h	rt rt	BINAP Tol-BINAP	1 1	85 (59) 84
10		$PhNH_2$		20 h	40 °C	BINAP	4	78
11				29 h	40 °C	BINAP	5	72

(a) Reaction Conditions: 1.0 equiv halide, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 1.4 equiv 18-Crown-6, 0.5-2.5 mol % $Pd_2(dba)_3$ (1-5 mol % Pd), 1.5-7.5 mol % ligand (1.5 L/Pd), THF (0.5 M), rt-40 °C. (b) Yields represent isolated yields (average of two experiments) unless otherwise noted. Yields in parentheses were obtained using the original iodide amination protocol.[12] (c) Isolated yield from a single experiment. (d) Product isolated as an 6.6/1 mixture (as determined by ^1H NMR) of *N*-methyl-*N*-(4-*t*-butylphenyl)aniline/*N*-methyl-diphenylamine.

temperature amination conditions were employed (Table 2, entry 1). This reaction afforded only a 19% isolated yield of the aniline derivative using the Pd/P(*o*-tol)$_3$ catalyst in dioxane at 100 °C.[12]

While we have not conducted a detailed study, we believe that the mechanism of this process is analogous to that of the catalytic amination of aryl bromides using BINAP as the supporting ligand.[14] Our current view is that the 18-Crown-6 activates the NaO*t*Bu by increasing solvation of the Na^+, thereby facilitating deprotonation of the coordinated amine.

It is interesting to note that the reaction of 4-bromoiodobenzene with piperidine only proceeded to 79% conversion in THF at 65 °C in the absence of 18-Crown-6 (1 mol % Pd catalyst). This coupling went to completion and afforded the product in high yield (Table 2, entry 8) when the room temperature/18-Crown-6 conditions were employed. In general, amination reactions of aryl iodides at 65–80 °C were less effective than the corresponding couplings of aryl bromide substrates. This is in contrast to what is observed in most palladium-catalyzed cross-coupling processes; typically aryl iodides are the most reactive substrates.[15] The cause for this discrepancy is not clear, although this trend was also observed with the Pd/P(*o*-tol)$_3$ catalyst system.[12,16]

Hartwig has recently reported examples of room-temperature catalytic aminations of aryl iodides.[17] Key to the success of these reactions is the use of the bulky, electron-rich phosphine 1,1'-bis(di-*t*-butylphosphino)ferrocene. The room-temperature catalytic amination of aryl bromides and chlorides using palladium catalysts supported by novel dialkyl(*o*-biphenyl)phosphine ligands is discussed in chapter 9.

Although the use of 18-Crown-6 with aryl iodide substrates provided an alternative to heating reactions, it did not resolve the issues of limited functional group tolerance. However, we found that palladium-catalyzed amination reactions tolerate

the presence of a wide variety of functional groups when the appropriate catalyst is used in combination with the weak base cesium carbonate. Reactions of electronically-neutral aryl bromides proceeded to completion in good yields using 1.5 mol % $Pd_2(dba)_3$/4.5 mol % (*rac*)-PPF-OMe[4] in the presence of cesium carbonate in dioxane at 100 °C . For electron-deficient aryl bromides, 0.5–1.5 mol % $Pd_2(dba)_3$/BINAP (L/Pd=1.5) in toluene at 100 °C was an effective catalyst system.

As shown in Table 3, these reaction conditions are sufficiently mild to tolerate the presence of methyl[18] and ethyl esters, aldehydes, enolizable ketones,[19] and nitro groups, which are incompatible with reaction conditions which employ sodium *t*-butoxide as the stoichiometric base. The reaction may be carried out using either electron-poor or electron-rich aryl bromides, and allows for the synthesis of a wide variety of anilines. While aryl bromides containing nitro groups are sufficiently activated to react slowly in toluene and fairly rapidly in DMF with amines in the absence of a palladium catalyst,[20] useful selectivity can be obtained using the catalytic protocol. For example, the palladium-catalyzed reaction of 2-bromo-4-chloro-5-nitrotoluene with 4-(2-aminoethyl)morpholine afforded exclusive substitution of the bromide (Table 3, entry 15). In the absence of a palladium catalyst, this substrate reacted slowly in toluene (~10% conversion/day) to form exclusively the product resulting from chloride substitution; no products resulting from bromide substitution were observed in DMF in the absence of a palladium catalyst. Similarly, selective substitution of bromide over chloride can be achieved in the reaction of 4-bromo-2-chlorobenzonitrile with benzylamine (entry 16).

Table 3: Catalytic Amination of Aryl Bromides[a]

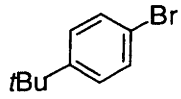
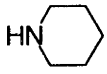
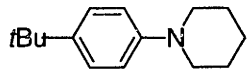
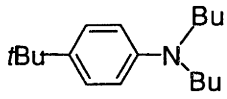
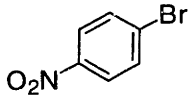
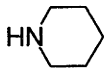
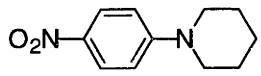
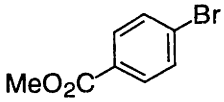
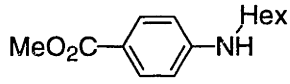
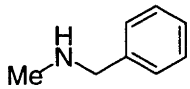
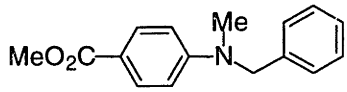
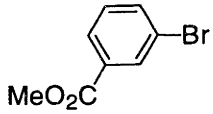
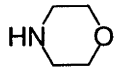
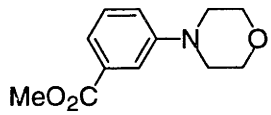
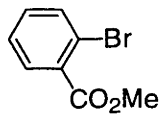
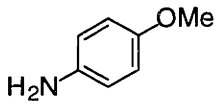
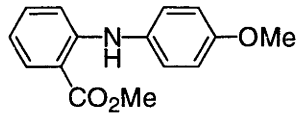
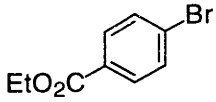
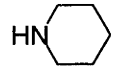
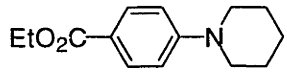
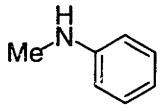
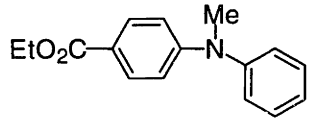
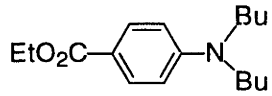
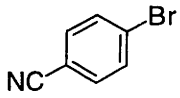
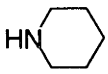
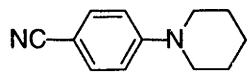
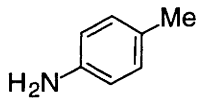
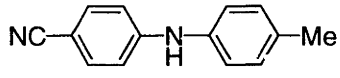
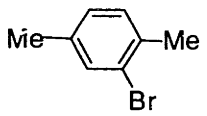
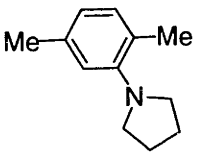
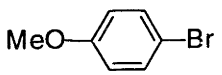
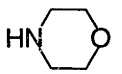
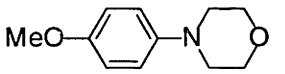
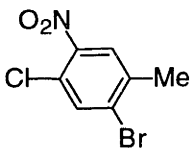
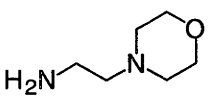
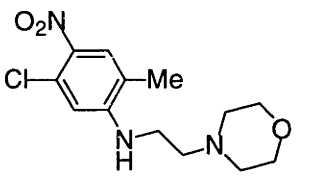
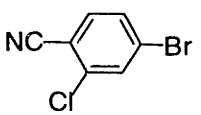
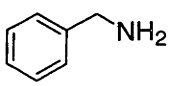
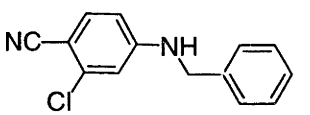
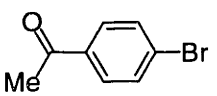
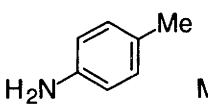
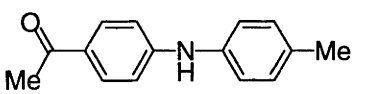
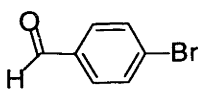
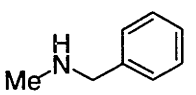
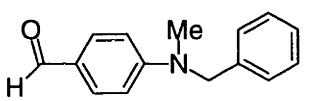
Entry	Halide	Amine	Product	catalyst[b]	mol% Pd	Rxn Time (h)	Yield(%)[d]
1				C[c]	3	15.5	92
2		Bu_2NH		C[c]	3	27	73
3				A	1	18	83
4		H_2NHex		A	2	21	72
5				B	3	16	75
6				B	1	20	86
7				B	3	20	92
8				C	3	26	80
9				A	1	24	87
10		Bu_2NH		D	4	24	73
11				A	1	26	87
12				A	1	26	80

Table 3: Catalytic Amination of Aryl Bromides (cont.)[a]

Entry	Halide	Amine	Product	catalyst[b]	mol% Pd	Rxn Time	Yield(%)[d]
13				B[c]	4	17	93
14				D[c]	4	7	73
15				A	2	16.5	75
16				A	1	20	84
17				A	1	15	73
18				A	1	22	54

(a) Reaction Conditions: 1.0 equiv halide, 1.2 equiv amine, 1.4 equiv Cs_2CO_3, cat. $Pd_2(dba)_3$ or $Pd(OAc)_2$, cat BINAP or PPFE (1.5 L/Pd), toluene (0.25 M), 100 °C. (b) A= $Pd_2(dba)_3$/BINAP; B=$Pd(OAc)_2$/BINAP; C= $Pd_2(dba)_3$/PPFE; D= $Pd(OAc)_2$/PPFE. (c) Reaction run in 1,4-dioxane. (d) All yields reported are isolated yields (average of two runs) of compounds estimated to be ≥95% pure as judged by ^1H NMR and either GC analysis or combustion analysis.

The use of cesium carbonate as the stoichiometric base was essential for high reactivity; other alkali metal carbonates provided only small amounts of the coupled products. This may be due to slightly higher solubility of cesium carbonate,[21] although none of the alkali metal carbonates appeared to be very soluble in toluene or dioxane. Unfortunately, the addition of 18-Crown-6 did not promote room-temperature coupling reactions of aryl iodides in the presence of cesium carbonate. Other weak bases

which were examined, such as tertiary amines or DBU, were not effective for these reactions. Although the pKa of cesium carbonate is lower than that of DBU in water,[22] it is expected that a charged base would be more strongly basic in a nonpolar solvent than in water.[23] Use of other solvents, or mixed solvent/water systems provided inferior results to the cesium carbonate/toluene (dioxane) system. As is commonly observed in heterogeneous reactions, rapid stirring of the reaction mixture was required for optimal results.

Premixing BINAP with palladium acetate before the addition of cesium carbonate resulted in slightly higher reaction rates, although this effect was less dramatic for these reactions than for reactions which employed NaO*t*Bu. The efficiency of primary aniline arylations was not substantially affected by the order of addition of the reagents to the reaction mixture; rates were slightly slower without use of a premixed catalyst, however reactions still proceeded to completion.

In conclusion, relatively mild reaction conditions have been developed using the Pd/BINAP catalyst system. Use of a stoichiometric amount of 18-Crown-6 allows for the room-temperature catalytic amination of aryl iodides. A number of base sensitive functional groups are tolerated in the palladium-catalyzed amination of aryl bromides if cesium carbonate is used as the base. These two protocols significantly expand the scope of the palladium-catalyzed amination of aryl halides.

Related studies by Dr. Jens Åhman demonstrated that improved yields could be obtained for catalytic aminations of aryl triflates when cesium carbonate was employed as the base.[24] Use of cesium carbonate with these substrates minimized the base-induced cleavage of the triflate moiety.

Experimental Section

General Considerations. The general considerations are the same as for the previous chapters with the following exceptions. Aryl iodides were purchased from commercial sources and were used without further purification except for 3-bromoiodobenzene which was passed through alumina before use. 18-Crown-6 was purchased from Lancaster Synthesis and was stored under nitrogen in a Vacuum Atmospheres glovebox. For reasons of convenience, the reaction vessels were charged with 18-Crown-6 in the glovebox. All other reagents were weighed and loaded into the reaction vessels in the air. A reaction employing 18-Crown-6 which had been stored and weighed in the air gave comparable results to the analogous reaction run with 18-Crown-6 from the glovebox. BINAP, Tol-BINAP, DPPF, and $Pd_2(dba)_3$ were purchased from Strem Chemical Company and used without further purification. Compounds 1-4, and 9 in Table 1 and compounds 1, 13, and 14 in Table 2 have been previously reported by this author and were characterized by proton NMR; full spectral data for these compounds is located in other chapters of this thesis. Compound 2 in Table 2 has been previously reported by this group and was characterized by comparison of its proton NMR spectrum with that of the previously described material.

General Procedure For Room-Temperature Catalytic Amination of Aryl Iodides. In a nitrogen-filled glovebox, an oven-dried Schlenk flask was charged with 18-Crown-6 (185 mg, 0.7 mmol), which was capped with a rubber septum and removed from the glovebox. The Schlenk flask was then charged with the aryl iodide (0.5 mmol), the amine (0.6 mmol), NaO*t*Bu (67 mg, 0.7 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol, 1 mol % Pd), BINAP (4.7 mg, 0.0075 mmol), and purged with argon. THF (1 mL) was added and the reaction mixture was stirred at room

temperature under argon until the reaction had proceeded to completion as judged by GC or TLC analysis. The reaction mixture was taken up in ether (20 mL), filtered, and concentrated *in vacuo*. The crude product was then purified by flash chromatography on silica gel.

***N,N*-Diethyl-*p*-(hexylamino)benzamide** (Table 1, entry 1).[12] The general procedure gave 119 mg (86%) of a purple solid, mp 37–38 °C (lit.=oil):[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.23 (m, 2H), 6.56–6.53 (m, 2H), 3.87 (s, br, 1H), 3.43 (q, 4H, *J*= 6.9 Hz), 3.11 (t, 2H, *J* = 7.2 Hz), 1.61 (quint, 2H, *J* = 6.9 Hz), 1.42–1.29 (m, 6H), 1.18 (t, 6H, *J*= 6.9 Hz), 0.90 (m, 3H).

***N*-(2,5-Xylyl)-pyrrolidine** (Table 1, entry 2).[25] The general procedure gave 74 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, 2H, *J* = 7.5 Hz), 6.69 (s, 1H), 6.64 (d, 1H, *J* = 7.5 Hz), 3.15–3.20 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 1.93–1.89 (m, 4H).

***N*-(2,5-Xylyl)-*p*-anisidine** (Table 1, entry 3).[25,26] The general procedure using 2 mol % $Pd_2(dba)_3$, 6 mol % BINAP, and a reaction temperature of 40 °C gave 95 mg (83%) of a white solid, mp 37°C (lit. mp 34–35 °C):[25] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (m, 3H), 6.89–6.82 (m, 3H), 6.63 (d, 1H, *J* = 7.0 Hz), 5.17 (s, br, 1H), 3.80 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H).

***N*-(4-Methoxyphenyl)pyrrolidine** (Table 1, entry 4).[25,27] The general procedure gave 76 mg (85%) of a white solid, mp 41–42 °C (lit. mp 41 °C):[25] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 2H, *J* = 9.1 Hz), 6.53 (d, 2H, *J* = 9.0 Hz), 3.76 (s, 3H), 3.28–3.20 (m, 4H), 2.02–1.90 (m, 4H).

4-(4-*t*-Butylphenyl)morpholine (Table 1, entry 5).[28] The general procedure gave 104 mg (95%) of a white solid, mp 59 °C (lit. mp 50–52 °C):[28] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, 2H, J = 8.9 Hz), 6.87 (d, 2H, J = 8.9 Hz), 3.86 (t, 4H, J = 4.7 Hz), 3.14 (t, 4H, J = 4.9 Hz), 1.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.9, 142.7, 125.9, 115.3, 66.7, 49.5, 33.9, 31.4; IR (KBr, cm^{-1}) 2961, 1521, 1238, 927, 820. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65. Found: C, 76.86; H, 9.87.

***N*-Methyl-*N*-(4-*t*butylphenyl)aniline** (Table 1, entry 6). The general procedure using 2.5 mol % $Pd_2(dba)_3$, 7.5 mol % BINAP, and a reaction temperature of 40 °C gave a 6.6/1 mixture (^{1}H NMR) of the title compound and *N*-methyldiphenylamine (84 mg, 68%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.31 (m, 4H), 6.86 (m, 5H), 3.32 (s, 0.45H), 3.30 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.8, 129.2, 129.0, 126.1, 121.2, 120.4, 120.2, 119.0, 40.2, 34.2, 31.4, 19.5; IR (neat, cm^{-1}) 2960, 1498, 1133; HRMS calcd for $C_{17}H_{21}N$ 239.167400, found 239.16762.

4-(2-Bromophenyl)morpholine (Table 1, entry 7).[29] The general procedure gave 100 mg (83%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57 (dd, 1H, J = 1.6 Hz, 8.0 Hz), 7.29 (dt, 1H, J = 1.1 Hz, 7.3 Hz), 7.05 (dd, 1H, J = 1.6 Hz, 7.9 Hz), 6.93 (dt, 1H, J = 1.6 Hz, 7.3 Hz), 3.88 (t, 4H, J = 4.6 Hz), 3.05 (t, 4H, J = 4.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.3, 133.9, 128.3, 124.6, 120.8, 119.8, 67.1, 52.1; IR (neat, cm^{-1}) 2853, 1475, 1115; GC/MS (*m/z*) 241, 243. Anal. Calcd for $C_{10}H_{12}BrON$: C, 49.61; H, 5.00. Found: C, 50.51; H, 5.20. The material was homogeneous by GC, ^{1}H NMR, and ^{13}C NMR. A small amount of material was Kugelrohr distilled and resubmitted for analysis. Found: C, 49.64; H, 5.00.

***N*-(4-Bromophenyl)piperidine** (Table 1, entry 8).[30] The general procedure gave 110 mg (92%) of a white solid, mp 69–70 °C (lit. mp 77 °C):[30] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, 2H, J = 8.6 Hz), 6.79 (d, 2H, J = 8.6 Hz), 3.12 (t, 4H, J = 5.2 Hz), 1.72–1.65 (m, 4H), 1.60–1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7, 118.0, 113.5, 111.0, 50.4, 25.6, 24.1; IR (KBr, cm^{-1}) 2939, 1494, 1244, 807; GC/MS (*m/z*) 238, 239, 240, 241. Anal. Calcd for $C_{11}H_{14}BrN$: C, 55.02; H, 5.88. Found: C, 55.23; H, 6.01.

***N*-(4-Methylphenyl)piperidine** (Table 1, entry 9).[26] The general procedure gave 74 mg (84%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, 2H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 3.09 (t, 4H, J = 5.4 Hz), 2.26 (s, 3H), 1.73–1.50 (m, 6H).

***N*-Phenyl-*p*-toluidine** (Table 1, entry 10).[31,32] The general procedure using 2 mol % $Pd_2(dba)_3$, 6 mol % BINAP, and a reaction temperature of 40 °C gave 74 mg (80%) of a white solid, mp 87–88 °C (lit. mp 89 °C):[32] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.21 (m, 2H), 7.10–6.90 (m, 6H), 6.88 (t, 1H, J = 7.3 Hz), 5.60 (s, br, 1H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.9, 140.2, 130.9, 129.8, 129.3, 120.2,118.9, 116.8, 20.6; IR (KBr, cm^{-1}) 3394, 1596, 1513, 1308, 746.

***N*-(3-Bromophenyl)-*o*-toluidine** (Table 1, entry 11). The general procedure using 2.5 mol % $Pd_2(dba)_3$, 7.5 mol % BINAP, and a reaction temperature of 40 °C gave 88 mg (67%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–6.92 (m, 7H), 6.80 (dd, 1H, J = 3.2 Hz, 8.9 Hz) 5.39 (s, br, 1H),2.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.0, 139.9, 131.1, 130.5, 130.0, 128.0, 126.9, 122.7, 120.9, 118.9, 114.9, 17.9; IR (neat, cm^{-1}) 3397, 3058, 1587, 1478, 1310, 1068; GC/MS (*m/z*) 261, 263. Anal. Calcd for $C_{13}H_{12}BrN$: C, 59.56; H, 4.61. Found: C, 59.74; H, 4.75.

General Procedure For Catalytic Amination with Cesium Carbonate as Base. An oven-dried Schlenk flask was charged with cesium carbonate which had been finely ground with a mortar and pestle (1.4 eq) in a nitrogen-filled glovebox. The flask was capped with a rubber septum and removed from the glovebox. The flask was then charged with $Pd_2(dba)_3$ or $Pd(OAc)_2$ and BINAP or PPF-OMe (see Table 2), and purged with argon. The aryl bromide (1.0 equiv), the amine (1.2 equiv), and toluene (4 mL/mmol halide) were added, and the mixture was heated to 100 °C with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (20 mL), filtered, and concentrated. The crude product was then purified by flash chromatography on silica gel. A reaction which employed cesium carbonate that had been finely ground in the air and stored in a dessicator outside of the glovebox gave comparable results to the analogous reaction which employed cesium carbonate from the glovebox.

***N*-(*p*-*t*-Butylphenyl)piperidine** (Table 2, entry 1)[33] The general procedure gave 101 mg (93%) of a white solid, mp 36–37 °C (lit. mp 37–38 °C): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26 (d, 2H, J = 9.8 Hz), 6.89 (d, 2H, J = 9.7 Hz), 3.11 (t, 4H, J = 5.5 Hz), 1.75–1.67 (m, 4H), 1.60–1.50 (m, 2H), 1.29 (s, 9H).

***N,N*-Dibutyl-(4-*t*-butyl)aniline** (Table 2, entry 2).[6] The general procedure gave 92 mg (70%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (d, 2H, J = 9.0 Hz), 6.59 (d, 2H, J = 8.7 Hz), 3.23 (t, 4H, J = 7.8 Hz), 1.62–1.50 (m, 4H), 1.41–1.28 (m, 4H), 1.28 (s, 9H), 0.94 (t, 6H, J = 7.5 Hz).

***N*-(4-Nitrophenyl)piperidine** (Table 2, entry 3).[30] The general procedure gave 87 mg (84%) of a yellow solid, mp 95 °C (lit. mp 104 °C):[30] ^{1}H NMR ($CDCl_3$,

300 MHz) δ 8.09 (d, 2H, J = 9.3 Hz), 6.79 (d, 2H, J = 9.9 Hz), 3.50 (m, 4H), 1.75–1.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 137.0, 125.9, 112.1, 48.3, 25.3, 24.2; IR (KBr, cm^{-1}) 2942, 1508, 1450, 1311, 1248, 1200, 1109;. Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.19; H, 6.72.

Methyl-(4-*n*-hexylamino)benzoate (Table 2, entry 4). The general procedure gave 88 mg (75%) of a white solid, mp 93–94 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.7 Hz), 4.01 (s, br, 1H), 3.85 (s, 3H) 3.15 (t, 2H, J = 6.9 Hz), 1.70–1.50 (m, 3H), 1.45–1.28 (m, 5H), 0.90 (t, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 152.0, 131.4, 117.8, 111.1, 51.5, 43.4, 31.6, 29.3, 26.8; IR (KBr, cm^{-1}) 3060, 1703, 1609, 1590, 1276, 1181. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 71.46; H, 8.99. Found: C, 71.47; H, 9.11.

***N*-Methyl-*N*-benzyl-(4-carbomethoxy)aniline** (Table 2, entry 5). The general procedure gave 87 mg (68%) of a white solid, mp 67–68 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, 2H, J = 9.0 Hz), 7.32–7.26 (m, 3H), 7.20–7.10 (m, 2H), 6.69 (d, 2H, J = 9.0 Hz), 4.62 (s, 2H), 3.84 (s, 3H), 3.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.2, 152.6, 137.7, 131.3, 128.7, 127.1, 126.4, 117.3, 110.8, 56.0, 51.5, 38.7; IR (KBr, cm^{-1}) 2948, 1702, 1608, 1286, 1181. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.38; H, 6.88.

***N*-(3-Carbomethoxy)morpholine** (Table 2, entry 6). The general procedure gave 97 mg (87%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58 (s, 1H), 7.54 (d, 1H, J = 6.9 Hz), 7.33 (t ,1H, J = 8.1 Hz), 7.09 (dd, 1H, J = 7.5 Hz, 1.8 Hz), 3.91 (s, 3H), 3.87 (t, 4H, J = 4.5 Hz), 3.21 (t, 4H, J = 5.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 151.0, 130.8, 129.0, 120.8, 119.8, 116.2, 66.7, 52.1, 49.0; IR (neat, cm^{-1})

2954, 1721, 1601, 1492, 1447, 1267, 1122. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.03; H, 6.79.

***N*-(2-Carbomethoxyphenyl)-*p*-ansidine** (Table 2, entry 7).[34] The general procedure gave 115 mg (89%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.26 (s, br, 1H), 7.93 (d, 1H, J = 8.1 Hz), 7.25 (t, 1H, J = 7.8 Hz), 7.17 (d, 2H, J = 8.7 Hz), 6.96 (d, 1H, J = 8.1 Hz), 6.90 (d, 2H, J = 8.7 Hz), 6.65 (t, 1H, J = 6.9 Hz), 3.90 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 156.5, 149.4, 134.0, 133.2, 125.8, 116.0, 114.5, 113.2, 110.7, 55.5, 51.7; IR (neat, cm^{-1}) 3324, 2950, 1682, 1513, 1243, 1162, 1084;. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 70.28; H, 5.95.

***N*-(4-Carboethoxyphenyl)piperidine** (Table 2, entry 8).[35] The general procedure gave 90 mg (77%) of a white solid, mp 78–79 °C (lit. mp 73–75 °C):[35] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (d, 2H, J = 9.1 Hz), 6.84 (d, 2H, J = 9.1 Hz), 4.31 (q, 2H, J = 6.9 Hz), 3.35–3.25 (m, 4H), 1.75–1.65 (m, 6H), 1.35 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 154.2, 130.9, 118.9, 113.4, 60.1, 48.8, 25.4, 24.4, 14.5; IR (KBr, cm^{-1}) 2934, 1698, 1610, 1286, 1126. Anal. Calcd for $C_{11}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 72.24; H, 8.11.

***N*-Methyl-*N*-(4-carboethoxyphenyl)aniline** (Table 2, entry 9).[36] The general procedure gave 114 mg (89%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 2H, J = 8.4 Hz), 7.41–7.36 (m, 2H), 7.22–7.19 (m, 3H), 6.77 (d, 2H, J = 8.7 Hz), 4.29 (q, 2H, J = 7.2 Hz), 3.36 (s, 3H), 1.36 (t, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.5, 152.3, 147.4, 130.8, 129.6, 125.6, 125.1, 119.5, 113.8, 60.2, 40.2, 14.5; IR (neat, cm^{-1}) 2949, 1682, 1600, 1172, 1109, 771. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.17; H, 6.51.

***N,N*-Dibutyl-(4-carboethoxyphenyl)aniline** (Table 2, entry 10). The general procedure gave 102 mg (73%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, 2H, J = 9.0 Hz), 6.57 (d, 2H, J = 9.0 Hz), 4.30 (q, 2H, J = 6.9 Hz), 3.31 (t, 4H, J = 7.2 Hz), 1.65–1.30 (m, 4H), 1.42–1.28 (m, 7H), 0.96 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8, 151.1, 131.2, 116.2, 110.1, 59.9, 50.7, 29.3, 20.3, 14.6, 14.0; IR (neat, cm^{-1}) 2956, 1702, 1605, 1276, 1182. Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81. Found: C, 73.65; H, 9.63.

***N*-(4-Cyanophenyl)-piperidine** (Table 2, entry 11).[30] The general procedure gave 77 mg (83%) of a white solid, mp 45 °C (lit. mp 56 °C):[30] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, 2H, J = 9.0 Hz), 6.83 (d, 2H, J = 9.0 Hz), 3.88–3.28 (m, 4H), 1.70–1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 133.3, 120.2, 113.9, 98.8, 48.4, 25.3, 24.3; IR (KBr, cm^{-1}) 2938, 2217, 1605, 1514, 1124. Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58. Found: C, 77.55; H, 7.41.

***N*-(4-Cyanophenyl)-*p*-toluidine** (Table 2, entry 12). The general procedure gave 84 mg (81%) of a yellow solid, mp 102–103 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, 2H, J = 9.0 Hz), 7.16 (d, 2H, J=8.5 Hz), 7.06 (d, 2H, J = 8.3 Hz), 6.89 (d, 2H, J = 9.0 Hz), 5.95 (s, br, 1H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.5, 137.0, 133.8, 133.5, 130.0, 121.9, 120.0, 114.2, 100.5, 20.9; IR (KBr, cm^{-1}) 3334, 2211, 1597, 1514. Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81. Found: C, 80.65; H, 5.91.

***N*-(2,5-xylyl)-pyrrolidine** (Table 2, entry 13).[25] The general procedure gave 82 mg (93%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, 2H, J = 7.5

Hz), 6.69 (s, 1H), 6.64 (d, 1H, J = 7.5 Hz), 3.15–3.20 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 1.93–1.89 (m, 4H).

***N*-(4-Methoxyphenyl)morpholine** (Table 2, entry 14).[12] The general procedure gave 74 mg (76%) of a white solid, mp 69–70 °C (lit. mp 73.3 °C):[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91–6.84 (m, 4H), 3.86 (t, 4H, J = 4.8 Hz), 3.78 (s, 3H), 3.06 (t, 4H, J = 4.5 Hz).

***N*-(1-Morpholinoethyl)-3-chloro-4-nitro-6-methylaniline** (Table 2, entry 15). The general procedure gave 108 mg (72%) of a yellow solid, mp 104–105 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.89 (s, 1H), 6.53 (s, 1H), 5.21 (s, br, 1H), 3.72 (t, 4H, J = 4.6 Hz), 3.24 (q, 2H, J = 5.1 Hz), 2.72 (t, 2H, J = 6.2 Hz), 2.46 (t, 4H, J = 4.7 Hz), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.4, 135.0, 128.5, 128.1, 120.1, 110.8, 67.0, 55.8, 53.0, 39.0, 16.6; IR (KBr, cm^{-1}) 3352, 2815, 1561, 1526, 1312, 1112; GC/MS (*m/z*) 301, 299. Anal. Calcd for $C_{13}H_{18}N_3O_3Cl$: C, 52.09; H, 6.05. Found: C, 52.33; H, 6.28.

***N*-Benzyl-3-chloro-4-cyanoaniline** (Table 2, entry 16). The general procedure gave 102 mg (84%) of a white solid, mp 91 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.27 (m, 6H), 6.65 (d, 1H, J = 2.3 Hz), 6.48 (dd, 1H, J = 8.6 Hz, 2.4 Hz), 4.67 (s, br, 1H), 4.36 (d, 2H, J = 4.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.7, 138.1, 137.0, 134.7, 128.9, 127.8, 127.2, 117.4, 112.5, 111.0, 100.0, 47.6; IR (KBr, cm^{-1}) 3356, 2216, 1603; GC/MS (*m/z*) 244,242. Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57. Found: C, 69.21; H, 4.52.

***N*-(4-Acetylphenyl)-*p*-toluidine** (Table 2, entry 17).[37] The general procedure gave 82 mg (73%) of an orange solid, mp 108 °C (lit. mp 115 °C):[37] ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, 2H, J = 9.0 Hz), 7.16 (d, 2H, J = 8.3 Hz), 7.08 (d, 2H, J = 8.5 Hz), 6.91 (d, 2H, J = 8.8 Hz), 5.98 (s, br, 1H), 2.52 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.1, 149.0, 137.7, 133.1, 130.4, 129.8, 128.1, 121.3, 113.6, 26.1, 20.9; IR (KBr, cm^{-1}) 3325, 1649, 1565, 1279, 1177;. Anal. Calcd for $C_{15}H_{15}NO$: C, 77.97; H, 6.71. Found: C, 80.19; H, 6.88.

***N*-Methyl-*N*-benzyl-(4-formyl)aniline** (Table 2, entry 18).[38] The general procedure gave 59 mg (52%) of a white solid, mp 53 °C (lit. mp 63 °C):[38] ^1H NMR ($CDCl_3$, 300 MHz) δ 9.73 (s, 1H), 7.71 (d, 2H, J=9.1 Hz), 7.33–7.26 (m, 3H), 7.17 (d, 2H, J = 6.8 Hz), 6.75 (d, 2H, J = 9.0 Hz), 4.66 (s, 2H), 3.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.9, 153.7, 137.0, 131.9, 128.7, 127.2, 126.2, 125.5, 111.1, 55.9, 38.9; IR (KBr, cm^{-1}) 2374, 1660, 1591, 1173, 1108. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 80.19; H, 6.95.

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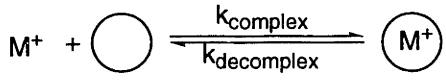
(6) K_S is the constant (eq 3) describing the equilibrium between free M^+ and bound M^+ (eq 2).



(2)

= crown ether

$k_{complex}$=rate of complexation

$k_{decomplex}$=rate of decomplexation

$$K_S = k_{complex}/k_{decomplex} \quad (3)$$

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(18) Differences in the reactivity of methyl-4-bromobenzoate purchased from different commercial sources were observed. Material purchased from Aldrich (99% pure) gave satisfactory results, however use of material purchased from Lancaster (98% pure) resulted in reactions which failed to go to completion and gave significantly different product distributions. The ^{1}H NMR spectra of the material from these sources were identical.

(19) Reactions of the enolizable ketone, 4'-bromoacetophenone, were only successful with 4-methylaniline. Attempts to couple this substrate with morpholine or piperidine afforded only low yields (~15 % by GC) of the desired product; however bulky, electron-rich phosphines function well for this transformation. See chapter nine.

(20) The reaction of 4-bromonitrobenzene with piperidine in DMF in the absence of a palladium catalyst proceeded to completion in 28 h and afforded a 78% isolated yield of *N*-(4-nitrophenyl)piperidine.

(21) Although data for the solubility of alkali metal carbonates in nonpolar solvents are not available, cesium carbonate is considerably more soluble than potassium carbonate in water or methanol. The solubility of cesium carbonate in water is 260.5 g/L while that of potassium carbonate is 112 g/L. In methanol the solubilties of cesium carbonate and potasssium carbonate are 56.1g/100 g MeOH, and 6.2g/100 g MeOH, respectively.

(22) The pKa of carbonate is 10.33 in water; see: March, J. *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure* , 4th ed., John Wiley and Sons: New York, 1992, Ch 8. The pKa of DBU has been measured or estimated to be 11.5–

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Chapter Six:

Benzophenone Imine as an Ammonia Equivalent in Pd-Catalyzed Amination Reactions

Introduction

Despite the utility of our palladium-catalyzed amination methodology for the synthesis of a wide variety of secondary or tertiary aniline derivatives, we were unable to produce primary anilines. Attempts to use ammonia as a coupling partner provided none of the desired primary aniline products. Although *t*-butylamine or benzylamine could be thought of as synthetic equivalents to ammonia, cleavage of aryl(*t*-butyl)amines to the corresponding primary anilines requires very harsh reaction conditions (e.g. refluxing HCl).[1] The benzyl protecting group may be removed from anilines using hydrogenolysis (which is often slow), Na/NH_3, photolysis, or certain chloroformates,[2] however, it was desirable to have a synthetic equivalent of ammonia which could easily be cleaved under a variety of conditions which are tolerant of many different functional groups.

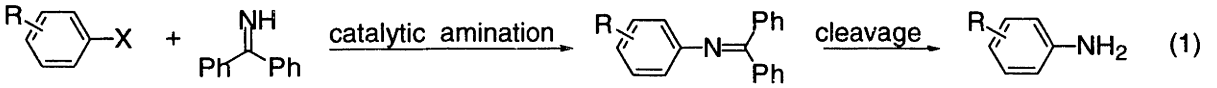
Benzophenone imine has proven to be a useful protecting group in the synthesis of complex molecules, and is stable to base and mild acid.[2,3] This protecting group has also been used in the synthesis of oligoaniline derivatives.[4] Amines which are protected as benzophenone imine derivatives are easily cleaved using a variety of different conditions,[2,3] however use of imines as coupling partners in catalytic amination reactions had not been previously examined.

The reactions discussed in this chapter are the result of a collaboration with Joseph Sadighi, Dr. Jens Åhman, and Dr. Robert Singer. The experiments performed by these individuals are identified by footnotes in Tables 1 and 2.

Results and Discussion

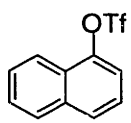
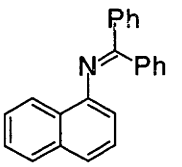
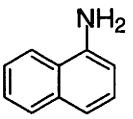
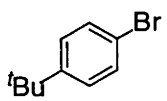
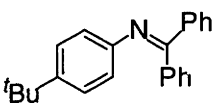
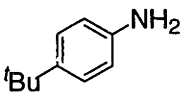
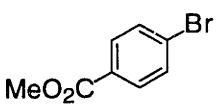
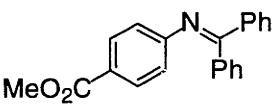
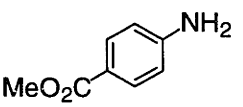
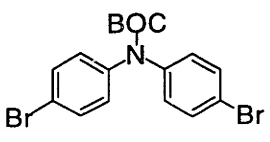
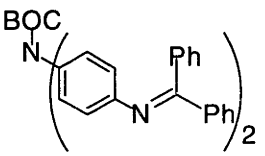
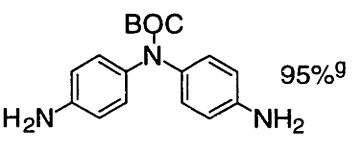
As shown below, benzophenone imine was coupled with aryl halides using our previously developed procedures for the catalytic amination of aryl halides. The

resulting N-aryl benzophenone imine products were then cleaved to liberate the primary anilines (eq 1).



Commercially available benzophenone imine proved to be an excellent substrate for palladium-catalyzed amination reactions. The resulting imine products were usually highly crystalline materials which could easily be isolated by recrystallization from methanol or hexanes (Table 1). Cleavage of the benzophenone imine products was accomplished either by acidic hydrolysis, hydrogenolysis, or by transamination with hydroxylamine.

