Scope and Limitations of the Pd/BINAP-Catalyzed Amination of Aryl Bromides

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Mixtures of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and BINAP catalyze the cross-coupling of amines with a variety of aryl bromides. Primary amines are arylated in high yield, and certain classes of secondary amines are also effectively transformed. The process tolerates the presence of several functional groups including methyl and ethyl esters, enolizable ketones, and nitro groups provided that cesium carbonate is employed as the base. Most reactions proceed to completion with 0.5−1.0 mol % of the palladium catalyst; in some cases, catalyst levels as low as 0.05 mol % Pd may be employed. Reactions are considerably faster if $Pd(OAc)_2$ is employed as the precatalyst, and the order in which reagents are added to the reaction has a substantial effect on reaction rate. It is likely that the catalytic process proceeds via bis(phosphine)palladium complexes as intermediates. These complexes are less prone to undergo undesirable side reactions which lead to diminished yields or catalyst deactivation than complexes of the corresponding monodentate triarylphosphines.

The catalytic amination of aryl halides represents a mild alternative to classical methods of aryl C−N bond formation and has many potential applications for the synthesis of aniline derivatives which are inaccessible through other routes.[1] The most commonly used catalysts for this transformation are based on chelating phosphines such as BINAP and DPPF,[1b] and aryl bromides are the most frequently employed substrates.[1] Recent reports have described the use of other catalyst systems based on bulky, electron-rich, phosphine ligands.[2] However, the BINAP catalyst system remains the most active and general catalyst for the coupling of aryl bromides with primary amines.[3a] Additionally, the BINAP catalyst system functions well in the presence of the weak base cesium carbonate, allowing for a high level of functional group tolerance.[3b] Although new catalyst systems tolerate the presence of functional groups when potassium phosphate is employed as the base,[2e,j] the BINAP system appears to give better results for reactions of primary amines with functionalized substrates. In this paper, we describe our studies on the scope and limitations of the Pd/BINAP-catalyzed amination of aryl bromides, as well as studies on the mechanism of this process.

In addition to its utility in catalytic amination reactions of aryl bromide substrates, the Pd/BINAP catalyst has previously been shown to be highly effective for a wide variety of carbon−heteroatom and carbon−carbon bond-forming processes.[1a,4−7] This catalyst allows for the catalytic amination of aryl triflates[4a,b] and halopyridines,[4c] catalyzes the room-temperature amination of aryl iodides,[4d] and is useful for the N-arylation of benzophenone imine,[4e] which can be cleaved to afford primary anilines.[5] BINAP has been shown to inhibit substrate racemization in the arylation of α-chiral amines[4f] and has been utilized for the N-arylation of benzophenone hydrazone in an improved version of the Fisher indole synthesis.[4g,h] Additionally, the Pd/BINAP catalyst promotes both inter- and intramolecular C−O bond-forming processes[6] and is useful for the Pd-catalyzed α-arylation of ketone enolates.[7] Racemic BINAP[8] is commercially available and is an air-stable, crystalline solid.

Results

Catalytic Amination of Aryl Bromides Using NaO-*t*-Bu as the Base. The Pd/BINAP catalyst system

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(8) (a) Miyashita, A.; Takaya, H.; Souchi, T.; Noyori, R. *Tetrahedron* **1984**, *40*, 1245−1253. (b) Racemic BINAP is commercially available from Strem Chemical Co.

10.1021/jo9916986 CCC: $19.00
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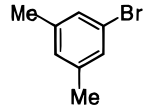
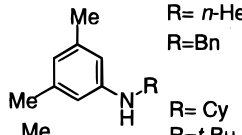
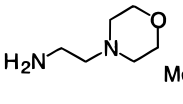
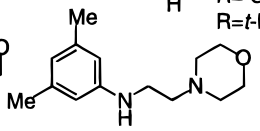
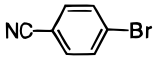
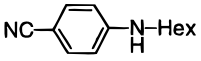
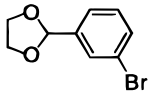
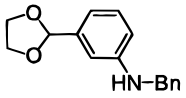
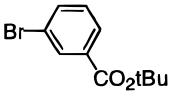
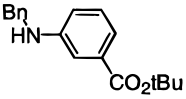
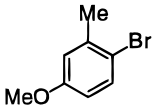
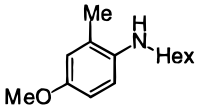
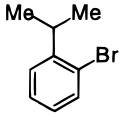
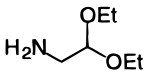
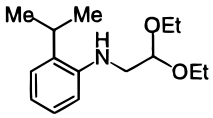
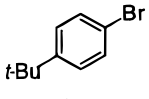
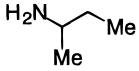
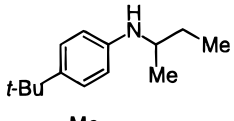
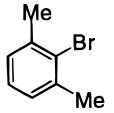
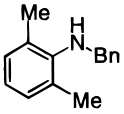
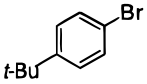
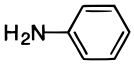
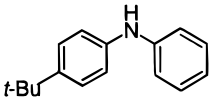
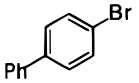
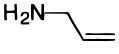
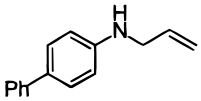
Table 1. BINAP/Pd-Catalyzed Arylation of Primary Amines

Entry	Halide	Amine	Product		Catalyst Loading (mol % Pd)	Rxn Time (h)	Isolated Yield (%)
1		RNH_2		R= *n*-Hexyl	0.5	2	88 (35)[b]
2				R=Bn	0.5	4	79
					0.5	1.5	91[e]
3					0.05	7	79
4				R= Cy	0.5	18	83
				R=*t*-Bu	4.0	25	76[d]
5					0.5	20	84
6		$nHexNH_2$			0.5	<1	98[c]
					0.05	1.5	97
7		H_2NBn			0.5	2	81
8		H_2NBn			0.5	3.5	71
9		$nHexNH_2$			0.5	6	95
10					0.5	17	90
11					2.0	18	79[d]
12		H_2NBn			0.5	18	87[d]
13					0.5	19	94[e]
14					0.5	3	83[e]

[a] Reaction conditions: 1.0 equiv of ArBr, 1.1−1.2 equiv of amine, 1.4 equiv of NaO-*t*-Bu, cat. $Pd_2(dba)_3$, cat. BINAP, toluene (2 mL/mmol halide), 80 °C. [b] Yields in parentheses refer to yields obtained when P(*o*-tol)$_3$ was used as the phosphine ligand. [c] Control experiments showed no formation of the desired product after 17 h at 100 °C in the absence of palladium. [d] Reaction conducted at 100 °C. [e] $Pd(OAc)_2$ used in place of $Pd_2(dba)_3$; base added last to reaction mixture.

is effective for the cross-coupling of a variety of primary amines with aryl bromides (Table 1). Significantly better results were obtained using this catalyst than with catalysts with P(*o*-tol)$_3$ as ligands.[9] For example, the reaction of *n*-hexylamine with 5-bromo-*m*-xylene using 0.5 mol % Pd/BINAP afforded the desired product in 88% yield; the P(*o*-tol)$_3$ catalyst system (2 mol % Pd) gave only 35% yield.

