ORGANIC LETTERS

2011
Vol. 13, No. 8
1984–1987

Palladium-Catalyzed C,N-Cross Coupling Reactions of 3-Halo-2-aminopyridines

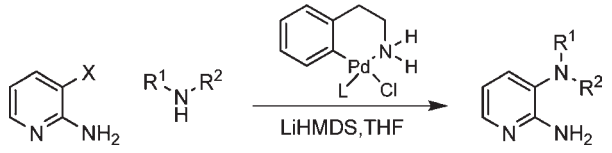
Felix Perez and Ana Minatti*

Department of Medicinal Chemistry, Amgen Inc., One Amgen Center Drive, Thousand Oaks, California 91320-1799, United States

aminatti@amgen.com

Received February 8, 2011

ABSTRACT



A simple approach toward N^3-substituted-2,3-diaminopyridines is presented, based on Pd-catalyzed C,N-cross coupling. The use of RuPhos- and BrettPhos-precatalysts in combination with LiHMDS allows for C,N-cross coupling reactions of unprotected 3-halo-2-aminopyridines with primary and secondary amines.

In the past decade, N^3-subsituted 2,3-diaminopyridines have been disclosed as potential therapeutics[1−3] for multiple indications. They also serve as versatile intermediates in the synthesis of further elaborated, biologically active heterocycles.[4−8]

Despite the emerging utility of N^3-substituted 2,3-diaminopyridines, the known synthetic routes remain mostly limited to two-step procedures: S_NAr reactions on 3-halo-2-nitropyridines followed by nitro reduction,[5,9] reductive alkylation[4,8,10] of 2,3-diaminopyridines, or amide coupling[6,8] of the aforementioned diamine followed by reduction.[11] Additionally, two modestly efficient copper-catalyzed aminations have been described, which are limited to 2-amino-3-iodopyridines[7] or the corresponding boronic ester.[2] Most importantly, all methods described to date are limited to the synthesis of N^3-alkylated 2,3-diaminopyridines while N^3-arylated products remain inaccessible.

Given the potential utility of N^3-subsituted 2,3-diaminopyridines, we felt that there was a need for a general and convenient synthetic method for their construction. We envisioned that a Pd-catalyzed C,N-cross coupling reaction of 3-bromo-2-aminopyridine might be amenable to the problem, given the maturity of the field and several recent advances.[12]

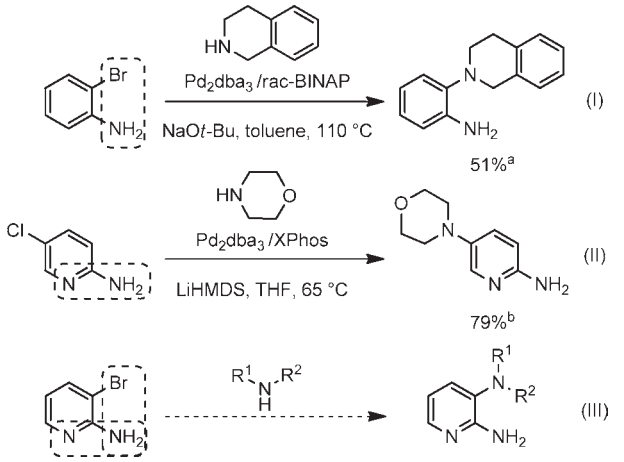
The potential challenges of 3-bromo-2-aminopyridine as the substrate in a Pd-catalyzed C,N-cross coupling reaction are 3-fold: (1) prevention or retardation of oxidative