Table 1: Synthesis and Cleavage of N-Aryl Benzophenone Imines

Entry	Substrate	Product	Yield (%)	Cleavage Conditions	Product	Yield (%)[e]
1			85%[a]	cat HCl wet THF rt		98%[f]
2			90%[b]	$NH_4^+ HCO_2^-$ cat Pd/C MeOH/60° C		84%
3			75%[c]	$NH_2OH•HCl$ NaOAc MeOH/rt		88%
4			91%[d]	$NH_4^+ HCO_2^-$ cat Pd/C MeOH/60° C		95%[g]

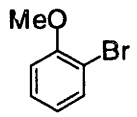
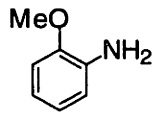
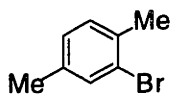
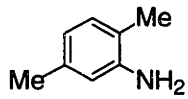
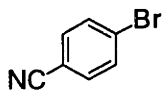
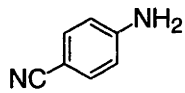
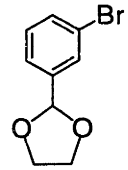
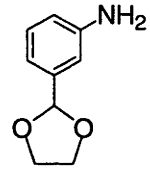
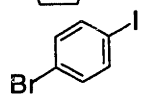
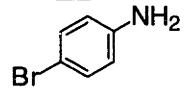
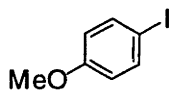
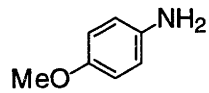
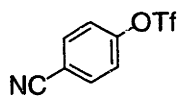
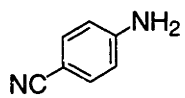
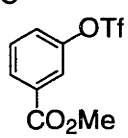
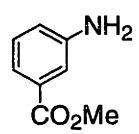
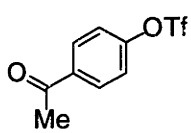
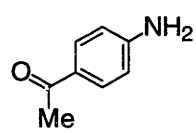
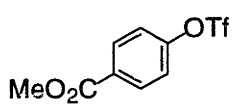
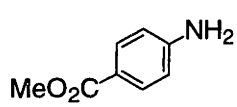
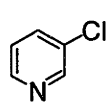
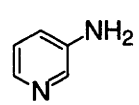
(a) 1 mol % $Pd(OAc)_2$, BINAP, Cs_2CO_3, THF, 65 °C, 16 h; (b) 0.25 mol % $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, toluene, 80 °C, 13 h; (c) 2 mol % $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 5 h. (d) 0.5 mol % $Pd_2(dba)_3$, BINAP, NaO*t*-Bu, toluene, 80 °C, 6 h; (e) Isolated yields are reported as the average of two runs; (f) The reactions described in entry 1 were performed by Dr. Robert Singer; (g)The reactions described in entry 4 were performed by Mr. Joseph Sadighi.

Although isolation of the pure benzophenone imine products was easily accomplished, it was not necessary to isolate these products prior to cleavage. A simple workup procedure involving filtration to remove halide salts followed by concentration afforded the crude imine products which were cleaved using the methods described above (Table 2).

As shown in Table 2, aryl iodides, bromides, and triflates could be employed in these reactions using the Pd/BINAP catalyst system. Reactions of iodides were efficient at room-temperature provided that a stoichiometric amount of 18-Crown-6 was employed as described in chapter 5; the selective substitution of iodide over bromide was achieved using these conditions (entry 5). Benzophenone imine was coupled with 3-chloropyridine using a nickel catalyst (see chapter 8 for further details of nickel-catalyzed amination reactions). A variety of base-sensitive functional groups were tolerated, including methyl esters and enolizable ketones, provided that cesium carbonate was used as the base for the coupling reaction; cesium carbonate was also used for triflate substrates to prevent cleavage of the triflate moiety.[5] Acetal functionality (entry 4) was also tolerated, provided that non-acidic conditions were used to cleave the imine protecting group. Interestingly, DBU proved to be an effective base for the coupling of 1-naphthyl triflate with benzophenone imine, although the use of DBU did not prove to be general in scope.

The benzophenone imine substrate possesses several properties which contribute to the efficiency of these reactions. The nitrogen is sp^2-hybridized, which increases the acidity of the N–H proton,[6] and may increase the facility of the C–N bond forming reductive elimination.[7] Furthermore, this substrate does not possess a hydrogen which could potentially lead to reduction of the aryl halide via a β-hydride elimination/reductive elimination process. Hartwig has reported related studies on the

Table 2: Synthesis of Primary Anilines

Entry	Substrate	Product	Time	Cleavage[e]	Yield (%)[f]
1			5 h[a']	B	87[f]
2			19 h[a]	B	77
3			1.5 h[a]	A	97[f]
4			1.5 h[a]	A	89[f]
5			48 h[b]	C	91[g]
6			14 h[b]	A	88
7			4.5 h[c]	A	84[g]
8			20 h[c]	A	80[g]
9			4 h[c]	C	83[g]
10			5 h[c]	A	89[g]
11			16 h[d]	A	81

(a) 0.25 mol % $Pd_2(dba)_3$, 0.38 mol % BINAP, 1.4 equiv NaO*t*Bu, toluene, 80 °C. (a') 0.5 mol % $Pd_2(dba)_3$, 0.75 mol % BINAP, 1.4 equiv NaO*t*Bu, toluene, 80 °C. (b) 1.0 mol % $Pd_2(dba)_3$, 1.5 mol % BINAP, 1.4 equiv NaO*t*Bu, 1.4 equiv 18-Crown-6, THF, rt. (c) 3 mol % $Pd(OAc)_2$, 4.5 mol % BINAP, 1.4 equiv Cs_2CO_3, THF, 65 °C. (d) 5 mol % $Ni(COD)_2$, 7.5 mol % DPPF, 1.4 equiv NaO*t*Bu, toluene, 100 °C. (e) Cleavage Methods: A: Hydroxylamine; B: Hydrogenolysis; C: Hydrolysis. (f) Isolated yields reported are an average of two runs. (g) The reactions depicted in entry 5 were performed by Dr. Robert Singer. (h) The reactions depicted in entries 7-10 were performed by Dr. Jens Åhman. (i) The reactions depicted in entries 1,3 and 4 were performed by Mr. Joseph Sadighi.

N-arylation of substrates bearing sp^2-hybridized nitrogen atoms,[7b] and demonstrated that although reactions of benzophenone imine work well, reductive elimination reactions involving azoles (e.g. pyrrole, indole) are much less facile and require high reaction temperatures (120 °C).[8]

In conclusion, benzophenone imine serves as a suitable ammonia equivalent in palladium-catalyzed amination reactions. The coupling reactions proceed in high yields, and cleavage of the imine products may be accomplished using a variety of techniques which allow for the synthesis of highly functionalized aniline derivatives.

Experimental Section

General Considerations The general considerations are the same as for the previous chapters with the following exceptions. Benzophenone imine, hydroxylamine HCl, and ammonium formate were purchased from Aldrich Chemical Co. Reactions employing $Ni(COD)_2$ were assembled in an argon-filled glovebox.

General Procedure for the coupling of aryl halides with benzophenone imine. An oven-dried Schlenk flask was charged with $Pd_2(dba)_3$ (0.00125 mmol) and BINAP (0.00375 mmol), and purged with argon. To the flask was added the aryl halide (1.00 mmol), benzophenone imine (1.20 mmol), NaO*t*Bu (1.40 mmol) and toluene (2 mL), and the mixture was heated to 80 °C with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (10 x volume of toluene), filtered, and concentrated. The crude imine product was then cleaved using one of the methods described below.

General Procedures for Imine Cleavage:

Method A (Transamination with Hydroxylamine) To a solution of the imine adduct in MeOH (0.1 M) at rt was added NaOAc (2.4 equiv) and hydroxylamine hydrochloride (1.8 eq). Oxime formation was usually complete in 15 to 30 minutes. The solution was then partitioned between 0.1 M NaOH and CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.

Method B (Hydrogenolysis) A solution of the imine adduct, ammonium formate (15 equiv) and 5% Pd/C (10 mol %) were heated to 60 °C in MeOH (0.2 M in imine). After 2 h reduction was usually complete. The solution was cooled to rt, diluted with CH_2Cl_2 (5 x volume MeOH), and passed through a plug of celite. The organic solution was washed with 0.1 M NaOH, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The product was purified by flash chromatography on silica gel.

Method C (Acidic Hydrolysis) To a solution of the imine adduct in THF (0.3 M) was added aqueous 2.0 M HCl (added 5% by volume of THF). After 5-20 minutes hydrolysis was complete and the reaction mixture was partitioned between 0.5 M HCl and 2:1 hexane/EtOAc. The aqueous layer was separated and made alkaline. The product aniline was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*.

***N*-(4-*t*-Butylphenyl)benzophenone imine** (Table 1, entry 2, imine). The general procedure gave a viscous, yellow oil which was crystallized from methanol to afford 277 mg (88%) of a yellow solid, mp 92–93 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 2H, J = 7.5 Hz), 7.45–7.35 (m, 3H), 7.30–7.20 (m, 3H), 7.18–7.10 (m, 4H), 6.65 (d, 2H, J=8.4 Hz), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 148.3, 145.9, 139.9, 136.3, 130.4, 129.5, 129.4, 129.2, 128.4, 128.0, 127.8, 125.2, 120.7, 34.1, 31.3;

IR (KBr, cm^{-1}) 2960, 1610, 1499. Anal. Calcd for $C_{23}H_{23}N$: C, 88.13; H, 7.40. Found: C, 88.11; H, 7.47.

4-*t*-Butylaniline (Table 1, entry 2, aniline).[9] *N*-(4-*t*-butylphenyl)benzophenone imine (244 mg, 0.775 mmol) was cleaved using method B to afford 96 mg (83%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.18 (d, 2H, *J* = 8.4 Hz), 6.65 (d, 2H, *J* = 8.1 Hz), 3.54 (s, br, 2H), 1.28 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7, 141.3, 126.0, 114.8, 33.8, 31.5; IR (KBr, cm^{-1}) 3424, 3356, 2960, 1517, 1266.

***N*-(4-Carbomethoxyphenyl)benzophenone imine** (Table 1, entry 3, imine). The general procedure conducted on a 0.5 mmol scale using 2 mol % $Pd(OAc)_2$, 3 mol % BINAP, cesium carbonate as the base, 2 mL toluene/mmol halide, and a reaction temperature of 100 °C gave a viscous, yellow oil which was crystallized from methanol to afford 123 mg (78%) of a white solid, mp 131–132 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, 2H, 8.1 Hz), 7.75 (d, 2H, *J* = 7.5 Hz), 7.65–7.35 (m, 3H), 7.30–7.20 (m, 3H), 7.15–7.05 (m, 2H), 6.74 (d, 2H, *J* = 8.7 Hz), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 166.7, 155.6, 138.8, 135.5, 130.9, 130.2, 129.3, 129.1, 128.7, 128.1, 127.9, 124.5, 120.4, 51.8; IR (KBr, cm^{-1}) 2954, 1709, 1633, 1594, 1280, 1115;. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43. Found: C, 80.16; H, 5.65.

Methyl-4-aminobenzoate (Table 1, entry 3, aniline).[10] *N*-(4-Carbomethoxyphenyl)benzophenone imine (79 mg, 0.25 mmol) was cleaved using method A to afford 35 mg (92%) of a white solid, mp 107–109 °C (lit. mp 112 °C):[10] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, 2H, *J* = 9.0 Hz), 6.63 (d, 2H, *J* = 8.7 Hz), 4.05 (s, br, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 150.8, 131.5, 119.6, 113.7, 51.5; IR (KBr, cm^{-1}) 3410, 3341 ,3328, 1686, 1597, 1287.

2,5-Dimethylaniline (Table 2, entry 2).[11] The general procedure using THF in place of toluene, and workup method B gave 91 mg (75%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H), J = 6.9 Hz), 6.53–6.50 (m, 2H), 3.53 (s, br, 2H), 2,24 (s, 3H), 2.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3, 136.6, 130.2, 119.3, 119.2, 115.7, 21.0, 16.8; IR (KBr, cm^{-1}) 3364, 2920, 1516, 1037. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15. Found: C, 79.55; H, 9.05.

***p*-Anisidine** (Table 2, entry 6).[12] An oven dried Schlenk flask was charged with 4-iodoansole (234 mg, 1.0 mmol), NaO*t*Bu (135 mg, 1.4 mmol), 18-Crown-6 (370 mg), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 2.0 mol % Pd), and BINAP (18.7 mg, 0.03 mmol) and was purged with argon. THF (2 mL), and benzophenone imine (0.20 mL, 1.2 mmol) were added and the mixture was stirred at rt for 17 h at which time GC analysis showed that the starting material had been completely consumed. The mixture was diluted with ether (30 mL), filtered, and concentrated *in vacuo*. The crude imine product was cleaved using method A to afford 115 mg (93%) of a brown solid, mp 55–58 °C (lit. mp 57 °C):[12] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74 (d, 2H, J = 8.8 Hz), 6.64 (d, 2H, J = 8.6 Hz), 3.74 (s, 3H), 3.50 (s, br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.7, 139.8, 116.3, 114.7, 55.6; IR (KBr, cm^{-1}) 3384, 3214, 2836, 1509, 1231.

3-Aminopyridine (Table 2, entry 11).[13] In an argon-filled glovebox, an oven-dried resealable Schlenk flask was charged with $Ni(COD)_2$ (15 mg, 0.05 mmol, 5 mol %), DPPF (55 mg, 0.1 mmol), NaO*t*Bu (135 mg), toluene (4 mL), 3-chloropyridine (0.95 mL, 1.0 mmol), and benzophenone imine (0.20 mL, 1.2 mmol). The flask was sealed with a teflon screwcap and removed from the glovebox. The flask was heated to 100 °C with stirring for 17 h at which time GC analysis showed that the starting aryl chloride had been completely consumed. The mixture was cooled to roomtemperature, diluted

with ether (30 mL), filtered, and concentrated *in vacuo* . The crude imine product was cleaved using method A to afford 77 mg (82%) of a brown solid, mp 55–58 °C (lit. mp 64 °C):[13] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.11, (d, 1H, J = 2.7 Hz), (8.04 (d, 1H, J = 3.9 Hz), 7.10–7.03 (m, 1H), 7.00–6.95 (m, 1H), 3.68 (s, br, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.6, 139.6, 137.3, 123.6, 121.3; IR (KBr, cm^{-1}) 3379, 3164, 1634, 1489. Anal. Calcd for $C_5H_6N_2$: C, 63.81; H, 6.43. Found: C, 64.04; H, 6.62.

References and Notes

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(2) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis* 2nd ed., John Wiley and Sons: New York, 1991, Ch 7.

(3) (a) Wessjohann, L.; McGaffin, G.; de Meijere, A. *Synthesis*, **1989**, 359. (b) Fasth, K.-J.; Antoni, G.; Långström, B. *J. Chem. Soc., Perkin Trans. I* **1988**, 3081. (c) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, 2641.

(4) (a) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 213–214; (b) Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 4960–4976.

(5) Åhman, J.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6363–6366.

(6) Bordwell has reported the pKa of benzophenone imine to be 31.0. See: Bordwell, F. G.; Algrim, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 2964–2968. By comparison, the pKa of ammonia is ~41, and the pKa of aniline is 30.6. See: Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–465.

(7) (a) In the analogous C–C bond forming processes, reductive elimination of sp^2-hybridized carbon is much more facile than reductive elimination of sp^3-hybridized carbon. See: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applictions of Organotransition Metal Chemistry*, University Science Books: Mill Valley, CA, 1987, Ch 5. (b) Hartwig has reported related studies on reductive elimination of

sp^2-hybridized nitrogen. Reductive elimination of benzophenone imine is relatively facile while that of azoles is slow. See: Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernandez-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827–828.

(8) Old and Buchwald have effected the N-arylation of indoles using catalysts based on 2-dimethylamino-2'-dicyclohexylphosphino-1,1'-biphenyl. Old, D. W.; Buchwald, S. L. Unpublished results.

(9) *Dictionary of Organic Compounds*, Cadogan, J. I. G.; Ley, S. V.; Pattenden, G.; Raphael, R. A.; Rees, C. W. eds.; 6th ed, 1996, Chapman & Hill, London, p 1159.

(10) Reference 9, p 124.

(11) Reference 9, p 2542.

(12) Reference 9, p 4190.

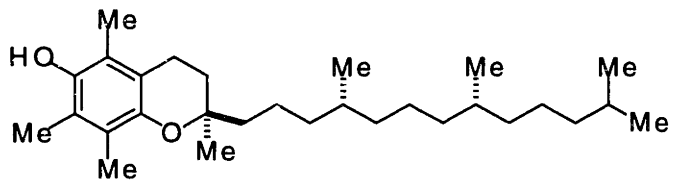
(13) Reference 9, p 399.

Chapter Seven:

Synthesis of Oxygen Heterocycles

Introduction

The aryl ether moiety is found in a wide variety of natural products and pharmaceuticals.[1,2] Oxygen heterocycles, in particular, are found in many important biologically active compounds, such as vitamin E (Figure 1), and also in many secondary metabolites.[2]



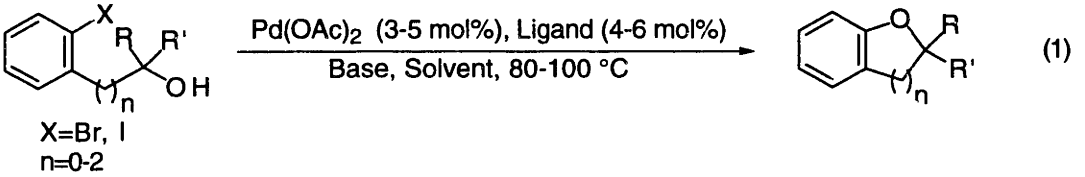
Vitamin E

Existing methods for the conversion of aryl halides to aryl ethers typically require harsh reaction conditions and/or activated substrates.[3] The most widely used methods for this transformation are copper catalyzed or mediated processes.[4,5] These procedures, aside from requiring relatively high reaction temperatures, also require the use of sodium alkoxides in a large excess of the alcohol solvent.[4] Additionally, these protocols have not been used in the synthesis of heterocycles, and their utility in the coupling of tertiary alcohols has not been demonstrated.

Initial attempts to effect the coupling of alcohols (either inter- or intramolecular) with aryl halides using the Pd/P(*o*-tol)$_3$ catalyst system failed to provide the desired product. However, Dr. Michael Palucki discovered that the Pd/BINAP catalyst efficiently promoted intramolecular C–O bond forming reactions of tertiary alcohols. The reactions discussed in this chapter are the result of our collaboration on this project, and the experiments performed by Dr. Palucki are identified in the footnotes in Table 1.

Results and Discussion

The intramolecular substitution of aryl halides with alcohols was effected using a palladium catalyst bearing a chelating phosphine ligand in the presence of a stoichiometric amount of base (eq 1). The ligands DPPF and Tol-BINAP were found to give the best results for these reactions. The halo-alcohol substrates were cyclized to form five-, six-, and seven-membered rings in good yields.

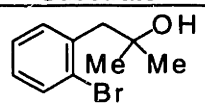
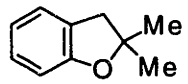
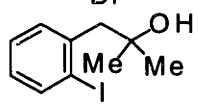
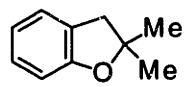
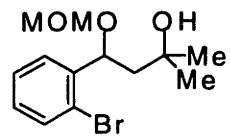
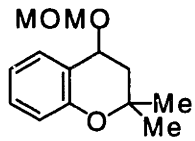
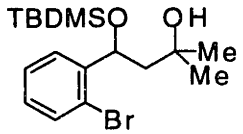
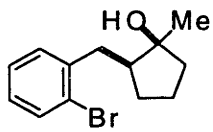
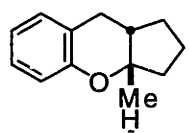
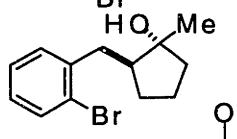
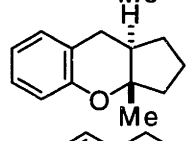
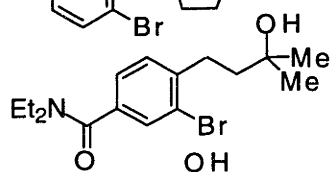
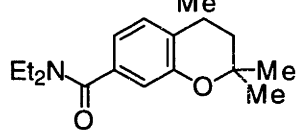
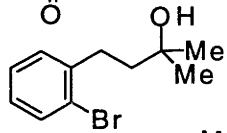
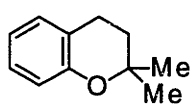
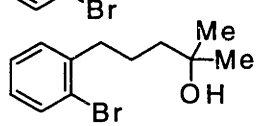
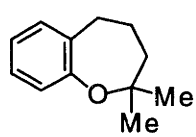
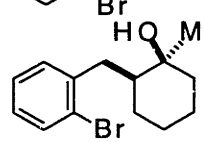
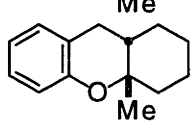
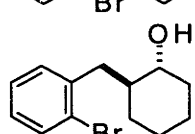
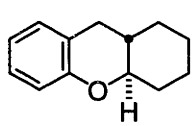
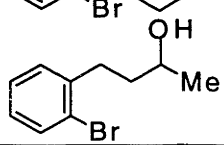
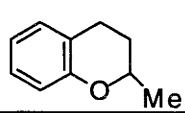


(1)

Typically the best results were obtained with substrates which contained tertiary alcohols, although in a few cases secondary alcohols could be cyclized in low to moderate yields (entries 11-12). Reactions of secondary alcohols required two equivalents of base and a L/Pd ratio of 2 to provide acceptable yields. Attempts to cyclize a primary alcohol (2-bromophenethyl alcohol) afforded only dehalogenated products; none of the desired heterocycle was obtained.

The main side products formed in the cyclization reactions resulted from the reduction of the aryl halide substrate. For substrates which contained secondary alcohols, ketone side products were also observed, suggesting that reduction of these substrates occurs via β-hydride elimination of the alcohol. However, for substrates bearing tertiary alcohols, the mechanism of reduction is not clear, as there is no available hydrogen to undergo β-hydride elimination. Experiments conducted on the intermolecular reaction of NaO*t*Bu with 1-bromo-4-*t*-butylbenzene showed only small amounts of deuterium incorporation in the arene side products when the reactions were conducted in toluene-d^8 or in the presence of NaO*t*Bu-d^9. Generation of

Table 1. Pd-Catalyzed Synthesis of Cyclic Aryl Ethers.

Entry	Substrate	Method	Product	Yield(%)
1		A		89[d]
2		A		60[d]
3		A		93[d]
4		A		90[d]
5		A		65[d]
6		A		73[d]
7		B		66
8		B		69
9		B		64
10		B		73
11		C		66
12		C		32

(a) Method A: 5 mol % $Pd(OAc)_2$, 6 mol % Tol-BINAP, 1.2 equiv of K_2CO_3 in toluene at 100 °C. Method B: 3 mol % $Pd(OAc)_2$, 3.6 mol % DPPF, 1.2 equiv NaO*t*-Bu in toluene at 80 °C. Method C: 5 mol % $Pd(OAc)_2$, 10 mol % DPPF, 2.0 equiv NaO*t*-Bu in toluene at 90 °C; (b) Yields refer to average isolated yields of two or more runs; (c) The reaction was performed in 1,4-dioxane; (d) The experiment was performed by Dr. Michael Palucki.

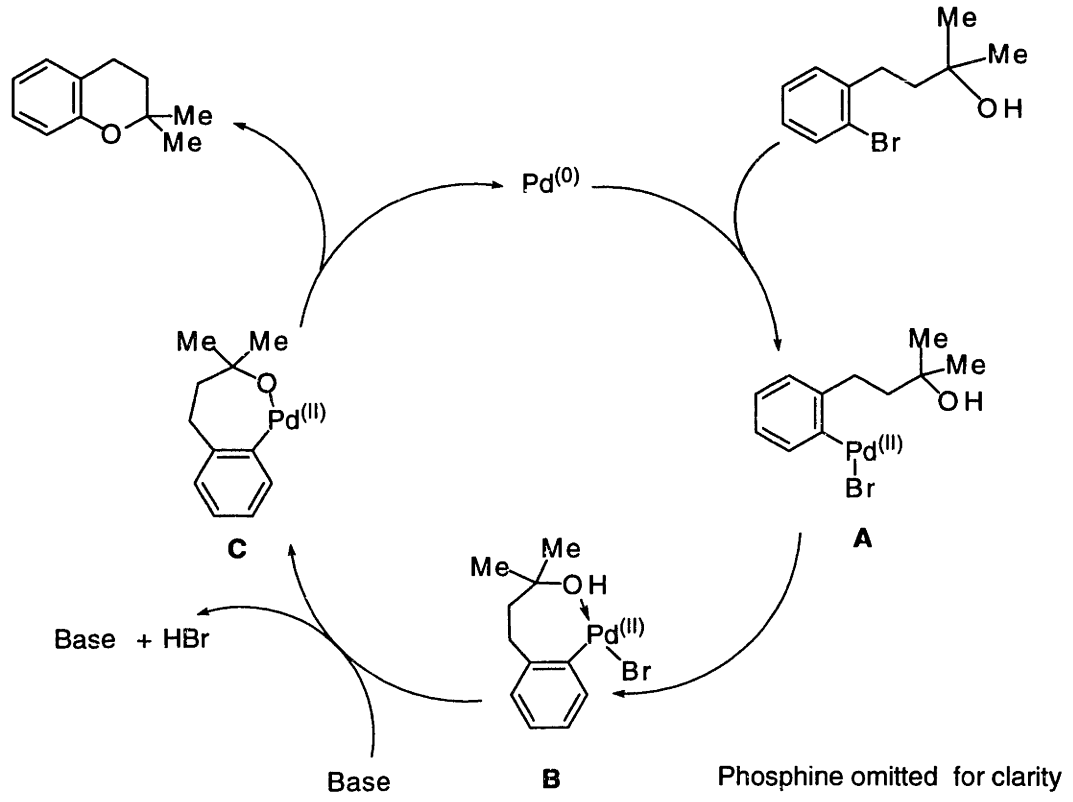
arylsodium species under these conditions seems unlikely, but this possibility has not been thoroughly examined and cannot be ruled out at this time.

The presence of functional groups such as acetals, silyl ethers, and amides was well tolerated. As was previously observed for intermolecular palladium-catalyzed C–N bond forming processes,[6] reactions of aryl iodides were greatly improved when conducted in dioxane. Use of $Pd(OAc)_2$ usually provided better results than were obtained with $Pd_2(dba)_3$. Reactions conducted using method A (5 mol % $Pd(OAc)_2$, 6 mol % Tol-BINAP, 1.2 equiv K_2CO_3, toluene, 100 °C) were slower than those run under the conditions of method B (3 mol % $Pd(OAc)_2$, 3.6 mol % DPPF, 1.2 equiv NaO*t*Bu, toluene, 80 °C), however method A typically afforded smaller amounts of undesired side products.

Presumably the mechanism for this process is similar to that of the palladium-catalyzed amination of aryl halides.[7] Oxidative addition of the aryl bromide to Pd(0), followed by complexation and deprotonation of the tethered alcohol (not necessarily in that order) affords oxymetallacycle **C** which then undergoes reductive elimination to form the heterocyclic product (Scheme 1). Intermediate **A** was independently synthesized and found to be a chemically and kinetically competent intermediate. Subsequent studies by Dr. Ross Widenhoefer led to the isolation of intermediate **C**, which upon heating undergoes reductive elimination to release the oxygen heterocycle.[8]

Continued research by Dr. Palucki led to the development of an intermolecular variant of this reaction which was effective for the coupling of alcohols with electron-deficient aryl halides,[9,10] although a general process for the efficient intermolecular reactions of primary and secondary alcohols with unactivated substrates has yet to be developed. Further mechanistic studies performed by Dr. Widenhoefer demonstrated

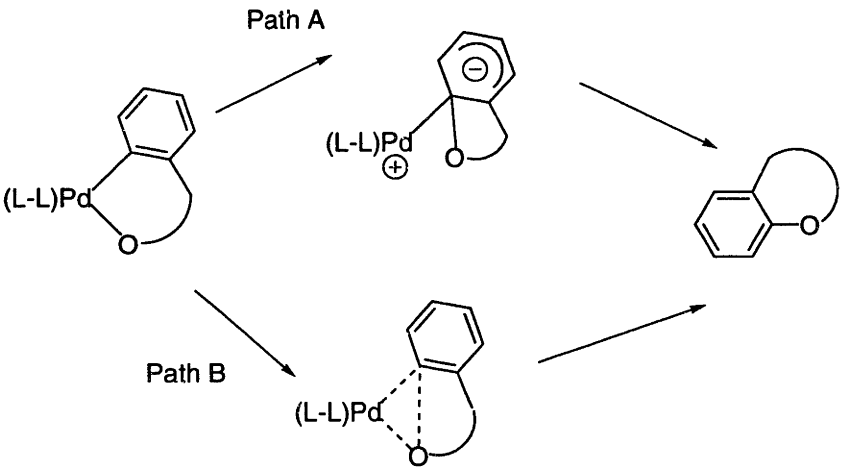
Scheme 1



that in intermolecular reactions, the reductive elimination is highly dependent on the electronic properties of the aromatic group;[8b] electron-withdrawing substituents accelerate the reductive elimination process, suggesting that the reaction may proceed through a zwitterionic intermediate similar to that formed in nucleophilic aromatic substitution reactions (Scheme 2, path A).[8b] However, the efficacy of the intramolecular reaction for the cyclization of unactivated substrates suggests that a concerted pathway may be viable for these reactions (Scheme 2, path B).[8]

Hartwig has reported related studies on palladium catalyzed reactions of halides with aliphatic alcohols.[11] The palladium-catalyzed coupling of phenols with aryl halides has also been reported by both Hartwig[12a,b] and Buchwald;[12c] the use of bulky, electron-rich ligands has been found to facilitate this process.[12a,c]

Scheme 2



In conclusion, the intramolecular palladium-catalyzed formation of oxygen heterocycles was achieved using a catalyst comprised of Pd/Tol-BINAP or Pd/DPPF. These were the first efficient palladium-catalyzed aryl C–O bond forming reactions to be reported.

Experimental Section

General Considerations The general considerations are the same as for the previous chapters with the following exceptions. Anhydrous diisopropylamine, anhydrous diemethoxyethane, anhydrous dimethylformamide, methylmagnesium bromide, 4-dimethylaminopyridine (DMAP), 2-bromobenzaldehye, cyclopentanone, 2-bromobenzylbromide, chloromethyl methyl ether, *tert*-butyl dimethylsilyl chloride, and 1,1'-bis(diphenylphosphino)ferrocene (DPPF) were purchased from Aldrich chemical company and used without further purification. Anhydrous potassium carbonate was purchased from Mallinckrodt Inc. *n*-BuLi in hexanes, and sodium borohydride were purchased from Strem chemical company and used without further purification.

***N,N*-Diethyl-3-bromo-4-(3-methyl-3-butanol)benzamide** (Table 1, entry 7 substrate) A resealable Schlenk flask was charged with *N,N*-diethyl-*p*-iodobenzamide[6] (5.15 g, 17 mmol), bromine (0.88 mL, 17 mmol), mercuric oxide (red) (9.20 g, 42.5 mmol), H_2SO_4 (1.7 mL), and chloroform (100 mL). The flask was sealed and heated to 80 °C. The reaction was monitored by GC, and additional portions of bromine, H_2SO_4, and HgO were added when conversion ceased (2 additional portions were required to achieve complete conversion). When the reaction was complete, the mixture was cooled to room temperature and filtered through celite. The residue was taken up in aqueous $NaHCO_3$ (50 mL), and the flask rinsed with chloroform. The aqueous layer was extracted with chloroform (3 x 50 mL), and the combined organic layers were washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on silica gel using 4/1 hexane/ethyl acetate as the eluant to afford *N,N*-diethyl-3-bromo-4-iodobenzamide (5.65 g, 87%) as an orange oil which solidified upon standing. ^1H NMR analysis showed slight impurities in the product. It was used without further purification. ^1H NMR ($CDCl_3$) δ 8.01 (d, 1H, J = 7.6 Hz), 7.64 (s, 1H), 7.10 (d, 1H, J = 8.5 Hz), 3.70–3.25 (br, 4H), 1.30–1.20 (m, 6H).

A Schlenk flask was charged with *N,N*-diethyl-3-bromo-4-iodobenzamide (3.736 g, 9.78 mmol), 1-buten-3-ol (1.27 mL, 14.67 mmol), sodium bicarbonate (2.05 g, 24.45 mmol), tetra-*n*-butyl ammonium chloride (2.72 g, 9.78 mmol), palladium acetate (66 mg, 0.293 mmol, 3 mol % Pd), and DMF (10 mL). The mixture was heated to 40 °C with stirring until the starting material had been consumed as judged by GC analysis (25 h). The mixture was taken up in ether (50 mL), washed with water (20 mL), washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The product was purified further by flash chromatography on silica gel using 3/1 hexane/ethyl acetate (200 mL), then 2/1 hexane/ethyl acetate (200 mL), then 2/1 ethyl acetate/hexane as the eluant to give *N,N*-diethyl-3-bromo-4-(3-methyl-3-

butanol)-benzamide as a colorless oil (1.95 g, 58%): ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.26–7.21 (m, 2H), 3.52 (s, br, 2H), 3.26 (s, br, 2H), 3.01 (t, 2H, J = 7.7 Hz), 2.77 (t, 2H, J = 7.4 Hz), 2.17 (s, 3H), 1.60–1.10 (br, 6H).

To a solution of *N,N*-diethyl-3-bromo-4-(3-methyl-3-butanol)benzamide (1.60 g, 4.91 mmol) in ether (25 mL) at –78 °C was slowly added methylmagnesium bromide (1.64 mL, 3.0 M in diethyl ether, 4.91 mmol). The mixture was stirred at –78 °C for 4 h, then warmed to room temperature and stirred for 1 h. GC analysis showed incomplete conversion of starting material. The reaction was cooled to 0 °C and methylmagnesium bromide (0.25 mL, 3.0 M in diethyl ether, 0.75 mmol) was added. The mixture was warmed to room temperature and stirred for an additional 2 h. The reaction was quenched with aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on silica gel using 3/1 hexane/ethyl acetate (150 mL), then 2/1 hexane/ethyl acetate (150 mL), followed by 1/1 hexane/ethyl acetate as the eluant to afford a colorless oil (1.23 g, 73%). ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1H), 7.27–7.24 (m, 2H), 3.53 (br, 2H), 3.27 (br, 2H), 2.87–2.81 (m, 2H) 1.77–1.72 (m, 2H), 1.60 (s, 6H), 1.32–1.14 (br, 6H); ^{13}C NMR ($CDCl_3$) δ 169.5, 143.0, 136.4, 130.6, 130.0, 125.4, 124.2, 70.5, 43.6, 43.2, 39.3, 31.1, 29.1, 14.1,12.8; IR (neat, cm^{-1}) 3418, 2970, 1633, 1614, 1470, 1288, 1040. Anal. Calcd. for $C_{16}H_{24}BrNO_2$: C, 56.15; H, 7.07. Found: C, 55.98; H, 7.14.

4-(2-bromophenyl)-2-methyl-2-butanol. (Table 1, entry 8 substrate) A Schlenk flask was charged with 2-bromoiodobenzene (3.85 mL, 30 mmol), methyl acrylate (4.05 mL, 45 mmol), sodium bicarbonate (6.3 g, 75 mmol), tetra-*n*-butyl ammonium chloride (8.34 g, 30 mmol), palladium acetate (135 mg, 0.6 mmol, 2 mol % Pd), and DMF (30 mL). The flask was purged with argon for 1 min, then heated to 40 °C with stirring until all starting material had been consumed (28 h) as judged by GC

analysis. The mixture was cooled to room temperature, taken up in ether (100 mL), washed with water (30 mL), washed with brine (30 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel using 15/1 hexane/ethyl acetate as the eluant to give methyl-*o*-bromo cinnimate[13] as a colorless oil (6.38g, 88%): ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1H, J = 16.0 Hz), 7.63–7.58 (m, 2H), 7.33–7.23 (m, 2H), 6.38 (d, 1H, J = 16.0 Hz), 3.83 (s, 3H).

To a suspension of sodium borohydride (1.18g, 31.14 mmol) in DME (25 mL) was added anhydrous methanol (1.26 mL). After evolution of H_2 ceased, a solution of methyl-*o*-bromo cinnimate (6.26g, 25.96 mmol) in DME (25 mL) was added slowly. The mixture was heated to 70 °C with stirring until the starting material had been consumed (14 h) as judged by GC analysis. The reaction was cooled to room temperature, and quenched with aqueous $NaHCO_3$ (30 mL). The mixture was taken up in ether (50 mL) and the layers were separated. The aqueous layer was extracted with ether (3 x 15 mL) and the combined organic layers were washed with brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 15/1 hexane/ethyl acetate as the eluant to afford methyl-3-(2-bromophenyl)propionate as a colorless oil (2.72 g, 43%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, J = 8.06 Hz), 7.26–7.23 (m, 2H), 7.11–7.08 (m, 1H), 3.68 (s, 3H), 3.07 (t, 2H, J = 8.1 Hz), 2.26 (t, 2H, J = 7.5 Hz).

To a solution of methyl-3-(2-bromophenyl)propionate (2.71 g, 11.2 mmol) in ether (12 mL) at 0 °C was slowly added methylmagnesium bromide (11.2 mL, 3.0 M in diethyl ether, 33.6 mmol). The mixture was stirred at 0 °C for 15 min, then warmed to room temperature and stirred until the reaction had gone to completion as judged by GC analysis. The mixture was quenched with aqueous NH_4Cl (15 mL), and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$,

filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 6/1 hexane/ethyl acetate as the eluant to give a colorless oil (2.08 g, 77%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, J = 7.8 Hz), 7.26–7.22 (m, 2H), 7.08–7.03 (m, 1H), 2.85–2.80 (m, 2H), 1.79–1.73 (m, 2H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.6, 132.6, 103.1, 127.4, 124.2, 70.7, 43.9, 31.2, 29.0; IR (neat, cm^{-1}) 3381, 2969, 1471, 1026, 746. Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.34; H, 6.22. Found: C, 54.63; H, 6.20.

4-(2-bromophenyl)-2-methyl-2-pentanol (Table 1, entry 9 substrate) To a solution of 4-(2-bromophenyl)butyric acid[14] (2.15 g, 8.85 mmol) in methanol (40 mL) was added concentrated H_2SO_4 (0.5 ml). The solution was heated to 65 °C with stirring until the starting material had been consumed as judged by TLC analysis (13 h). The mixture was cooled to room temperature and taken up in ether (100 mL), washed with aqueous $NaHCO_3$ (25 mL), and washed with brine (25 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 2% ethyl acetate/hexane as the eluant to afford methyl-4-(2-bromophenyl)butyrate as a colorless oil (1.92 g, 85%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, J = 8.1 Hz), 7.24–7.22 (m, 2H), 7.08–7.05 (m, 1H), 3.68 (s, 3H), 2.78 (t, 2H, J = 8.0 Hz), 2.38 (t, 2H, J = 7.5 Hz),1.96 (p, 2H, J = 7.5 Hz).

To a solution of methyl-4-(2-bromophenyl)butyrate (1.40 g, 5.45 mmol) in ether (6 mL) at 0 °C was slowly added methylmagnesium bromide (5.45 mL, 3.0 M in diethyl ether, 16.34 mmol). The mixture was stirred at 0 °C for 15 min, then warmed to room temperature and stirred until the reaction had proceeded to completion as judged by GC analysis. The mixture was quenched with aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 8/1 hexane/ethyl acetate as the eluant to give a colorless oil (1.28 g, 92%): ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, J = 7.8 Hz), 7.23 (d, 2H, J = 4.2 Hz), 7.09–7.01

(m, 1H), 2.74 (t, 2H, J = 7.3 Hz), 1.71–1.53 (m, 4H), 1.22 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.5, 132.6, 130.2, 127.4, 127.2, 124.3, 70.7, 43.3, 36.4, 29.1, 24.6; IR (neat, cm^{-1}) 3374, 2968, 1470, 1021, 750. Anal. Calcd for $C_{12}H_{17}BrO$: C, 56.05; H, 6.66. Found: C, 55.84; H, 6.59.