Most reactions proceeded to completion in <24 h using 0.5 mol % of the Pd/BINAP catalyst, although substrates that contained more than one ortho substituent required higher reaction temperatures (100 °C) and primary amines that were branched at the α position usually required longer reaction times, higher temperatures, and/or greater quantities of catalyst. Electronically neutral or electron-deficient aryl bromides are efficiently transformed; however, reactions of electron-rich aryl bromides gave poor results unless the aryl bromide also contained an ortho substituent. For example, the reaction of 4-bromoanisole with *n*-hexylamine using 0.5 mol % of the palladium catalyst proceeded to 26% conversion affording a ∼1/1 mixture of the desired product and anisole. In contrast, the reaction of 4-bromo-3-methylanisole with *n*-hexylamine proceeded to completion in 6 h with the same catalyst loading; the desired product was obtained in 95% yield. Functional groups, which were not sensitive to the strong base NaO-*t*-Bu tolerated by the reaction

(9) (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (b) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612.

conditions included aryl halides containing acetals, nitriles, and *tert*-butyl esters in reactions with primary amines.[10] Amine substrates containing acetal, olefin, or tertiary amine functionality were efficiently arylated. Ortho substitution of the aryl halide substrate was also well tolerated and in some instances (see above) was beneficial. In some cases, it was possible to conduct the reactions using only 0.05 mol % of the palladium catalyst (Table 1, entries 2 and 6), although the generality of this protocol has not yet been established.

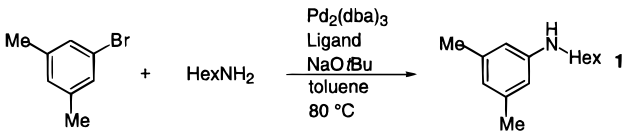
For most reactions, $Pd_2(dba)_3$ was employed as the precatalyst, although $Pd(OAc)_2$ usually provided similar results. Faster reactions were observed with $Pd(OAc)_2$ if the Pd and ligand were mixed in toluene prior to the addition of the other reagents; this protocol is especially important for the arylation of primary anilines (see below). Typically, a 1.5/1 ratio of BINAP to Pd was employed, although ratios of 1.0−2.0 L/Pd gave similar results. Both racemic and nonracemic BINAP give similar results for these transformations, although use of (±)-BINAP with $Pd(OAc)_2$ necessitates the use of a modified procedure (see below).

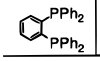
We felt that it was important to determine the effects, if any, of large excesses of the amine component of the reaction. Previously, we have shown that large excesses of amines inhibit reactions that employ catalysts that contain P(*o*-tol)$_3$ ligands.[11c] Neither the reaction of 5-bromo-*m*-xylene with *n*-hexylamine (see below) nor the reaction of 5-bromo-*m*-xylene with benzylamine using the $Pd_2(dba)_3$/BINAP catalyst (0.5 mol % Pd) were inhibited by excess amine (4.0 equiv).

$Pd_2(dba)_3$ was a more effective precatalyst for reactions that used low levels of the palladium catalyst (0.05 mol %Pd); thus, the effect of adding additional dba (dba = *trans*,*trans*-dibenzylideneacetone) to the reaction of 5-bromo-*m*-xylene with benzylamine using 0.5 mol % $Pd_2(dba)_3$ was examined. Addition of 5 mol % of dba (relative to substrate) dramatically decreased the reaction rate. The reaction proceeded to completion in <4 h with no dba added, but with 5 mol % added dba the reaction required ∼22 h to proceed to completion.

The main side products in the arylations of primary amines were diaryl(alkyl)amines resulting from overarylation of the primary amine substrate. 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.[12] The other ligands examined all provided larger amounts of diarylated side products than were observed with BINAP. With 0.5 mol % of the palladium catalyst, ratios of monoaryl/diaryl products were typically ∼10−30/1 in procedures that employ only a slight excess of the amine (1.1−1.2 equiv) in arylations with para- or meta-substituted aryl bromides. Although a ratio of monoarylation/diarylation of 39/1 was obtained for the

Table 2. Ligand Effects on Arylation of *n*-Hexylamine[a]



Ligand	% Conversion (Time)	Ratio[b] of Product/ Reduced S.M.	Ratio[b] of Product/ Doubly Arylated Amine	Isolated Yield 1
BINAP	100% (2 h)	40/1	39/1	88%
P(o-tol)$_3$	88% (22 h)	1.5/1	7.6/1	35%[c]
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	54%
	22% (12 h)	2.5/1	10/1	—

[a] Reaction conditions: 1.0 equiv of ArBr, 1.1 equiv of amine, 1.4 equiv of NaO-*t*-Bu, 1 mol % $Pd_2(dba)_3$, 3 mol % ligand, toluene (9 mL/mmol halide), 80 °C. [b] Uncorrected GC ratio. [c] Ratio of L/Pd = 2/1.

reaction of *n*-hexylamine with 5-bromo-*m*-xylene using 2 mol % Pd under relatively dilute conditions (0.11 M, 9 mL toluene/mmol halide), a ratio of ∼11.5/1 was obtained for the same reaction using 0.5 mol % Pd under more concentrated conditions (0.5 M, 2 mL toluene/mmol halide). However, by employing an excess of amine (4.0 equiv) under the conditions of higher concentration (0.5 M), an ∼80/1 ratio of monoaryl/diaryl product was produced. Use of 1.5 equiv of allylamine was employed to minimize overarylation with 4-bromobiphenyl (a ratio of ∼30/1 was observed by ^{1}H NMR analysis in this instance). Diarylated side products were not observed in reactions of ortho-substituted or electron-deficient aryl bromides. Primary amines with branching at the α-position also gave little or no overarylation. A small amount of phenylated amine side product (3%) was observed in the reaction of 5-bromo-*m*-xylene with *tert*-butylamine, presumably resulting from aryl exchange from the phosphine ligand.[13] This problem is most likely a result of the relatively high catalyst loading required for this reaction; phenylation was not observed in reactions which employed only 0.5 mol % of the Pd catalyst.

Certain types of secondary amines were also efficiently arylated using the Pd/BINAP catalyst system (Table 3). These reactions provided the best results when conducted without solvent. Considerably improved results were obtained for several substrate combinations that gave low yields with catalysts supported by P(*o*-tol)$_3$ ligands. For example, the reaction of *N*-methylaniline with 2-bromoanisole afforded the desired product in 75% isolated yield using 0.5 mol % of the Pd/BINAP catalyst. In comparison, the Pd/P(*o*-tol)$_3$ catalyst did not produce the desired product even with 2 mol % Pd. It was also possible to couple *N*-methylpiperazine with 2-bromo-*p*-xylene in 94% yield using only 0.05 mol % of the Pd/BINAP catalyst. Acyclic secondary amines are, however, usually problematic substrates. For example, the reaction of 4-*tert*-butylbromobenzene with di-*n*-butylamine affords a 1/5.2 ratio of the desired product/arene

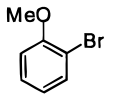
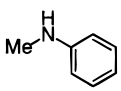
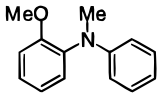
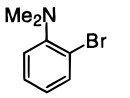
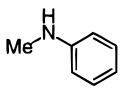
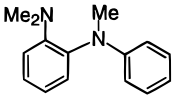
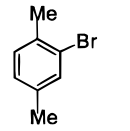
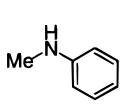
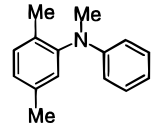
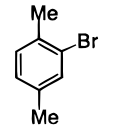
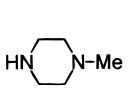
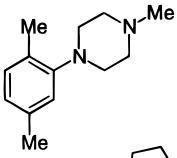
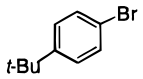
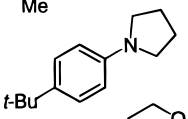
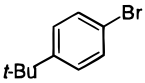
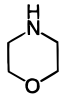
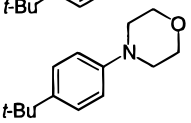
(10) Cyano groups are not tolerated in reactions of primary anilines when NaO-*t*-Bu is employed as the base. Amidine side products resulting from the addition of the primary aniline to the nitrile are formed under these conditions.