(1) Kanai, K.; Hashimoto, K.; Goto, K. JP Patent 62223173, 1987.
(2) Steinig, A. G.; Mulvihill, M. J.; Wang, J.; Werner, D. S.; Weng, Q.; Kan, J.; Coate, H.; Chen, X. U.S. Patent 2009197862, 2009.
(3) (a) Illig, C. R.; Ballentine, S. K.; Chen, J.; Meegalia, S,; Rudolph, J.; Wall, M. J.; Wilson, K. J.; Desjarlais, R.; Manthey, C. L.; Flores, C. M.; Molloy, C. J. WO Patent 2006047504, 2006. (b) Illig, C. R.; Chen, J.; Wall, M. J.; Wilson, K. J.; Ballentine, S. K.; Rudolph, M. J.; DesJarlais, R. L.; Chen, Y.; Schubert, C.; Petrounia, I.; Crysler, C. S.; Molloy, C. J.; Chaikin, M. A.; Manthey, C. L.; Player, M. R.; Tomczuk, B. E.; Meegalla, S. K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1642.
(4) Goehring, R. R.; Matsumura, A. A,; Shao, B.; Taoda, Y.; Tsuno, N.; Whitehead, J. W. F.; Yao, J. WO Patent 2009027820, 2009.
(5) Jones, E. D.; Coates, J. A. V.; Rhodes, D. I.; Deadman, J. J.; VanDegraff, N. A.; Winfiled, L. J.; Thienthong, N.; Issa, W.; Choi, N.; Macfarlane, K. WO Patent 2008077188, 2008.
(6) Grewal, G,; Hennessy, E,; Kamhi, V.; Li, D.; Lyne, P.; Oza, V.; Saeh, J. C.; Su, Q.; Yang, B. WO Patent 2008056150, 2008.
(7) Shipps, G. W. Jr.; Cheng, C. C.; Huang, X.; Fischmann, T. O.; Duca, J. S.; Richards, M.; Zeng, H.; Sun, B.; Reddy, P. A.; Wong, T. T.; Tadikonda, P. K.; Siddiqui, M. A.; Labroli, M. M.; Poker, C.; Guzi, T. J. WO Patent 2008054702, 2008.
(8) Ohtsuka, M.; Haginoya, N.; Ichikawa, M.; Matsunaga, H.; Saito, H.; Shibata, Y.; Tsunemi, T.; Ishibashi, K. WO Patent 2010016490, 2010.
(9) Exception: For an S_NAr on 3-bromo-2-amino-5-phenylpyridine under harsh reaction conditions, seeChrisman, W.; Knize, M. G.; Tanga, M. J. *J. Heterocyclic Chem.* **2008**, *45*, 1641.
(10) Khanna, I. K.; Weier, R. M.; Lentz, K. T.; Swenton, L.; Lankin, D. C. *J. Org. Chem.* **1995**, *60*, 960.
(11) Additionally, the synthesis of 3-butylamino-2-amino-pyridine via nucleophilic substitution has been reported: Liu, Y.; Zhang, W.; Sayre, L. M *J. Heterocycl. Chem.* **2010**, *47*, 683.
(12) (a) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (b) Tasler, S.; Mies, J.; Langa, M. *Adv. Synth. Catal.* **2007**, *349*, 2286. (c) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (d) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *2*, 27.

10.1021/ol200371n
Published on Web 03/25/2011

addition due to potential coordination/chelation of palladium by the amidine-like structure, (2) hindrance of transmetalation due to coordination of the proximal amino group to the Pd(II) center after oxidative addition, and (3) formation of homocoupling product due to competition of 2-amino-halopyridine as the nucleophilic component. While there are few reports of each of these scenarios (Scheme 1, equations I[13] and II[14]), there is no precedent for a Pd-catalyzed C,N-cross coupling with a substrate that combines all three challenges (Scheme 1, equation III).

Scheme 1. Proposed Pd-Catalyzed Amination Reaction of 3-Bromo-2-aminopyridine and Potential Challenges



[a] See ref 13.
[b] See ref 14.

We decided to react 3-bromo-2-aminopyridine with morpholine under the same conditions as described previously for 5-chloro-2-aminopyridine[14] [Pd_2dba_3 (2 mol %)/XPhos (**L1**, 8 mol %) and LiHMDS (2.5 equiv) in THF at 65 °C for 16 h]. We were pleased to obtain 40% of the desired product along with unreacted starting material and 2-aminopyridine. Encouraged by this result, we examined structurally related biarylmonophosphine ligands **L1**–**L8** and palladacycles **Pre-L1, -L3, -L4, -L8**[15] leaving all the other reaction parameters unchanged (Figure 1). As palladium complexes of bidentate phosphine ligands have proven to be competent catalysts in the *N*-arylation of 2-aminopyridine itself and in the amination of 2-bromoaniline (Scheme 1, equation I), three representative ligands **L9**–**L11** of this class were also included in the catalyst screen.[16]