***Cis*-1-Methyl-2-(2-bromobenzyl)cyclohexanol** (Table 1, entry 10 substrate) To a solution of diisoproyplamine (3.7 mL, 28.0 mmol) in THF (50 mL) at –78 °C was slowly added *n*-BuLi (14.2 mL, 1.6 M in hexanes, 22 mmol). The mixture was stirred at –78 °C for 30 min, then cyclohexanone (2.0 mL, 20 mmol) in THF (25 mL) was added dropwise at –78 °C. The mixture was stirred at –78 °C for 10 min, and 2-bromobenzylbromide (7.5 g, 30 mmol) in THF (25 mL) was added dropwise at –78 °C. The mixture was then allowed to warm to room temperature and stirred until the starting material had been consumed as judged by GC analysis (25 h). The reaction was quenched with water (10 mL), and taken up in ether (200 mL). The layers were separated, and the organic layer was washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography on silica gel using 20/1 hexane/ethyl acetate as the eluant to give 2-(*o*-bromobenzyl)-cyclohexanone[15] as a colorless oil (3.902 g, 73%): ^1H NMR ($CDCl_3$) δ 7.55–7.50 (m, 1H), 7.09–7.01 (m, 2H), 3.39–3.30 (m, 1H), 2.70–1.20 (m, 10 H).

To a solution of 2-(2-bromobenzyl)-cyclohexanone (1.76 g, 6.6 mmol) in ether (7 mL) at 0 °C was slowly added methylmagnesium bromide (2.9 mL, 3.0 M in diethyl ether, 8.6 mmol). The mixture was stirred at 0 °C for 15 min, then warmed to room temperature and stirred until the reaction was complete as judged by GC analysis. The mixture was quenched with aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel

using 2% ethyl acetate/hexane (200 mL), then 10/1 hexane/ethyl acetate as the eluant to give the cis diastereomer (777 mg, 42%), and a mixture of diastereomers (464 mg, 25%) as colorless oils. Data for the cis diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.52 (d, 1H, *J* = 6.8 Hz), 7.26–7.16 (m, 2H), 7.06–7.04 (m, 1H), 3.19 (dd, 1H, *J* = 3.6 Hz, 13.2 Hz), 2.48 (dd, 1H, *J* = 11.3 Hz, 13.2 Hz), 1.67–1.59 (m, 6H), 1.58 (s, 3H), 1.57–1.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 140.7, 132.8, 132.0, 127.4, 126.9, 124.9, 71.5, 45.2, 40.5, 36.2, 28.8, 26.4, 25.6, 21.9; IR (neat, cm^{-1}) 3472, 2931, 1470, 1445, 1023, 755. Anal. Calcd for $C_{14}H_{19}BrO$: C, 59.37; H, 6.76. Found: C, 59.18; H, 6.63.

***Trans*-2-(2-bromobenzyl)cyclohexanol** (Table 1, entry 11 substrate) To a solution of 2-(2-bromobenzyl)-cyclohexanone[15] (2.14 g, 8.0 mmol) in ethanol (16 mL) was slowly added sodium borohydride (333 mg, 8.8 mmol). The mixture was stirred at room temperature until the starting material had been consumed as judged by GC analysis (17 h). The reaction was quenched with aqueous $NaHCO_3$ (10 mL), and extracted with ether (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. GC analysis revealed a 4:1 ratio of trans:cis diastereomers. The product was purified by flash chromatography on silica gel using 2% ethyl acetate/hexane (200 mL), then 10/1 hexane/ethyl acetate as the eluant to give the trans diastereomer (747 mg, 35%) as a colorless oil. Data for the trans diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.53 (d, 1H, *J* = 8.3 Hz), 7.22–7.19 (m, 2H), 7.08–7.03 (m, 1H), 3.44–3.34 (m, 2H), 2.47–2.40 (m, 1H), 2.05–1.95 (m, 1H), 1.80–0.96 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 140.3, 132.8, 131.6, 127.5, 127.0, 124.9, 75.0, 45.8, 38.9, 35.8, 29.8, 25.3, 24.8; IR (neat, cm^{-1}) 3356, 2924, 1446, 1067, 1022, 749. Anal. Calcd for $C_{13}H_{17}BrO$: C, 58.01; H, 6.37. Found: C, 58.20; H, 6.43.

4-(2-bromophenyl)-2-butanol.[16] (Table 1, entry 12 substrate) To a solution of 3-(2-bromophenyl)propanal[14] (2.13g, 10.0 mmol) in ether (10 mL) at 0 °C was

slowly added methylmagnesium bromide (4.3 mL, 3.0 M in diethyl ether, 13.0 mmol). The mixture was stirred at 0 °C for 10 min, then warmed to room temperature and stirred until the reaction had proceeded to completion as judged by GC analysis. The mixture was quenched with aqueous NH_4Cl (10 mL), and the layers were separated. The aqueous layer was extracted with ether (3 x 10 mL), and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel using 10/1 hexane/ethyl acetate as the eluant to give a colorless oil (1.65 g, 72%): ^1H NMR ($CDCl_3$) δ 7.53 (d, 1H, J = 8.4 Hz), 7.26–7.23 (m, 2H), 7.08–7.03 (m, 1H), 3.88–3.84 (m, 1H), 2.89–2.76 (m, 2H), 1.80–1.72 (m, 2H), 1.47 (d, 1H, J = 4.3 Hz), 1.26 (d, 3H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 141.2, 132.5, 130.1, 127.32, 127.25, 124.2, 67.1, 39.0, 32.2, 23.2; IR (neat, cm^{-1}) 3356, 2965, 2928, 1471, 1129, 1022, 747. Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72. Found: C, 52.59; H, 5.76.

(DPPF)Pd(Br)[2-(2-methyl-2-butanol)benzene] A Schlenk flask was charged with tris(dibenzylideneacetone)dipalladium(0) (400 mg, 0.44 mmol), tri-*o*-tolyl phosphine (536 mg, 1.76 mmol), 4-(2-bromophenyl)-2-methyl-2-butanol (536 mg, 2.2 mmol), and benzene (30 mL). The mixture was stirred at room temperature for 1 h, and then heated to 40 °C for 1h, until the purple color had changed to dark green. The mixture was filtered through celite under an argon atmosphere into a Schlenk flask, and DPPF (488 mg, 0.88 mmol) was added. The mixture was stirred at room temperature for 1.5 h. An orange precipitate formed during stirring. The solvent was removed *in vacuo* , and ether (60 mL) was added. An orange precipitate formed. The precipitate was collected on a fritted funnel and rinsed with ether to afford a yellow solid (480 mg, 60%): ^1H NMR ($CDCl_3$) δ 8.22–8.15 (m, 2H), 8.00–7.82 (m, 4H), 7.55–7.05 (m, 11 H), 6.90–6.80 (m, 2H), 6.77–6.52 (m, 4H), 6.40–6.37 (m, 1H), 5.14 (s, 1H), 4.65 (s, 1H), 4.37 (s, 1H), 4.34 (s, 1H), 4.19–4.11 (m, 2H), 3.62 (s, 1H), 3.56 (s, 1H),

3.18–3.06 (m, 1H), 2.30–2.15 (m, 2H), 1.56 (s, 1H), 1.43 (dt, 1H, J = 8.4 Hz, 13.2 Hz), 1.32 (d, 6H, J=14.1 Hz); ^{31}P NMR ($CDCl_3$) δ 30.6 (d, J = 40.3 Hz), 9.2 (d, J = 40.3 Hz); IR (KBr, cm^{-1}) 3468, 1481, 1435, 1096, 742, 695. Anal. Calcd for $C_{45}H_{43}BrFeOP_2Pd$: C, 59.79; H, 4.79. Found: C, 59.98; H, 4.78.

General Procedures For The Cyclization of Bromo-Alcohols

General Procedure using Method A. An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (5 mol %), Tol-BINAP (6 mol %) and K_2CO_3 (1.2 equiv). To this was added the bromo-alcohol (0.1–0.2 M) in toluene (1–2 mL). The resulting mixture was heated at 100 °C with stirring until the starting material had been consumed as judged by GC analysis. Upon completion, the solution was cooled to room temperature, taken up in diethyl ether (10 mL), filtered through celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

General Procedure using Method B. A Schlenk flask was charged with sodium *t*-butoxide (1.2 equiv), palladium acetate (0.03 equiv, 3 mol %), DPPF (0.036 equiv, 3.6 mol %), followed by a solution of the bromo-alcohol (1 equiv) in toluene (2 mL/mmol substrate). The mixture was heated to 80 °C under argon with stirring until the starting material had been consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with ether (15 mL), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

General Procedure using Method C. A Schlenk flask was charged with sodium *t*-butoxide (2.0 equiv), palladium acetate (0.05 equiv, 5 mol %), DPPF (0.1 equiv, 10 mol %), followed by a solution of bromo-alcohol (1 equiv) in toluene (4 mL/mmol substrate). The mixture was heated to 80 °C under argon with stirring until the starting material had been consumed as judged by GC analysis. The mixture was

cooled to room temperature, diluted with ether (15 mL), filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

2,2-Dimethyl-(7-*N,N*-diethylamido)chroman (Table 1, entry 7). Procedure C (on a 0.25 mmol scale) gave 44 mg (68%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.03 (d, 1H, J = 7.7 Hz), 6.78 (d, 1H, J = 7.7 Hz), 6.74 (s, 1H), 3.55–3.15 (br, 4H), 2.75 (t, 2H, J = 6.7 Hz), 1.78 (t, 2H, J = 6.7 Hz), 1.30 (s, 6H), 1.20–1.00 (br, 6H); ^{13}C NMR ($CDCl_3$) δ 171.0, 153.8, 136.3, 129.4, 121.9, 117.4, 115.1, 74.4, 43.1, 38.9, 32.5, 26.8, 22.3, 14.1, 12.8; IR (neat, cm^{-1}) 2974, 1633, 1427, 1306, 1219, 1088. Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87. Found: C, 73.53; H, 8.96.

2,2-Dimethylchroman.[17] (Table 1, entry 8). Procedure A (on a 0.5 mmol scale) gave 54 mg (67%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.08–7.04 (m, 2H), 6.84–6.76 (m, 2H), 2.78 (t, 2H, J = 6.7 Hz), 1.80 (t, 2H, J = 6.7 Hz),1.33 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.0, 129.4, 127.2, 120.9, 119.6, 117.2, 74.1, 32.8, 26.9, 22.4; IR (neat, cm^{-1}) 2975, 1488, 1220, 1122, 756.

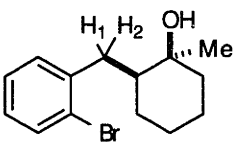
2,3,4,5-Tetrahydro-2,2-dimethyl-1-benzoxepine.[18] (Table 1, entry 9). Procedure A (on a 1 mmol scale) gave 127 mg (72%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.08–6.86 (m, 4H), 2.74 (t, 2H, J = 5.9 Hz), 1.81–1.54 (m, 4H), 1.23 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.6, 136.2, 129.4, 126.9, 123.4, 123.3, 41.8, 33.4, 27.7, 22.0; IR (neat, cm^{-1}) 2928, 1487, 1239, 1155, 912, 761.

***Cis*-12-methyl-1,2,3,4,11,12-hexahydroxanthene.**[19] (Table 1, entry 10). Procedure A (on a 0.66 mmol scale) gave 103 mg (77%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.09–7.02 (m, 2H), 6.84–6.79 (m, 2H), 3.13 (dd, 1H, J = 6.5 Hz, 17.0 Hz), 2.35 (d, 1H, J = 16.8 Hz), 1.99–1.92 (m, 1H), 1.73–1.22 (m, 8H), 1.21 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.2, 129.9, 127.0, 119.8, 119.6, 117.0, 74.8, 36.8, 29.2, 28.4, 25.6, 21.7; IR (neat, cm^{-1}) 2929, 1486, 1248, 1143, 998, 751. Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.93; H, 8.91.

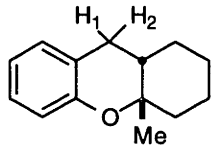
***Trans*-1,2,3,4,11,12-hexahydroxanthene.**[20] (Table 1, entry 11). Procedure B (on a 0.5 mmol scale) gave 65 mg (69 %) of a white solid, mp 75–76 °C (lit. mp 78 °C):[20] ^{1}H NMR ($CDCl_3$) δ 7.10–7.00 (m, 2H), 6.88–6.78 (m, 2H), 3.60 (dt, *J* = 4.5 Hz, 10.4 Hz 1H), 2.68 (dd, *J* = 4.9 Hz, 16.1 Hz, 1H), 2.46 (dd, *J* = 11.7 Hz, 16.1 Hz, 1H), 2.22–2.15 (m, 1H), 1.99–1.85 (m, 2H), 1.78–1.61 (m, 2H), 1.50–1.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 154.8, 129.4, 127.1, 122.4, 119.9, 116.3, 79.0, 37.0, 32.5, 32.3, 31.8, 25.4, 24.6; IR (KBr, cm^{-1}) 2909, 1470, 1240, 1056, 858. Anal. Calcd. for $C_{13}H_{16}O$: C, 82.94; H, 8.57. Found: C, 83.16; H, 8.76.

2-methylchroman.[21] (Table 1, entry 12) Procedure B (on a 1 mmol scale) gave 51 mg (34%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.10–7.01 (m, 2H), 6.85–6.72 (m, 2H), 4.19–4.08 (m, 1H), 2.91–2.69 (m, 2H), 2.02–1.94 (m, 1H), 1.81–1.65 (m, 1H),1.39 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 129.5, 127.1, 121.8, 119.9, 116.7, 72.1, 29.2, 24.8, 21.4; IR (neat, cm^{-1}) 2973, 1488, 1237, 1118, 754.

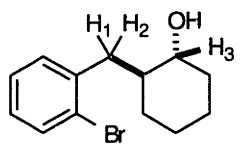
Explanation of Stereochemical Assignments



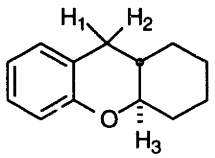
***Cis*-1-Methyl-2-(2-bromobenzyl)cyclohexanol** (Table 1, entry 10, substrate) Stereochemical assignment is based on the stereochemical configuration of the product (*cis*-12-methyl-1,2,3,4,11,12-hexahydroxanthene) obtained from the Pd-catalyzed cyclization of the title compound and the assumption that cyclization occurs with preservation of the stereochemical integrity of the substrate (see below). Other supporting evidence includes studies which show that Grignard addition to 2-substituted cyclohexanones provides as the major product, the cis isomer, resulting from equatorial attack to the most stable conformer.[22]



***Cis*-12-methyl-1,2,3,4,11,12-hexahydroxanthene** (Table 1, entry 10, product) Stereochemistry of the title compound was assigned as cis based on comparison of ^{1}H NMR chemical shifts of the benzylic protons with those of known compound *cis*-1,2,3,4,11,12-hexahydroxanthene (see below). Data for title compound: δ H_1: 3.13, J = 17.0 Hz, 6.5 Hz; δ H_2: 2.35, J = 17.0 Hz, 0 Hz. Data for *cis*-1,2,3,4,11,12-hexahydroxanthene: δ H_1: 2.93, J = 16.6 Hz, 6.2 Hz; δ H_2: 2.41, J = 16.6, 2.2 Hz.



***Trans*-2-(2-bromobenzyl)cyclohexanol** (Table 1, entry 11, substrate). Stereochemistry of the title compound was assigned as trans by comparison of chemical shifts of the benzylic (H_1, H_2) and CHOH (H_3) protons with literature data for the related known compound 2-benzylcyclohexanol. Data for 2-(2-bromobenzyl)-cyclohexanol: δ H_1: 3.35; δ H_2: 2.42; δ H_3: 3.4. Literature[23] values for *trans*-2-benzylcyclohexanol: δ H_1: 3.1; δ H_2: 2.3; δ H_3: 3.2. Literature values for *cis*-2-benzylcyclohexanol: δ H_1: 2.6; δ H_2: 2.5; δ H_3: 3.7. Additionally, the title compound was predicted to be the major diastereomer resulting from $NaBH_4$ reduction of the corresponding ketone based on previous studies of hydride reductions of 2-substituted cyclohexanones.[24] Furthermore, inversion of stereochemistry is unlikely in the cyclization of *trans*-2-(2-bromobenzyl)cyclohexanol to *trans*-1,2,3,4,11,12-hexahydroxanthene (Table 1, entry 11, product).



***Trans*-1,2,3,4,11,12-hexahydroxanthene** (Table 1, entry 11, product) Although the title compound is known, a slight discrepancy between our NMR data and the literature exists (see below). The NMR data of the title compound matched more closely to the literature values for *trans*-1,2,3,4,11,12-hexahydroxanthene than for *cis*-1,2,3,4,11,12-hexahydroxanthene.[23] The stereochemistry of the title compound was assigned as trans by comparison of ^{1}H NMR chemical shifts of benzylic (H_1, H_2) and R_2**C**H**O**R (H_3)protons, as well as comparison of coupling constants of the R_2**C**H**O**R proton. Data for title compound: δ H_1: 2.68, J = 16.1 Hz, 4.9 Hz; δ H_2: 2.46, J = 16.1 Hz, 11.7 Hz; d H_3: 3.60, J = 4.5, 10.4 Hz. Literature values for trans: δ H_1: 2.6, J = 16.4 Hz, 7.2 Hz; δ H_2: 2.49, J = 16.4 Hz, 2.2 Hz; δH_3: 3.53, J = 10 Hz. Literature values for cis: δH_1: 2.93, J = 16.6 Hz, 6.2 Hz; δH_2: 2.41, J = 16.6, 2.2 Hz; δH_3: 3.53, J = 4 Hz. The coupling constants of the benzylic protons were reported incorrectly in the literature. This discrepancy may be due to the fact that the spectra described in the literature were recorded on a 60 MHz NMR instrument, however, these were not the basis for the stereochemical assignments in the literature.

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Part Three:

Development of Highly Active Catalysts for C–N and C–C Bond Forming Reactions of Aryl Bromides and Chlorides

Chapter Eight:

Nickel-Catalyzed Amination of Aryl Chlorides

Introduction

Aryl chlorides are both the most widely available and least expensive aryl halides. However, aryl chlorides are also the least reactive of the aryl halides; oxidative addition of aryl chlorides to Pd(0) is often problematic.[1] For example, oxidative addition of aryl chlorides to $Pd(PPh)_3$ or $(Ph_3P)_2Pd(dba)$ typically requires temperatures of 100-140 °C.[2] This process is more facile if electron-rich phosphine ligands are employed,[3] for example, Osborn has demonstrated the oxidative addition of chlorobenzene to $(Cy_3P)_2Pd(dba)$ at 60 °C,[3b] and Milstein demonstrated the oxidative addition of chlorobenzene to $(dippe)_2Pd$[3c] at temperatures as low as 38 °C.[3c] Milstein employed $(dippe)_2Pd$ and other related catalysts for several palladium catalyzed C–C bond forming reactions of aryl chlorides[4] such as carbonylations[4a-b] and Heck olefinations.[4c]

Despite the ability of electron-rich phosphines to promote the oxidative addition of aryl chlorides, these ligands did not appear to be viable for palladium-catalyzed amination reactions. Electron-rich phosphine ligands increase the electron density of the metal center which facilitates oxidative addition,[3] but decrease the rate of reductive elimination relative to β-hydride elimination[5] which leads to lower yields of coupled products and large amounts of arene side products. Furthermore, Milstein's ligands are air-sensitive and difficult to prepare,[4] and the related ligands dppe and dppp were usually ineffective for the catalytic amination of aryl bromides.

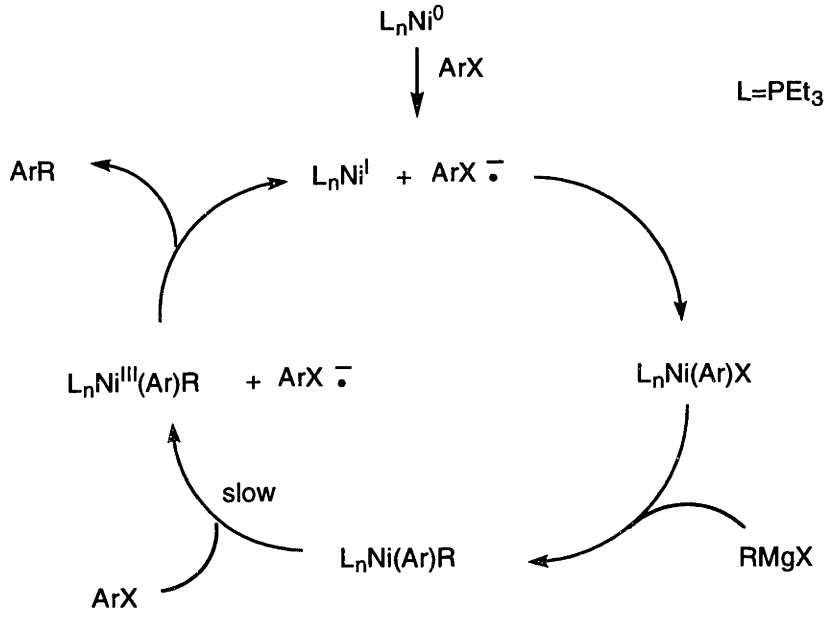
Our initial attempts to utilize aryl chlorides as substrates with palladium catalysts resulted in low conversion when P(*o*-tolyl)$_3$ or BINAP-based catalyst systems were employed as ligands. For example, the reaction of 4-chlorotoluene and *N*-methyl benzylamine at 100 °C resulted in low conversion (<10%) when the $Pd_2(dba)_3$/P(*o*-tolyl)$_3$ catalyst system was employed (4 mol % Pd). When P(cyclohexyl)$_3$ was used as

a ligand, the reaction proceeded to completion, but the yield of desired product was low (<30% by GC). Subsequent work by Reddy and Tanaka showed that aryl chlorides could be coupled with amines in moderate yields with $(Cy_3P)_2PdCl_2$ provided that an excess (2.0 equiv) of the aryl chloride was employed.[6] Herrmann and Beller have also demonstrated the catalytic amination of aryl chlorides using a palladacycle catalyst and reaction temperatures of 135-140 °C,[7] but mixtures of regioisomers were obtained under these conditions, presumably arising from competing benzyne formation.[7] Improved results have been obtained by Nishiyama, Yamamoto, and Koie with catalysts based on P(*t*-Bu)$_3$,[8] although these reactions were usually conducted at 120-130 °C and only a few examples of aryl chloride aminations were reported.

Despite the low reactivity of aryl chlorides towards palladium catalysts, nickel complexes are frequently used in C–C bond forming reactions of aryl chlorides.[9] Early studies of nickel-catalyzed cross-coupling focused on reactions of aryl halides with Grignard reagents,[10] although more recently nickel catalysts have been employed for the coupling of arylboronic acids,[11] or aryl(tributyl)tin reagents with aryl halides.[12] An additional advantage of nickel catalysts arises from the low cost of nickel relative to palladium.

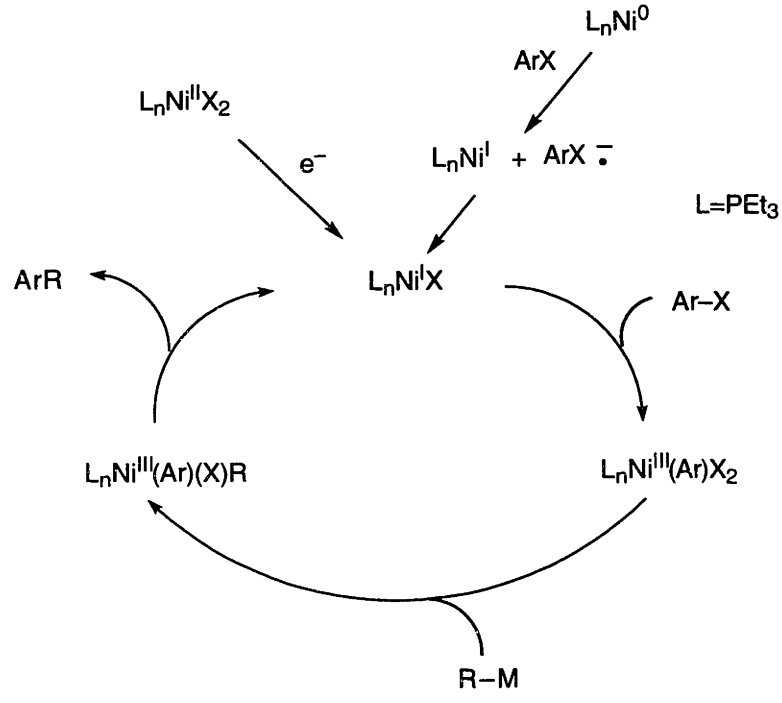
Kochi has performed mechanistic studies on the nickel catalyzed coupling of Grignard reagents with aryl halides and has determined that electron-transfer processes occur during the catalytic cycle.[13] Oxidative addition of aryl halides to Ni(0) proceeds via initial electron transfer from the nickel to the arene, followed by collapse of the resulting intermediates to form the Ni(II) complex.[13b] Transmetallation of a Grignard reagent to the Ni(II) complex is a facile process, however reductive elimination from the Ni(II)(Ar)(Me) species is slow.[13c] A second, rate limiting electron transfer step is believed to occur, followed by reductive elimination of the resulting Ni(III) intermediate to form a Ni(I) species which undergoes oxidative addition to

Scheme 1: Catalytic Cycle Proposed by Kochi for Kumada Coupling



complete the catalytic cycle (Scheme 1).[13a,c] An alternative catalytic cycle has also been proposed by Kochi for the nickel-catalyzed homocoupling of aryl halides.[13d]

Scheme 2: Ni(I)/Ni(III) cataytic cycle Proposed for the Homocoupling of Aryl Halides



This process is believed to involve a Ni(I)-Ni(III) catalytic cycle as depicted in Scheme 2.

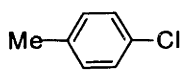
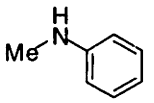
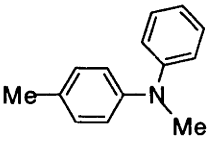
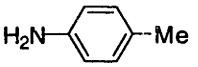
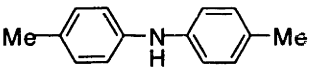
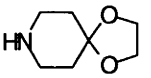
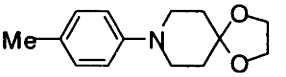
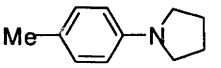
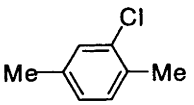
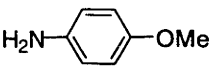
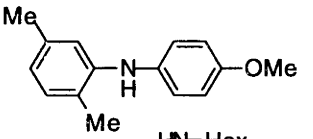
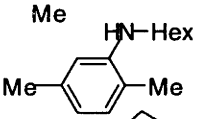
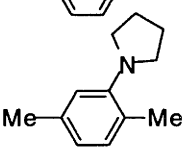
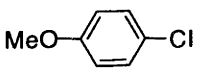
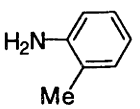
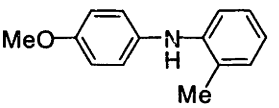
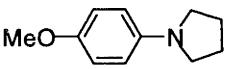
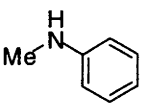
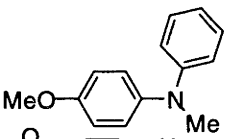
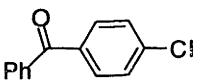
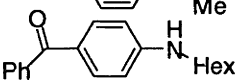
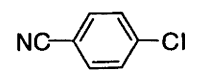
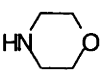
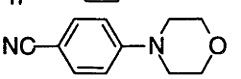
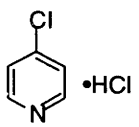
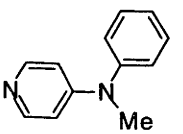
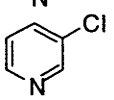
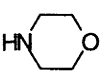
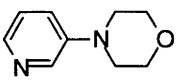
Although there existed considerable precedent for nickel-catalyzed C–C bond formation,[9-12] and nickel-catalyzed C–S bond forming reactions had also been reported,[14] little research had been conducted on the analogous C–N bond forming reactions. Previous reports of nickel-catalyzed aryl carbon-nitrogen bond formation consist of a few examples with no isolated yields of products given.[15,16] The only example of a nickel-catalyzed amination of an aryl chloride was the reaction of chlorobenzene with dimethylamine, which required 10 equivalents of dimethylamine and only proceeded to 68% conversion after 6 h at 200 °C.[15] Cristau and Desmurs have reported nickel catalyzed amination reactions of aryl halides at 165 °C using $(bipy)_2NiBr_2$, however no specific aryl halides were mentioned.[16] Instead, the generic example "Ar-Br" was used, and no experimental details were given. Hillhouse has previously reported stoichiometric C–N bond forming reductive elimination reactions from Ni(II) amido complexes which are promoted either by thermolysis or by oxidation;[17] however, catalytic reactions were not described.

Results and Discussion

After some initial experimentation, we found that mixtures of $Ni(COD)_2$ and DPPF[18] effectively promote the coupling of aryl chlorides with amines (eq 1). For example, the reaction of 4-chlorotoluene and *N*-methyl aniline

$$\text{Ar-Cl} + \text{HN(R)R'} \xrightarrow[\text{NaO}t\text{Bu}]{\text{cat. Ni(COD)}_2,\ \text{Ligand}}{\text{Toluene}\atop 70\text{-}100\ ^\circ\text{C}} \text{Ar-N(R)R'} \qquad (1)$$

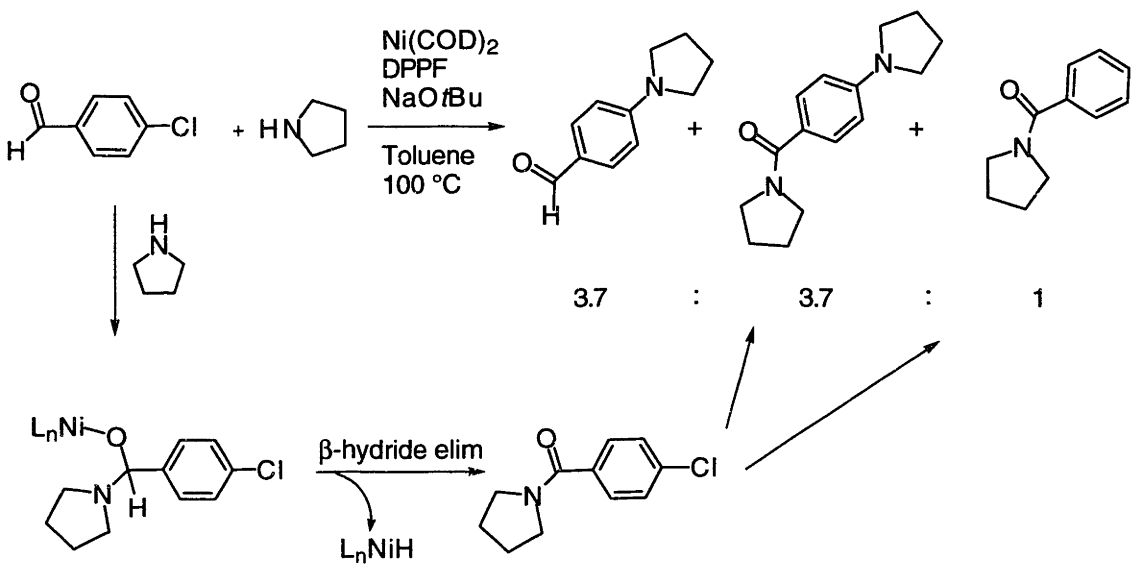
Table 1: Nickel Catalyzed Amination of Aryl Chlorides

entry	halide	amine	product	catalyst loading	method[a]	rxn time	iso. yield
1				2 mol %	A	18.5 h	80%
2				2 mol %	A	19 h	91%
3				5 mol %	A	21.5 h	81%
4				2 mol % 5 mol % 2 mol % 7 mol %	A B C D	15 h 19 h 19 h 21 h	58% 84% 54% 86%
5				2 mol % 3 mol %	A C	19 h 21.5 h	96% 83%
6		$HexNH_2$		5 mol % 6 mol %	A[b] B[b]	15 h 30 h	50% 63%
7				5 mol %	B	18 h	82%
8				3 mol %	A	15 h	88%
9				5 mol %	B	36 h	56%
10				3 mol %	A	23 h	55%
11		$HexNH_2$		2 mol % 2 mol %	A C	22 h 16 h	91% 85%
12				2 mol % 2 mol %	A B	15 h 5 h	86% 82%
13				5 mol %	A	20 h	79%
14				5 mol %	A	19 h	87%

(a) Method A: 1 equiv halide, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 2-5 mol % $Ni(COD)_2$, 4-10 mol % DPPF, toluene (0.25 M), 100 °C. Method B: 1 equiv halide, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 2-5 mol % $Ni(COD)_2$, 4-10 mol % 1,10-Phenanthroline, pyridine (0.25 M), 100 °C. Method C: Same as method A, but $(DPPF)NiCl_2$/MeMgBr used in place of $Ni(COD)_2$. Method D: Same as method B, but $(Phen)NiCl_2$/MeMgBr used in place of $Ni(COD)_2$. (b) 3.0 eq of amine used.

(Table 1, entry 1) affords the desired tertiary amine in 80% yield when 2 mol % $Ni(COD)_2$/2 DPPF is employed in the presence of a stoichiometric amount of NaO*t*Bu at 100 °C in toluene. This method effectively couples both electron-rich (entries 1-10) and electron-poor aryl chlorides (entries 11-12), as well as chloropyridine derivatives (entries 13-14) with amines in moderate to excellent yields (Table 1). The reaction conditions are sufficiently mild to tolerate a variety of functional groups including ethers, nitriles, acetals, and non-enolizable ketones. The main side products of the reaction are arenes resulting from reduction of the aryl halides, although in some cases small amounts of homocoupled arenes were produced. Attempts to couple 4-chlorobenzaldehyde with pyrrolidine resulted in the formation of amide side products which may arise from β-hydride elimination of a hemi-aminal intermediate as shown in Scheme 3. Primary amines with β-hydrogens give large amounts of reduced side products, unless electron-deficient aryl chlorides are used as coupling partners.

Scheme 3



Additionally, when primary amines with β-hydrogens are coupled with electronically-neutral aryl chlorides, imine side products resulting from oxidation of the coupled

amine were also detected. Formation of these side products is significantly decreased when the couplings were performed with an excess (3 equiv) of the amine.

Other phosphine ligands examined (BINAP, PPFA, PPFE, DPPP, DPPE, PPh_3, and P(*o*-tol)$_3$)[18] gave either low conversion or poor product/reduced substrate ratios for the coupling reaction. However, the chelating nitrogen ligand 1,10-phenanthroline (phen), which was not an effective ligand in palladium-catalyzed aminations, proved quite useful for nickel-catalyzed C–N bond forming procedures (Table 1, entries 4,6,7,9,12). With this ligand substantially higher yields of desired products could be obtained for some substrates than with the $Ni(COD)_2$/DPPF catalyst system. For example, the attempted reaction of 2-chloro-*p*-xylene with pyrrolidine afforded a 1:2 ratio[19] of the desired product/arene side product using the $Ni(COD)_2$/DPPF combination. With the $Ni(COD)_2$/1,10-phenanthroline catalyst, a 12:1 ratio of desired product/arene was obtained; *N*-(2,5-xylyl)pyrrolidine was isolated in 82% yield. In most cases, reactions which employed 1,10-phenanthroline required a higher catalyst loading than those using DPPF (5% vs 2%). In addition, it was necessary to employ pyridine as a solvent to obtain complete consumption of the starting aryl chloride. However, 1,10-phenanthroline is much less expensive than either BINAP or DPPF, and its high polarity allows for its easy chromatographic separation from the desired products.[20] The use of other 1,10-phenanthroline derivatives such as neocuproine hydrate and 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline afforded little or no desired products. While 1,10-phenanthroline proved to be a superior ligand for some coupling reactions, attempts to use it in procedures to couple aryl chlorides with anilines failed under these conditions, giving mainly homocoupled byproducts.

Due to the air sensitivity, thermal instability, and high cost of $Ni(COD)_2$, we felt it would be desirable to develop conditions to carry out this transformation with air stable (L-L)$NiCl_2$ precatalysts. Attempts to directly employ these complexes without additional additives resulted in no reaction. Use of activated zinc[14a,21] to reduce the

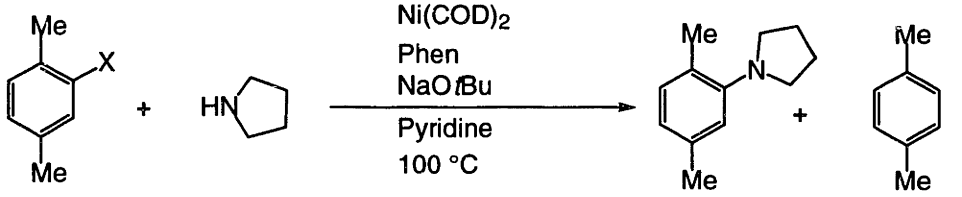
Ni(II) precatalysts *in situ* also failed, resulting in low conversion of the aryl chloride to the desired aniline. However, MeMgBr (2 equiv/Ni) proved to be an effective reagent for the activation of these complexes (eq 2).[22] Use of the *in situ* generated catalyst provided yields which were generally comparable to those obtained with $Ni(COD)_2$, although sometimes slightly higher catalyst levels were required. While this method proved satisfactory for some coupling reactions (Table 1, entries 4, 5, 11), it did not provide reproducible results for the attempted combination of 4-chloroanisole with *o*-toluidine.

$$\text{Ar-Cl} + \text{HN(R)R'} \xrightarrow[\text{cat. MeMgBr}\\ \text{Ligand}\\ \text{NaO}t\text{Bu}\\ \text{Toluene}\\ 100\ ^\circ\text{C}]{\text{cat. (L-L)NiCl}_2} \text{Ar-N(R)R'} \qquad (2)$$

We currently have little mechanistic information about this transformation. The reaction sequence may be similar to the one proposed for the palladium-catalyzed amination of aryl halides,[23] or it may proceed through Ni(I) and Ni(III) intermediates as proposed by Kochi for the nickel-catalyzed coupling of aryl halides with Grignard reagents.[13] A mechanism which involves electron transfer from Ni to an aryl halide is consistent with the fact that reaction of 2-bromo-*p*-xylene with pyrrolidine afforded mainly xylene and only a small amount of the desired product under conditions which gave excellent yields for the coupling of the corresponding chloride (Scheme 4). These results are consistent with the observations made by Kumada on reactions of halobenzenes with *n*-butylmagnesium bromide, although the differences between the results obtained with the aryl chloride and aryl bromide are more dramatic in this case.[22]

One of the principal limitations of this method is the lack of functional group tolerance caused by the use of NaO*t*Bu. Unfortunately, use of weaker bases such as cesium carbonate proved to be ineffective for these reactions. Despite this limitation, a

Scheme 4



X=Cl	12.3	:	1	100% conversion 86% GC yield
X=Br	1	:	3.2	72% conversion 8% GC yield

variety of aniline derivatives can be prepared from aryl chlorides in good to excellent yields using this method for nickel catalyzed amination reactions.