(11) (a) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745−2754. (b) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 3534−3542. (c) Widenhoefer, R. A.; Buchwald, S. L. Unpublished results.

(12) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218.

(13) Aryl exchange from phosphine ligands to palladium oxidative addition complexes has been previously observed. See: Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441−12453.

Table 3. BINAP/Pd-Catalyzed Arylation of Secondary Amines

Entry	Halide	Amine	Product	Catalyst Loading (mol % Pd)	Rxn Time (h)	Isolated Yield (%)
1				0.5[c] 2.0	29 14	75 61 (0)[a]
2				1.0[c] 2.0	39 36	66 65 (0)[a]
3				0.5[c] 2.0	36 4	94 79 (5)[a]
4				0.5[c] 2.0 0.05[c]	4 15 6	98 98 (47)[a] 94
5				0.5	20	83
6				0.5	22	93[c]

[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.

side product,[14] and attempts to use *N*-methylaniline as the substrate were, in general, only effective with ortho-substituted aryl bromides (activated substrates exhibit somewhat different reactivity; see below). Additionally, while pyrrolidine and morpholine were coupled with 4-*tert*-butylbromobenzene in high yield, the analogous reaction with piperidine gave a large amount of reduced side products. Other catalyst systems have subsequently been developed that are effective for reactions of acyclic secondary amines, as well as piperidine.[2d−j,14]

Catalytic Amination of Functionalized Aryl Bromides Using Cs_2CO_3. Although use of NaO-*t*-Bu as the stoichiometric base in catalytic amination reactions provides for the fastest reactions and allows for use of low catalyst loadings (0.05 mol % Pd) in some cases, its basicity greatly limits the functional group tolerance of the process. For example, methyl and ethyl esters react to form amides or *tert*-butyl esters (depending on the amine coupling partner), enolizable ketones are deprotonated, and nitroarenes decompose under these reaction conditions. However, when the weak base Cs_2CO_3 is employed, a much wider variety of functional groups are tolerated. As shown in Table 4, substrates containing methyl[15] and ethyl esters or nitro groups are efficiently coupled with a variety of amines. Although 4-bromonitrobenzene is sufficiently active to react slowly in toluene,[16] and rapidly in polar solvents in the absence of a palladium catalyst, selective substitution of bromide in the presence of chloride is obtained under catalytic conditions. Interestingly, while piperidine, *N*-methylaniline, and *N*-methylbenzyamine do not react well with unactivated aryl bromides, their reaction with electron-deficient aryl bromides gives functionalized aniline derivatives in high yields (entries 1, 3, 6, 7, and 13). Acetophenone derivatives are efficiently coupled with anilines under these conditions, although reactions with aliphatic amines do not work well.[17] Reactions of aryl bromides containing ortho functional groups are often problematic when aliphatic amines are employed. With anilines, however, they are more favorable; the reaction of methyl-2-bromobenzoate with *p*-anisidine provided the diarylamine product in 92% yield. Anilines containing base-sensitive functional groups were also arylated in good yields. In our studies, we also screened a variety of other weak bases such as alkali metal carbonates and phosphates,[2e,j] as well as organic bases such as tertiary amines and DBU. These generally gave poorer results in the amination reactions. The activated substrate 4-bromobenzonitrile was efficiently coupled with *p*-toluidine in the presence of K_2CO_3; however, this protocol was not generally effective even for other activated substrates.

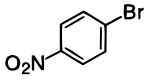
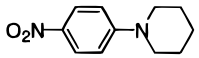
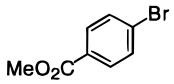
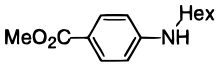
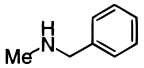
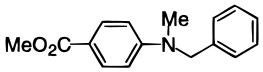
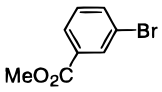
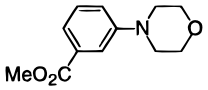
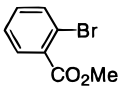
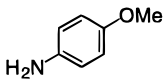
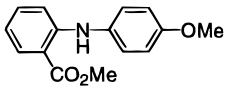
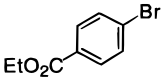
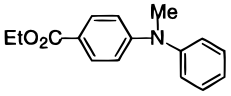
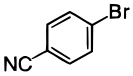
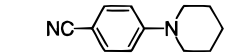
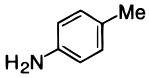
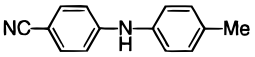
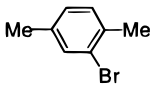
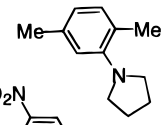
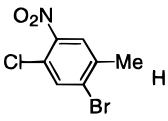
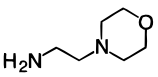
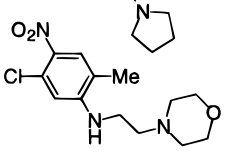
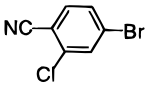
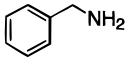
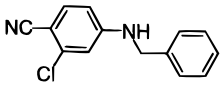
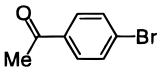
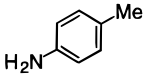
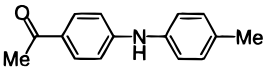
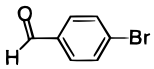
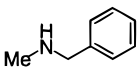
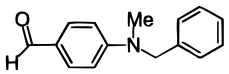
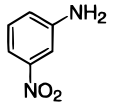
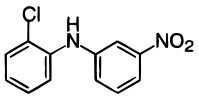
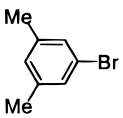
(14) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568−1569.

(15) 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.

(16) 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.

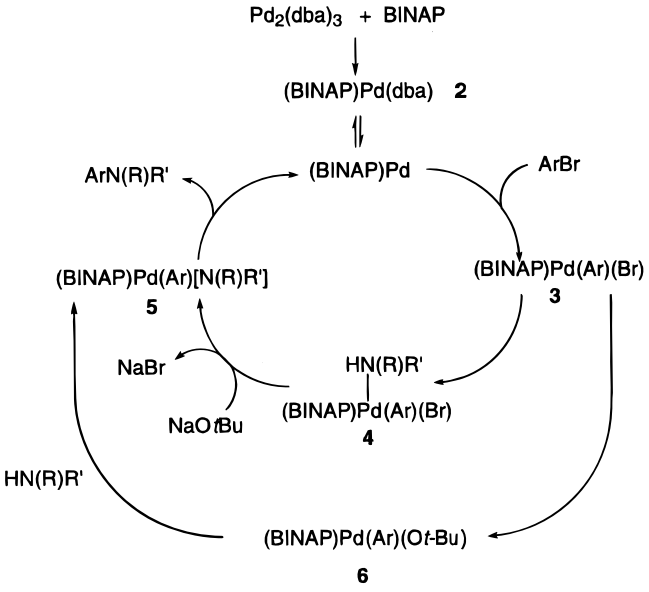
(17) Reactions of the enolizable ketone, 4′-bromoacetophenone, were only successful with 4-methylaniline. Attempts to couple this substrate with morpholine or piperidine afforded only low yields (∼15% by GC) of the desired product.

Table 4. Catalytic Amination of Aryl Bromides Using Weak Bases

Entry	Halide	Amine	Product	catalyst[b]	mol% Pd	Rxn Time (h)	Yield(%)[d]
1				A	1	18	83
2		H_2NHex		A	2	21	72
3				B C	3 3	16 22	75 87[f]
4				B	1	20	86
5				B	3	20	92
6				A	1	24	87
7				A	1	26	87
8				A B	1 1	26 16	80 88[e,g]
9				B[c]	4	17	93
10				A	2	16.5	75
11				A	1	20	84
12				A	1	15	73
13				A	1	22	54
14				A	1	21	80
15				B	3	20	88[f]

[a] Reaction conditions: 1.0 equiv of halide, 1.2 equiv of amine, 1.4 equiv of Cs_2CO_3, cat. $Pd_2(dba)_3$ or $Pd(OAc)_2$, cat. BINAP (1.5 L/Pd), toluene (0.25 M), 100 °C. [b] A = $Pd_2(dba)_3$/(*S*)-BINAP; B = $Pd(OAc)_2$/(*S*)-BINAP; C = $Pd(OAc)_2$/(±)-BINAP. [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. [e] K_2CO_3 used in place of Cs_2CO_3. [f] Base added last to the reaction mixture. [g] Isolated yield from a single experiment.

Scheme 1

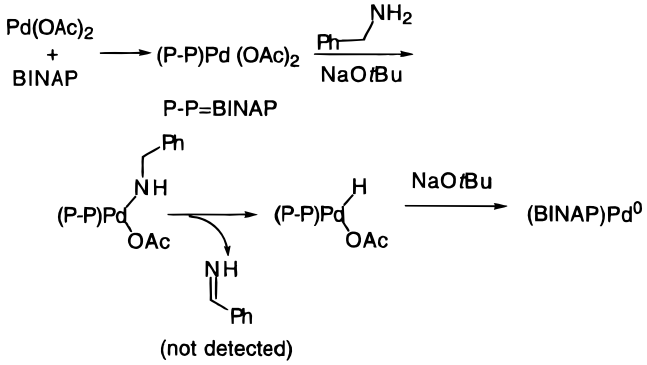


Mechanistic Studies

Catalytic Cycle. We believe the catalytic cycle for this process is similar to that postulated for many palladium-catalyzed C−C bond-forming processes (Scheme 1).[18] Mixing BINAP with $Pd_2(dba)_3$ initially leads to the formation of the isolable complex (BINAP)Pd(dba) (**2**).[19] This complex probably undergoes dissociation of a dba ligand prior to oxidative addition of the aryl bromide to form the isolable oxidative addition complex **3**. However, Amatore has shown that direct oxidative addition to (L−L)Pd(dba) is possible.[19] Coordination of the amine to **3**,[20] followed by deprotonation, would form amido complex **5**, which then undergoes reductive elimination to form the desired product and to regenerate the Pd(0) catalyst. Alternatively, Hartwig has recently demonstrated that treatment of (DPPF)Pd(Ar)(O-*t*-Bu) with amine leads to the formation of arylamine products.[21] Thus, it is also possible that the reaction proceeds via *tert*-butoxide complex **6** when NaO-*t*-Bu is used as the base. Treatment of **3** (Ar = 4-*t*-BuPh) with an excess of benzylamine did not lead to the detectable formation of an amine complex; however, addition of NaO-*t*-Bu to this mixture afforded the arylamine product. Both **2** and **3** 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 what has been observed with Pd/P(*o*-tol)$_3$ complexes,[1b,22] it is likely that all steps in the catalytic cycle occur via 4-coordinate intermediates without prior dissociation of a phosphine.

Use of $Pd(OAc)_2$ as a Precatalyst: Effect of the Order of Addition on Reaction Rate and Evidence for Rate-Limiting Oxidative Addition. In many cases, $Pd(OAc)_2$ is an effective precatalyst and often provides faster reactions than are observed when $Pd_2(dba)_3$ is employed. This process also presumably proceeds through a catalytic cycle involving Pd(0)−Pd(II) complexes as intermediates. Studies were undertaken to determine what was responsible for the initial reduction of $Pd(OAc)_2$ to the active catalyst using ^{31}P NMR.[23] Mixing $Pd(OAc)_2$ and (*S*)-BINAP in a 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 observed 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 result in a change in the ^{31}P NMR spectrum. 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 causes reduction of the precatalyst, presumably by a mechanism involving formation of a Pd(amido)complex that then undergoes β-hydride elimination 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

(18) Farina, V. in *Comprehensive Organometallic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1995; Vol. 12, pp 161−240.

(19) Amatore has reported detailed studies on (L−L)Pd(dba) complexes. See: (a) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176−5185. (b) Amatore, C.; Jutand, A. *Coord. Chem. Rev.* **1998**, *178*−*180*, 511−528.

(20) Associative reactions of square-planar, d^8 transition metal complexes typically proceed via five-coordinate intermediates. See: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987; Chapter 5.

(21) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110.

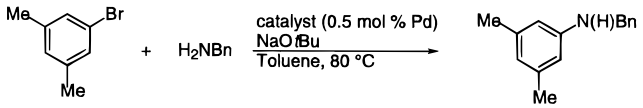
(22) (a) Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc.* **1995**, *117*, 5373−5374. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969−5970. (c) Louie, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 11598-11599. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1995**, *117*, 4708−4709. (e) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794−2805. (f) Hartwig, J. F. *Synlett* **1997**, 329−340.

(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.

Table 5

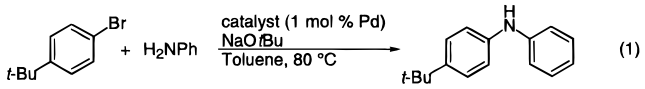


catalyst	catalyst and ligand mixed before addn of other reagents	k_{obs} (min^{-1})	relative rate
$Pd_2(dba)_3$/(±)-BINAP	no	0.017 ± 0.001	1.0 ± 0.1
$Pd_2(dba)_3$/(S)-BINAP	no	0.019 ± 0.001	1.1 ± 0.1
$Pd(OAc)_2$/(±)-BINAP	no	0.044 ± 0.003	2.6 ± 0.2
$Pd(OAc)_2$/(S)-BINAP	no	0.044 ± 0.005	2.6 ± 0.3
$Pd_2(dba)_3$/(±)-BINAP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

new ^{31}P NMR signals, and after heating to 40 °C for 20 min, ^1H NMR analysis did not show formation of the arylamine product. Heating this mixture to 80 °C also did not produce new ^{31}P NMR signals; however, after heating for 10−15 min at this temperature, 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 that then undergoes rapid oxidative addition of the aryl halide.[27]

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 significantly 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 10 min 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 above in Table 5. 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 precatalyst mixture when (±)-BINAP was employed, due to the low solubility of the (±)-BINAP. Reactions which used $Pd_2(dba)_3$ as a precatalyst were much slower, and premixing the catalyst did not affect reaction rates; (±)-BINAP provided reaction rates similar 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-*tert*-butylbenzene. This reaction proceeded to completion in high yield in <20 h if the BINAP and $Pd(OAc)_2$ were premixed (eq 1). However, if the catalyst



(1)

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

precursors were not mixed prior to the addition of the other reagents, the reaction did not proceeded to completion. This effect was also observed for the arylation of aniline derivatives using a catalyst comprised of $Pd(OAc)_2$/DPE-Phos.[28] 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 (see below for discussion of this effect).