Following the completion of this work, Fort reported related studies on the nickel-catalyzed amination of aryl chlorides using a catalyst comprised of mixtures of NaH/*t*-AmONa/$Ni(OAc)_2$/BIPY in a ratio of 2/2/1/2.[24] Reactions conducted using 20 mol % of the nickel catalyst gave moderate to good yields for the amination of electronically neutral or electron-deficient aryl chlorides with cyclic secondary amines. Reaction of an electron-rich substrate (4-chloroanisole) with pyrrolidine provide the product in a low yield (37%). Hartwig has also reported related studies on nickel-catalyzed C–O bond forming processes.[25]

Experimental Section

General Considerations All reactions were carried out under an argon atmosphere in oven-dried glassware. Reactions catalyzed by mixtures of $Ni(COD)_2$ and DPPF or 1,10-phenanthroline were run in Schlenk flasks equipped with a teflon screwcap, and were mixed and sealed in a Vacuum Atmospheres glovebox prior to heating in an oil bath outside of the glovebox. Reactions in which (L-L)$NiCl_2$

complexes were employed as catalysts were run in Schlenk flasks equipped with rubber septa, and were assembled outside of the glovebox. Elemental analyses were performed by E & R Microanalytical Laboratory Inc., Corona, N.Y. Toluene was distilled under nitrogen from molten sodium, degassed under vacuum, and stored under argon in a Vacuum Atmospheres glovebox. Pyridine was distilled under argon from CaH_2, degassed under vacuum, and stored under argon in a Vacuum Atmospheres glovebox. All amines were purchased from commercial sources. Amines which were liquids at ambient temperature were distilled from CaH_2 under argon or vacuum, degassed under vacuum, and stored under argon in a Vacuum Atmospheres glovebox. Amines which were solids at ambient temperature were stored under argon in a Vacuum Atmospheres glovebox and used without further purification. Sodium *t*-butoxide was purchased from Aldrich chemical company and stored in a Vacuum Atmospheres glovebox under nitrogen or argon. For reactions which employed (L-L)$NiCl_2$ precatalysts, small amounts of sodium *t*-butoxide were removed from the glovebox, stored in a dessicator for up to one week, and weighed in the air. Bis(1,5-cyclooctadiene)Nickel was purchased from Strem Chemical Company, stored in the freezer of a Vacuum Atmospheres glovebox under argon and used without further purification. DPPF was purchased from Strem Chemical Company and used without further purification. 1,10-phenanthroline was purchased from Lancaster Synthesis Inc. and used without further purification. Aryl chlorides were purchased from commercial sources, degassed under vacuum, and stored under argon in a Vacuum Atmospheres glovebox. Methylmagnesium bromide (3M solution in Et_2O) was purchased from Aldrich chemical company. The paramagnetic complexes (DPPF)$NiCl_2$[26] and (phen)$NiCl_2$[27] were prepared by slightly modified literature procedures and characterized by IR and elemental analysis. For example, the (phen)$NiCl_2$ obtained from the literature procedure was found to contain large amounts of alcohol by IR analysis. This compound was dried under vacuum at 180 °C

overnight. The preparation of (DPPF)$NiCl_2$ was carried out in a 1:1:1 mixture of ethanol:*n*-butanol:CH_2Cl_2 due to the low solubility of the phosphine in ethanol. Preparative flash chromatography was performed on ICN Biomedicals Silitech 32-63d silica gel. Yields in table 1 refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^1H NMR and either capillary GC (known compounds) or combustion analysis (new compounds). The procedures described in supplementary material are representative, thus the yields may differ from those given in Table 1.

General Procedure for the Catalytic Amination of Aryl Chlorides, Method A. A resealable Schlenk flask was charged with Bis(1,5-cyclooctadiene)Nickel (6 mg, 0.02 mmol, 2 mol %), DPPF (22 mg, 0.04 mmol, 4 mol %), and sodium *t*-butoxide (135 mg, 1.4 mmol) under argon in a Vacuum Atmospheres glovebox. Toluene (1 mL) was added, followed by the aryl chloride (1.0 mmol), the amine (1.2 mmol), and additional toluene (3 mL). The flask was sealed, removed from the glovebox, and heated to 100 °C with stirring until the starting halide had been consumed as judged by GC analysis.

Workup method 1. The reaction mixture was cooled to room temperature, diluted with ether (10 mL), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel. Products which were inseparable from DPPF by silica gel chromatography were purified according to one of the following workup procedures.

Workup method 2. The reaction mixture was cooled to room temperature, diluted with ether (20 mL), and poured into a separatory funnel. The mixture was extracted with 1M HCl (3 x 10 mL). The organic layer was discarded after confirming that no desired product remained. The aqueous extracts were then combined and taken to pH 12 with 3M NaOH. The aqueous solution was extracted with ether (3 x 20

mL), and the combined ether extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated.

Workup method 3. The reaction mixture was cooled to room temperature, diluted with ether (10 mL), filtered, and concentrated. The product was then taken up in ether (20 mL), and 30% H_2O_2 (5 mL) was added to oxidize the phosphine. The mixture was stirred at room temperature for 10 min, then poured into a separatory funnel. The aqueous layer was drained, and the ether layer was washed with distilled water (10 mL), and saturated aqueous $FeSO_4$ (20 mL) (CAUTION: The reaction between H_2O_2 and $FeSO_4$ is vigorously exothermic, and both the washing of the organic layer with aqueous $FeSO_4$ and the mixing of the aqueous washes should be done with care). The aqueous washes were combined, the aqueous mixture was allowed to cool to room temperature, and then was extracted with ether (3 x 20 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was then purified by flash chromatography on silica gel.

General Procedures for the Catalytic Amination of Aryl Chlorides, Method B. A resealable Schlenk flask was charged with Bis(1,5-cyclooctadiene)Nickel (15 mg, 0.05 mmol, 5 mol %), 1,10-phenanthroline (18 mg, 0.10 mmol, 10 mol %), and sodium *t*-butoxide (135 mg, 1.4 mmol) under argon in a Vacuum Atmospheres glovebox. Pyridine (1 mL) was added, followed by the aryl chloride (1.0 mmol), the amine (1.2 mmol), and additional pyridine (3 mL). The flask was sealed, removed from the glovebox, and heated to 100 °C with stirring until the starting halide had been consumed as judged by GC analysis. The mixture was cooled to room temperature, taken up in ether (10 mL), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel.

Method C. A Schlenk flask was charged with (DPPF)$NiCl_2$ (14 mg, 0.02 mmol, 2 mol %), DPPF (11 mg, 0.02 mmol, 2 mol %), and sodium *t*-butoxide (135 mg, 1.4 mmol)

and purged with argon. Toluene (2 mL) was added, followed by methylmagnesium bromide (13 μL, 3.0 M in diethyl ether, 0.04 mmol, 4 mol %), and additional toluene (2 mL). The mixture was stirred at room temperature for 15 min, then the aryl halide (1.0 mmol) and amine (1.2 mmol) were added. The mixture was heated to 100 °C with stirring until the starting aryl halide had been consumed as judged by GC analysis. The mixture was cooled to room temperature, taken up in ether (10 mL), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel.

Method D. A Schlenk flask was charged with (phen)$NiCl_2$ (22 mg, 0.07 mmol, 7 mol %), 1,10-phenanthroline (13 mg, 0.07 mmol, 7 mol %), and sodium *t*-butoxide (135 mg, 1.4 mmol) and purged with argon. Pyridine (2 mL) was added, followed by methylmagnesium bromide (47 μL, 3.0 M in diethyl ether, 0.14 mmol, 14 mol %), and additional pyridine (2 mL). The mixture was stirred at room temperature for 15 min, then the aryl halide (1.0 mmol) and amine (1.2 mmol) were added. The mixture was heated to 100 °C with stirring until the starting aryl halide had been consumed as judged by GC analysis. The mixture was cooled to room temperature, taken up in ether (10 mL), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel.

***N*-Methyl-*N*-phenyl-*p*-toluidine** (Table 1, entry 1).[28] The general procedure A using workup 1 gave 152 mg (77%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.22 (m, 5H), 7.03 (d, 2H, J = 8.73 Hz), 6.68 (d, 2H, J = 8.67 Hz), 4.49 (s, 2H), 2.97 (s, 3H), 2.25 (s, 3H).

Di-*p*-tolylamine (Table 1, entry 2).[29] The general procedure A using workup 1 gave 186 mg (94%) of a white solid, mp 77 °C (lit mp 77–78 °C):[29] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, 4H, J = 8.6 Hz), 6.93 (d, 4H, J = 8.5 Hz), 5.54 (s, br, 1H), 2.29 (s,

6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.1, 130.1, 129.7, 117.9, 20.6; IR (KBr, cm^{-1}) 3418, 1610, 1518, 1320, 807.

***N*-(*p*-Methylphenyl)-1,4-dioxa-8-azaspiro[4.5]decane** (Table 1, entry 3).[28] The general procedure A using 5 mol % $Ni(COD)_2$, 10 mol % DPPF, and workup 1 gave 188 mg (88%) of a white solid, mp 65 °C (lit mp 64.8–65.6 °C):[28] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, 2H, J = 8.4 Hz), 6.86, (d, 2H, J = 8.7 Hz), 3.99 (s, 4H), 3.26 (t, 4H, J = 5.7 Hz), 2.26 (s, 3H), 1.85 (t, 4H, J = 5.7 Hz).

***N*-*p*-Tolylpyrrolidine** (Table 1, entry 4).[30] The general procedure A using workup 2 gave 91 mg (57%) of a tan solid, mp 34–35 °C (lit=oil):[30] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.03 (d, 2H, J = 8.1 Hz), 6.50 (d, 2H, J = 8.2 Hz), 3.29–3.22 (m, 4H), 2.25 (s, 3H), 2.05–1.95 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.1, 129.6, 124.4, 111.7, 47.8, 25.4, 20.3; IR (KBr, cm^{-1}) 2964, 1624, 1523, 1370, 1187, 801.

***N*-(2,5-Dimethylphenyl)-*p*-anisidine** (Table 1, entry 5).[31] The general procedure A using workup 1 gave 216 mg (95%) of a pale yellow solid, mp 37 °C (lit mp 34–35 °C):[31] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.02 (m, 3H), 6.89–6.82 (m, 3H), 6.63 (d, 1H, J = 7.0 Hz), 5.17 (s, br, 1H), 3.80 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.9, 143.1, 136.4, 130.5, 122.3, 122.0, 120.7, 115.9, 114.6, 55.5, 21.2, 17.3; IR (KBr, cm^{-1}) 3419, 2928, 1526, 1509, 1246, 826.

***N*-(2,5-Dimethylphenyl)hexylamine** (Table 1, entry 6).[28] The general procedure A using 3 mmol of amine, 5 mol % $Ni(COD)_2$, 10 mol % DPPF, and workup 3 gave 107 mg (52%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H, J = 7.5 Hz),6.47–6.43 (m, 2H), 3.38 (s, 1H, br), 3.13 (t, 2H, J = 7.2 Hz), 2.29 (s, 3H), 2.09 (s, 3H), 1.66 (p, 2H, J = 7.8 Hz), 1.45–1.30 (m, 6H), 0.91 (m, 3H).

***N*-(2,5-Xylyl)pyrrolidine** (Table 1, entry 7).[32] The general procedure B gave 143 mg (82%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.99 (d, 2H, J = 7.5 Hz), 6.69 (s, 1H), 6.64 (d, 1H, J = 7.5 Hz), 3.15–3.20 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 1.93–1.89 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 135.6, 131.5, 125.5, 120.8, 116.5, 50.9, 24.9, 21.2, 20.1; IR (neat, cm^{-1}) 2964, 1505, 1312. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.30; H, 9.71.

***N*-(2-Methylphenyl)-*p*-anisidine** (Table 1, entry 8). The general procedure A using 3 mol % $Ni(COD)_2$, 6 mol % DPPF, and workup 1 gave 187 mg (88%) of a white solid, mp 78 °C: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16–6.67 (m, 8H), 5.20 (s, br, 1H), 3.80 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.0, 143.3, 136.2, 130.7, 126.7, 125.2, 122.0, 119.9, 115.1, 114.6, 55.5, 17.7; IR (KBr, cm^{-1}) 3392, 2997, 1514, 1236. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C,78.85; H, 6.83.

***N*-(4-Methoxyphenyl)pyrrolidine** (Table 1, entry 9).[30] The general procedure B gave a white solid which was contaminated with the byproduct 4,4'-dimethoxybiphenyl. This material was taken up in ether (20 mL), and extracted with 1M HCl (3 x 10 mL). The organic layer was discarded after confirming that no desired product remained. The aqueous extracts were then combined and taken to pH 12 with 3M NaOH. The aqueous solution was extracted with ether (3 x 20 mL), and the combined ether extracts were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give 98 mg (55%) of a white solid, mp 41 °C (lit=oil):[30] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 2H, J = 9.1 Hz), 6.53 (d, 2H, J = 9.0 Hz), 3.76 (s, 3H), 3.28–3.20 (m, 4H), 2.02–1.90 (m, 4H).

***N*-Methyl-*N*-phenyl-*p*-anisidine** (Table 1, entry 10). The general procedure A using 3 mol % $Ni(COD)_2$, 6 mol % DPPF, and workup 3 gave 120 mg (56%) of a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.20–6.76 (m, 9H), 3.81 (s, 3H), 3.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75MHz) δ 156.2, 149.7, 142.2, 128.9, 126.2, 118.3, 115.7, 114.7, 55.5, 40.4; IR (neat, cm^{-1}) 2932, 1596, 1508, 1243. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.77; H, 7.22.

***N*-(4-Benzoylphenyl)hexylamine** (Table 1, entry 11).[33] The general procedure A using workup 1 gave 262 mg (93%) of a yellow solid, mp 55–56 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.79–7.71 (m, 4H), 7.52–7.42 (m, 3H), 6.57 (d, 2H, J = 8.8 Hz), 4.22 (s, br, 1H), 3.19 (t, 2H, J = 7.3 Hz), 1.69–1.30 (m, 8H), 0.91 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.0, 152.3, 139.2, 133.0, 131.1, 129.4, 127.9, 125.6, 111.1, 43.2, 31.5, 29.2, 26.7, 22.5, 14.0; IR (KBr, cm^{-1}) 3354, 2924, 1635, 1586, 1321, 1285. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 81.35; H, 8.02.

***N*-(4-Cyanophenyl)morpholine** (Table 1, entry 12).[34] The general procedure A using workup 1 gave 163 mg (87%) of a white solid, mp 77–78 °C (lit mp 75–76.5 °C):[34] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, 2H, J = 9.5 Hz), 6.81 (d, 2H, J = 9.6 Hz), 3.82 (t, 4H, J = 4.8 Hz), 3.23 (t, 4H, J=4.9 Hz).

***N*-Methyl-*N*-(4-pyridyl)aniline** (Table 1, entry 13). A resealable Schlenk flask was charged with 4-chloropyridine•HCl (150 mg, 1.0 mmol), NaO*t*Bu (135 mg, 1.4 mmol) and toluene (1 mL) under argon in a Vacuum Atmospheres glovebox. The mixture was stirred for 2 min at ambient temperature, then $Ni(COD)_2$ (15 mg, 0.05 mmol, 5 mol %), DPPF (55 mg, 0.10 mmol, 10 mol %), NaO*t*Bu (96 mg, 1.0 mmol), and toluene (3 mL) were added. The flask was sealed, removed from the glovebox, and heated to 100 °C with stirring until the halide had been consumed as judged by GC

analysis. The product was isolated using workup 1 to give 138 mg (75%) of a pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (s, br, 2H), 7.45–7.40 (m, 2H), 7.26–7.19 (m, 3H), 6.54 (d, 2H, J = 5.2 Hz), 3.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.6, 149.8, 146.1, 129.9, 126.6, 126.3, 108.2, 39.3; IR (neat, cm^{-1}) 3030, 1587, 1504, 1363. Anal. Calcd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57. Found: C, 78.34; H, 6.54.

***N*-(3-Pyridyl)morpholine** (Table 1, entry 14).[35] The general procedure A using 5 mol % $Ni(COD)_2$, 10 mol % DPPF, and workup 1 gave a yellow oil which contained slight impurities as judged by ^{1}H NMR. The oil was then Kugelrohr distilled to give 141 mg (86%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32–8.30 (m, 1H), 8.13 (t, 1H, J = 3.0 Hz), 7.19–7.17 (m, 2H), 3.90–3.86 (m, 4H), 3.21–3.17 (m, 4H).

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(18) DPPF= 1,1'-Bis(diphenylphosphino)ferrocene, BINAP= 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl, PPFA= N,N-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine, PPFE= 1-[2-(diphenylphosphino)ferrocenyl] ethyl methyl ether, DPPP= 1,3-Bis(diphenylphosphino)propane, DPPE= 1,2-Bis(diphenylphosphino)ethane.

(19) Ratios are not corrected for GC response factors.

(20) DPPF is relatively non-polar, and separation of the excess DPPF from non-polar aryl amines occasionally required an additional step in the workup to oxidize the phosphine.

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Chapter Nine:

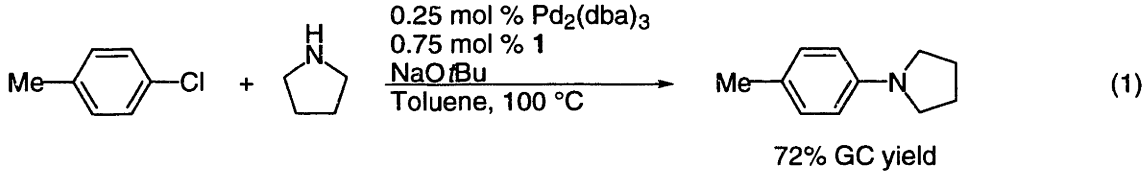
Palladium-Catalyzed Amination of Aryl Chlorides

Introduction

Despite the utility of our nickel catalyst system for aminations of aryl chlorides, the method was limited to substrates which did not contain base-sensitive functional groups. Additionally, the $Ni(COD)_2$ precatalyst was air sensitive, and air-stable nickel precatalysts required activation with Grignard reagents. In light of these drawbacks we sought to develop a more efficient palladium catalyst for aminations of aryl chlorides.

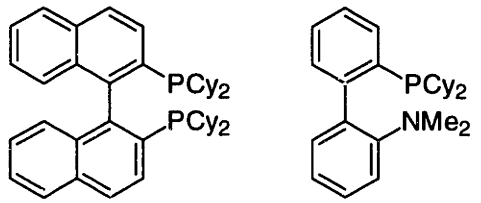
Results and Discussion

As described in chapter 4, NMR studies had suggested that oxidative addition (or ligand dissociation prior to oxidative addition) was rate limiting; oxidative addition of aryl chlorides was expected to be less facile than for aryl bromide substrates (see chapter 8). We reasoned that an electron-rich derivative of BINAP should accelerate oxidative addition,[1] thus, we synthesized (±)-2,2'-bis(dicyclohexylphosphino)-1,1'-binaphthyl (**1**), which had previously been prepared in optically active form by Akutagawa, et al [2] Initial experiments with this ligand demonstrated its utility for the palladium-catalyzed amination of aryl chlorides; 4-chlorotoluene was coupled with pyrrolidine in 72 % GC yield at 100 °C using this catalyst system (eq 1). During the course of these experiments, Dr. David Old prepared a related phosphine,



72% GC yield (1)

2-dicyclohexylphosphino-2'-dimethylaminobiphenyl (**2**) and found that catalysts supported by this ligand frequently were more reactive than those based on **1**.



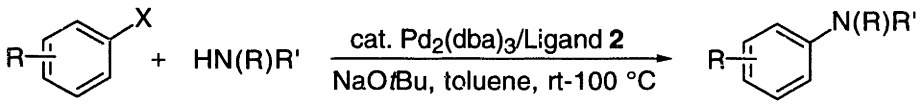
1 2

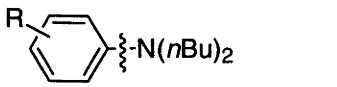
A number of catalytic amination reactions using **2** as ligand were examined by Dr. Old and myself; experiments described as entries 1-3, 6-7, 9-11, and 15 in Table 1 were performed by Dr. Old. Catalysts supported by **2** were effective for the amination of a variety of aryl chloride substrates (Table 1). Secondary amines are efficiently coupled under these conditions, however reactions of primary anilines required temperatures of 100 °C to proceed to completion. Reactions of primary aliphatic amines with unhindered aryl halides were marred by the formation of large amounts of doubly arylated products when **2** was employed, however use of **1** afforded the desired products in high yields (entries 14,17). Functionalized aryl bromides or chlorides were viable substrates provided that either cesium carbonate or potassium phosphate was employed. Curiously, while cesium carbonate worked well with catalysts based on **1**, it was not effective for reactions which employed **2**; potassium phosphate was employed for these latter reactions.

Dr. Old also demonstrated that catalytic aminations of aryl bromides could be conducted at room temperature[3] if reactions were run in DME using slightly more concentrated reaction conditions (1-2 M) than were normally employed (0.5 M). Unlike room-temperature reactions of aryl iodides,[4] use of crown ether additives was not required. Additionally, the first room-temperature catalytic amination of an aryl chloride (albeit an activated one) was effected using this catalyst; 4-chlorobenzonitrile was coupled with morpholine in 96% yield using 5 mol % $Pd_2(dba)_3$ and 7.5 mol % **2** (entry 9). It was somewhat curious that other aminations of aryl chlorides could not be

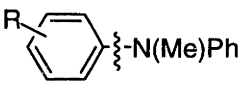
effected at room-temperature in light of our results in room-temperature Suzuki coupling reactions of aryl chlorides (see chapter 10).

Table 1: Catalytic Amination[a] of Aryl Chlorides and Bromides

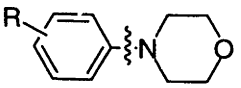




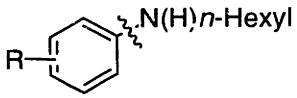
1: R=4-Me, X=Cl; 95% (95%)[b,c,o]
2: R=4-MeO, X=Cl; 90%[o]
3: R=4-Me, X=Br; 96%[d,e,l,o]



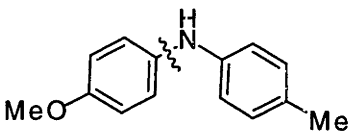
4: R=4-Me, X=Cl; 98%
5: R=4-MeO, X=Cl; 95%
6: R=2,5-Me2, X=Cl; 96%[o]
7: R=4-Me, X=Br; 95%[d,m,o]



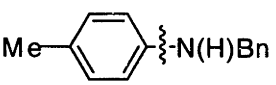
8: R=4-MeO, X=Cl; 91%
9: R=4-CN, X=Cl; 96%[d,f,l,o]
10: R=2,5-Me2, X=Br; 97%[d,e,m,o]
11: R=4-CO2Me, X=Br; 81%[g,o]
12: R=4-C(O)Me, X=Br; 82%[h,i]



13: R=2,5-Me2, X=Cl; 99%
14: R=4-CO2Me, X=Cl; 83%[c,j]
15: R=2,6-Me2, X=Br; 88%[d,f,l,o]



16: X=Cl, 93%[c]



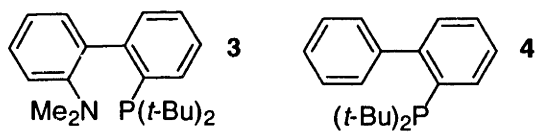
17: X=Cl, 89%[c,k,n]

□ = Reaction run at rt.

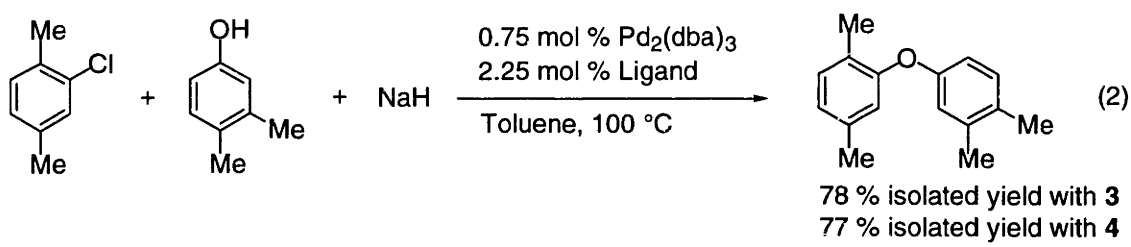
(a) Reaction Conditions: 1.0 equiv aryl halide, 1.2 equiv amine,1.4 equiv NaO*t*Bu, 0.5 mol % $Pd_2(dba)_3$, 1.5 mol % ligand (1.5L/Pd), toluene (2 mL/mmol halide), 80 °C. Reactions were complete in 11-27 h; reaction times have not been minimized. (b) Reaction run with 0.025 mol % $Pd_2(dba)_3$. (c) Reaction run at 100 °C. (d) Reaction run at room temperature in DME solvent. (e) Reaction run with 1.5 mol % $Pd_2(dba)_3$. (f) Reaction run with 2.5 mol % $Pd_2(dba)_3$. (g) Reaction run using K_3PO_4, DME solvent. (h) Reaction run using $Pd(OAc)_2$, K_3PO_4, DME solvent. (i) One of two runs only proceeded to 98% conversion. (j) Reaction run with $Pd(OAc)_2$, ligand **1**, Cs_2CO_3 as catalyst, ligand, and base. (k) Using **1** as ligand. (l) [ArBr]=1M. (m) [ArBr]=2M. (n) 1.5 equiv. benzylamine used. (o) This experiment was performed by Dr. David Old.

Control experiments using commercially available phenyldicyclohexylphosphine were conducted by Dr. Old to determine if the amino group on the ligand was important for catalysis. These reactions were considerably less efficient than those which employed **2**, giving low conversion and large amounts of arene side products, and suggested that the amino moiety was necessary for high reactivity. Subsequent experiments with ligands **4** and **5** demonstrated that this hypothesis was incorrect (see below).

Related studies of palladium-catalyzed C–O bond forming reactions led to the development of catalysts even more active than those based on **2**. Although **2** was not effective for the coupling of aryl halides with phenols, the bulky ligands **3** and **4** worked well for this process. For example, the reaction of 2-chloro-*p*-xylene with 3,4-dimethyl phenol using 0.75 mol % $Pd_2(dba)_3$ and 2.25 mol % **3** provided the



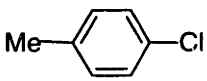
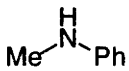
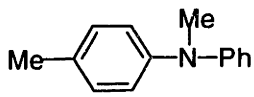
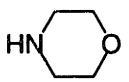
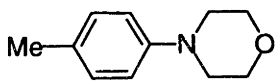
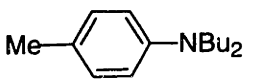
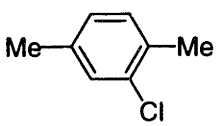
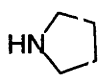
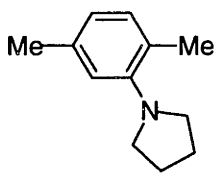
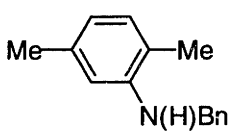
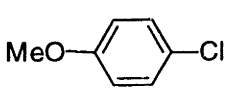
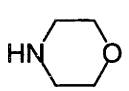
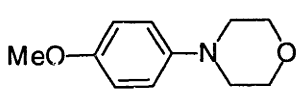
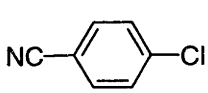
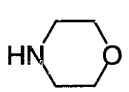
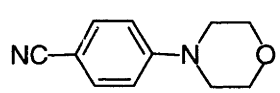
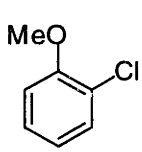
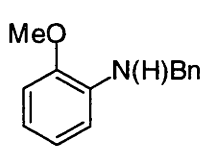
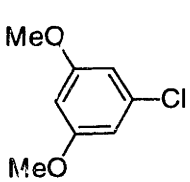
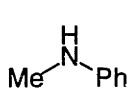
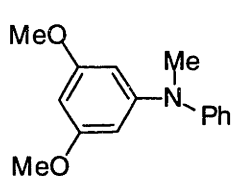
diarylether product in 78% yield. Ligand **4** gave similar results for this reaction; the diarylether was obtained in 77% yield (eq 2).[5]



(2)

In light of the effectiveness of ligand **4** in C–O bond forming processes, its use in catalytic amination reactions was examined. Catalysts based on **4** proved to be considerably more active in room-temperature reactions of aryl chlorides than those which employed **2**. Mixtures of $Pd(OAc)_2$/**4** catalyzed the room-temperature amination of a variety of unactivated aryl chlorides, including substrates which are electron-rich and/or ortho-substituted. Secondary amines were found to be effective coupling partners, and primary amines were successfully arylated with ortho-substituted aryl halides (Table 2).

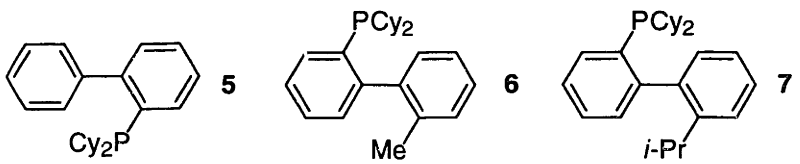
Table 2: Room-Temperature Catalytic Amination of Aryl Chlorides[a]

Entry	Halide	Amine	Product	%Pd	Rxn Time	Yield
1				1.0	19 h	98
2				1.0	20 h	94
3		$HNBu_2$		2.0	18 h	81
4				1.0	21 h	98
5		H_2NBn		2.0	18 h	99
6				2.0	20 h	90
7				1.0	15 h	86
8		H_2NBn		1.0	14 h	99
9				1.0	16 h	97

(a) Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 1-2 mol % $Pd(OAc)_2$, 2-4 mol % **4**, toluene (1 mL/mmol halide), rt. Reaction times have not been minimized. Yields represent isolated yields (average of two or more experiments) of compounds estimated to be ≥95 % pure as judged by ^1H NMR and GC analysis (known compounds) and combustion analysis (new compounds).

To date, the scope of the room-temperature amination of aryl chlorides is somewhat limited. For example, primary amines are not efficiently arylated with unhindered aryl chlorides, and primary anilines reacted poorly at room temperature. Additionally, the functional group tolerance of this process is limited due to the requirement to use the strong base NaO*t*Bu.

Aminations of aryl chlorides were also examined at 80-100 °C using catalysts based on either **4**, or the related *o*-(dicyclohexylphospino)biphenyl **5**. Reactions



which were inefficient with **4** or **5** often succeeded when **2** was employed; use of **6** or **7** occasionally gave better results than were obtained with **5** (Table 3, entry 6). These studies were done in collaboration with Dr. Hiroshi Tomori, and Joseph Sadighi; experiments which were performed by them are identified in the footnotes of Table 3.

As shown in Table 3, the scope of the aryl chloride amination process was considerably broader at 80–100 °C than at room temperature. Catalysts comprised of $Pd(OAc)_2$ or $Pd_2(dba)_3$ and either **4**, **5**, or **2** function well with 0.5–1.0 mol % catalyst for a variety of substrates including those which are electron-rich and/or ortho-substituted. Even the very hindered 2,6-dimethylchlorobenzene reacted effectively, although higher temperatures (110 °C) and/or higher catalyst loadings (1–4 mol %) were required for reactions to proceed to completion in a reasonable period of time.

A variety of amine coupling partners may be used including primary and secondary anilines, primary amines, cyclic secondary amines, and diarylamines. Benzophenone imine, which serves as an NH_3 equivalent,[6] is also a suitable

Table 3: Palladium-catalyzed amination of unactivated aryl chlorides[a]

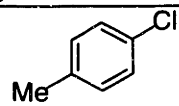
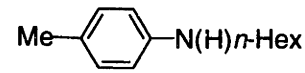
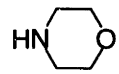
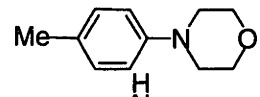
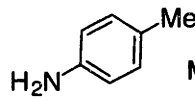
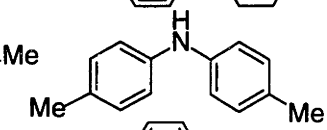
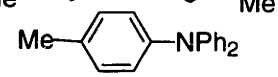
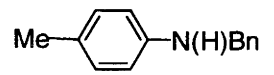
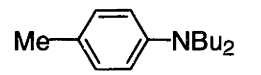
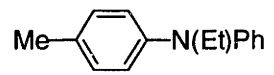
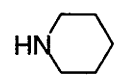
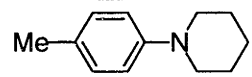
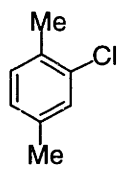
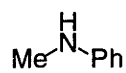
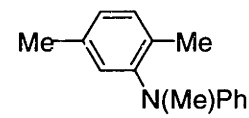
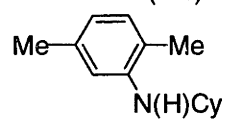
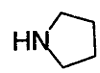
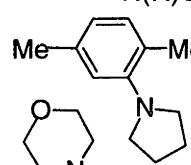
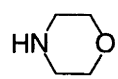
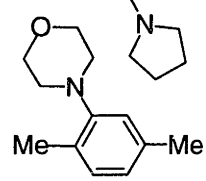
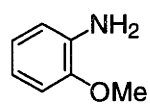
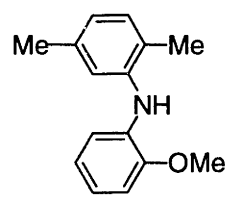
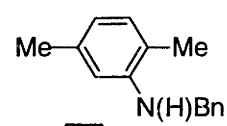
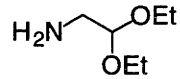
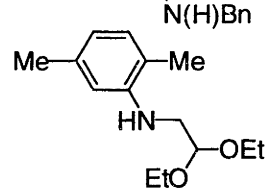
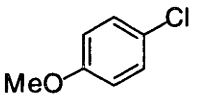
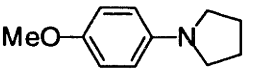
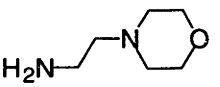
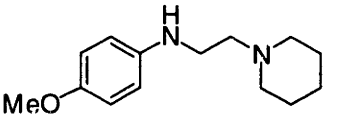
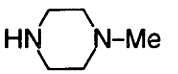
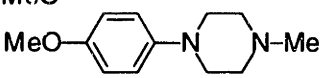
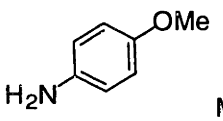
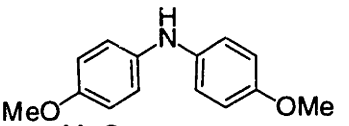
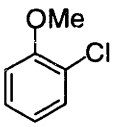
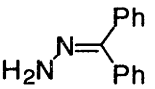
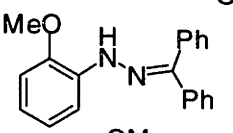
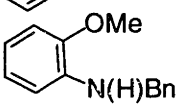
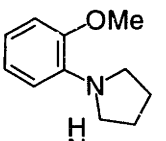
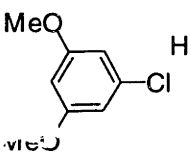
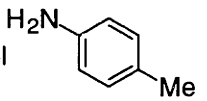
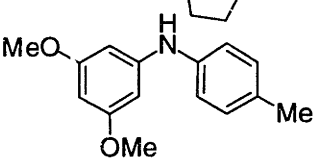
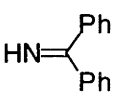
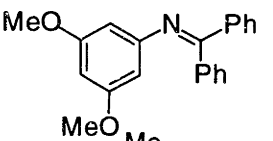
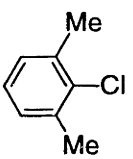
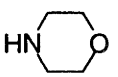
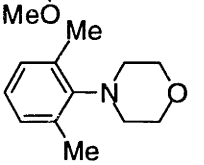
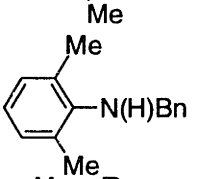
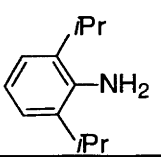
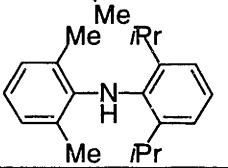
Entry	Halide	Amine	Product	mol % Pd	Rxn Time	Yield (%)
1		H_2NHex		0.5	19 h	85
2				0.5	4 h	93
3				0.5	2.5 h	90[b,f]
4		$HNPh_2$		0.5	12 h	90[e]
5		H_2NBn		0.5	5 h	89
6		$HNBu_2$		0.5/**6** 0.5/**7**	22 h 22 h	89[b] 91[b]
7		HN(Et)Ph		0.5	18 h	93
8				0.5	23 h	86
9				0.5	3 h	90
10		H_2NCy		1.0	19 h	98
11				0.5	3h	98[e]
12				0.5	24 h	89[e]
13				0.5	2.5 h	97[b,f]
14		H_2NBn		0.5	24 h	96
15				0.5	15 h	100[b,e]

Table 3: Palladium-catalyzed amination of unactivated aryl chlorides (cont.)[a]

Entry	Halide	Amine	Product	mol % Pd	Rxn Time	Yield (%)
16				1.0	23 h	92
17				0.5	24 h	86[d,e]
18				0.5/**5**	21 h	82[c,e]
19				0.5	8 h	94[b,f]
20				0.5	2.5 h	91[b,f]
21		H_2NBn		0.5	18 h	96
22				0.5	16 h	88
23				0.5	2.5 h	95[b,f]
24				1.0/**5**	18 h	>99[b,e]
25				1.0/**2**	20 h	86[d,e]
26		H_2NBn		1.0	24 h	86[d,e]
27				4.0	20 h	73[b,f]

(a) Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, cat. $Pd(OAc)_2$, cat **4** (2L/Pd), toluene (2mL/mmol halide), 80 °C. Reaction times have not been minimized. (b) $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$; (c) The reaction was conducted at 100 °C; (d) The reaction was conducted at 110 °C; (e) The reaction was conducted by Dr. Hiroshi Tomori; (f) The reaction was conducted by Mr. Joseph Sadighi.

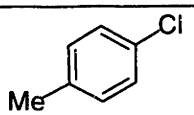
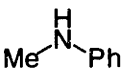
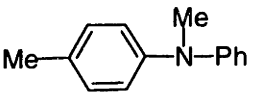
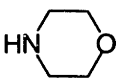
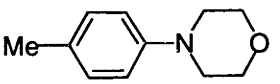
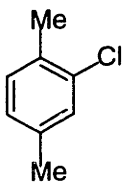
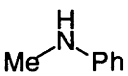
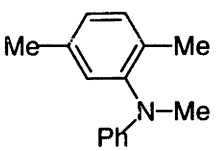
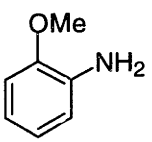
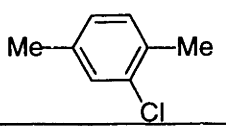
substrate. Use of **6** or **7** for the coupling of di-*n*-butylamine with 4-chlorotoluene gave higher yields than were obtained with **4** or **5** (Entry 6); use of the latter resulted in the formation of aryl(*t*-butyl)ether byproducts (~10%). Reactions of primary aliphatic amines with unhindered aryl halides afforded good yields of the aryl(alkyl)amine products with the **4**/Pd catalyst at 80 °C; 1.5-3.0 equiv of amine was employed to minimize the formation of diarylated side products in these reactions. Sadighi found that reactions of primary anilines were inefficient if $Pd(OAc)_2$ was employed as a precatalyst, but use of $Pd_2(dba)_3$ for these reactions provided excellent results.