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. For example, the reaction of methyl-3 bromobenzoate with morpholine proceeded to 87% conversion after 22 h with 1 mol % $Pd(OAc)_2$/(±)-BINAP when the catalyst was not premixed. When a procedure was employed in which the $Pd(OAc)_2$ and (±)-BINAP were mixed prior to adding the other reagents, the above reaction proceeded to completion in 22 h affording the desired product in 93% GC yield. Similar effects are observed for the catalytic amination of aryl triflates using Cs_2CO_3 as the base. For example, the reaction of 4-acetylphenyl triflate with *p*-anisidine catalyzed by 3 mol % $Pd(OAC)_2$/(±)-BINAP with THF as solvent at 65 °C stopped at 90% conversion when the catalyst was not premixed; however, this reaction proceeded to completion in 3 h when the catalyst was premixed; 76% yield of the desired product was obtained. Due to the increased solubility of (±)-BINAP in THF, it was not necessary to heat the precatalyst mixture. In contrast to what was seen using 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 for reactions with Cs_2CO_3 as base. For example, the reaction of 4-bromobenzonitrile with *p*-toluidine proceeded to ~25% conversion in 1 h using 1 mol % $Pd(OAc)_2$/(±)-BINAP regardless of the order in which reagents were added to the reaction mixture; both reactions proceeded to completion in <18 h.

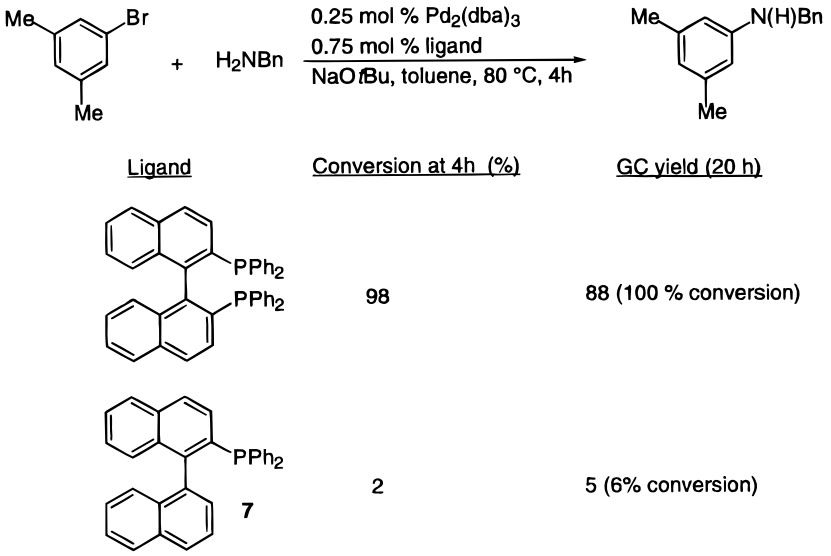
Examination of the Role of P−C Bond Cleavage in the Catalytic Process. As stated above, side prod-

(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.

(27) Hartwig has described similar NMR experiments. See ref 2d.

(28) DPE-Phos= 1, 1′-bis(diphenylphosphino)diphenyl ether: Sadighi, J. P.; Harris, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1998**, *39*, 5327−5330.

Scheme 3



ucts are occasionally observed in Pd/BINAP-catalyzed aminations of aryl bromides in which the amine has been arylated with a phenyl group rather than the aryl group from the substrate. These products usually form in small amounts (<5%) when relatively high levels of the palladium catalyst are employed. As these side products presumably arise from P−C bond cleavage of the phosphine ligand,[13] it is possible that one of the phosphines may be cleaved from the BINAP ligand to form 2-diphenylphosphino-1,1′-binaphthyl[29] (**7**) (Scheme 3). Our recent results with bulky, electron-rich, monodentate phosphine also suggested that some monophosphine ligands function well for a variety of catalytic amination reactions.[2j] To determine whether the actual catalyst in this system is the Pd/BINAP complex or a Pd complex of **7**, we prepared **7** and compared its reactivity to BINAP in the reaction of 5-bromo-*m*-xylene with benzylamine. As shown above in Scheme 3, the reaction proceeded to 98% (average) conversion in >4 h with the Pd/(±)-BINAP catalyst, affording the desired product in 88% GC yield after 20 h (100% conversion was obtained). In contrast, use of **7** as a ligand provided only small amounts (∼2% average) of the desired product in 4 h and gave a GC yield of 5% (6% conversion) after 20 h. This experiment suggests that palladium complexes of the bis(phosphine) ligand are the catalytically active species in the reactions, and while **7** may form under some conditions, it does not appear to be important for catalysis.

In a separate experiment, the above reaction was conducted using 5 mol % $Pd_2(dba)_3$ and 15 mol % (*S*)-BINAP. Following completion of the reaction, the phosphine ligand was displaced from the metal by treatment with an ethanolic solution of sodium cyanide. Analysis of the mixture by ^{31}P NMR showed no evidence for the formation of **7** under these conditions; the only detectable phosphorus-containing species were BINAP, BINAP(monooxide), and BINAP(bisoxide).[30] Use of $Pd(OAc)_2$ as the precatalyst led to the formation of many phosphorus-containing side products consistent with P−C bond cleavage; however, the majority of the BINAP (∼70%) remained unchanged after the reaction. It is difficult to say what percentage of P−C bond cleavage occurred during the reaction and what percentage occurred following consumption of the aryl bromide starting material; no products resulting from P−C bond cleavage were detected during the NMR experiments to ascertain the resting state of the catalyst as described above.

Discussion

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[11b] and bridging amido complexes,[11c] presumably through chelation of both phosphine groups of the ligand to the metal. This is highlighted by the differences in reactivity between BINAP and 2-diphenylphosphino-1,1′-binaphthyl (**7**). The inefficiency of **7** in the reaction of benzylamine with 5-bromo-*m*-xylene is most likely due to the formation of bis(amine)-complexes similar to those observed with other monodentate phosphines.[11b]

We believe that structural features specific to BINAP are also key to the success of this catalyst system. Dissociation of one arm of a chelating ligand (dechelation) could lead to increased amounts of β-hydride elimination;[31] thus, the rigidity of the binaphthyl backbone and the small bite angle[32a] of BINAP (92.7 °)[32b] relative to DPPF (99.1 °)[32c] presumably lead to the formation of a tight chelate. The large size of BINAP relative to other chelating ligands also disfavors double arylation of the

(29) Uozumi, Y.; Suzuki, N.; Ogiwara, A.; Hayashi, T. *Tetrahedron* **1994**, *50*, 4293−4302.

(30) Phosphine oxides may form during the workup of the reaction.

(31) (a) Whitesides has demonstrated that β-hydride elimination in platinum complexes requires an open coordination site. See: Whitesides, G. M.; Gaasch, J. F.; Stedronsky, E. R. *J. Am. Chem. Soc.* **1972**, *94*, 5258−5270. (b) β-hydride elimination of Pd(II) complexes may occur either via 3-coordinate intermediates or via 4-coordinate intermediates. In $L_2Pd(X)alkyl$ complexes (X = OAc, phenoxide) β-hydride elimination has been shown to occur predominantly through the 3-coordinate pathway; however, in $L_2Pd(alkyl)_2$ complexes the major pathway involves 4-coordinate intermediates. See: (c) Kawataka, F.; Kayaki, Y.; Shimuzu, I.; Yamamoto, A. *Organometallics* **1994**, *13*, 3517−3524. (d) Ozawa, F.; Ito, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1980**, *102*, 6457−6463.

(32) (a) Bite angle is defined as the P−Pd−P angle; (b) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188−4196. (c) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.

primary amine substrate and should promote reductive elimination to form the arylamine product.

The increased rates of reactions that employ $Pd(OAc)_2$ instead of $Pd_2(dba)_3$ as the precatalyst, along with the resting-state NMR experiments, support a mechanism that involves rate-limiting oxidative addition of the aryl bromide (for reactions of primary amine substrates).[33] This is also supported by the fact that added dba decreases the rate of the reaction. However, the fact that bulky primary amines or secondary amines react much more slowly than unbranched primary amines suggest that the rate-limiting step of the reaction may be substrate dependent. The relatively slow reactions observed when Cs_2CO_3 is used in place of NaO-*t*-Bu also suggests that the rate-limiting step of the catalytic cycle changes when a weaker base is employed; it seems likely that deprotonation is rate limiting in amination reactions that employ weak bases.

The reasons for the increased efficiency of cesium carbonate relative to other weak bases are not entirely clear. Its increased solubility relative to other alkali metal carbonates[34] may play a role in its activity, although none of the alkali metal carbonates are very soluble in toluene or dioxane. The efficacy of cesium carbonate relative to "stronger" organic bases such as DBU may be related to its ionic character. Even though the pK_a of cesium carbonate is lower than that of DBU in water,[35] it is expected that a charged base would be more strongly basic in a nonpolar solvent than in water.[36] Moreover, in toluene formation of the ammonium salt from DBU may be unfavorable.[37]

One possible explanation for the slower reaction rates observed in reactions catalyzed by BINAP and palladium acetate when the base is added without premixing the catalyst is that the formation of $Pd(O\text{-}t\text{-}Bu)_n$ 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 presumed catalytically active species slowly increased upon heating (in the absence of an aryl halide). It is likely that the *tert*-butoxide complexes may undergo decomposition to catalytically inactive species under the conditions of the catalytic reactions; thus, faster reaction 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 that did not employ preformed catalysts did not increase with time, suggesting that the *tert*-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, the Pd/BINAP catalyst system is highly effective for the arylation of primary amine substrates. A variety of substrate combinations are tolerated, including amines that are branched or contain functional groups such as olefins or acetals. Good results are also obtained for the arylations of cyclic secondary amines, although acyclic secondary amines often react poorly under these conditions. A wide variety of functional groups such as esters, nitriles, nitro groups, and enolizable ketones are tolerated under the reaction conditions when the mild base cesium carbonate is employed. In some cases, reactions can be run at low catalyst loadings (0.05 mol %) Pd. A combination of the chelating ability of the phosphine groups, the rigidity of the ligand backbone, and the small bite angle of the ligand are most likely responsible for the utility of this ligand in catalytic amination reactions. Either racemic or nonracemic BINAP may be employed for the catalytic amination reactions, and both function equally well. Despite the development of several new catalysts for amination reactions, BINAP continues to be the most generally efficacious ligand for the arylation of primary amines with aryl bromides and is highly effective for the transformation of functionalized aryl halides.

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, NY, or by Atlantic Microlabs Inc., Norcross, GA. All amines were purchased from commercial sources and were purified either by distillation from CaH_2 or by passing through a short column of alumina. Aryl halides (except *tert*-butyl-3-bromobenzoate) were purchased from commercial sources and used without further purification. Toluene, benzene, and ether were continuously refluxed and freshly distilled from sodium or sodium benzophenone ketyl under nitrogen or argon. *tert*-Butyl alcohol was purchased from Mallinckrodt Chemical Co. and dried over 3 Å molecular sieves. Sodium *tert*-butoxide was purchased from Aldrich Chemical Co.; 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. Lithium *tert*-butoxide was purchased from Aldrich Chemical Co. and stored under nitrogen in a vacuum atmosphere glovebox. Ligand **7** was prepared according to the previously published procedure[29] and was characterized by ^1H and ^{31}P NMR and elemental analysis. Tris(dibenzylideneacetone)dipalladium(0), tri-*o*-tolylphosphine, and (±)-BINAP were purchased from Strem Chemical Co. and used without further purification. Preparative flash chromatography was performed on ICN Biomedicals Silitech 32−63d silica

(33) Amatore has previously shown dba to decrease the rate of oxidative addition of aryl halides to Pd(0). See ref 15 and: Amatore, C.; Jutand, A.; Khalil, F.; M′Barki, M. A.; Mottier, L. *Organometallics* **1993**, *12*, 3168−3178.

(34) 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/dL while that of potassium carbonate is 112 g/dL. In methanol the solubilties of cesium carbonate and potasssium carbonate are 56.1 g/100 g MeOH, and 6.2 g/100 g MeOH, respectively. See: (a) *CRC Handbook of Chemistry and Physics*, 72nd ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 1991−1992; **4**-51, **4**-85. (b) Stenger, V. A. *J. Chem. Eng. Data* **1996**, *41*, 1111−1113.

(35) The pK_a 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; Chapter 8. The pK_a of DBU has been measured or estimated to be 11.5−14.3 in water; see: (a) Hermecz, I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: Orlando, 1987; Vol. 42, p 91. (b) Leffek, K. T.; Pruszynski, P.; Thanapaalasingham, K. *Can J. Chem.* **1989**, *67*, 590−595.

(36) Dyumaev, K. M.; Korolev, B. A. *Russ. Chem. Rev.* **1980**, *49*, 1021−1032.

(37) We thank Dr. Robert Singer for this suggestion.

gel. IR spectra reported in this paper for neat solids were obtained by placing neat samples directly on the DiComp probe of an ASI REACTIR in situ IR instrument. Yields refer to isolated yields (average of two runs) of compounds estimated to be ~95% pure as determined by ^{1}H NMR and either capillary GC (known compounds) or combustion analysis (new compounds). The procedures described in this section are representative; thus, the yields may differ from those given in Tables 1, 3, and 4.

Pd[(R)-BINAP](dba) (2). 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 that was dissolved in ether (5 mL). The precipitate that formed over 4 h was collected, washed with ether, and dried under vacuum to give **2** (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-*tert*-butylphenyl)(Br) (3). A solution of BINAP (100 mg, 0.16 mmol) and {Pd[P(*o*-tolyl)$_3$](*p*-C_6H_4-CMe_3)(μ-Br)}$_2$[11a] (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 that was dissolved in ether (20 mL). A white precipitate formed quickly and was collected, washed with ether, and dried under vacuum to give **3** (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-Bromobenzoate**[38] To a solution of lithium *tert*-butoxide (401 mg, 5.0 mmol) in *tert*-butyl alcohol (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 18 h, diluted with ether (20 mL), and poured into a separatory funnel. The solution was washed with brine (3 × 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 the title compound as 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 Primary Amines. A Schlenk flask was charged with aryl halide (1.0 mmol), amine (1.1−1.2 mmol), sodium *tert*-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 using (*S*)-BINAP gave 176 mg (86%) of the title compound as 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, 1601, 1188. 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 using (*S*)-BINAP gave 177 mg (84%) of the title compound as 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, 1605, 1182. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.04; H, 8.25.