Curiously, some substrate combinations which gave outstanding results with the BINAP system (for the analogous aryl bromides) were either inefficient, or required high temperatures. For example, the reaction of 4-bromobenzonitrile with *n*-hexylamine proceeds to completion rapidly and in high yield using the BINAP catalyst (0.05 mol % Pd).[7] However, the reaction of 4-chlorobenzonitrile with *n*-hexylamine required 40 h at 110 °C to proceed to completion (Table 5, entry 10). Reactions of unactivated aryl bromides with aliphatic amines were considerably slower than the reactions of the corresponding aryl chlorides. This suggests that the Pd–N bond forming process is less facile for aryl bromide substrates, since the oxidative addition of aryl bromides is faster than that of aryl chlorides,[8] and the reductive elimination should proceed at the same rate for both bromides and chlorides (presumably through the same intermediate). It appears that the BINAP catalyst is more effective for arylation of aliphatic amines with bromide substrates than catalysts based on **2**–**5**.

Sadighi demonstrated that reactions of anilines with electron-rich substrates (bromides or chlorides) were much more efficient with Pd/**4** than with previously developed catalysts. Arylations of primary anilines were considerably faster with aryl bromide substrates than with the analogous aryl chlorides. It is possible that the increased acidity of anilines relative to aliphatic amines[9] increases the rate of Pd–N bond formation.

For some substrates it is possible to conduct reactions at relatively low catalyst loadings (0.05 mol % Pd), although to date these conditions are only effective for a

Table 4: Amination of Aryl Chlorides at Low Catalyst Loading[a]

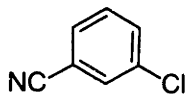
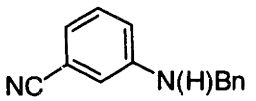
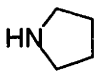
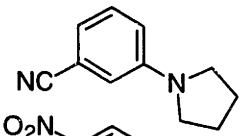
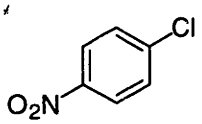
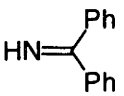
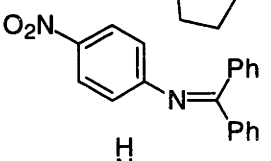
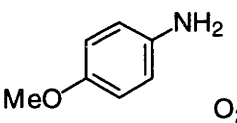
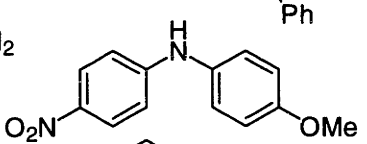
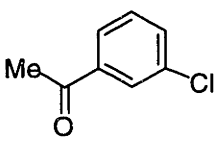
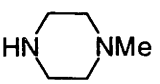
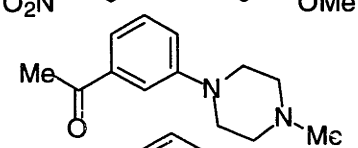
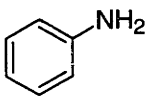
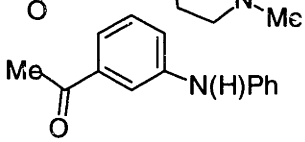
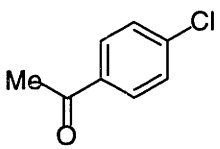
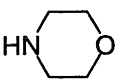
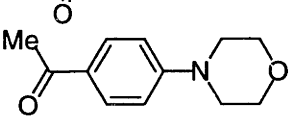
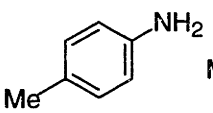
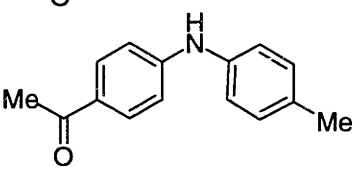
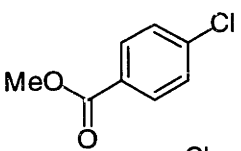
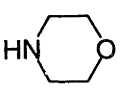
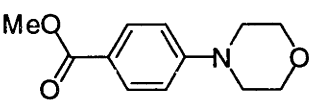
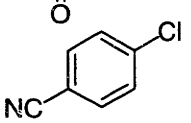
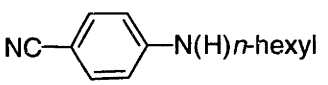
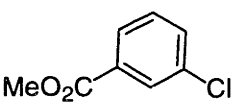
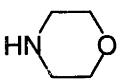
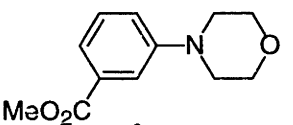
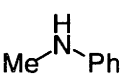
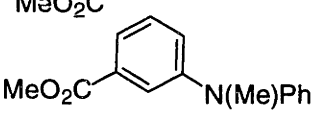
Entry	Halide	Amine	Product	%Pd	Rxn Time	Yield
1				0.05	22 h	95[b]
2				0.05/**5**	19 h	89[b]
3				0.05	22 h	95
4				0.05	14 h	97[c,d]

(a) Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv amine, 1.4 equiv NaO*t*Bu, 0.025 mol % $Pd_2(dba)_3$, 0.1 mol % **4**, toluene (1 mL/mmol halide),110 °C. Reaction times have not been minimized. Yields represent isolated yields (average of two or more experiments) of compounds estimated to be ≥95 % pure as judged by ^1H NMR and GC analysis (known compounds) and combustion analysis (new compounds); (b) The reaction was conducted at 100 °C; (c) The reaction was conducted at 80 °C; (d) This experiment was performed by Mr. Joseph Sadighi.

limited number of substrates (Table 4). For example, the reaction of *N*-methyl aniline with 4-chlorotoluene proceeds to completion in 22 h using 0.05 mol % $Pd_2(dba)_3$ and 0.1 mol % **4** at 100 °C affording the desired product in 95% yield. However, although the reaction of 4-chlorotoluene with *p*-toluidine is efficient with 0.5 mol % Pd (Table 3, entry 3), it only proceeds to 41 % conversion in 48 h at 110 °C using 0.05 mol % Pd.

Catalytic amination of aryl chloride substrates bearing a variety of base-sensitive functional groups was achieved using catalysts derived from **4**, **5**, and **2** when K_3PO_4 was employed as the stoichiometric base (Table 5) in DME. The reaction

Table 5 : Palladium-catalyzed amination of functionalized aryl chlorides[a]

Entry	Halide	Amine	Product	mol % Pd	Rxn Time	Yield (%)
1				2.0/**5**	25 h	72[b,g]
2				1.0/**5**	40 h	81[g]
3				1.0/**2**	16 h	82[h]
4				1.0	17 h	91[h]
5				1.0/**2**	21 h	77[g]
6				1.0/**5** 1.0/**2**	22 h 22 h	81[g] 84[g]
7				1.0	21 h	91[d]
8				1.0/**5**	18 h	95[d,g]
9				1.0/**5**	18 h	90[d]
10		*n*-HexylNH$_2$		0.5	40 h	72[e,f,g]
11				1.0/**5**	20 h	93[g]
12				1.0/**5** 1.0/**2**	20 h 20 h	88[b,g] 83[g]

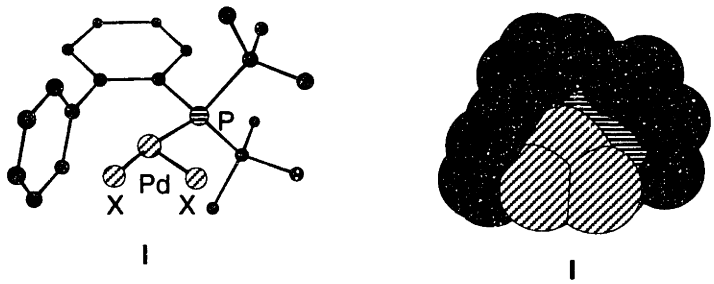
(a) Reaction conditions: 1.0 equiv aryl chloride, 1.2 equiv amine, 1.4 equiv K_3PO_4, cat $Pd(OAc)_2$, cat **4**, DME (2 mL/mmol halide), 100 °C; (b) The reaction proceeded to 99 % conversion; (c) $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$; (d) The reaction was conducted at 80 °C; (e) The reaction was conducted at 110 °C; (f) The reaction was conducted with 3.0 equiv amine; (g) The reaction was conducted by Dr. Hiroshi Tomori; (h) The reaction was conducted by Mr. Joseph Sadighi.

conditions tolerated the presence of enolizable ketones, methyl esters, nitriles, and nitro groups; a variety of amines were efficient coupling partners, but reactions of primary aliphatic amines usually required longer reaction times, higher temperatures, and/or larger catalyst loadings. Although the Pd/**4** catalyst was useful for some substrate combinations, the best results in reactions which employed K_3PO_4 were generally obtained with either **5** or **2**; catalysts based on **2** were slightly more reactive than those derived from **5**. Reactions which proved to be inefficient when $Pd(OAc)_2$ was employed as a precatalyst were often improved when $Pd_2(dba)_3$ was used.

Although the reasons for the high reactivity of catalysts based on **2**, **4**, and **5** are not well understood, several structural features of these ligands presumably contribute to their effectiveness. The electron-rich phosphine group serves to accelerate the oxidative addition process, and allows for the transformation of aryl chloride substrates which react sluggishly when palladium complexes bearing triarylphosphine ligands are used.[10] The steric bulk of the ligands may accelerate the C–N bond forming reductive elimination,[11a] as well as promote reactivity via (monophosphine)palladium complexes.[11b-h] Although attempts to isolate palladium complexes of these ligands have thus far been unsuccessful due to the high solubility of these complexes as well as a competing cyclometallation reaction, circumstantial evidence suggests that monophosphine complexes are involved in these reactions; the amination reactions proceed at roughly the same rate regardless of the ratio of **4**/Pd which is employed.

The π-system of the *o*-aromatic group on these ligands may participate in an interaction with the unoccupied metal d-orbital.[12] Examination of molecular models suggest that this interaction is sterically favorable (Figure 1), and further circumstantial evidence for this interaction is provided by the fact that room-temperature reactions

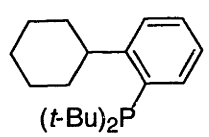
Figure 1: Chem 3-D Representation of $LPdX_2$



I I

X= Ar, N(R)R', halide, solvent

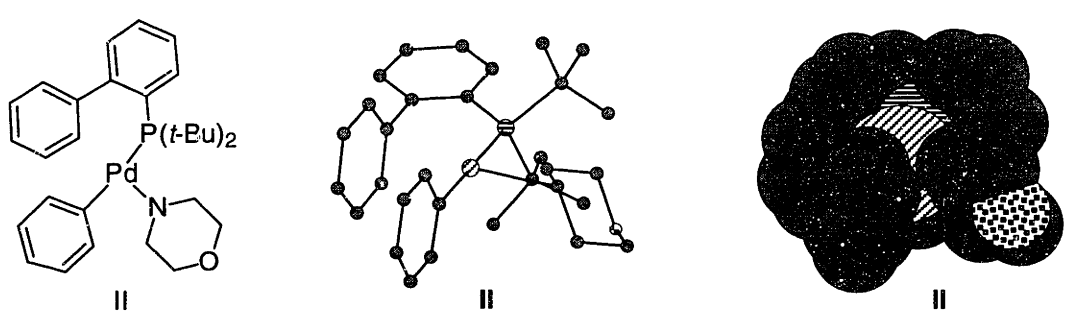
conducted with ligand **8** are generally much less efficient than those which employ **4**. For example, the reaction of 4-chlorotoluene with morpholine proceeds to completion



8

in 20 h and affords the desired product in 94% isolated yield when **4** is employed. Use of **8** for this coupling afforded only 33% conversion (33% GC yield) in 22h. The metal-arene interaction presumably serves to stabilize the catalyst, and may force the substrate arene into a perpendicular orientation which may facilitate reductive elimination (Figure 2).

Figure 2: Chem 3-D Representation of LPd(Ar)(morpholine)



II II II

In conclusion, use of **1**, **2**, **4**, and **5** allows for the efficient palladium-catalyzed amination of aryl chloride substrates. Catalysts based on **4** effect this transformation at room temperature for some substrate combinations, and work well for reactions of primary amines with unhindered aryl chlorides and arylations of aniline substrates at 80 °C. Reactions of functionalized substrates with potassium phosphate as the base at 80-100 °C are most effective with **2** and **5**; these ligands frequently work for reactions of secondary amines which are inefficient with **4**. Reactions of di-*n*-butylamine are improved with the use of **6** or **7**. Certain substrate combinations react efficiently at low catalyst loadings (0.05 mol % Pd), although most reactions require moderate levels of palladium (0.5-1.0 mol %).

Hartwig has reported related studies using bulky, electron rich bis-phosphines,[3] although he has not demonstrated any examples of room-temperature aminations of aryl chloride substrates; most reactions were conducted at 85–110 °C using 1-3 mol % Pd). Furthermore, the scope of catalytic aminations with these ligands is not clear; only a few examples were reported, none of which involved substrates containing base-sensitive functional groups.

Experimental Section

General Considerations The general considerations are the same as for the previous chapters with the following exceptions. Aryl halides were purchased from Aldrich Chemical company except for 4-chloroacetophenone which was purchased from Fluka Chemical company. Tribasic potassium phosphate was purchased from Fluka Chemical company. Cesium carbonate was obtained from Chemetal and was ground with a mortar and pestle before use. Chlorodicyclohexylphosphine, palladium acetate, tris(dibenzylideneacetone)dipalladium(0), (±)-2,2'-dibromo-1,1'-binaphthyl, and *n*-butyllithium were purchased from Strem Chemical company. Trimethyl borate,

triisopropyl borate, 9-BBN (0.5 M THF solution), NaHMDS (95%), 2-methyl-3-pentanone, 3-methyl-2-butanone, anhydrous dioxane, anhydrous DME, dicyclohexylphenylphosphine, and 1-hexene were purchased from Aldrich Chemical company. (±)-2,2'-Bis(dicyclohexylphosphino)-1,1'-binaphthyl **1**[2] was prepared by metallation of the corresponding dibromobinaphthyl with *t*-butyllithium and quenching with chlorodicyclohexylphosphine using a procedure analogous to the synthesis of (±)-BINAP.[13] It was characterized by elemental analysis and by comparison of its ^{1}H and ^{31}P NMR spectra with literature data.[2] Tetrakis(triphenylphosphine)palladium was prepared according to a literature procedure.[14] 2-(*N,N*-Dimethylamino)-2'-(dicyclohexylphosphino)biphenyl (2) was prepared according to the published procedure.[15] IR spectra reported in this chapter were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR *in situ* IR instrument.

2-(*N,N*-Dimethylamino)-2'-di-*t*-butylphosphinobiphenyl (3). An oven-dried Schlenk flask was purged with argon and charged with 2-(*N,N*-dimethylamino)-2'-bromobiphenyl (1.104 g, 4.0 mmol).[15] The flask was purged with argon and ether (18 mL) was added *via* syringe. The resulting solution was cooled to –78 °C and *n*-butyllithium in hexanes (1.6 M, 2.75 mL, 4.4 mmol) was added dropwise with stirring. The mixture was stirred at –78 °C for 30 min, then warmed to 0 °C. Di-*t*-butylchlorophosphine (0.96 mL, 5.0 mmol) was added *via* syringe, and the mixture was allowed to slowly warm to room temperature overnight (17 h). The mixture was quenched with saturated aqueous ammonium chloride (10 mL), diluted with ether (40 mL), and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (1 x 20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting oil was taken up in a small amount of hot methanol (ca. 10 mL), the bottom of the flask was scratched with a spatula, and crystallization was allowed to occur slowly

in a –20 °C freezer. The resulting crystals were washed with cold methanol and dried under vacuum to afford 683 mg (50%) of a white solid, mp 116–117 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.75 (m, 1H), 7.40–7.26 (m, 4H), 7.00–6.90 (m, 3H), 2.44 (s, 6H), 1.26 (d, 9H, J = 11.4 Hz), 0.90 (d, 9H, J = 11.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 25.3; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.53, 151.5, 150.3, 149.8, 137.1, 137.0, 136.9, 136.7, 135.6, 135.5, 132.7, 131.0, 130.9, 128.7, 127.8, 125.2, 120.9, 117.4, 43.2, 33.4, 33.1, 31.5, 31.3, 31.1, 30.0, 29.8 (observed complexity due to P–C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2941, 1416, 947, 745. Anal. Calcd for $C_{22}H_{32}NP$: C, 77.38; H, 9.45. Found: C, 77.16; H, 9.56.

2-(Di-*t*-butylphosphino)biphenyl (4).[5a] An oven-dried round-bottomed flask equipped with a magnetic stirbar and a rubber septum was allowed to cool to rt under an argon purge. The flask was charged with magnesium turnings (617 mg, 25.4 mmol) and a small crystal of iodine. The flask was purged with argon and a solution of 2-bromobiphenyl (5.38 g, 23.1 mmol) in THF (40 mL) was added. The mixture was heated to reflux with stirring for 2 h, then allowed to cool to rt. The septum was removed and anhydrous copper (I) chloride (2.40 g, 24.2 mmol) was added. The flask was capped with the septum and purged with argon for 2 min. Di-*t*-butylchlorophosphine (5.0 g, 27.7 mmol) was added via syringe, and the mixture was heated to reflux with stirring for 8 h. The mixture was cooled to rt and diluted with 1:1 hexanes:ether (200 mL). The resulting suspension was filtered, and the solids were washed with hexanes (60 mL). The solid material was transferred to a flask containing 1:1 hexane:ethyl acetate (150 mL) and water (100 mL) and 30% aqueous ammonium hydroxide (60 mL) were added. The resulting slurry was stirred at rt for 5 min then transferred to a separatory funnel. The layers were separated and the organic phase was washed with brine (100 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting solid was recrystallized from methanol (2 crops

of crystals were collected) to afford 4.46 g (67%) of a white solid, mp 86–86.5 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.85 (m, 1H), 7.40–7.21 (m, 8H), 1.15 (d, 18H, J = 11.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 18.7; ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 150.9, 143.6, 143.5, 135.6, 135.2, 135.0, 130.5, 130.4, 130.1, 128.3, 127.0, 126.7, 126.5, 126.2, 126.0, 125.6, 32.7, 32.4, 30.8, 30.6 (observed complexity due to P–C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2956, 1459, 1362, 1173. Anal. Calcd for $C_{20}H_{27}P$: C, 80.50; H, 9.12. Found: C, 80.67; H, 9.36.

***o*-(Dicyclohexylphosphino)biphenyl (5).** An oven-dried round-bottomed flask equipped with a magnetic stirbar and a rubber septum was allowed to cool to rt under an argon purge. The flask was charged with 2-bromobiphenyl (0.69 mL, 4.0 mmol) and THF (10 mL), and cooled to -78 °C in a dry ice/acetone bath. *n*-Butyllithium in hexanes (1.6 M, 2.75 mL, 4.4 mmol) was added dropwise with stirring. The resulting yellow solution was stirred at –78 °C for 45 min, during which time a yellow precipitate formed. A solution of dicyclohexylchlorophosphine (1.16 g, 5.0 mmol) in THF (2 mL) was added to the mixture dropwise at –78 °C, and the resulting solution was stirred at –78 °C for 15 min. The solution was then warmed to 0 °C in an ice water bath and allowed to warm slowly to rt overnight (14 h). The reaction was quenched with saturated aqueous ammonium chloride (10 mL), diluted with ether (50 mL), and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to give a colorless oil. Methanol (5 mL) was added, and a white precipitate formed. The material was then recrystallized from hot methanol (two crops of crystals were collected) to afford 994 mg (71%) of a white solid, mp 103 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.51 (m, 1H), 7.40–7.10 (m, 8H), 1.95–1.45 (m, 13H), 1.35–0.95 (m, 9H) ; ^{31}P NMR (121 MHz, $CDCl_3$) δ –12.7; ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 150.4,

142.9, 142.8, 134.1, 133.8, 132.8, 130.61, 130.55, 130.5, 130.2, 1301, 128.1, 127.3, 127.14, 127.05, 126.7, 126.4, 34.7, 34.5, 30.5, 30.2, 29.3, 29.1, 27.3, 27.2, 27.1, 26.4 (observed complexity due to P–C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2916, 1441, 749. Anal. Calcd for $C_{24}H_{31}P$: C, 82.25; H, 8.92. Found: C, 82.18; H, 9.04.

2-Dicyclohexylphosphino-2'-methylbiphenyl (6). A flame-dried flask was cooled to rt under an argon purge and charged with tetrakis(triphenylphosphine)palladium (425 mg, 0.37 mmol), sodium carbonate (3.9 g, 36.8 mmol), and *o*-tolylboronic acid (1.0 g, 7.36 mmol). The flask was purged with argon and a degassed mixture of DME (60 mL), water (18 mL), and ethanol (3 mL) was added to the flask *via* cannula. 1-Bromo-2-iodobenzene (1.13 mL, 8.83 mmol) was added to the flask *via* syringe and the mixture was heated to 90 °C for 42 h. The mixture was cooled to rt, diluted with ether (50 mL) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with aqueous sodium hydroxide (3 x 75 mL). The organic layer was concentrated *in vacuo* and the crude material was dissolved in 1:1 ether:dichloromethane (200 mL), washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 1.57 g of 2-bromo-2'-methylbiphenyl which contained ~5% of 2-bromoiodobenzene as judged by GC analysis. This material was used without further purification.

An oven-dried Schlenk flask was cooled to rt under an argon purge and charged with 2-bromo-2'-methylbiphenyl (682 mg, 2.76 mmol) and THF (7 mL). The mixture was cooled to –78 °C with stirring and *n*-butyllithium (1.6 M, 1.9 mL, 3.04 mmol) was added dropwise. The mixture was stirred at –78 °C for 70 min, then a solution of dicyclohexylchlorophosphine (803 mg, 3.45 mmol) in THF (2 mL) was added dropwise at –78 °C *via* syringe. The mixture was stirred at –78 °C for 20 min,

warmed to 0 °C and stirred for 20 min, then warmed to rt and stirred for 18 h. The mixture was quenched with saturated aqueous ammonium chloride (5 mL), diluted with ether (50 mL), and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was crystallized from ethanol to afford 754 mg (65% overall yield) of the title compound as a white solid, mp 107–109 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.56 (s, br, 1H), 7.37–7.30 (m, 2H), 7.28–7.10 (m, 4 H), 7.06 (d, 1H, J = 7.3 Hz), 2.06 (s, 3H), (1.99–1.80 (m, 1H), 1.80–1.45 (m, 11H), 1.40–0.85 (m, 10H); ^{31}P NMR (121 MHz, $CDCl_3$) δ –10.97; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 149.5, 142.4, 142.3, 135.5, 134.5, 134.2, 132.5, 130.7, 130.0, 129.9, 129.3, 128.2, 127.2, 126.3, 124.5, 35.4, 35.2, 33.2, 33.0, 30.8, 30.6, 30.0, 29.8, 29.7, 29.6, 28.8, 28.7, 27.6, 27.44, 27.39, 27.2, 27.0, 26.4, 26.3, 20.7, 20.6 (observed complexity due to P–C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2927, 1445, 1177, 1007, 766. Anal. Calcd for $C_{25}H_{33}P$: C, 82.38; H, 9.13. Found: C, 82.11; H, 9.21.

2-Dicyclohexylphosphino-2'-isopropylbiphenyl (7). An oven-dried flask was cooled to rt under an argon purge and charged with 2-bromoisopropyl benzene (4.0 g, 20.0 mmol) and THF (80 mL). The solution was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (1.65 M, 12.7 mL, 21.0 mmol) was added dropwise. The mixture was stirred at –78 °C for 1 h, then transferred *via* cannula to a separate flask containing a solution of triisopropyl borate (9.2 mL, 40.0 mmol) in THF (40 mL) under argon which had been cooled to –78 °C. The reaction mixture was stirred at –78 °C for 15 min, then warmed to rt and allowed to stir overnight (14 h). Aqueous HCl (1 M, 250 mL) was added and the mixture was stirred at rt for 15 min. The mixture was basicified to pH 14 with aqueous NaOH (6 M) and the mixture was transferred to a

separatory funnel. The mixture was extracted with ether (100 mL), and the organic layer was discarded. The aqueous phase was acidified to ~pH 7 with aqueous HCl (1 M) and was extracted with ether (2 x 150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was precipitated from ether/pentane to give 2-isopropylphenylboronic acid (2.4 g) which was used without further purification.

An oven-dried flask was charged with the crude 2-isopropylphenylboronic acid (2.4 g), tetrakis(triphenylphosphine) palladium (840 mg, 0.61 mmol, 5 mol %), and K_3PO_4 (4.6 g, 21.9 mmol). The flask was purged with argon, then DMF (100 mL) and 2-bromoiodobenzene (1.88 mL, 14.6 mmol) were added *via* syringe. The mixture was heated to 100 °C for 48 h, then cooled to rt, diluted with ether (200 mL) and water (100 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (200 mL). The combined organic layers were washed with aqueous NaOH (1 M), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to give 2-bromo-2'-isopropylbiphenyl (1.5 g). The crude material was used without further purification.

An oven-dried flask was cooled to rt under an argon purge and charged with the crude 2-bromo-2'-isopropylbiphenyl (1.1 g, 4.0 mmol), and THF (10 mL). The mixture was cooled to –78 °C and a solution of *n*-butyllithium in hexanes (1.6 M, 2.8 mL, 4.4 mmol) was added dropwise. The mixture was stirred at –78 °C for 1 h, then a solution of dicyclohexylchlorophosphine (1.16 g, 5.0 mmol) in THF (2 mL) under argon was added dropwise. The mixture was stirred at –78 °C for 15 min, then warmed to rt and stirred for 20 h. Aqueous ammonium chloride (10 mL) was added, and the mixture was diluted with ether (50 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with ether (20 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in*

vacuo. The crude material was crystallized from ethanol to afford 877 mg (~11% overall yield from 2-isopropylbromobenzene) of a white crystalline solid, mp 104 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (s, br, 1H), 7.36–7.10 (m, 6H), 7.00 (d, 1H, J = 7.5 Hz), 2.65 (p, 1H, J = 6.8 Hz), 1.99–1.85 (m, br, 1H), 1.75–1.45 (m, 11H), 1.28–0.85 (m, 17H); ^{31}P NMR (121 MHz, $CDCl_3$) δ –12.75; ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 149.5, 146.2, 141.15, 141.07, 134.9, 134.7, 132.7, 132.6, 130.9, 130.4, 130.3, 127.9, 127.6, 126.3, 124.7, 124.3, 35.8, 35.6, 33.9, 33.7, 30.9, 30.8, 30.3, 30.0, 29.9, 29.7, 29.6, 29.5, 28.9, 28.8, 27.6, 27.5, 27.4, 27.3, 27.2, 27.0, 26.5, 26.4, 25.3, 22.6 (observed complexity due to P–C splitting; definitive assignments have not yet been made); IR (neat, cm^{-1}) 2921, 1443, 1003, 753. Anal. Calcd for $C_{27}H_{37}P$: C, 82.61; H, 9.50. Found: C, 82.35; H, 9.55.

***o*-(Di-*t*-butylphosphino)cyclohexylbenzene (8).** An oven-dried Schlenk flask was allowed to cool to room temperature under an argon purge, and was charged with 1,2-dibromobenzene (1.2 mL, 10.0 mmol), ether (20 mL), and THF (20 mL). The mixture was cooled to –119 °C with stirring using an ethanol/N_2 cold bath. A solution of *n*-butyllithium in hexanes (1.6 M, 5.8 mL, 9.3 mmol) was added slowly dropwise. The mixture was stirred at –119 °C for 45 min, then cyclohexanone (0.98 mL, 9.5 mmol) was added to the mixture. The mixture was stirred at –78 °C for 30 min, then warmed to room temperature and stirred for 17 h. The mixture was quenched with saturated aqueous ammonium chloride (20 mL), diluted with ether (50 mL), and poured into a separatory funnel. The layers were separated and the aqueous phase was extracted with ether (20 mL). The organic layers were combined and washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 1.91 g of 1-(*o*-bromophenyl)cyclohexanol which was judged to be ~86% pure by GC analysis. This material was used without further purification.

A round bottomed flask was purged with argon and charged with 1-(*o*-bromophenyl)cyclohexanol (1.78 g, 7.0 mmol), dichloromethane (28 mL), triethylsilane (1.5 mL, 9.1 mmol), and trifluoroacetic acid (1.1 mL, 14.7 mmol). The mixture was stirred at room temperature for 1.5 h, then was quenched with solid potassium carbonate (ca 2 g). The mixture was diluted with ether (50 mL) and transferred to a separatory funnel. The mixture was washed with saturated aqueous $NaHCO_3$ (50 mL), and the organic phase was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford a mixture of 1-bromo-2-cyclohexylbenzene and 1-(2-bromophenyl)cyclohexene. The crude material was placed into a round bottomed flask, and the flask was purged with argon. THF (2 mL) was added, and the mixture was cooled to 0 °C with stirring. A solution of BH_3 in THF (1 M, 7.0 mL, 7.0 mmol) was added dropwise to the mixture. The mixture was stirred at 0 °C for 1.5 h, then warmed to room temperature and stirred for 19 h. Acetic acid (4 mL) was added and the mixture was stirred at room temperature for 6 h. The mixture was then diluted with ether (50 mL) and poured into a separatory funnel. The mixture was washed with aqueous NaOH (1M, 50 mL), the layers were separated, and the aqueous phase was extracted with ether (50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 555 mg of 1-bromo-2-cyclohexylbenzene which was judged to be 93% pure by GC analysis. This material was used without further purification.

An oven-dried Schlenk flask was cooled to room temperature under an argon purge, and was charged with magnesium turnings (27 mg, 1.1 mmol), THF (1 mL), and 1,2-dibromoethane (8 µL). The mixture was stirred at room temperature for 10 min, then 1-bromo-2-cyclohexylbenzene (239 mg, 1.0 mmol) was added in one portion. The mixture was stirred at room temperature for 20 min, then immersed in a 60 °C oil bath for 15 min. The mixture was cooled to room temperature, the septum was

removed from the flask, and copper (I) chloride (104 mg, 1.05 mmol) was added. The flask was capped with the septum and purged with argon for 1 min. The flask was charged with di-*t*-butylchlorophosphine (0.23 mL, 1.2 mmol) and additional THF (1 mL). The mixture was immersed in a 60 °C oil bath with stirring for 26 h, then cooled to room temperature, filtered, and the solids were washed with 1:1 ether:hexanes (50 mL). The organic solution was poured into a separatory funnel and washed with 30% aqueous ammonium hydroxide solution (3x50 mL), and brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo.* The crude material was purified by flash chromatography on silica gel to afford the title compound as a white solid (141 mg), which was judged to be 92% pure by GC analysis. This material was recrystallized from methanol to afford 101 mg (~3% overall from 1,2-dibromobenzene) of the title compound as a white, crystalline solid, mp 101–102 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75–7.65 (m, 1H), 7.40–7.20 (m, 2H), 7.15–7.05 (m, 1H), 4.05–3.90 (m, 1H), 1.85–1.60 (m, 5H), 1.51–1.25 (m, 5H), 1.14 (d, 18H, *J* = 11.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 13.0; ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 155.4, 135.0, 134.7, 128.8, 126.34, 126.27, 123.85, 40.8, 40.3, 34.4, 32.3, 31.9, 30.7, 30.5, 26.7, 26.3; IR (neat, cm^{-1}) 2927, 1461, 1175, 768. Anal. Calcd for $C_{20}H_{33}P$: C, 78.90; H, 10.93. Found: C, 78.96; H, 11.31.

General procedure for the palladium-catalyzed amination of aryl chlorides using ligand 2: An oven-dried Schlenk flask or test tube fitted with a rubber septum was purged with argon and charged with $Pd_2(dba)_3$ (0.005 mmol, 1 mol % Pd), **2** (0.015 mmol, 1.5 mol %), and NaO*t*-Bu (1.4 mmol). The flask was purged with argon, and toluene (2.0 mL), the aryl chloride (1.0 mmol) and the amine (1.2 mmol) were added. The mixture was stirred in an 80 °C oil bath until the starting aryl chloride had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with ether (20 mL), filtered

through celite and concentrated *in vacuo*. The crude material was then purified by flash chromatography on silica gel.

***N*-Methyl-*N*-phenyl-*p*-methylaniline** (Table 1, entry 4).[16] The general procedure gave 189 mg (96%) of a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25–6.86 (m, 9H), 3.28 (s, 3H), 2.32 (s, 3H).

***N*-Methyl-*N*-phenyl-*p*-anisidine** (Table 1, entry 5).[17] The general procedure gave 204 mg (94%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–6.76 (m, 9H), 3.81 (s, 3H), 3.26 (s, 3H).

4-(4-Methoxyphenyl) morpholine (Table 1, entry 8).[16] The general procedure gave 172 mg (89%) of a tan solid; mp 72 ° C (lit. mp 73.3 °C):[16] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91–6.84 (m, 4H), 3.86 (t, 4H, J = 4.8 Hz), 3.78 (s, 3H), 3.06 (t, 4H, J= 4.5 Hz).

***N*-(4-Acetylphenyl)morpholine** (Table 1, entry 12).[18] An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (2.2 mg, 0.10 mmol), **2** (5.9 mg, 0.015 mmol), K_3PO_4 (297 mg, 1.4 mmol), and 4'-bromoacetophenone (199 mg, 1.0 mmol). The flask was purged with argon and DME (2 mL), and morpholine (0.10 mL, 1.2 mmol) was added. The mixture was heated to 80 °C with stirring until the reaction had stopped progressing (98 % consumption of the aryl halide was obtained after 39 h). The mixture was cooled to rt, diluted with 1/1 ether/ethyl acetate (50 mL), filtered through celite, and concentrated. The crude material was purified by flash chromatography on silica gel to afford 169 mg (82%) of a pale yellow solid, mp 93–94 °C (lit. mp 97–98 °C);[18] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, 2H, J = 9.1 Hz), 6.87 (d, 2H, J = 9.1 Hz), 3.86 (t, 4H, J = 4.8 Hz), 3.31 (t, 4H, J = 5.1 Hz), 2.54 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 196.4, 154.1, 130.2, 128.1, 113.2, 66.5, 47.5, 26.0; IR (neat, cm^{-1}) 2972, 1660, 1243, 1119, 818. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.31; H, 7.22.

***N*-(2,5-Xylyl)-hexylamine** (Table 1, entry 13).[16] The general procedure gave 201 mg (98%) of a pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (d, 1H, J = 7.5 Hz),6.47–6.43 (m, 2H), 3.38 (s, 1H, br), 3.13 (t, 2H, J = 7.2 Hz), 2.29 (s, 3H), 2.09 (s, 3H), 1.66 (p, 2H, J= 7.8 Hz), 1.45–1.30 (m, 6H), 0.91 (m, 3H).

Methyl-(4-*n*-hexylamino)benzoate (Table 1, entry 14).[19] An oven-dried Schlenk flask was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol %), **1** (9.6 mg, 0.015 mmol, 1.5 mol %), cesium carbonate (456 mg, 1.4 mmol), and methyl 4-chlorobenzoate (171 mg, 1.0 mmol) and was purged with argon. Toluene (2 mL), and *n*-hexylamine (0.16 mL, 1.2 mmol) was added and the mixture was heated to 100 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis (17 h). The mixture was cooled to rt, diluted with ether (30 mL), filtered through celite, and concentrated. The crude material was crystallized from hot hexanes to afford 203 mg (86%) of a white solid, mp 93–94 °C: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, J=8.7 Hz), 4.01 (s, br, 1H), 3.85 (s, 3H) 3.15 (t, 2H, J = 6.9 Hz), 1.70–1.50 (m, 3H), 1.45–1.28 (m, 5H), 0.90 (t, 3H, J = 6.6 Hz).

***N*-(4-Methylphenyl)-*p*-anisidine** (Table 1, entry 16).[20] The general procedure was employed using a reaction temperature of 100 °C to give 198 mg (93%) of a tan solid, mp 80–81 °C (lit. mp 84–85 °C):[20] ^1H NMR (300 MHz, $CDCl_3$) δ 6.98–7.05 (m, 4H), 6.80–6.86 (m, 4H), 5.37 (s, br 1H), 3.76 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 142.4, 136.7, 129.7, 129.3, 121.1, 116.6, 114.7, 55.6, 20.5; IR (neat, cm^{-1}) 3416, 2910, 1513, 1304, 815.

***N*-Benzyl-*p*-toluidine** (Table 1, entry 17).[21] The general procedure was employed using **1** as the ligand and 1.5 equiv. amine to give 177 mg (90%) of a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25–7.39 (m, 5H), 6.98 (d, 2H, J = 8.1 Hz), 6.56 (d, 2H, J = 8.5 Hz), 4.31 (s, 2H), 3.90 (br s, 1H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.9, 139.7, 129.7, 128.5, 127.4, 127.1, 126.7, 113.0, 48.6, 20.3; IR (neat, cm^{-1}) 3416, 3026, 1521, 807.

2,3',4',5-Tetramethyldiphenyl ether (the reaction shown in equation 2 using ligand **3**). An oven-dried resealable Schlenk flask was charged with sodium hydride (dry 95%, 36 mg, 1.4 mmol) in a nitrogen-filled glovebox. The flask was sealed and removed from the glovebox, then fitted with a rubber septum and purged with argon. Toluene (1 mL) was added, followed by a solution of 3,4-dimethylphenol (147 mg, 1.2 mmol) in toluene (2 mL). The mixture was stirred at room temperature for 2 min, then heated to 100 °C with stirring for 15 min. The reaction mixture was allowed to cool to room temperature, then the septum was removed and $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol, 1.5 mol % Pd) and **3** (7.7 mg, 0.0225 mmol, 2.25 mol %) were added. The flask was capped with the septum and purged with argon. 2-chloro-*p*-xylene (0.135 mL, 1.0 mmol) and additional toluene (1 mL) were added, and the flask was sealed with a teflon screwcap. The mixture was heated to 100 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis (19 h). The mixture was cooled to room temperature, diluted with ether (30 mL), filtered through celite, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 177 mg (78%) of the title compound as a colorless oil. See below for characterization data.

2,3',4',5-Tetramethyldiphenyl ether (the reaction shown in equation 2 using ligand **4**). An oven-dried resealable Schlenk flask was charged with sodium hydride (dry 95%, 36 mg, 1.4 mmol) in a nitrogen-filled glovebox. The flask was sealed and removed from the glovebox, then fitted with a rubber septum and purged with argon. 3,4-Dimethylphenol (147 mg, 1.2 mmol) and toluene (2.0 mL) were added and the resulting mixture was stirred at 100 °C for 15 min under argon. The reaction mixture was allowed to cool to room temperature, then the septum was removed and $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol, 1.5 mol % Pd), **4** (6.7 mg, 0.0225 mmol) were added. The flask was capped with the septum and purged with argon. 2-chloro-*p*-xylene (135 μL, 1.0 mmol) was added, then the flask was sealed with a teflon screwcap and the reaction mixture was stirred at 100 °C for 14 h. The mixture was allowed to cool to room temperature, then water (5 mL) and ether (40 mL) were added and the resulting solution was poured into a separatory funnel. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel to afford 175 mg (77%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, 1H, J = 7.5 Hz), 7.05 (d, 1H, J = 8.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.74 (d, 1H, J = 3.0 Hz), 6.70 (broad s, 1H), 6.64 (dd, 1H, J = 8.1, 3.0 Hz), 2.27 (s, 3H), 2.23 (s, 6H), 2.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 155.8, 154.7, 138.0, 136.9, 131.0, 130.42, 130.41, 126.4, 124.2, 119.9, 118.8, 114.7, 21.0, 20.0, 18.9, 15.8; IR (neat, cm^{-1}) 2923, 1495, 1256; Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.67; H, 8.03.