***N*-Benzyl-3,5-xylidene (Table 1, Entry 2).** The general procedure conducted on a 10 mmol scale using 0.025 mol % $Pd_2(dba)_3$ and 0.075 mol % (*S*)-BINAP gave 1.66 g (79%) of the title compound as a colorless oil. See above for NMR data.

***N*-Cyclohexyl-3,5-xylidene (Table 1, Entry 3).**[39] The general procedure using (*S*)-BINAP gave 172 mg (85%) of the title compound as a white solid: mp 49.7−51.6 °C (lit. mp 50−52 °C);[39] ^{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, 1603, 1338.

***N*-*tert*-Butyl-3,5-xylidene (Table 1, Entry 4).**[40] The general procedure using 2 mol % $Pd_2(dba)_3$, 6 mol % (±)-BINAP, and a reaction temperature of 100 °C gave 137 mg (76%) of the title compound as a yellow oil. This material contained 3% *N*-*tert*-butylaniline as judged by GC analysis: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (s, 1H), 6.39 (s, 2H), 2.23 (s, 6 H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.7, 138.3, 120.1, 115.3, 51.4, 30.2, 21.6; IR (KBr, cm^{-1}) 3405, 2968, 1602, 1224.

***N*-(2-Ethylmorpholino)-3,5-xylidene (Table 1, Entry 5).** The general procedure using (*S*)-BINAP gave 193 mg (82%) of the title compound as 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, 1602, 1120. 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 6).** The general procedure using (*S*)-BINAP gave 196 mg (97%) of the title compound as 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.

***N*-(4-Cyanophenyl)hexylamine (Table 1, Entry 6).** The general procedure conducted on a 10 mmol scale using 0.025 mol % $Pd_2(dba)_3$ and 0.075 mol % (*S*)-BINAP gave 1.95 g (97%) of the title compound as a white solid. See above for NMR data.

2-(3-*N*-Benzylanilino)-1,4-dioxolane (Table 1, Entry 7). The general procedure using (*S*)-BINAP gave 213 mg (84%) of the title compound as 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. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.54; H, 6.67.

***tert*-Butyl-3-(*N*-benzylamino)benzoate (Table 1, Entry 8).** The general procedure using (*S*)-BINAP gave 201 mg (71%) of the title compound as 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 =

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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, 1298, 1116. 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 9).** The general procedure using (*S*)-BINAP gave 207 mg (94%) of the title compound as a colorless oil: ^{1}H 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.

***N*-(2-Isopropylphenyl)aminoacetaldehyde Diethyl Acetal (Table 1, Entry 10).** The general procedure using (±)-BINAP gave 232 mg (92%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, 1H, J = 7.5 Hz), 7.09 (d, 1H, J = 7.5 Hz), 6.75 (t, 1H, J = 7.3 Hz), 6.64 (d, 1H, J = 7.9 Hz), 4.76 (t, 1H, J = 5.7 Hz), 4.00 (s, br, 1H), 3.80−3.50 (m, 4H), 3.28 (d, 2H, J = 5.7 Hz), 2.95−2.80 (m, 1H), 1.26−1.22 (m, 12 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.6, 132.5, 126.7, 125.0, 117.6, 110.7, 100.8, 62.2, 46.3, 27.2, 22.2, 15.4; IR (neat, cm^{-1}) 3432, 2972, 1509, 1061. Anal. Calcd for $C_{15}H_{26}NO_2$: C, 71.67; H, 10.02. Found: C, 71.59; H, 10.03.

***N*-(4-*t*-Butylphenyl)-*s*-butylamine (Table 1, Entry 11).** The general procedure using 1 mol % $Pd_2(dba)_3$, 3 mol % (±)-BINAP, and a reaction temperature of 100 °C gave 167 mg (81%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.6 Hz), 3.40−3.28 (m, 2H), 1.60−1.45 (m, 2H), 1.27 (s, 9H), 1.15 (d, 3H, J = 6.2 Hz), 0.94 (t, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.3, 139.4, 126.0, 112.7, 49.9, 33.8, 31.6, 29.8, 20.4, 10.4; IR (neat, cm^{-1}) 3405, 2961, 1613, 1192. Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29. Found: C, 81.83; H, 11.27.

***N*-Benzyl-2,6-xylidene (Table 1, Entry 12).** The general procedure using (±)-BINAP, 1 mL/mmol halide of toluene as solvent, and a reaction temperature of 100 °C gave 188 mg (89%) of the title compound as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.26 (m, 5H), 7.01 (d, 2H, J = 7.3 Hz), 6.85 (t, 1H, J = 7.8 Hz), 4.11 (s, 2H), 3.21 (s, br, 1H), 2.07 (S, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.8, 140.4, 129.8, 128.8, 128.5, 127.9, 127.2, 122.1, 52.8, 18.4; IR (neat, cm^{-1}) 3366, 2945, 1475, 1216. Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11. Found: C, 85.10; H, 8.06.

General Procedures for Arylation of Secondary Amines. Method A. No Solvent. An oven-dried glass vial was charged with aryl halide (1.0 mmol), amine (1.2 mmol), sodium *tert*-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 *tert*-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 3, Entry 1). The general procedure A gave 172 mg (77%) of the title compound as 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, 1260, 1027. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09. Found: C, 78.96; H, 7.22.

2-Methoxy-*N*-methyldiphenylamine (Table 3, Entry 1). The general procedure B using 1.0 mol % $Pd_2(dba)_3$ and (±)-BINAP gave 143 mg (61%) of the title compound as a colorless oil. See above for NMR data.

2-(Dimethylamino)-*N*-methyldiphenylamine (Table 3, Entry 2).[41] The general procedure A using 0.5 mol % $Pd_2(dba)_3$ gave 143 mg (63%) of the title compound as 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, 1138.

2-(Dimethylamino)-*N*-methyldiphenylamine (Table 3, Entry 2).[41] The general procedure B using 1.0 mol % $Pd_2(dba)_3$ and (±)-BINAP gave 147 mg (65%) of the title compound as a colorless oil. See above for NMR data.

***N*-Methyl-*N*-phenyl-2,5-xylidene (Table 3, Entry 3).** The general procedure A gave 201 mg (95%) of the title compound as 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, 1340. 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-xylyl)piperazine (Table 3, Entry 4).** The general procedure A gave 197 mg (97%) of the title compound as 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, 1505, 1150. Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87. Found: C, 76.31; H, 9.71.

***N*-Methyl-*N*′-(2,5-xylyl)piperazine (Table 3, Entry 4).** The general procedure B using 1 mol % $Pd_2(dba)_3$ and (±)-BINAP gave 199 mg (98%) of the title compound as a colorless oil. See above for NMR data.

***N*-Methyl-*N*′-(2,5-xylyl)piperazine (Table 3, Entry 4).** The general procedure A conducted on a 10 mmol scale using 0.025 mol % $Pd_2(dba)_3$ and 0.075 mol % (*S*)-BINAP gave 1.91 g (94%) of the title compound as a colorless oil. See above for NMR data.