General procedure for room-temperature catalytic amination of aryl chlorides. An oven-dried resealabale Schlenk flask was evacuated and backfilled with argon. The flask was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1 mol %), **4** (6.0 mg, 0.02 mmol, 2 mol %), and NaO*t*Bu (135 mg, 1.4 mmol). The flask was evacuated and backfilled with argon, then capped with a rubber septum. Toluene (0.5 mL), the

aryl chloride (1.0 mmol) (aryl chlorides which were solids at room temperature were added as solids following the addition of NaO*t*Bu), the amine (1.2 mmol), and additional toluene (0.5 mL) were added through the septum. The septum was replaced with a teflon screwcap, the flask was sealed, and the mixture was stirred at room temperature until the starting aryl chloride had been completely consumed as judged by GC analysis. During the course of the reaction the mixture was observed to form a gel (at around 50% conversion) and then liquefy again as the reaction proceed to completion. Following the complete consumption of the aryl chloride starting material, the mixture was diluted with ether (20 mL), filtered through celite, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

***N*-Methyl-*N*-phenyl-*p*-toluidine** (Table 2, entry 1).[16] The general procedure was modified such that when the aryl halide had been completely consumed, the mixture was diluted with ether (50 mL) and transferred to a separatory funnel. The mixture was washed with aqueous HCl (1 M, 2x20 mL), washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel to give 197 mg (100%) of the title compound as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.19 (m, 2H), 7.15–7.09 (m, 2H), 7.02–6.82 (m, 5H), 3.28 (s, 3H), 2.32 (s, 3H).

***N*-(4-Methylphenyl)morpholine** (Table 2, entry 2).[16] The general procedure gave 166 mg (94%) of the title compound as a white solid, mp 47–48 °C (lit mp 48 °C):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 2H, J = 8.5 Hz), 6.84 (d, 2H, J = 8.2 Hz), 3.86 (t, 4H, J = 4.7 Hz), 3.11 (t, 4H, J = 4.6 Hz), 2.28 (s, 3H).

***N,N*-Dibutyl-*p*-toluidine** (Table 2, entry 3).[16] The general procedure was modified such that 2 mol % $Pd(OAc)_2$ and 3 mol % **4** were employed. When the aryl halide had been completely consumed, 30% H_2O_2 (1 mL) was added to the reaction mixture to

oxidize the phosphine (to facilitate purification). The mixture was stirred at room temperature for 5 min, then diluted with ether (20 mL) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with water (20 mL), and saturated aqueous $Fe(SO)_4$ (20 mL). The combined aqueous layers were extracted with ether; the organic extracts were combined and the aqueous layer was discarded. The combined organic extracts were extracted with aqueous HCl (1 M, 4x50 mL), the organic layer was discarded, and the aqueous extracts were combined and basicified to pH 14. The aqueous layer was extracted with ether (4x50 mL), and the combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered through a plug of silica gel, and concentrated *in vacuo* to afford 172 mg (79%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, 2H, J = 8.6 Hz), 6.57 (d, 2H, J = 8.6 Hz), 3.22 (t, 4H, J = 7.7 Hz), 2.23 (s, 3H), 1.56–1.48 (m, 4H), 1.37–1.29 (m, 4H), 0.94 (t, 6H, J = 7.4 Hz).

***N*-(2,5-Xylyl)pyrrolidine** (Table 2, entry 4).[17] The general procedure gave 169 mg (97%) of the title compound as a colorless oil which was determined to contain ≤1% of **4** as judged by ^{1}H NMR and GC analysis: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.99 (d, 1H, J = 7.5 Hz), 6.69–6.63 (m, 2H), 3.25–3.10 (m, 4H), 2.29 (s, 3H), 2.28 (s, 3H), 1.95–1.85 (m, 4H).

***N*-(2,5-Xylyl)benzylamine** (Table 2, entry 5). The general procedure was modified such that 2 mol % $Pd(OAc)_2$ and 4 mol % **4** were employed. When the aryl halide had been completely consumed, 30% H_2O_2 (2 mL) and THF (1 mL) was added to the reaction mixture. The mixture was stirred at room temperature for 5 min, then diluted with ether (20 mL) and transferred to a separatory funnel. The layers were separated and the organic layer was washed with water (20 mL), and saturated aqueous $Fe(SO)_4$ (20 mL). The combined aqueous layers were extracted with ether; the organic extracts were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was then purified by flash

chromatography on silica gel to afford 196 mg (99%) of the title compound as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41–7.26 (m, 5H), 6.96 (d, 1H, J = 7.3 Hz), 6.51–6.46 (m, 2H), 4.36 (s, 2H), 3.790 (s, br, 1H), 2.26 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 139.5, 129.9, 128.6, 127.6, 127.2, 118.9, 117.8, 110.8, 48.3, 21.5, 17.1; IR (neat, cm^{-1}) 3438, 1582, 1453, 795. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.14; H, 8.12.

***N*-(4-Methoxyphenyl)morpholine** (Table 2, entry 6).[16] The general procedure was modified such that 2 mol % $Pd(OAc)_2$ and 4 mol % **4** were employed. The procedure afforded 173 mg (90%) of the title compound as a white solid, mp 73–74 °C (lit mp 73.3 °C):[16] ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.81 (m, 4H), 3.88–3.85 (m, 4H), 3.78 (s, 3H), 3.08–3.05 (m, 4H).

***N*-(4-Cyanophenyl)morpholine** (Table 2, entry 7).[22] The general procedure gave 158 mg (84%) of the title compound as a white solid, mp 85 °C (lit mp 65–66 °C):[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, 2H, J = 9.1 Hz), 6.86 (d, 2H, J = 9.1 Hz), 3.87–3.84 (m, 4H), 3.29–3.26 (m, 4H).

***N*-(2-Methoxyphenyl)benzylamine** (Table 2, entry 8) The general procedure gave 211 mg (99%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.20 (m, 5H), 6.86–6.76 (m, 2H), 6.70–6.57 (m, 2H), 4.66 (s, br, 1H), 4.35 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.7, 139.5, 138.0, 128.5, 127.4, 127.0, 121.2, 116.5, 110.0, 109.3, 55.3, 47.9; IR (neat, cm^{-1}) 3425, 2937, 1511, 1027, 735. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.54; H, 6.79.

***N*-Methyl-*N*-(3,5-dimethoxyphenyl)aniline** (Table 2, entry 9). The general procedure gave 238 mg (98%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.26 (m, 2H), 7.10–7.01 (m, 3H), 6.12–6.06 (m, 3H), 3.73 (s, 6H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.3, 150.9, 148.6, 129.2, 122.3, 97.5, 92.4, 55.2, 40.3; IR (neat, cm^{-1}) 2939, 1586, 1150, 1065, 700. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.90; H, 7.01.

General Procedure for the catalytic amination of aryl chlorides at 80–110 °C.

An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with palladium acetate (0.5 mol %), **4** (1.0 mol %), NaO*t*Bu (1.4 equiv), and evacuated and backfilled with argon. The flask was capped with a rubber septum and toluene (2 mL/mmol halide), the aryl halide (1.0 equiv), and the amine (1.2 equiv) were added through the septum. The septum was replaced with a teflon screwcap, the flask was sealed, and the mixture was heated to 80 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis. The mixture was cooled to rt, diluted with ether (30 mL), filtered through celite, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

***N*-(4-Methylphenyl)hexylamine** (Table 3, entry 1).[16] The general procedure was conducted on a 2 mmol scale using 1.5 equiv amine. Following completion of the reaction, the mixture was cooled to room-temperature, diluted with ether (40 mL), and extracted with 1 M aqueous HCl (3x50 mL). The organic phase was discarded, and the aqueous layer was basicified to pH 14 with 6 M aqueous NaOH. The aqueous phase was extracted with ether (3 x 50 mL), and the ether layers were combined, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford 318 mg (83%) of a white solid, mp 37 °C (lit mp 37.1–37.3 °C).[16] This material contained 1% **4** as judged by GC and ^{1}H NMR analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (d, 2H, J = 8.89 Hz), 6.54 (d, 2H, J = 8.7 Hz), 3.45 (s, br, 1H), 3.07 (t, 2H, J= 7.5 Hz), 1.64–1.26 (m, 8H), 0.89 (m, 3H).

***N*-Benzyl-*p*-toluidine** (Table 3, entry 5). The general procedure was conducted on a 2 mmol scale using 1.5 equiv amine. The reaction was subjected to the same workup described above for *N*-(4-methylphenyl)hexylamine to afford 344 mg (87%) of a pale yellow oil. This material contained 1% **4** as judged by GC and ^{1}H NMR analysis. See above for NMR data.

***N,N*-Dibutyl-*p*-toluidine** (Table 3, entry 6). The general procedure using $Pd_2(dba)_3$ and **6** gave 193 mg (88%) of a pale yellow oil. See above for NMR data.

***N,N*-Dibutyl-*p*-toluidine** (Table 3, entry 6). The general procedure using $Pd_2(dba)_3$ and **7** gave 199 mg (91%) of a pale yellow oil. See above for NMR data.

***N*-Ethyl-*N*-phenyl-*p*-toluidine** (Table 3, entry 7).[23] The general procedure gave 196 mg (93%) of a pale yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25–7.18 (m, 4H), 7.11 (d, 2H, J = 8.3 Hz), 6.99–6.79 (m, 3H), 3.74 (q, 2H, J = 7.1 Hz), 2.32 (s, 3H), 1.20 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 145.0, 132.1, 130.0, 129.0, 123.4, 119.3, 118.2, 46.4, 20.8, 12.6; IR (neat, cm^{-1}) 2974, 1599, 1498, 1259, 810. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.25; H, 8.15.

***N*-(4-Methylphenyl)piperidine** (Table 3, entry 8).[16] The general procedure gave 149 mg (85%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, 2H, J = 8.4 Hz), 6.85 (d, 2H, J = 8.4 Hz), 3.09 (t, 4H, J = 5.4 Hz), 2.26 (s, 3H), 1.73–1.50 (m, 6H).

***N*-Methyl-*N*-phenyl-2,5-xylidene** (Table 3, entry 9).[7] The general procedure conducted on a 2 mmol scale gave 374 mg (89%) of a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.14 (m, 3H), 7.01–6.95 (m, 2H), 6.72–6.67 (m, 1H), 6.54–6.51 (m, 2H), 3.20 (s, 3H), 2.30 (s, 3H), 2.09 (s, 3H).

***N*-(2,5-Xylyl)-cyclohexylamine** (Table 3, entry 10). The general procedure gave 197 mg (97%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92 (d, 1H, J = 7.4 Hz), 6.45–6.40 (m, 2H), 3.35–3.25 (m, 2H), 2.28 (s, 3H), 2.08 (s, br, 5H), 1.80–1.55 (m, 3H), 1.45–1.10 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 136.6, 130.0, 118.6, 116.8, 110.9, 51.4, 33.6, 26.0, 25.0, 21.6, 17.1; IR (neat, cm^{-1}) 3427, 2927, 1520, 789. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.51; H, 10.78.

N-*p*-Anisidylpyrrolidine (Table 3, entry 16).[22] The general procedure gave 159 mg (90%) of a white solid, mp 40–41 °C (lit mp 40–41 °C):[22] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.84 (d, 2H, J = 9.1 Hz), 6.53 (d, 2H, J = 9.0 Hz), 3.76 (s, 3H), 3.28–3.20 (m, 4H), 2.02–1.90 (m, 4H).

***N*-(2-Methoxyphenyl)benzylamine** (Table 3, entry 21) The general procedure conducted on a 2 mmol scale gave 423 mg (99%) of the title compound as a colorless oil. See above for NMR data.

***N*-(2-Methoxyphenyl)pyrrolidine** (Table 3, entry 22) The general procedure conducted on a 2 mmol scale gave 314 mg (89%) of the title compound as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91–6.77 (m, 4H), 3.84 (s, 3H), 3.35–3.25 (m, 4H), 1.95–1.85 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 139.9, 121.0, 119.6, 115.4, 111.6, 55.5, 50.4, 24.6; IR (neat, cm^{-1}) 2960, 1596, 1503, 1229, 735. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53. Found: C, 74.63; H, 8.46.

Procedures for the Catalytic Amination of Aryl Chlorides at Low Catalyst Loadings

***N*-Methyl-*N*-phenyl-*p*-toluidine**[16] (Table 4, entry 1) An oven-dried Schlenk flask was evacuated and backfilled with Argon. The flask was charged with NaO*t*Bu (270 mg, 2.8 mmol), then evacuated and backfilled with argon and toluene (1 mL), 4-chlorotoluene (0.24 mL, 2.0 mmol), and *N*-methyl aniline (0.26 mL, 2.4 mmol) were added through a rubber septum. A separate flask was charged with $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol) and ligand **4** (12.0 mg, 0.04 mmol), and was purged with argon. Toluene (4 mL) was added, the mixture was stirred for 1 minute at rt, then 200 µL of this solution (0.05 mol % Pd, 0.1 mol % ligand **4**) was added to the Schlenk flask followed by additional toluene (1 mL). The septum was removed; the flask was sealed with a teflon screwcap and the mixture was stirred at rt for 2 minutes, then heated to 100 °C with stirring until the starting aryl chloride had been completely consumed as judged by GC analysis. The mixture was cooled to room-temperature, diluted with ether, and filtered through celite. The crude product was purified by flash chromatography on silica gel to give 378 mg (96%) of the title compound as a colorless oil. See above for NMR data.

***N*-(4-Methylphenyl)morpholine**[16] (Table 4, entry 2) An oven-dried Schlenk flask was evacuated and backfilled with Argon. The flask was charged with NaO*t*Bu (270 mg, 2.8 mmol), then evacuated and backfilled with argon and toluene (1 mL), 4-chlorotoluene (0.24 mL, 2.0 mmol), and morpholine (0.20 mL, 2.4 mmol) were added through a rubber septum. A separate flask was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and ligand **5** (7.0 mg, 0.02 mmol), and was purged with argon. THF (1 mL) was added, the mixture was stirred for 1 minute at rt, then 100 µL of this solution (0.05 mol % Pd, 0.1 mol % ligand **5**) was added to the Schlenk flask followed by additional toluene (1 mL). The septum was removed; the flask was sealed with a teflon screwcap and the mixture was stirred at rt for 2 minutes, then heated to 100 °C with stirring until the starting aryl chloride had been completely consumed as judged by GC analysis.

The mixture was cooled to room-temperature, diluted with ether, and filtered through celite. The crude product was purified by flash chromatography on silica gel to give 311 mg (88%) of the title compound as a white solid. See above for NMR data.

***N*-Methyl-*N*-phenyl-2,5-xylidene**[7] (Table 4, entry 3) An oven-dried Schlenk flask was evacuated and backfilled with Argon. The flask was charged with NaO*t*Bu (270 mg, 2.8 mmol), then evacuated and backfilled with argon and toluene (1 mL), 2-chloro-*p*-xylene (0.24 mL, 2.0 mmol), and *N*-methyl aniline (0.26 mL, 2.4 mmol) were added through a rubber septum. A separate flask was charged with $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol) and ligand **4** (12.0 mg, 0.04 mmol), and was purged with argon. Toluene (4 mL) was added, the mixture was stirred for 1 minute at rt, then 200 µL of this solution (0.05 mol % Pd, 0.1 mol % ligand **4**) was added to the Schlenk flask followed by additional toluene (1 mL). The septum was removed; the flask was sealed with a teflon screwcap and the mixture was stirred at rt for 2 minutes, then heated to 100 °C with stirring until the starting aryl chloride had been completely consumed as judged by GC analysis. The mixture was cooled to room-temperature, diluted with ether, and filtered through celite. The crude product was purified by flash chromatography on silica gel to give 391 mg (93%) of the title compound as a colorless oil. See above for NMR data.

General procedure for the catalytic amination of functionalized aryl chlorides

An oven-dried resealable Schlenk flask was evacuated and backfilled with argon. The flask was charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **4** (4.5 mg, 0.015 mmol), K_3PO_4 (297 mg, 1.4 mmol). The flask was evacuated and backfilled with argon and capped with a rubber septum. DME (2 mL), the aryl halide (1.0 mmol), and the amine (1.2

mmol) were added through the septum, the septum was removed, and the flask was sealed with a teflon screwcap. The mixture was heated to 80 °C with stirring until the starting aryl chloride had been completely consumed as judged by GC analysis. The mixture was cooled to room temperature, diluted with 1/1 ether/ethyl acetate (40 mL), filtered through celite, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

***N*-(4-Acetylphenyl)morpholine** (Table 5, entry 7).[18] The general procedure gave 187 mg (91%) of a pale yellow solid: mp 96-97 °C (lit. mp 97–98 °C).[18] See above for NMR data.

***N*-(4-Carbomethoxyphenyl)morpholine** (Table 5, entry 9).[15] The general procedure using ligand **5** gave 198 mg (90%) of a pale yellow solid, mp. 162-163 °C: (lit mp 152–154 °C)[15] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 2H, J = 9.1 Hz), 6.86 (d, 2H, J = 9.1 Hz), 3.87 (s, 3H), 3.87–3.84 (m, 4H), 3.30–3.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 154.1, 131.2, 120.2, 113.4, 66.6, 51.7, 47.6; IR (neat, cm^{-1}) 2970, 1700, 1115, 770. Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.18; H, 6.78.

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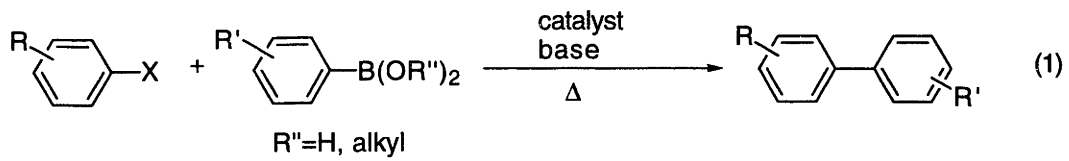
Chapter Ten:

Palladium-Catalyzed Suzuki Coupling of Aryl Chlorides

Introduction

After the discovery of new, highly active palladium-catalysts for C–N bond forming reactions of aryl chlorides, we proceeded to study their use in C–C bond forming reactions of aryl chlorides. We chose to first examine Suzuki coupling due to its widespread use in organic synthesis for the synthesis of biaryl compounds, as well as dienes and styrene derivatives.[1]

Suzuki coupling is the palladium-catalyzed cross-coupling of boronic acids or esters with aryl or vinyl halides (eq 1).[1] As shown in Scheme 1, the mechanism of this process involves oxidative addition of the aryl halide to a Pd(0) species, followed by

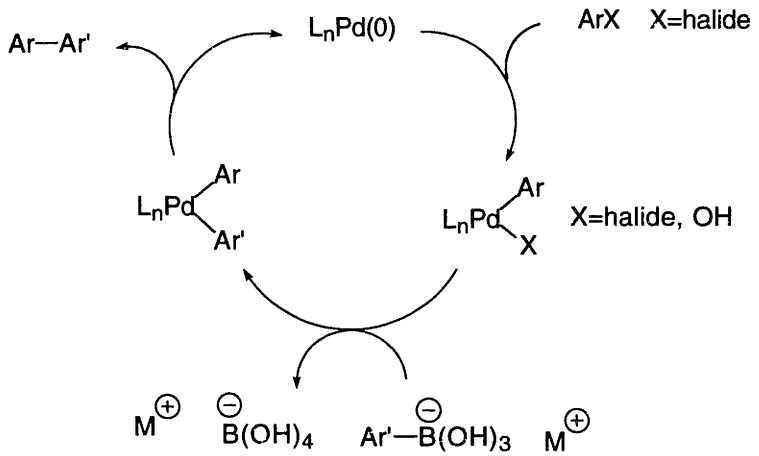


(1)

transmetallation of the aryl group from boron to palladium, and reductive elimination to form the desired product and regenerate the Pd(0) catalyst.[1,2] A base is required for these reactions, as transmetallation of the organoboron species is believed to take place from a four-coordinate ate complex.[1] Some mechanistic studies have also indicated that transmetallation occurs to a palladium hydroxide complex rather than a palladium halide complex.[1,3] Numerous bases have been used for this process, although Na_2CO_3 and K_3PO_4 are employed most frequently.[1] The pKa of a boronic acid (to form the ate complex) is in the range of ~9,[4] and strong bases such as alkoxides or hydroxides have been reported to improve reactivity in hindered systems.[1] The use of KF or CsF as bases for these reactions has also been described.[5] Most reactions are run under biphasic conditions, although a variety of organic solvents have also been employed in the absence of water.[1]

Triphenylphosphine-based catalyst systems are typically used for these reactions, although in some cases use of DPPF,[6] or ligandless conditions[7] give improved results.

Scheme 1



Although there have been several reports of Suzuki coupling reactions of aryl chlorides, many of these methods are limited by the requirement for high reaction temperatures and/or activated substrates.[8] Shen has reported that aryl chlorides bearing electron-withdrawing groups undergo Suzuki coupling reactions in the presence of palladium catalysts bearing either dppp or PCy_3 ligands at 100 °C, however these reactions are ineffective for the coupling of unactivated or electron-rich aryl chlorides.[8a] Related studies on the coupling of boronate ester substrates with aryl chlorides using PCy_3 ligated catalysts at 100 °C have been described by Firooznia, but yields are typically low to moderate for unactivated substrates.[8e] Bumagin has found that a ligandless palladium catalyst is effective for Suzuki reactions of aryl chlorides when sodium tetraphenyl borate is used as a coupling partner; poor yields are obtained at 100-140 °C with electron-rich aryl chlorides.[8c] Mitchell has reported the arylation of chloropyridine derivatives with boronic acids in good yields with dppb ligated palladium catalysts,[8d] and Cornils has used palladium catalysts bearing

sulfonated triphenylphosphine ligands for the reaction of 2-chlorobenzonitrile with *p*-tolylboronic acid in water,[8f] although detailed reaction conditions were not described in either of these reports. Beller and Herrmann have described the Coupling of 4-chloroacetophenone with phenylboronic acid in the presence of a palladacycle catalyst at 135 °C.[8b] Herrmann has also employed chelating, heterocyclic, stabilized carbene ligands for the Suzuki coupling of 4-chloroacetophenone with phenylboronic acid (60% yield was obtained after 48 h at 120 °C).[8i] Fu has recently reported the use of P(*t*-Bu)$_3$ as a ligand for palladium-catalyzed Suzuki coupling.[8g] This catalyst system is effective for reactions of both electron-rich and electron-poor aryl chlorides at 80 °C. Guram has recently reported an aryl(dicyclohexyl)phosphine catalyst for Suzuki coupling of aryl chlorides; although both electron-poor and electron-rich aryl chlorides afford coupled products in high yields, reaction temperatures of 100–130 °C are required.[8h]

A few protocols for nickel-catalyzed Suzuki coupling reactions have also been described.[9] Indolese[9a] and Miyaura[9b] independently discovered that (dppf)NiCl$_2$ is an effective catalyst for this process, however reaction temperatures of 70-95 °C were required, and sterically encumbered systems were not efficiently transformed. Genêt[9c] has recently reported a nickel catalyst which was effective for Suzuki coupling reactions of aryl chlorides with some hindered boronic acids, although 10 mol % (dppe)NiCl$_2$ and 50 mol % of a sulfonated triphenylphosphine ligand were required.

Examples of room-temperature Suzuki coupling reactions are relatively rare. Use of the highly toxic additive thallium hydroxide to promote room-temperature transformations was first reported by Kishi[10c] and subsequently studied in detail by Anderson.[10b] Ligandless systems for room-temperature Suzuki coupling have also been described, although their scope has not been well established.[10a] Bedford has reported the room-temperature Suzuki coupling of 4-bromoacetophenone with phenylboronic acid in the presence of a cyclometallated tris(2,4-di-*t*-

butylphenyl)phosphite palladium catalyst.[10d] No examples of room-temperature Suzuki coupling reactions of aryl chloride substrates have previously been demonstrated.

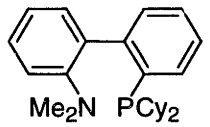
Although examples of Suzuki coupling to form very hindered biphenyls from aryl iodides or bromides have been reported,[10b,11] reactions of this type are often problematic.[1,10b,11f] In some cases the use of certain bases (TlOH,[10b] $Ba(OH)_2$,[11f] or K_3PO_4[11f]), or solvent combinations (e.g., toluene/water/ethanol 3/3/1)[11e] have been reported to give improved results, although the generality of these protocols is not clear. To the best of our knowledge, only one example of the synthesis of biphenyls bearing three ortho substituents from aryl chloride substrates has been previously reported.[9c]

The use of palladacycle catalysts for Suzuki coupling at very low catalyst loading (<0.1 mol % Pd) have been described by Beller and Herrmann,[8b] and Bedford.[10d] While in some cases these catalysts provide high turnover numbers for aryl bromide substrates, the best results are usually obtained with the highly activated 4-bromoacetophenone at very high temperatures (135 °C). The Beller-Herrmann catalyst is much less effective for Suzuki coupling of aryl chlorides, and the Bedford system has not been reported to function for aryl chloride substrates.

To avoid confusion, ligands in this chapter are referred to by the same numbers used in the previous chapter. Compounds **1**, **3**, and **8** from the previous chapter are not discussed in this chapter, hence these numbers are not used.

Results and Discussion

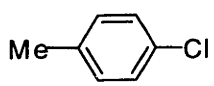
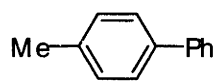
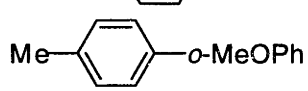
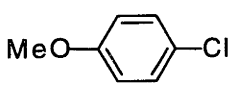
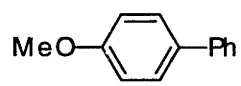
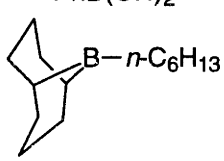
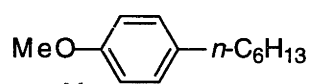
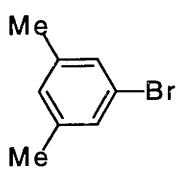
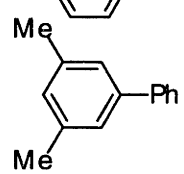
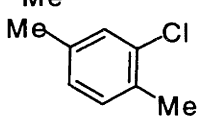
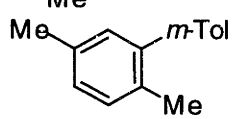
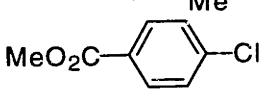
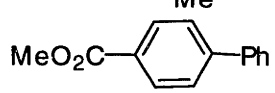
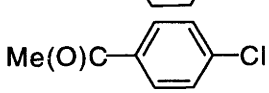
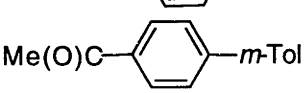
Catalysts based on ligand **2** (described in the previous chapter) proved to be highly effective for Suzuki coupling. Reactions of both aryl bromides and aryl



2

chlorides proceed in high yield at room temperature using the **2**/Pd(0) catalyst system (1-2 mol % Pd) and CsF[5] in dioxane solvent (Table 1, entries 2, 5, 7-10).[12] These conditions allow for the coupling of both electron-rich and electron-deficient aryl chlorides, and tolerate the presence of base-sensitive functional groups and ortho substituents. An aryl-alkyl coupling reaction of an aryl chloride using an alkylboron reagent generated *in situ* from 1-hexene and 9-BBN[6] was achieved at 50 °C (entry 6).

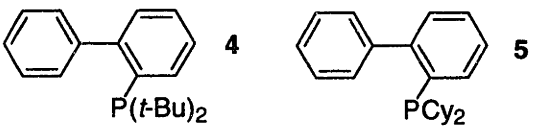
Table 1: Suzuki Coupling

Entry	Halide	Coupling Partner	Temp	mol% Pd	Yield	Product
1		$PhB(OH)_2$	100	0.5	96[b]	
2			rt	2.0	94	
3		*o*-$MeOPhB(OH)_2$	100	1.0	94[c]	
4		$PhB(OH)_2$	100	0.5	93[b]	
5			rt	2.0	92	
6			50	2.0	88[c]	
7		$PhB(OH)_2$	rt	1.0	92	
8		*m*-$TolB(OH)_2$	rt	2.0	94	
9		$PhB(OH)_2$	rt	2.0	90	
10		*m*-$TolB(OH)_2$	rt	2.0	92	

(a) Reaction Conditions: 1.0 equiv aryl halide, 1.5 equiv boron reagent, 3.0 equiv CsF, 0.5-2.0 mol % $Pd(OAc)_2$, 0.75-3.0 mol % **2** (1.5L/Pd), dioxane (3 mL/mmol halide). Reactions were complete in 19-30h; reaction times have not been minimized. (b) 2.0 equiv. K_3PO_4 used in place of CsF. (c) One of two runs only proceeded to 98% conversion.

Suzuki coupling reactions of electron-rich aryl chlorides could also be carried out using inexpensive K_3PO_4 with only 0.5 mol % palladium catalyst, although temperatures of 100 °C were required.

The effectiveness of **4** and **5** for Suzuki coupling was also studied. This work was done in collaboration with Dr. Robert Singer and Dr. Bryant Yang; experiments which they performed are identified in the footnotes of Tables 2–4.

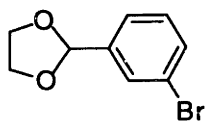
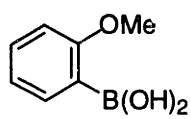
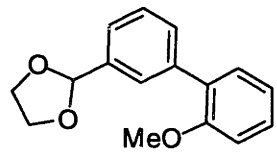
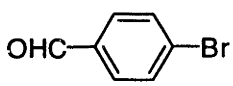
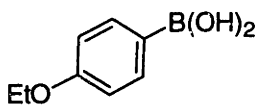
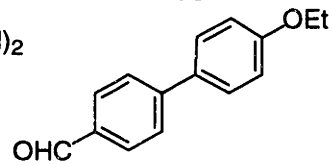
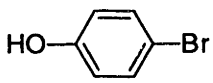
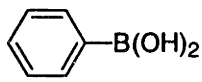
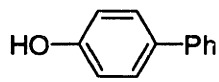
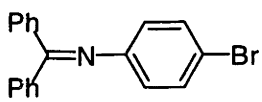
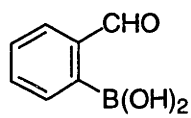
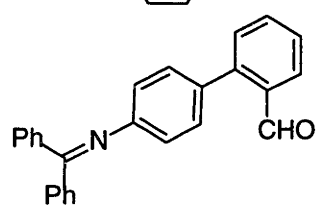
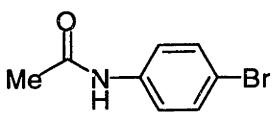
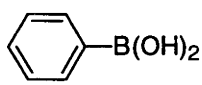
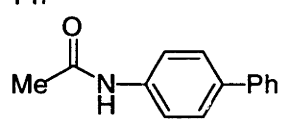
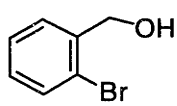
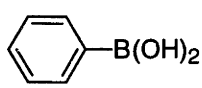
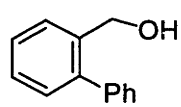
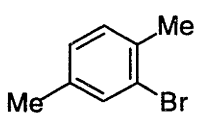
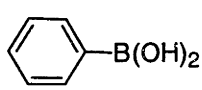
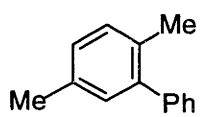
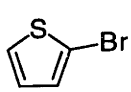
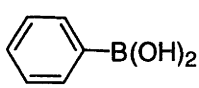
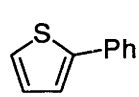
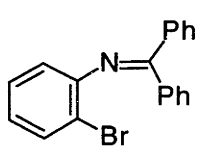
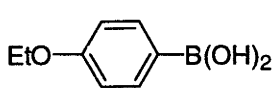
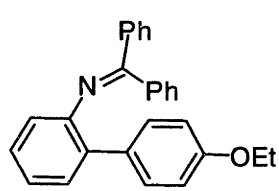


4 **5**

The reaction of a wide variety of aryl halides and boronic acids was examined using conditions optimized for room-temperature Suzuki coupling; the results are shown in Tables 2 and 3. A catalyst comprised of $Pd(OAc)_2$/**4** efficiently promotes the room-temperature Suzuki coupling of both electron-rich and -poor aryl bromides (Table 2) and chlorides (Table 3). As is usually the case in Suzuki coupling reactions conducted under non-aqueous conditions,[1,5] a wide variety of functional groups are tolerated, and the catalyst is also active for heterocyclic halide substrates. Aryl halides with ortho substituents are usually efficiently coupled, although heating was occasionally required for reactions to proceed to completion. Reactions of ortho-substituted halides were often more efficient if **5** was used in place of **4** (see below). Cross-coupling of chloropyridine derivatives, or aryl halides containing acidic protons were slow at room temperature, and heating was required for reactions to proceed to completion in a reasonable amount of time. The coupling of an aryl chloride with an alkyl 9-BBN derivative[6] (generated *in situ*) was effected at 65 °C (Table 3, entry 11).

During the course of our studies, we examined several different bases for the Suzuki coupling reactions. For room-temperature reactions, KF or CsF[5] were found to be the most effective of these. Other bases such as K_3PO_4, alkali metal carbonates, and sodium *t*-butoxide were substantially less effective at room-temperature, and alkali

Table 2: Room-Temperature Suzuki Coupling of Aryl Bromides[a]

Entry	Halide	Boronic Acid	Product	Ligand	Time (h)	Yield (%)
1				4 $(ArO)_3P$[b]	2.5 2.5	86[c] 83[c]
2				4 $(ArO)_3P$[b]	2 2	90 82
3				4	12	90[d,h]
4				4	20	89[i]
5				4	11	88[d,h]
6				4	11	83[d,h]
7				4 4 5	40 12 22	82[h] 94[e,h] 93[h]
8				4	3	98[i]
9				5	17	87[f,g]

(a) Reaction conditions: 1.0 equiv aryl bromide, 1.5 equiv boronic acid, 3.0 equiv KF, 1 mol % $Pd(OAc)_2$, cat ligand (2L/Pd), THF (1 mL/mmol aryl bromide, rt; reaction times have not been minimized. Yields in tables 1-4 represent isolated yields (average of two or more experiments) of compounds estimated to be ≥95 % pure as judged by ^1H NMR and GC analysis (known compounds) and combustion analysis (new compounds); (b) ArO_3P= Tris(2,4-di-*t*-butylphenyl)phosphite; (c) The reaction was conducted with 0.5 mol % $Pd(OAc)_2$; (d) The reaction was conducted at 50 °C; (e) The reaction was conducted at 45 °C; (f) The reaction was conducted at 80 °C; (g) K_3PO_4 (2.0 equiv) was used in place of KF; (h) This experiment was performed by Dr. Bryant Yang; (i) This experiment was performed by Dr. Robert Singer.

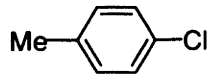
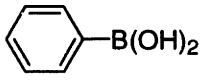
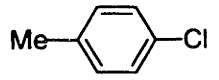
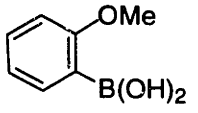
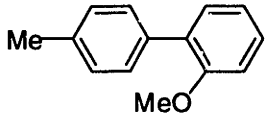
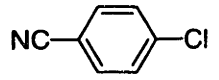
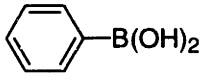
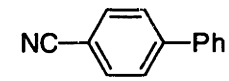
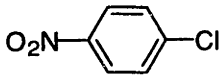
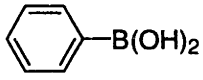
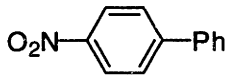
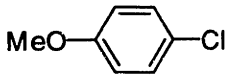
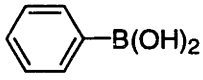
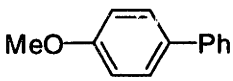
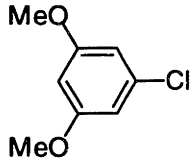
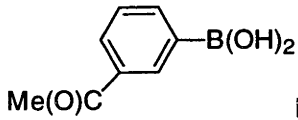
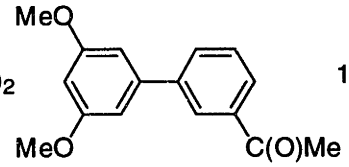
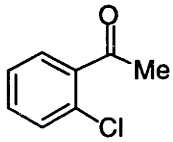
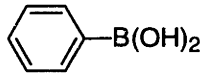
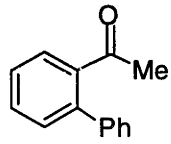
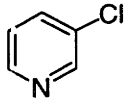
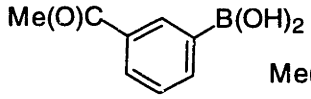
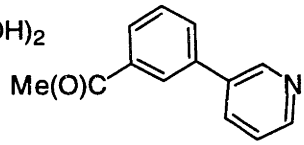
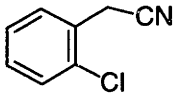
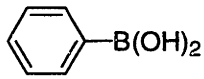
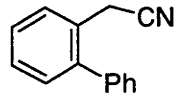
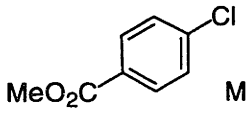
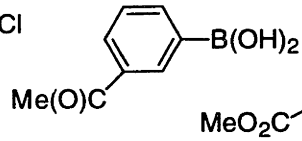
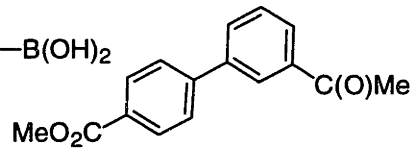
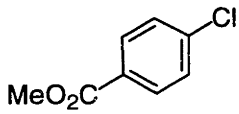
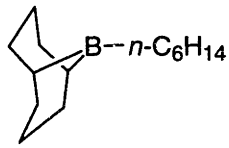
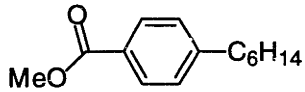
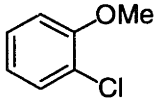
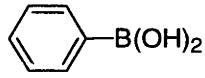
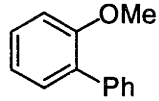
metal acetates failed to promote the reaction. Reactions conducted at room-temperature were most efficient in THF or dioxane. Use of DME or CH_3CN as solvent led to slower reactions, while reactions run in toluene or NMP gave very low conversions. Alcohols (MeOH, EtOH, *i*-PrOH) were poor solvents for the room-temperature Suzuki coupling, and their use led to reduction of the starting aryl halide.[13]

The correct combination of solvent and base was extremely important. While KF was ineffective in toluene, it was the most efficient promoter of room-temperature Suzuki coupling reactions in THF. Furthermore, while K_3PO_4 was less useful than KF for reactions in THF, reactions could be run at very low catalyst loadings using K_3PO_4 in toluene solvent at elevated temperatures (see below). Reactions conducted with low catalyst loadings were much less efficient in oxygenated solvents, such as THF, DME, or dioxane when K_3PO_4 was employed as the base. Use of biphasic solvent systems generally gave inferior results compared to reactions run without added water.

With respect to precatalyst, $Pd(OAc)_2$ was more effective than $Pd_2(dba)_3$; catalysts derived from the latter did not catalyze room-temperature couplings of aryl chlorides for the systems examined. The use of $Pd_2(dba)_3$ for reactions of aryl bromides at low catalyst loadings gave better results than $Pd(OAc)_2$ in THF at 65 °C, although $Pd(OAc)_2$ was a superior palladium source for reactions conducted in toluene at 100 °C.

Reactions of 5-chloro-1,3-dimethoxybenzene with phenylboronic acid at room-temperature proceeded more rapidly as the amount of boronic acid and KF added to the reaction mixture was increased; 21±1% conversion was obtained after 1 h with 1.5 equiv boronic acid and 3.0 equiv KF while 32±2% conversion was observed after the same period of time when 3.0 equiv boronic acid and 6.0 equiv KF was employed (after 4 h 66±2% and 96±3% conversion were observed, respectively). This trend

Table 3: Room-Temperature Suzuki Coupling of Aryl Chlorides[a]

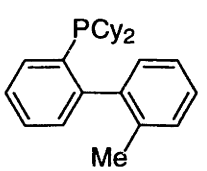
Entry	Halide	Boronic Acid	Product	mol% Pd	Time (h)	Yield (%)
1				1 0.5	6 19	95 97
2				1	24	95[e]
3				1	2	88
4				1 0.2	4 8	98[e] 98[e]
5				1 1.5	6 21	93[b,e] 92[e]
6				1	7	90
7				1	2.5	93[f]
8				1	9	94[c]
9				1	20	91
10				1	2	91
11				1	20	83[d,f]
12				1	24	96[f]

(a) Reaction conditions: 1.0 equiv aryl chloride, 1.5 equiv boronic acid, 3.0 equiv KF, cat $Pd(OAc)_2$, cat **4** (2L/Pd), THF (1 mL/mmol aryl chloride), rt; reaction times have not been minimized; (b) reaction conducted at 45 °C; (c) The reaction was conducted at 50 °C; (d) The reaction was conducted at 65 °C; (e) This experiment was performed by Dr. Bryant Yang; (f) This experiment was performed by Dr. Robert Singer.

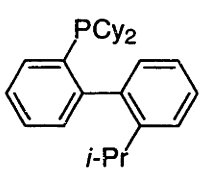
suggests that transmetallation may be the rate limiting step for this substrate combination. However, it is possible that the rate limiting step in the catalytic cycle may change when other substrates or reaction conditions are used.

A recent report described the use of a cyclometallated tris(2,4-di-*t*-butylphenyl)phosphite palladium complex as a highly active catalyst for the Suzuki coupling of aryl bromides.[10d] The authors reported that the cyclometallated complex was sufficiently active to promote the room-temperature Suzuki coupling of 4-bromoacetophenone with phenylboronic acid, and speculated that the palladacycle was probably being cleaved *in situ* to a non-cyclometallated catalyst.[10d] We examined the use of mixtures of palladium acetate and tris(2,4-di-*t*-butylphenyl)phosphite as a catalyst under our reaction conditions and found that this system gave results comparable to those obtained with **4**/$Pd(OAc)_2$ in room-temperature Suzuki couplings of aryl bromides (Table 2, entries 1-2), but was unreactive towards aryl chlorides. Even at 100 °C, the coupling of 4-chlorotoluene with phenylboronic acid catalyzed by 1 mol % palladium acetate and 2 mol % tris(2,4-di-*t*-butylphenyl)phosphite proceeded only to 5% conversion.

Using our conditions, substrates with more than one ortho substituent were substantially less reactive than other aryl halides, and the **4**/$Pd(OAc)_2$ catalyst system was usually not very effective for reactions of these types of substrates. However, catalysts employing ligands **2**, **5**, **6**, or **7** functioned well for reactions of 2,6-disubstituted halides, 2,6-disubstituted boronic acids, and the coupling of *o*-substituted halides with *o*-substituted boronic acids. Ligands **2**, **6** and **7** were equally effective for these reactions, while **5** provided catalysts which were slightly less efficient (Table 4,

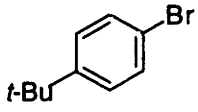
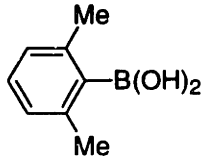
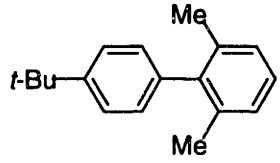
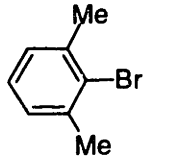
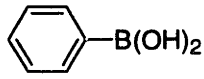
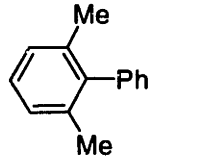
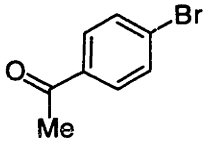
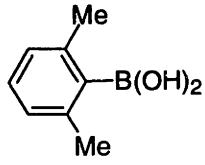
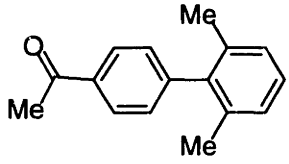
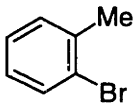
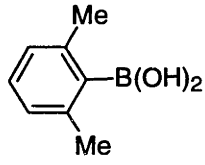
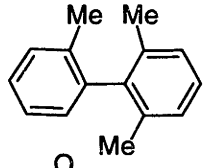
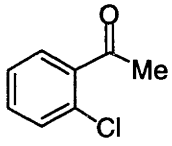
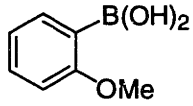
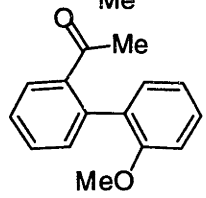
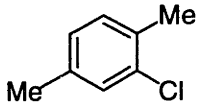
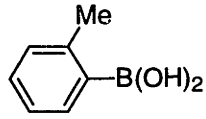
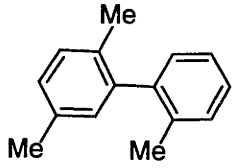
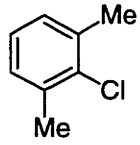
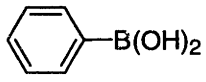
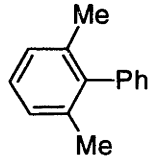
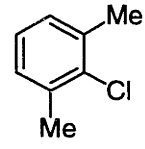
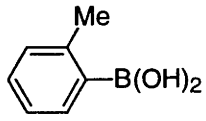
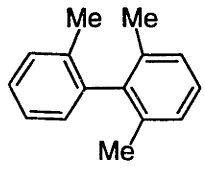


6



7

Table 4: Suzuki Coupling of Sterically Hindered Substrates[a]

Entry	Halide	Boronic Acid	Product	Ligand	Temp (°C)	Time (h)	Yield (%)
1				2	100	16	97[g]
2				4 5	65 rt	19 13	81[b,c,h] 92[b,c,h]
3				4	80	16	88[d,g]
4				2	100	20	86[g]
5				4	65	6	90
6				5	80	15	96
7				2 5	100 100	22 22	91 85[e]
8				7 5	100 100	3 17	92 88[f]

(a) Reaction conditions: 1.0 equiv aryl halide, 1.5 equiv boronic acid, 2.0 equiv K_3PO_4, 1 mol % $Pd(OAc)_2$, cat ligand (4L/Pd), toluene (3 mL/mmol halide); reaction times have not been minimized; (b) KF (3.0 equiv) was used in place of K_3PO_4; (c) A ratio of L/Pd=2/1 was used; (d) The reaction was conducted with 2 mol % $Pd(OAc)_2$; (e) One experiment proceeded to 93% conversion, the other proceeded to 97% conversion; (f) One experiment proceeded to 97% conversion; (g) This experiment was performed by Dr. Robert Singer; (h) This experiment was performed by Dr. Bryant Yang

entries 7-8). The best results in reactions of hindered substrates were usually obtained with K_3PO_4 as the base in toluene solvent. While L/Pd ratios of 2/1 were usually employed, occasionally it was found that use of a 3-4/1 ratio was beneficial.

While reactions which formed biaryls containing three ortho substituents were fairly efficient, reactions which formed tetra-ortho substituted biaryls were problematic and typically proceeded to <40% conversion.[14] Surprisingly, use of an increased quantity of catalyst did not give improved results.

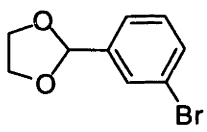
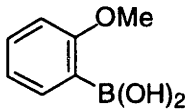
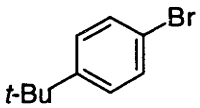
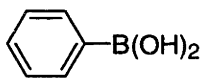
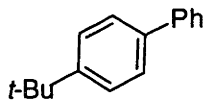
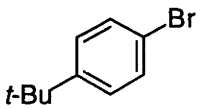
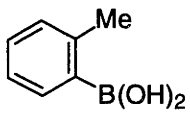
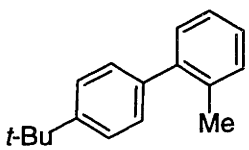
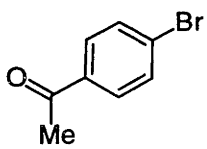
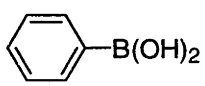
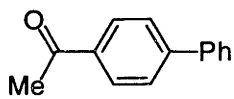
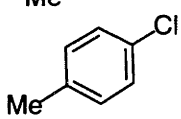
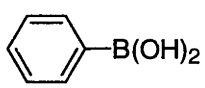
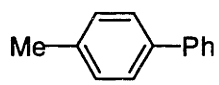
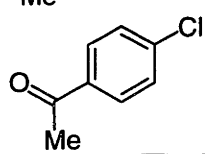
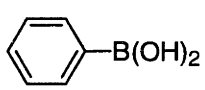
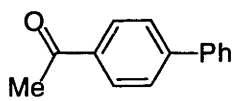
Studies to minimize the quantity of catalyst necessary further demonstrated the high activity of catalysts based on the dialkylphosphino(*o*-biphenyl) ligands. When **4** was used as the supporting ligand, reactions of electronically-neutral aryl bromides proceeded to completion with 0.025-0.05 mol % $Pd_2(dba)_3$ at 65 °C in THF, or with 0.1 mol % $Pd(OAc)_2$ in toluene at 100 °C in <24 h; the activated aryl chloride 4-chloroacetophenone was coupled with phenylboronic acid in 92% yield using 0.02 mol % Pd (Table 5, entry 6). Generally the best results were obtained with K_3PO_4 as the stoichiometric base in toluene solvent.

Higher turnover numbers were achieved when ligand **5** was employed in place of ligand **4**. Reactions of unactivated aryl bromides proceeded to completion with 0.005 mol % Pd (Table 5, entries 1-3), while the coupling of 4-chlorotoluene proceeded to 99% conversion (93% isolated yield) with 0.05 mol % Pd (Table 5, entry 5). Tris(2,4-di-*t*-butylphenyl)phosphite proved to be inferior to **5** for the coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid when a catalyst loading of 0.001 mol % Pd was employed (Table 5, entry 2); the reaction catalyzed by Pd/**5** proceeded to an average of 92% conversion (93% avg. GC yield) while the Pd/phosphite catalyst system afforded an average conversion of 43% (44% avg. GC yield); the reaction was only slightly improved with 0.005 mol % of the Pd/phosphite catalyst (52% conversion, 54% GC yield). Interestingly, the reaction of 1-bromo-4-*t*-butylbenzene with *o*-

tolylboronic acid proceeded to 89% conversion (88% GC yield) under these conditions (entry 3).

Remarkably low catalyst loadings could be used for the cross-coupling of 4'-bromoacetophenone with phenylboronic acid. Previous reports have described

Table 5: Suzuki Coupling at Low Catalyst Loading

Entry	Halide	Boronic Acid	Product	mol% Pd	Ligand	Time (h)	Yield (%)
1				0.005	5	18	87
2				0.1 0.05 0.02 0.005 0.001 0.001 0.005	4 4 4 5 5 ArO_3P ArO_3P	20 24 26 16 20 20 24	96[b,c,d] 94[b,c,d,e] 92 93 92[f,h] 43[f,i,j] 54[f,j,l]
3				0.1 0.005 0.005	4 5 ArO_3P	25 20 24	94[b,c,d] 96 88[f,j,m]
4				0.001 0.001 0.000001	4 – 4	19 19 24	96 100[f] 89[k]
5				0.1 0.05	4 5	25 25	95 94[g]
6				0.02	4	23	92

(a) Reaction conditions: 1.0 equiv aryl halide, 1.5 equiv boronic acid, 2.0 equiv K_3PO_4, cat $Pd(OAc)_2$, cat ligand (2L/Pd), toluene (3 mL/mmol halide), 100 °C; reaction times have not been minimized. All reactions proceed to completion unless otherwise noted; (b) $Pd_2(dba)_3$ used in place of $Pd(OAc)_2$; (c) THF used in place of toluene; (d) The reaction was conducted at 65 °C; (e) CsF (3.0 equiv) used in place of K_3PO_4; (f) GC yield; (g) The reaction proceeded to 99% conversion; (h) The reaction proceeded to 92% (average) conversion; (i) The reaction proceeded to 44% (average) conversion; (j) ArO_3P=tris(2,4-di-*t*-butylphenyl)phosphite; (k) Of two experiments, one proceeded to only 99% conversion; (l) The reaction proceeded to 52% (average) conversion; (m) The reaction proceeded to 89% (average) conversion.

catalyst systems which provide 74,000 or 1,000,000 turnovers for this reaction at 135 °C.[8b,10d] We were able to reproducibly obtain 100,000,000 turnovers in <24 h at 100 °C using the (*o*-biphenyl)P(*t*-Bu)$_2$ catalyst system for this reaction; a control experiment conducted in the absence of a phosphine ligand showed that 100,000 turnovers could be obtained using only Pd(OAc)$_2$ as the catalyst for this reaction. These exceptionally high turnover numbers were only obtained for this substrate combination suggesting that it is not a useful benchmark for new catalysts in Suzuki couplings.

It is clear that catalysts supported by ligands **2**, **4** or **5** are substantially more active for Suzuki coupling than catalysts based on triarylphosphines or trialkylphosphines which have been previously described.[1] The efficiency of catalysts based on **4** or **5** is most likely due to the combination of a number of factors. The electronic properties of the ligand are certainly of importance, as most triarylphosphines are not sufficiently electron-rich to promote the oxidative addition of aryl chlorides, particularly at room temperature.[15,16] However, previous studies have shown that electron-rich trialkylphosphines such as PCy$_3$ are rather inefficient ligands for the Suzuki coupling of electron-rich aryl halides;[8a,e] although these electron-rich ligands facilitate oxidative addition[17] they also decrease the rate of reductive elimination processes.[18]

Ligands **4** and **5** possess a fine balance of steric and electronic properties which allow for significantly accelerated oxidative addition while facilitating the other steps (transmetallation, reductive elimination) in the catalytic cycle. The basic phosphine group promotes oxidative addition, and binds tightly to the metal (relative to a triarylphosphine) to prevent precipitation of the catalyst. We believe that the ortho-phenyl moiety may provide a stabilizing interaction between the aromatic π-system and one of the metal d-orbitals (see chapter 9),[19] and increases the steric bulk around the metal, which promotes reductive elimination and favors monophosphine palladium species.[20a-c] This interaction also causes the aryl group of the substrate to be

oriented perpendicular to the coordination plane which may be the most favorable conformation for reductive elimination (see chapter 9).[20d]

Room-temperature Suzuki coupling reactions catalyzed by Pd/**4** were faster than those catalyzed by Pd/**5**. However, ligands **2**, **5**, **6**, and **7** were more effective for the Suzuki coupling of hindered substrates. Presumably this latter set of ligands are more efficient than **4** because their smaller size allows for relatively facile transmetallation to the $L_nPd(Ar)X$ intermediate when sterically encumbered aryl halides or boronic acids are used; the decreased steric properties of the ligand allows for the transformation of larger substrates. The ability of the electron-rich ligands to prevent precipitation of the palladium also contributes to their efficiency in reactions of hindered substrates.

In general, **5** gave better results at low catalyst loading than were obtained with **4**. The larger *o*-(di-*t*-butylphosphino)biphenyl ligand (**4**) may tend to dissociate from the metal more readily than the smaller *o*-(dicyclohexylphosphino)biphenyl ligand (**5**) to form unligated palladium complexes which are unstable and lead to the precipitation of the metal. Therefore, catalysts based on the smaller dicyclohexylphosphino moiety are more stable than those based on larger ligands and thus allow for higher turnover numbers in reactions run at low catalyst loadings.

The fact that significantly higher turnover numbers are obtained with the electron-rich dialkyl(biphenyl)phosphine ligands than with less electron-rich phosphine or phosphite ligands is due in part to the basic nature of **4** and **5**. These ligands bind to the metal more tightly than triarylphosphine derivatives and may help to increase catalyst lifetime by keeping the metal in solution for extended periods of time. Although steric influences on coordination number are important for reactivity,[20] the basic phosphine is necessary to promote the oxidative addition step in the catalytic cycle.[15,17] This is highlighted by the results obtained with the tris(2,4-di-*t*-butylphenyl)phosphite ligand. While the steric bulk of the phosphite ligand may lead to

pathways favoring the more reactive L_1 palladium complexes, it is not as electron-rich as **2-7**, and is ineffective as a ligand for Suzuki coupling reactions of aryl chloride substrates.

In conclusion, we have developed a new, highly active catalyst system for Suzuki coupling of aryl halides based on ligands **2**, **4** and **5**; ligands **4** and **5** are easily prepared in one step and are commercially available.[21] While the use of **4** generally gives faster reaction rates in room-temperature Suzuki couplings, **5** is more effective for hindered substrates and operates more efficiently at low catalyst loadings.

Experimental Section

General Considerations. All reactions were carried out under an argon atmosphere in oven-dried glassware. Elemental analyses were performed by E & R Microanalytical Laboratory Inc., Parsippany, N.J. Toluene was distilled under nitrogen from molten sodium. THF was distilled under argon from sodium benzophenone ketyl. Unless stated otherwise, commercially obtained materials were used without purification. Aryl halides were purchased from Aldrich Chemical company except for 4-chloroacetophenone which was purchased from Fluka Chemical company. Tribasic potassium phosphate was purchased from Fluka Chemical company. Cesium fluoride was purchased from Strem Chemical company and was ground with a mortar and pestle before use. Cesium carbonate was obtained from Chemetal and was ground with a mortar and pestle before use. Phenylboronic acid, chlorodicyclohexylphosphine, palladium acetate, tris(dibenzylideneacetone)dipalladium(0), and *n*-butyllithium were purchased from Strem Chemical company. 2-Methoxyphenylboronic acid[22] and 3-methylphenylboronic acid[22] were prepared by lithiation of the corresponding halide and reaction with $B(OMe)_3$ according to a general literature procedure.[22] These

boronic acids were obtained in ~85–95% purity following crystallization from pentane/ether and were used without further purification. Trimethyl borate, triisopropyl borate, 9-BBN (0.5 M THF solution), anhydrous dioxane, anhydrous DME, dicyclohexylphenylphosphine, and 1-hexene were purchased from Aldrich Chemical company. Tetrakis(triphenylphosphine)palladium was prepared according to a literature procedure[23] or purchased from Strem Chemical Co. IR spectra reported in this chapter were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR *in situ* IR instrument. Yields in Tables 1 and 2 refer to isolated yields (average of two runs) of compounds estimated to be ≥95% pure as determined by ^{1}H NMR, and GC analysis or combustion analysis. The procedures described in this section are representative, thus the yields may differ from those given in Tables 1 and 2.

General procedure for the room-temperature Suzuki coupling of aryl halides using CsF and Ligand 2: An oven-dried resealable Schlenk flask was purged with argon and charged with $Pd(OAc)_2$ (0.02 mmol, 2 mol %), **2** (0.03 mmol, 3 mol %), the boronic acid (1.5 mmol), and cesium fluoride (3.0 mmol). The flask was purged with argon, and dioxane (3 mL) and the aryl halide (1.0 mmol) were added through a rubber septum. The septum was removed, the flask was sealed with a teflon screwcap and the mixture was stirred at room temperature until the starting aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then diluted with ether (20 mL) and poured into a separatory funnel. The mixture was washed with 1 M NaOH (20 mL), and the layers were separated. The aqueous layer was extracted with ether (20 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was then purified by flash chromatography on silica gel.

4-Methylbiphenyl (Table 1, entry 2).[24] The general procedure gave 157 mg (93 %) of a white solid, mp 45–46 °C (lit. mp 49-50 °C).[24] See below for data.

4-Methoxybiphenyl (Table 1, entry 5).[25] The general procedure gave 167 mg (91 %) of a white solid, mp 83–84 °C (lit. mp 87 °C).[25] See below for data.

4-Hexylanisole (Table 1, entry 6).[26] An oven-dried resealable Schlenk flask was capped with a rubber septum, cooled under an argon purge, charged with 1-hexene (0.19 mL, 1.5 mmol), and cooled to 0 °C. A solution of 9-BBN in THF (3 mL, 1.5 mmol, 0.5 M) was added, the flask was stirred at 0 °C for 15 min, then warmed to room temperature and stirred for 5 h. 4-Chloroanisole (0.12 mL, 1.0 mmol) was added, the septum was removed, and palladium acetate (4.4 mg, 0.02 mmol, 2 mol %), **2** (11.9 mg, 0.03 mmol, 3 mol %), and cesium fluoride (456 mg, 3.0 mmol) were added under a stream of argon. The septum was replaced and the flask was purged with argon for 30 s. Dioxane (2 mL) was added, the septum was removed, the flask was sealed with a teflon screw cap, and the mixture was stirred at rt for 2 min. The reaction mixture was then heated to 50 °C with stirring for 22 h, at which time GC analysis showed the aryl chloride had been completely consumed. The mixture was cooled to room temperature, diluted with ether (20 mL), and poured into a separatory funnel. The mixture was washed with 1 M aqueous NaOH (20 mL), the layers were separated, and the aqueous phase was extracted with ether (20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography to afford 170 mg (89%) of a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.6 Hz), 3.78 (s, 3H), 2.54 (t, 2H, J = 7.5 Hz), 1.54–1.60 (m, 2H), 1.28–1.35 (m, 6H), 0.88 (t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 135.0, 129.2, 113.6,

55.2, 35.0, 31.73, 31.70, 28.9, 22.6, 14.1; IR (neat, cm^{-1}) 2926, 1513, 1243, 1038, 822. Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.19; H, 10.62.

3,5-Dimethylbiphenyl (Table 1, entry 7).[27] The general procedure using 1 mol % $Pd(OAc)_2$ and 1.5 mol % **2** gave 171 mg (94%) of a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 6.8 Hz), 7.42 (t, 2H, J = 7.2 Hz), 7.31–7.34 (m, 1H), 7.21 (s, 2H), 7.00 (s, 1H), 2.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5, 141.3, 138.2, 128.9, 128.6, 127.2, 127.0, 125.1, 21.4; IR (neat, cm^{-1}) 3030, 1602, 849, 760. Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 91.98; H, 8.02.

2,5,3'-Trimethylbiphenyl (Table 1, entry 8).[28] The general procedure gave 192 mg (98%) of a colorless oil which contained 4% 3,3'-dimethylbiphenyl as determined by ^1H NMR: ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.28 (m, 1H), 7.04–7.16 (m, 6H), 2.39 (s, 3H), 2.34 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.1, 141.9, 137.5, 135.0, 132.1, 130.5, 130.2, 129.9, 127.85, 127.80, 127.3, 126.2, 21.4, 20.9, 19.9; IR (neat, cm^{-1}) 2949, 1451, 811, 703. Anal. Calcd for $C_{15}H_{15}$: C, 92.26; H, 7.74. Found: C, 92.34; H, 7.66.

Methyl 4-phenylbenzoate (Table 1, entry 9).[29] The general procedure (except using water for the aqueous workup in place of 1 M aqueous NaOH) gave 193 mg (91%) of a white solid, mp 113 °C (lit. mp 117–118 °C):[29] ^1H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, 2H, J = 8.3 Hz), 7.61–7.68 (m, 4H), 7.39–7.49 (m, 3H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 145.5, 139.9, 130.0, 128.8, 128.1, 127.2, 126.9, 52.0; IR (neat, cm^{-1}) 2945, 1710, 1270, 1112, 749. Anal. Calcd for $C_{14}H_{13}O_2$: C, 78.85; H, 6.14. Found: C, 79.04; H, 6.16.

4-Acetyl-3'-methylbiphenyl (Table 1, entry 10).[30] The general procedure gave 190 mg (90%) of a white solid, mp 84–86 °C (lit. mp 92 °C):[30] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (d, 2H, J = 8.5 Hz), 7.68 (d, 2H, J = 8.5 Hz), 7.33–7.44 (m, 3H), 7.20–7.26 (m, 1H), 2.64 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 145.8, 139.7, 138.5, 135.7, 128.9, 128.8, 127.9, 127.1, 124.3, 26.5, 21.4; IR (neat, cm^{-1}) 3019, 1683, 1270, 787. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.79; H, 6.92.

General procedure for K_3PO_4 promoted Suzuki coupling of aryl chlorides using ligand 2: An oven-dried resealable Schlenk flask was purged with argon and charged with $Pd(OAc)_2$ (0.01 mmol, 0.5 mol %), **2** (0.015 mmol, 0.75 mol %), the boronic acid (3.0 mmol), and K_3PO_4 (4.0 mmol). The flask was purged with argon, and dioxane (6 mL) and 4-chlorotoluene (2.0 mmol) were added through a rubber septum. The septum was removed, the flask was sealed with a teflon screw cap and the mixture was stirred at room temperature for 2 min, then heated to 100 °C with stirring until the starting aryl chloride had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with ether (20 mL) and poured into a separatory funnel. The mixture was washed with 1 M NaOH (20 mL), and the layers were separated. The aqueous layer was extracted with ether (20 mL), and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was then purified by flash chromatography on silica gel.

4-Methylbiphenyl (Table 1, entry 2).[28] The general procedure gave 319 mg (95%) of a white solid, mp 44–46 °C (lit. mp 49–50 °C):[28] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.8 Hz), 7.39–7.51 (m, 4H), 7.23–7.35 (m, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2, 138.4, 136.9, 129.4, 128.7, 126.94, 126.92, 21.0; IR (neat,

cm^{-1}) 3030, 1486, 822, 753. Anal. Calcd for $C_{13}H_{12}$: C, 92.81; H, 7.19. Found: C, 92.86; H, 7.15.

4-Methyl-2'-methoxybiphenyl (Table 1, entry 3).[31] The general procedure was conducted on a 1 mmol scale using 1 mol % $Pd(OAc)_2$, 1.5 mol % **2**, and 3 eq CsF in place of K_3PO_4 to give 196 mg (99%) of a white solid, mp 74–75 °C (lit. mp 70–72 °C),[31] ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.1 Hz), 7.21–7.33 (m, 4H), 7.16–7.04 (m, 2H), 3.81 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 136.5, 135.6, 130.7, 129.4, 128.6, 128.3, 120.8, 111.2, 55.5, 21.2; IR (neat, cm^{-1}) 2964, 1227, 1023, 757. Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 84.94; H, 7.36.

4-Methoxybiphenyl (Table 1, entry 4).[25] The general procedure gave 347 mg (94%) of a white solid, mp 83–84 °C (lit. mp 87 °C):[25] ^1H NMR (250 MHz, $CDCl_3$) δ 7.52–7.58 (m, 4H), 7.42 (t, 2H, J = 7.8 Hz), 7.26–7.38 (m, 1H), 6.97 (d, 2H, J = 6.7 Hz), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3; IR (neat, cm^{-1}) 3003, 1251, 1034, 834, 760. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 85.06; H, 6.72.

General Procedure for the Suzuki Coupling of Aryl Halides Using KF as base. An oven-dried resealable Schlenk flask was evacuated and backfilled with argon[32] and charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1.0 mol %), ligand **4** (6.0 mg, 0.020 mmol, 2.0 mol %), the boronic acid (1.5 mmol), and potassium fluoride (174 mg, 3.0 mmol). The flask was evacuated and backfilled with argon, and THF (1 mL) and the aryl halide (1.0 mmol) were added through a rubber septum (aryl halides which were solids at rt were added prior to the second evacuation/backfill cycle). The flask was sealed with a teflon screwcap, and the reaction mixture was stirred at rt until the

starting aryl chloride had been completely consumed as judged by GC analysis. The reaction mixture was diluted with ether (30 mL) and poured into a separatory funnel. The mixture was washed with aqueous NaOH (1 M, 20 mL), and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

2-Methoxy-3-(1,3-dioxolane)-biphenyl (Table 2, entry 1). The coupling of 2-(3-bromophenyl)-1,3-dioxolane with 2-methoxyphenylboronic acid was effected using the general procedure with 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % **4** to afford 215 mg (84%) of the title compound as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.55–7.50 (m, 1H), 7.43–7.40 (m, 2H), 7.38–7.28 (m, 2H), 7.06–6.96 (m, 2H), 5.59 (s, 1H), 4.17–4.01 (m, 4H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 138.5, 137.6, 0.8, 130.3, 130.2, 128.6, 127.8, 127.5, 124.8, 120.7, 111.1, 103.7, 65.1, 55.4; IR , cm^{-1}) 2887, 1598, 1239, 1100, 753. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.92; H, 6.49.

2-Methoxy-3-(1,3-dioxolane)-biphenyl (phosphite ligand used). The coupling of 2-(3-bromophenyl)-1,3-dioxolane with 2-methoxyphenylboronic acid was effected using the general procedure with 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % tris(2,4-di-*t*-butylphenyl)phosphite to afford 211 mg (82%) of the title compound as a colorless oil.

4-Formyl-4'-ethoxybiphenyl (Table 2, entry 2). The coupling of 4-bromobenzaldehyde with 4-ethoxyphenylboronic acid was effected using the general procedure with 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % **4** to afford 203 mg (90%) of the title compound as a white solid, mp 102–103 °C: ^1H NMR (300 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.92 (d, 2H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.3 Hz), 7.58 (d, 2H, J = 8.8 Hz), 6.99

(d, 2H, J = 8.8 Hz), 4.10 (q, 2H, J = 7.1 Hz), 1.45 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 159.5, 146.7, 134.7, 131.8, 130.2, 128.4, 126.9, 115.0, 63.6, 14.7; IR (neat, cm^{-1}) 2984, 1679, 1602, 1185, 822. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 80.02; H, 6.47.

4-Formyl-4'-ethoxybiphenyl (Phosphite ligand used). The coupling of 4-bromobenzaldehyde with 4-ethoxyphenylboronic acid was effected using the general procedure with 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % tris(2,4-di-*t*-butylphenyl)phosphite to afford 178 mg (79%) of the title compound as a white solid.

4-Methylbiphenyl (Table 3, entry 1).[24] The coupling of 4-chlorotoluene with phenylboronic acid was effected using the general procedure to afford 161 mg (96%) of the title compound as a white solid, mp 42–45 °C (lit mp 44–46 °C).[24] See above for NMR data.

4-Methylbiphenyl.[24] The coupling of 4-chlorotoluene with phenylboronic acid was effected using the general procedure with 0.5 mol % $Pd(OAc)_2$ and 1.0 mol % **4** to afford 161 mg (96%) of the title compound as a white solid.

4-Cyanobiphenyl (Table 3, entry 3).[33] The coupling of 4-chlorobenzonitrile with phenylboronic acid was effected using the general procedure to afford 156 mg (87%) of the title compound as a white solid, mp 86–87 °C (lit mp 82–84 °C):[33] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76–7.68 (m, 4H), 7.60–7.58 (m, 2H), 7.52–7.43 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 139.1, 132.5, 129.0, 128.6, 127.6, 127.4, 118.9, 110.8; IR (neat, cm^{-1}) 2227, 1605, 1485, 768. Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06. Found: C, 87.04; H, 5.06.

3-(3-Acetylphenyl)pyridine (Table 3, entry 8). The coupling of 3-chloropyridine with 3-acetylphenylboronic acid was effected using the general procedure with a reaction temperature of 50 °C to afford 181 mg (92%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (d, 1H, J = 2.3 Hz), 8.64 (d, 1H, J = 4.7 Hz), 8.18 (s, 1H), 8.00 (d, 1H, J = 7.7 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.79 (d, 1H, J = 7.7 Hz), 7.60 (t, 1H, J = 7.8 Hz), 7.43–7.39 (m, 1H), 2.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 149.0, 148.2, 138.4, 138.3, 135.7, 134.4, 131.5, 129.3, 127.9, 126.8, 123.6, 26.6; IR (neat, cm^{-1}) 3034, 1683, 1239, 791. Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62. Found: C, 79.12; H, 5.62.

2-Cyanomethylbiphenyl (Table 3, entry 9).[34] The coupling of 2-chlorobenzyl cyanide with phenylboronic acid was effected using the general procedure to afford 177 mg (92%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56–7.53 (m, 1H), 7.48–7.38 (m, 5H), 7.30–7.26 (m, 3H), 3.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 139.9, 130.4, 128.9, 128.6, 128.2, 127.7, 118.1, 22.0; IR (neat, cm^{-1}) 3061, 2250, 1482, 749. Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74. Found: C, 87.25; H, 5.60.

4-Carbomethoxy-3'-acetylbiphenyl (Table 3, entry 10). The coupling of methyl-4-chlorobenzoate with 3-acetylphenylboronic acid was effected using the general procedure to afford 229 mg (90%) of the title compound as a white solid, mp 109–110 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.12 (d, 2H, J = 8.3 Hz), 7.96 (d, 1H, J = 7.8 Hz), 7.82 (d, 1H, J = 6.5 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.57 (t, 1H, J = 7.7 Hz), 3.94 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 166.6, 144.3, 140.3, 137.7, 131.5, 130.1, 129.3, 129.1, 127.9, 126.9, 126.8, 52.0, 26.6; IR (neat, cm^{-1}) 3003, 1722, 1679, 1293, 1111, 768. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.96; H, 5.27.

General Procedure for the Suzuki Coupling of Aryl Halides Using K_3PO_4 as Base with ligands 4–7. An oven-dried resealable Schlenk flask was evacuated and backfilled with argon and charged with $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 1.0 mol %), ligand **4** (6.0 mg, 0.020 mmol, 2.0 mol %), the boronic acid (1.5 mmol), and K_3PO_4 (425 mg, 2.0 mmol). The flask was evacuated and backfilled with argon, and toluene (3 mL) and the aryl halide (1.0 mmol) were added through a rubber septum (aryl halides which were solids at rt were added prior to the second evacuation/backfill cycle). The flask was sealed with a teflon screwcap, and the reaction mixture was heated to 65 °C with stirring until the starting aryl halide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to rt, diluted with ether (30 mL) and poured into a separatory funnel. The mixture was washed with aqueous NaOH (1 M, 20 mL), and the aqueous layer was extracted with ether (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel.

2-(Diphenylketimine)-4'-ethoxybiphenyl (Table 2, entry 9). The coupling of *N*-(diphenylmethylene)-2-bromoaniline, with 4-ethoxyphenylboronic acid was effected using the general procedure with ligand **5** and a reaction temperature of 80 °C to afford 328 mg (87%) of the title compound as a yellow solid, mp 97–98 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 6.7 Hz), 7.49–7.30 (m, 3H), 7.20–6.90 (m, 8H), 6.86 (d, 1H, J = 7.9 Hz), 6.77 (d, 2H, J = 6.8 Hz), 6.65 (d, 2H, J = 7.0 Hz), 3.99 (q, 2H, J = 7.0 Hz), 1.39 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 157.4, 148.9, 139.3, 136.3, 132.2, 131.0, 130.3, 129.8, 129.1, 128.7, 128.2, 128.0, 127.3, 126.9, 63.2, 14.8; IR (neat, cm^{-1}) 2983, 1607, 1470, 1243, 1052. Anal. Calcd for $C_{27}H_{23}NO$: C, 85.91; H, 6.14. Found: C, 85.81; H, 6.08.

2-Methoxy-2'-acetylbiphenyl (Table 4, entry 5). The coupling of 2-chloroacetophenone with 2-methoxyphenyl boronic acid was effected using the general procedure to afford 201 mg (89%) of the title compound as a white solid, mp 83 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, 1H, J = 7.7 Hz), 7.54–7.49 (m, 1H), 7.42–7.26 (m, 4H), 7.06 (t, 1H, J = 7.3 Hz), 6.92 (d, 1H, J = 8.2 Hz), 3.73 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 155.8, 140.7, 136.7, 131.1, 130.8, 130.5, 129.9, 129.3, 127.3, 127.1, 121.0, 110.6, 55.0, 28.8; IR (neat, cm^{-1}) 3003, 1695, 1243, 757. Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.89; H, 6.02.

2,5-Dimethyl-2'-Methylbiphenyl (Table 4, entry 6). The coupling of 2-chloro-*p*-xylene with *o*-tolylboronic acid was effected using the general procedure with **5** as the supporting ligand and a reaction temperature of 80 °C to afford 185 mg (94%) of the title compound a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.04 (m, 6H), 6.93 (s, 1H), 2.33 (s, 3H), 2.06 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.7, 141.4, 135.8, 134.9, 132.6, 129.9, 129.7, 129.6, 129.2, 127.8, 127.0, 125.5, 20.9, 19.8, 19.3; IR (neat, cm^{-1}) 3041, 2921, 1482, 1032, 810. Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.68; H, 8.17.

2,6-Dimethylbiphenyl (Table 4, entry 7).[35] The coupling of 2-chloro-*m*-xylene with phenylboronic acid was effected using the general procedure with **2** as the supporting ligand and a reaction temperature of 100 °C to afford 164 mg (90%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.5–7.0 (m, 8H), 2.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 141.0, 136.0, 129.0, 128.4, 127.2, 127.0, 126.6. IR (neat, cm^{-1}) 3057, 3022, 1463, 1444, 768; Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 91.92; H, 7.87.

2,6-Dimethylbiphenyl.[35] The coupling of 2-chloro-*m*-xylene with phenylboronic acid was effected using the general procedure with **5** as the supporting ligand and a reaction temperature of 100 °C to afford 135 mg (85%) of the title compound as a colorless oil. A small amount of the starting aryl chloride (7%) was not consumed during the course of the reaction.

2,6-Dimethyl-2'-methyl biphenyl (Table 4, entry 8).[35] The coupling of 2-chloro-*m*-xylene with *o*-tolylboronic acid was effected using the general procedure with **7** as the supporting ligand and a reaction temperature of 100 °C to afford 180 mg (92%) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.24 (m, 3H), 7.22–7.12 (m, 3H), 7.06–7.03 (m, 1H), 2.00 (s, 3H), 1.98 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 140.4, 135.8, 135.5, 129.9, 128.7, 127.1, 126.9, 126.8, 126.0, 20.4, 19.4; IR (neat, cm^{-1}) 3060, 1583, 1462, 1120, 760. Anal. Calcd for $C_{15}H_{16}$: C, 91.78; H, 8.22. Found: C, 91.82; H, 8.27.

2,6-Dimethyl-2'-methyl biphenyl.[35] The coupling of 2-chloro-*m*-xylene with *o*-tolylboronic acid was effected using the general procedure with **5** as the supporting ligand and a reaction temperature of 100 °C to afford 174 mg (89%) of the title compound as a colorless oil.