***N*-(4-*tert*-Butylphenyl)pyrrolidine (Table 3, Entry 5).**[4a] The general procedure B using 0.25 mol % $Pd_2(dba)_3$ and 0.75 mol % (±)-BINAP gave 161 mg (79%) of the title compound as a white solid: mp 38−40 °C (lit.[4a] 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).

***N*-(4-*tert*-Butylphenyl)morpholine (Table 3, Entry 6).**[4d] The general procedure A using (±)-BINAP gave 203 mg (93%) of the title compound as a white solid: mp 60−61 °C (lit.[4d] mp 59 °C); ^{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).

General Procedure for Catalytic Amination with Cesium Carbonate as Base. An oven-dried Schlenk flask was charged with cesium carbonate that had been finely ground with a mortar and pestle (1.4 equiv) 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 (see Table 4) and purged with argon. The aryl bromide (1.0 equiv), the amine (1.2 equiv), and toluene (2−4 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

(41) Pilgram, K. H.; Skiles, R. D. *Phosphorous Sulfur* **1988**, *36*, 117−124.

then purified by flash chromatography on silica gel. A reaction that employed cesium carbonate that had been finely ground in the air and stored in a desiccator outside of the glovebox gave results comparable to the analogous reaction that employed cesium carbonate from the glovebox.

***N*-(4-Nitrophenyl)piperidine (Table 4, Entry 1).**[42] The general procedure gave 87 mg (84%) of the title compound as a yellow solid: mp 95 °C (lit.[42] mp 104 °C); ^{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 4, Entry 2). The general procedure gave 88 mg (75%) of the title compound as a white solid: mp 93−94 °C; ^{1}H 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, 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 4, Entry 3).** The general procedure gave 87 mg (68%) of the title compound as a white solid: mp 67−68 °C; ^{1}H 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, 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-Carbomethoxyphenyl)morpholine (Table 4, Entry 4).** The general procedure gave 97 mg (87%) of the title compound as a colorless oil: ^{1}H 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, 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 4, Entry 5).**[43] The general procedure gave 115 mg (89%) of the title compound as 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, 1084. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88. Found: C, 70.28; H, 5.95.

***N*-Methyl-*N*-(4-carbethoxyphenyl)aniline (Table 4, Entry 6).**[44] The general procedure gave 114 mg (89%) of the title compound as 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. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71. Found: C, 75.17; H, 6.51.

***N*-(4-Cyanophenyl)piperidine (Table 4, Entry 7).**[42] The general procedure gave 77 mg (83%) of the title compound as a white solid: mp 45 °C (lit.[42] mp 56 °C); ^{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, 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 4, Entry 8).** The general procedure gave 84 mg (81%) of the title compound as 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 4, Entry 9).**[45] The general procedure gave 82 mg (93%) of the title compound as 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*-(1-Morpholinoethyl)-3-chloro-4-nitro-6-methylaniline (Table 4, Entry 10).** The general procedure gave 108 mg (72%) of the title compound as 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 4, Entry 11).** The general procedure gave 102 mg (84%) of the title compound as 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 4, Entry 12).**[46] The general procedure gave 82 mg (73%) of the title compound as an orange solid: mp 108 °C (lit.[46] mp 115 °C); ^{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, 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-formylaniline (Table 4, Entry 13).**[47] The general procedure gave 59 mg (52%) of the title compound as a white solid: mp 53 °C (lit.[47] mp 63 °C); ^{1}H 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, 1108. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71. Found: C, 80.19; H, 6.95.

***N*-(2-Chlorphenyl)-*m*-nitroaniline (Table 4, Entry 14).** The general procedure using 1 mol % $Pd_2(dba)_3$ and 3 mol % (±)-BINAP (the product was isolated by recrystallization from methanol instead of by chromatography) gave 196 mg (79%) of the title compound as a yellow solid: mp 93−94 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.05−7.95 (m, 1H), 7.82−7.75 (m, 1H), 7.50−7.30 (m, 5H), 6.99−6.93 (m, 1H), 6.24 (s, br, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 143.5, 138.1, 130.1, 127.7, 123.7, 123.6, 122.8, 117.9, 116.1, 112.1; IR (neat, cm^{-1}) 3397, 3061, 1532, 1336; GC/MS (*m*/*z*) 250, 248. Anal. Calcd for $C_{12}H_9ClN_2O_2$: C, 57.96; H, 3.65. Found: C, 58.14; H, 3.72.

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

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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 and 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 room temperature for ~1 min, 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 and 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*-Benzyl-3,5-xylidene (Table 1, Entry 2).** The general procedure gave 189 mg (90%) of the title compound as a colorless oil. See above for NMR data.

***N*-(4-*tert*-Butylphenyl)aniline (Table 1, Entry 13).**[48] 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.[48] mp 66−67 °C); ^{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. Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found: C, 84.98; H, 8.52.

***N*-Allyl-4-phenylaniline (Table 1, Entry 14)**.[49] The general procedure using 1.5 equiv allylamine gave 174 mg (83%) of the title compound as a white solid: mp 66−68 °C (lit.[49] mp 55−57 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.53 (d, 2H, J = 7.3 Hz), 7.45−7.35 (m, 4H), 7.27−7.22 (m, 1H), 6.69 (d, 2H, J = 6.71 Hz), 6.03−5.93 (m 1H), 5.31 (d, 1H, J = 17.1 Hz), 5.19 (d, 1H, J = 10.3 Hz), 3.90 (s, br, 1H), 3.83 (d, 2H, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.4, 141.2, 135.3, 1304., 128.6, 127.9, 126.2, 126.0, 116.3, 113.2, 46.5; IR (neat, cm^{-1}) 3408, 3027, 2825, 1611, 1160. Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.12. Found: C, 85.68; H, 7.15.

***N*-(3-Carbomethoxyphenyl)-3,5-xylidene (Table 4, Entry 15).** The general procedure using Cs_2CO_3 as the base gave 220 mg (86%) of the title compound as a white solid: mp 107−109 °C; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.68 (s, 1H), 7.55 (d, 1H, J = 7.04 Hz), 7.34−7.25 (m, 2H), 6.72 (s, 2H), 6.63 (s, 1H), 5.62 (S, br, 1H), 3.90 (s, 3H), 2.28 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.1, 143.7, 142.2, 139.0, 131.2, 129.2, 123.5, 121.4, 121.3, 118.2, 116.2, 52.1, 21.3; IR (neat, cm^{-1}) 3362, 2949, 1714, 1583, 1309. Anal. Calcd for $C_{16}H_{16}NO_2$: C, 75.23; H, 6.71. Found: C, 75.19; H, 6.72.

***N*-Methyl-*N*-benzyl-(4-carbomethoxy)aniline (Table 4, Entry 3)**. The general procedure using Cs_2CO_3 as the base gave 219 mg (86%) of a white solid: mp 67−68 °C. See above for NMR data.

Procedures for the Relative Rate Experiments Shown in Table 5. 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 (0.575 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 room temperature, and the IR acquisition was begun. After five 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*)-BINAP (11.7 mg, 0.0188 mmol, 0.75 mol %), and toluene (2.5 mL). The mixture was stirred at room temperature for ~1 min, and 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, NaO-*t*-Bu (336 mg, 3.5 mmol) was added, and 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 room temperature, and the IR acquisition was begun. After five 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, 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 room temperature, 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 room temperature for ~1 min, and 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, NaO-*t*-Bu (336 mg, 3.5 mmol) was added, and 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 room temperature, and the IR acquisition was begun. After five 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 were 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 tTime 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.

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