General Procedure for the Suzuki Coupling of Aryl Halides at Low Catalyst Loadings (≤0.1 mol % Pd) An oven-dried resealable Schlenk flask was evacuated and backfilled with argon and charged with the boronic acid (1.5 mmol) and K_3PO_4 (2.0 mmol). The flask was evacuated and backfilled with argon, and THF (1.5 mL) and the aryl halide (1.0 mmol) were added through a rubber septum. A separate flask was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and ligand **4** (4.5 mmol, 0.015 mmol), and was purged with argon. THF (1 mL) was added, the mixture was stirred for

1 minute at rt, then 100 μL of this solution (0.1 mol % Pd, 0.15 mol % ligand **4**) was added to the Schlenk flask followed by additional THF (1.5 mL). The septum was removed; the flask was sealed with a teflon screwcap and the mixture was stirred at rt for 2 minutes, then heated to 65 °C with stirring until the starting aryl bromide had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to rt, diluted with ether (20 mL) and poured into a separatory funnel. The mixture was washed with aqueous NaOH (1 M, 20 mL), and the layers were separated. The aqueous layer was extracted with ether (20 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material was then purified by flash chromatography on silica gel to give

4-*t*-Butylbiphenyl[36] (0.1 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure to afford 199 mg (95%) of a glassy solid, mp 47–49 °C (lit mp 51–52 °C):[36b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58–7.51 (m, 4H), 7.46–7.38 (m, 4H), 7.30–7.26 (m, 1H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 141.1, 138.3, 128.7, 127.0, 126.9, 126.8, 125.7, 34.5, 31.4; IR (neat, cm^{-1}) 2961, 1486, 834, 764. Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.42; H, 8.69.

4-*t*-Butylbiphenyl[36] (0.05 mol % Pd, CsF as base). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with CsF (3.0 mmol) as the base and a 50 μL of a catalyst solution comprised of $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), ligand **4** (4.5 mmol, 0.015 mmol), in THF (1 mL) to afford 202 mg (96%) of a glassy solid.

4-*t*-Butylbiphenyl[36] (0.02 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 80 °C, and 20 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **4** (6.0 mg, 0.02 mmol), and THF (2 mL) to afford 196 mg (93 %) of a glassy solid.

4-*t*-Butylbiphenyl[36] (0.005 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **5** (7.0 mg, 0.02 mmol), and THF (10 mL) to afford 198 mg (94%) of a glassy solid.

4-*t*-Butylbiphenyl[36] (0.001 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 10 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **5** (7.0 mg, 0.02 mmol), and THF (10 mL). When the reaction was no longer progressing, the mixture was cooled to room-temperature and dodecane (0.23 mL) was added as an internal standard; GC analysis showed 93% conversion (96% GC yield).

4-*t*-Butylbiphenyl[36] (0.001 mol % Pd, K_3PO_4 as base, phosphite ligand). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 10 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(2,4-di-*t*-butylphenyl)phosphite (13.0 mg, 0.02 mmol), and THF (10 mL). When the reaction was no longer progressing, the mixture was cooled to room-temperature and

dodecane (0.23 mL) was added as an internal standard; GC analysis showed 40% conversion (42% GC yield).

4-*t*-Butylbiphenyl[36] (0.005 mol % Pd, K_3PO_4 as base, phosphite ligand). The coupling of 1-bromo-4-*t*-butylbenzene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(2,4-di-*t*-butylphenyl)phosphite (13.0 mg, 0.02 mmol), and THF (10 mL). When the reaction was no longer progressing, the mixture was cooled to room-temperature and dodecane (0.23 mL) was added as an internal standard; GC analysis showed 47% conversion (49% GC yield).

2-Methyl-4'-*t*-butylbiphenyl (0.1 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with *o*-tolylboronic acid was effected using the general procedure with 100 μL of a catalyst solution comprised of $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), ligand **4** (4.5 mmol, 0.015 mmol), and THF (1 mL) to afford 210 mg (94%) of a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 8.2 Hz), 7.27–7.22 (m, 6H), 2.29 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 141.9, 139.0, 135.4, 130.3, 129.9, 128.8, 127.0, 125.7, 124.9, 34.5, 31.4, 20.5; IR (neat, cm^{-1}) 2961, 1482, 1112, 838. Anal. Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 91.11; H, 9.21.

2-Methyl-4'-*t*-butylbiphenyl (0.005 mol % Pd, K_3PO_4 as base). The coupling of 1-bromo-4-*t*-butylbenzene with *o*-tolylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **5** (7.0 mg, 0.02 mmol), and THF (10 mL) to afford 216 mg (96%) of a glassy solid.

2-Methyl-4'-*t*-butylbiphenyl (0.005 mol % Pd, K_3PO_4 as base, phosphite ligand). The coupling of 1-bromo-4-*t*-butylbenzene with *o*-tolylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), tris(2,4-di-*t*-butylphenyl)phosphite (13.0 mg, 0.02 mmol), and THF (10 mL). When the reaction was no longer progressing, the mixture was cooled to room-temperature and dodecane (0.23 mL) was added as an internal standard; GC analysis showed 87% conversion (84% GC yield).

2-Methoxy-3-(1,3-dioxolane)-biphenyl (0.005 mol % Pd, K_3PO_4 as base). The coupling of 2-(3-bromophenyl)-1,3-dioxolane with *o*-methoxyphenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **5** (7.0 mg, 0.02 mmol), and THF (10 mL) to afford 223 mg (87%) of a glassy solid. See above for NMR data.

4-Acetylbiphenyl[29] (0.02 mol % Pd, K_3PO_4 as base, from the aryl chloride). The coupling of 4-chloroacetophenone with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 100 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **4** (6.0 mg, 0.02 mmol), and THF (5 mL) to afford 178 mg (91%) of the title compound as a white solid, mp 120–121 °C (lit mp 109–110 °C):[29] ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, 2H, J = 8.6 Hz), 7.71–7.62 (m, 4H), 7.50–7.40 (m, 3H), 2.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5, 145.7, 139.8, 135.9, 128.9, 128.8, 128.2, 127.2, 127.1, 26.5; IR (neat, cm^{-1}) 2999, 1679, 764. Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.62; H, 6.07.

4-Acetylbiphenyl[29] (0.001 mol % Pd, K_3PO_4 as base, from the aryl bromide). The coupling of 4-bromoacetophenone with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 50 μL of a catalyst solution prepared as follows: a flask was charged with $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) and ligand **4** (4.5 mg, 0.015 mmol) and was purged with argon. THF (5 mL) was added and the mixture was stirred for 1 min at rt, then 50 μL of this solution (0.01 mol % Pd, 0.02 mol % **4**) was added to a second flask containing 1 mL THF. The title compound was obtained as a white solid (187 mg, 95 %).

4-Acetylbiphenyl[29] (0.000001 mol % Pd, K_3PO_4 as base, from the aryl bromide). The coupling of 4-bromoacetophenone with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 10 μL of a catalyst solution prepared as follows: in a flask in a argon filled glovebox, $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and ligand **4** (12.0 mg, 0.04 mmol) were dissolved in THF (20 mL) under argon. A portion of this solution (10 μL, 0.00001 mmol Pd, 0.001 mol % Pd, 0.002 mol % **4**) was added to a second flask containing THF (10 mL). The title compound was obtained as a white solid (176 mg, 90 %).

4-Acetylbiphenyl[29] (0.001 mol % Pd, no ligand). The coupling of 4-bromoacetophenone with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 10 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol) and THF (10 mL). When the aryl halide had been completely consumed, the mixture was cooled to room-temperature and dodecane (0.23 mL) was added as an internal standard; the GC yield was determined to be 101%.

4-Methyl biphenyl[24] (0.1 mol % Pd, ligand 4). The coupling of 4-chlorotoluene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 100 μL of a catalyst solution comprised of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), ligand **4** (12.0 mg, 0.04 mmol), and THF (2 mL) to afford 161 mg (96%) of the title compound.

4-Methyl biphenyl[24] (0.05 mol % Pd, ligand 5). The coupling of 4-chlorotoluene with phenylboronic acid was effected using the general procedure with toluene solvent, a reaction temperature of 100 °C, and 100 μL of a catalyst solution comprised of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), ligand **5** (7.0 mg, 0.02 mmol), and THF (2 mL) to afford 158 mg (94%) of the title compound.

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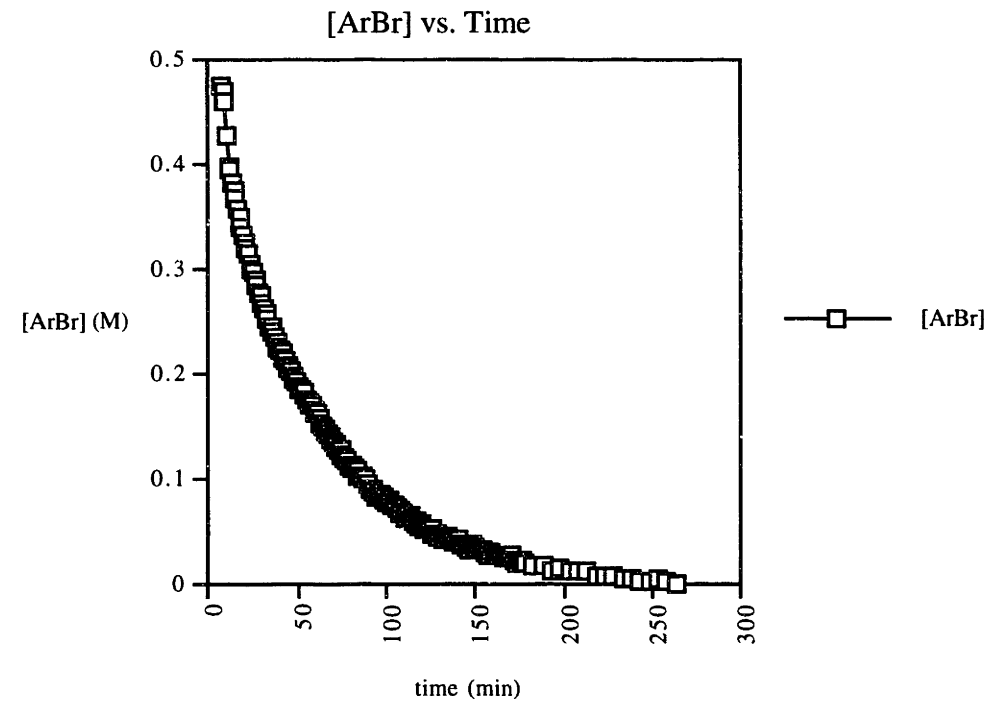
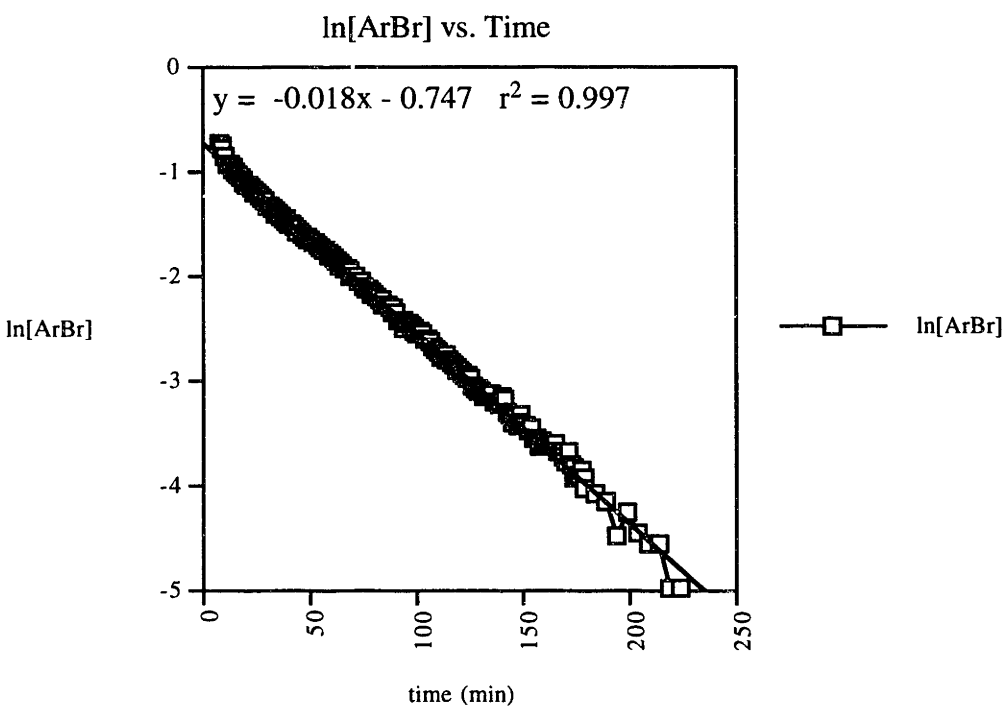
Appendix One:

Plots of [ArBr] vs Time and ln[ArBr] vs Time for the Relative Rate Experiments Described in Chapter Three

$Pd_2(dba)_3$/(±)-BINAP; Catalyst Not Premixed





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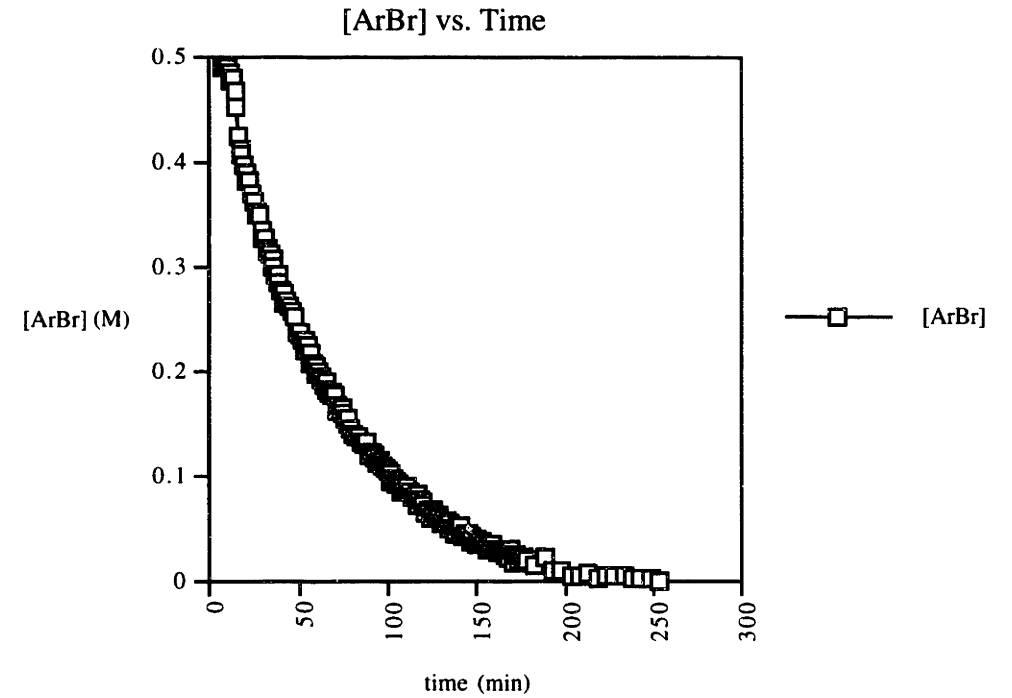

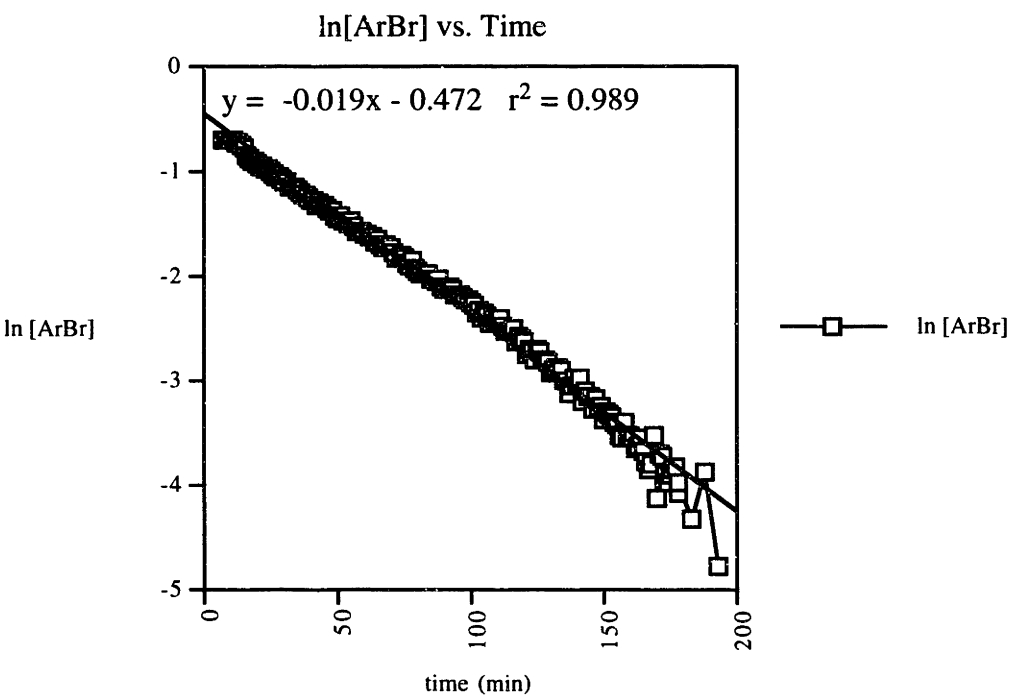

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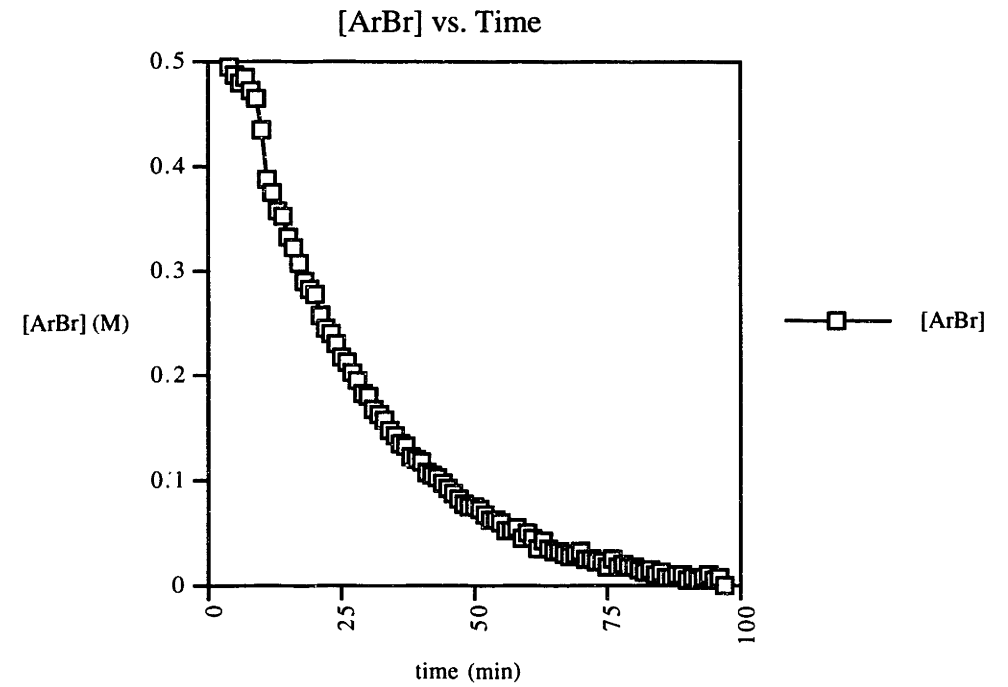

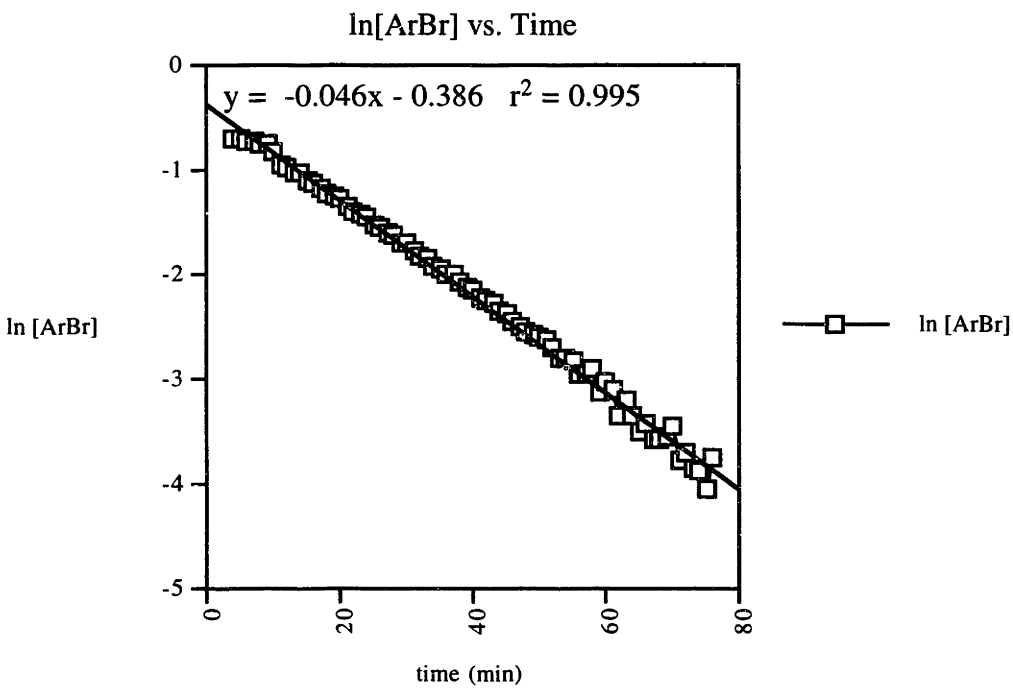

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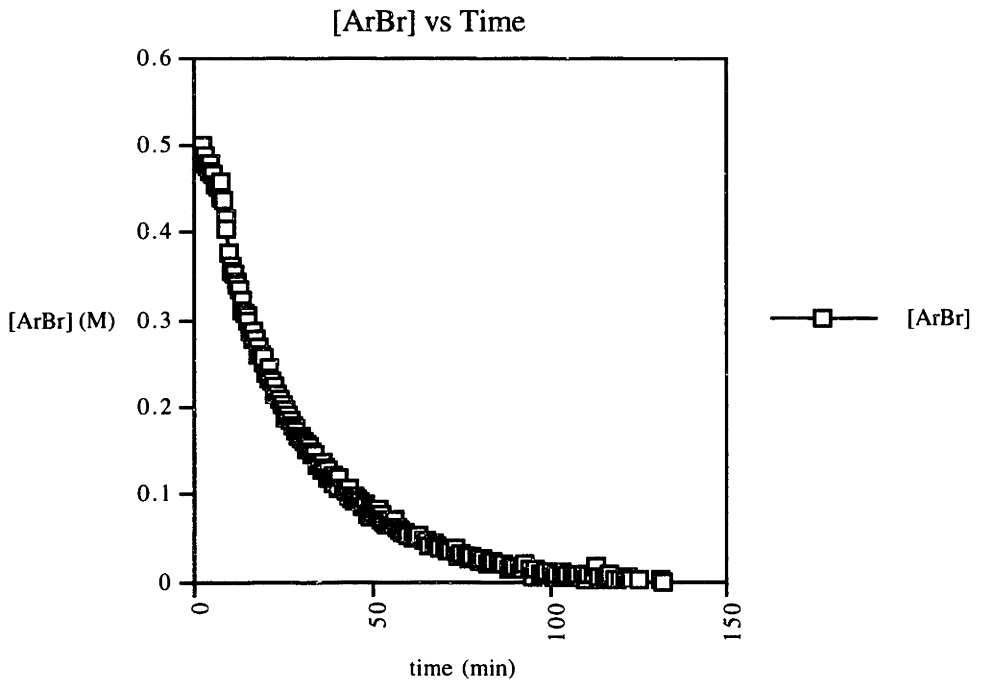

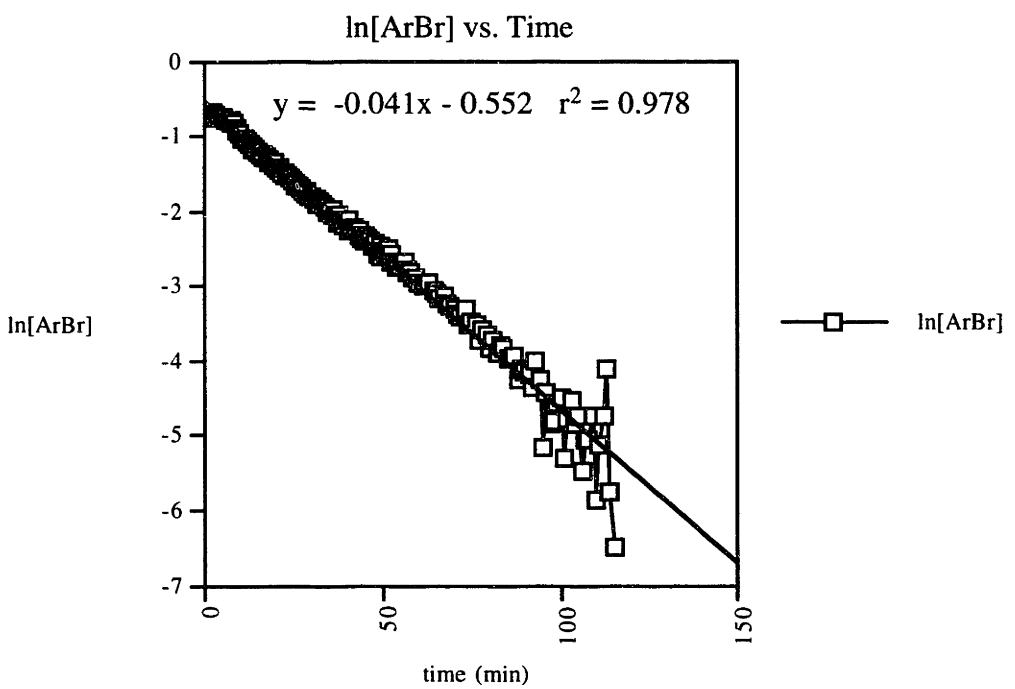

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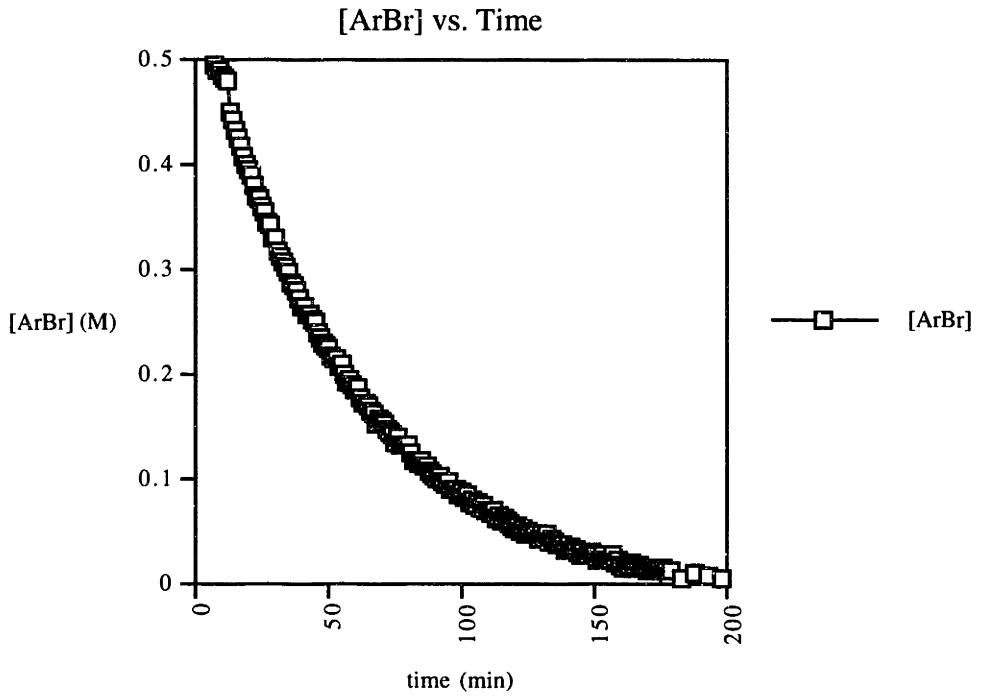

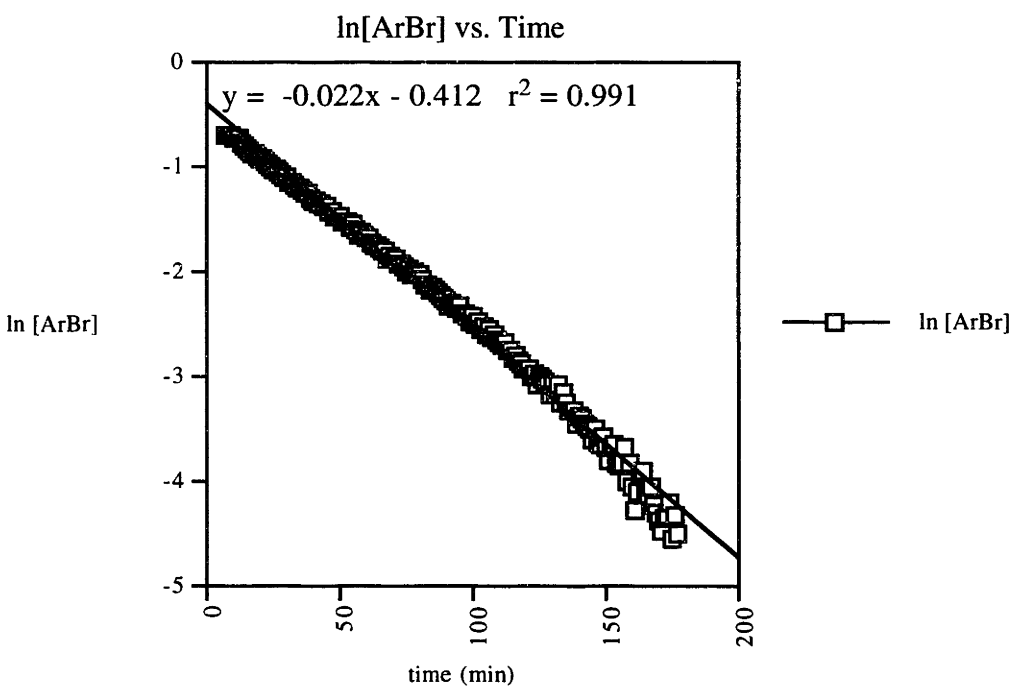

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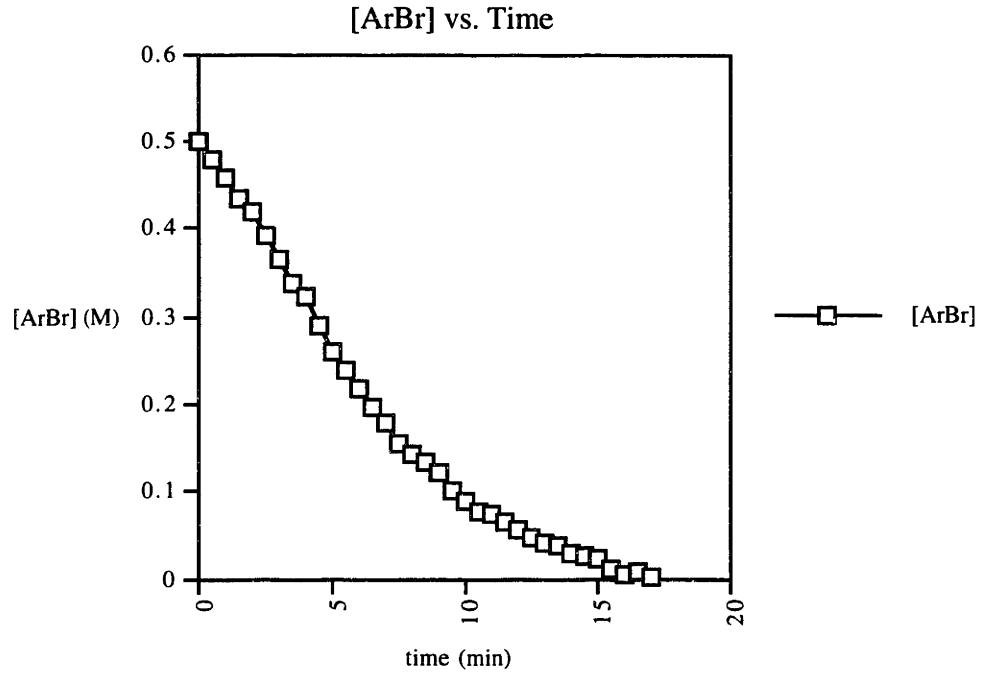

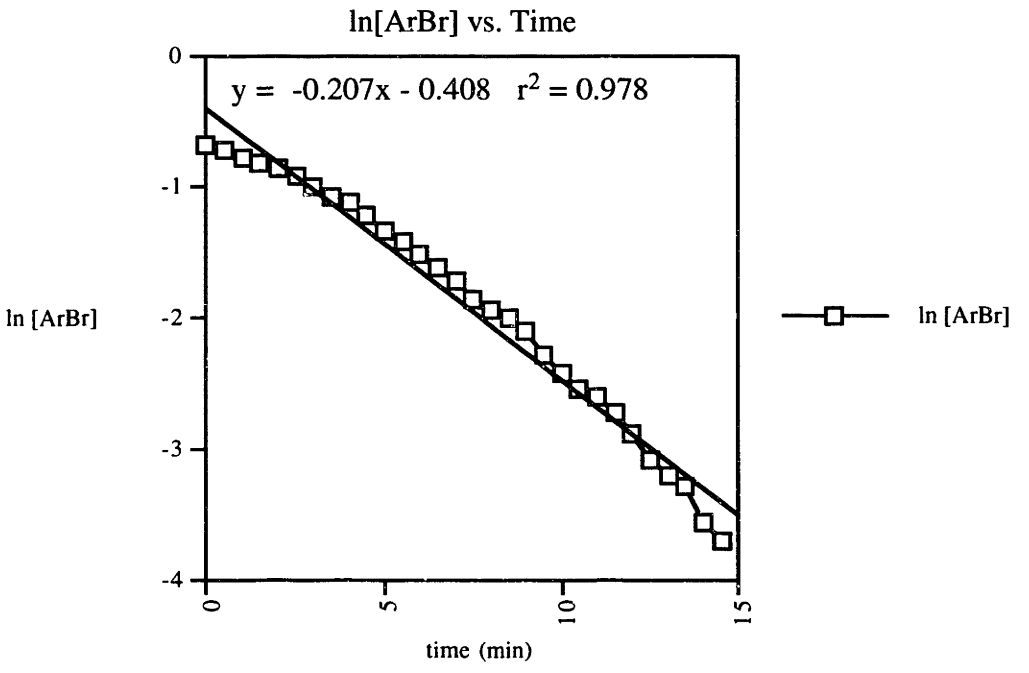

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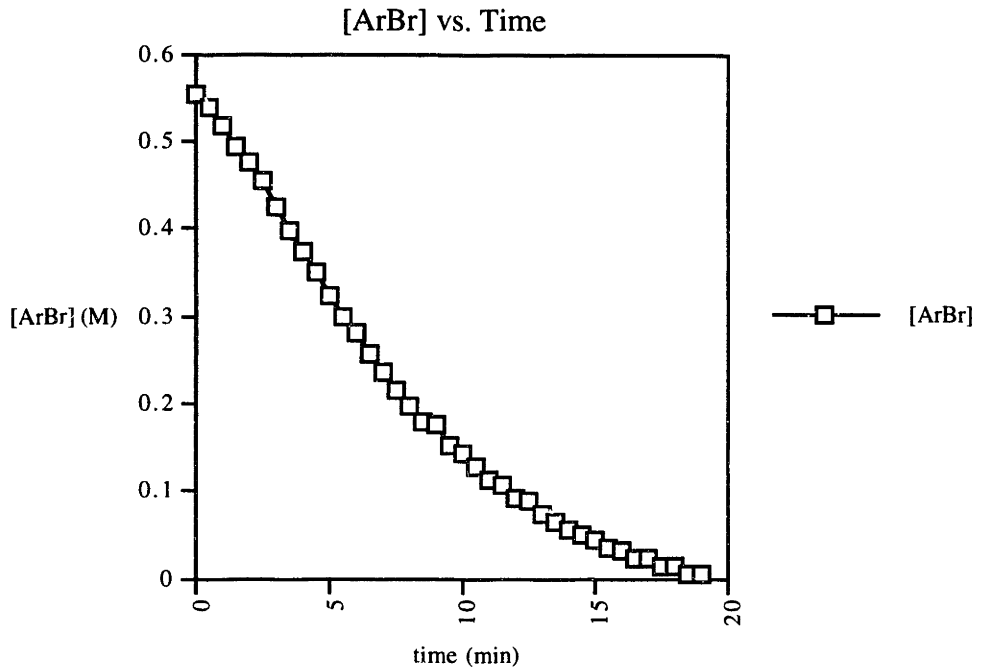

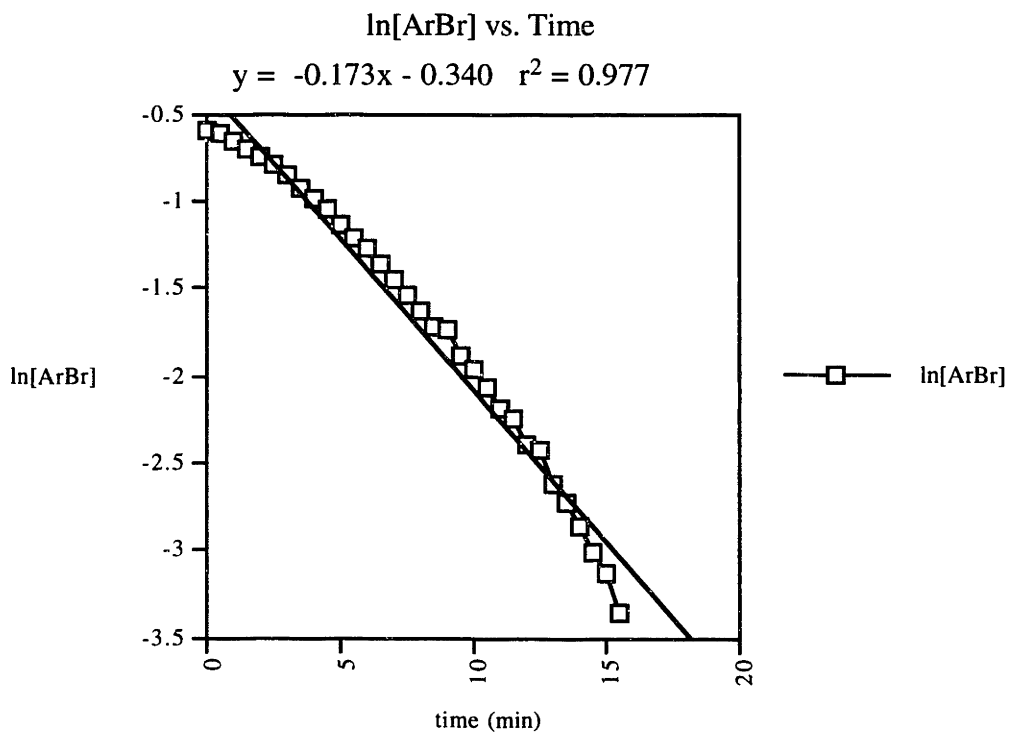

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