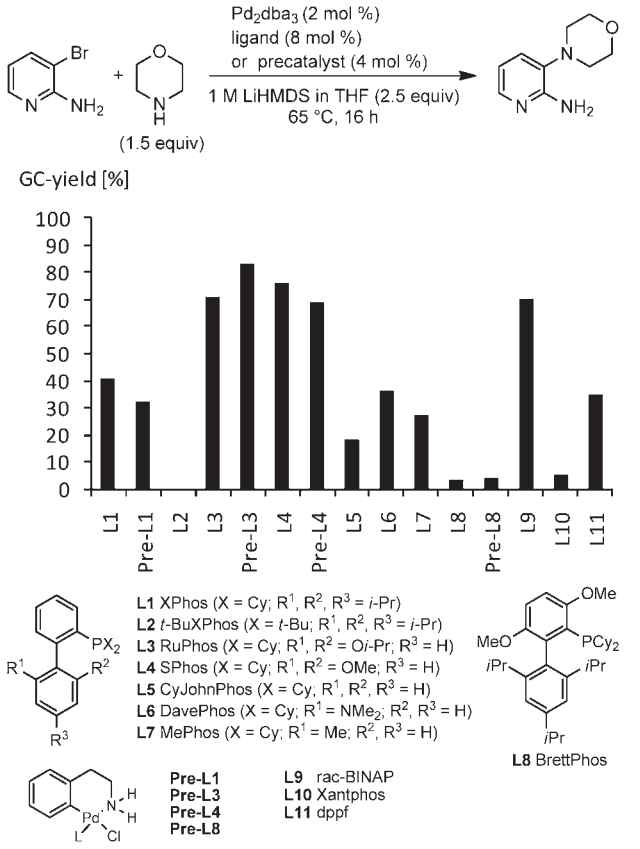


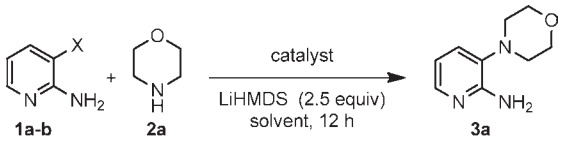
Figure 1. Ligand screen for C,N-cross coupling of morpholine to 3-bromo-2-aminopyridine. Yields are an average of two runs and were determined by GC analysis using dodecane as an internal standard.

The screening study revealed that the ligands RuPhos (**L3**), SPhos (**L4**), and BINAP (**L9**) performed similarly, affording the desired product in high yield (71, 76, and 71%, respectively) after 16 h (Figure 1). The yields obtained with the precatalysts were slightly lower in comparison to the corresponding Pd_2dba_3/ligand catalyst system, except for the RuPhos–precatalyst (**Pre-L3**), which exhibited a ~10% increase resulting in the highest yield (83%). Notably, at no point did we observe formation of "homocoupling product" due to 2-amino-halopyridine competing as the nucleophilic component nor the formation of 2,3-diaminopyridine as a consequence of LiHMDS functioning as an ammonia surrogate.

The superior performance of the RuPhos-precatalyst (**Pre-L3**, Table 1, entry 2) compared to the catalyst system Pd_2dba_3/BINAP (**L9**, Table 1, entry 3) was further demonstrated by its ability to effectively catalyze the reaction at room temperature (Table 1, entries 4 and 5) and to even couple 3-chloro-2-aminopyridine (Table 1, entries 6 and 7)

(13) Buckley, R. B.; Christie, S. D. R.; Elsegood, M. R. J.; Gillings, C. M.; Page, P. C. B.; Pardoe, W. J. M. *Synlett* **2010**, *6*, 939.
(14) Anderson, K. W.; Tundel, R. E.; Ikawa, T; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523.
(15) Palladacycles based upon biarylmonophosphines are operationally simple to handle precatalysts which are, easily acivated and ensure formation of the catalytically active monoligated Pd(0) species: (a) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686. (b) Fors, B, P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552. (c) Lee, B. K.; Biscoe, M. R.; Buchwald, S. L. *Tetrahedron Lett.* **2009**, *50*, 3672.
(16) (a) Jonckers, T. H. M.; Maes, B. U. W.; Guy, L. F.; Dommisse, L.; Dommisee, R. *Tetrahedron* **2001**, *57*, 7027. (b) Yin, J; Zhao, M. M.; Huffman, M. A.; McNamara, J. M. *Org. Lett.* **2002**, *4*, 3481. (c) Usui., S; Suzuki, T.; Hattori, Y.; Etoh, K.; Fujieda, H.; Nishizuka, M.; Imagawa, M.; Nakagawa, H.; Kohda, K.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1547. (d) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586.

Table 1. Variation of Reaction Parameters for the Coupling of Morpholine to 3-Halo-2-aminopyridine[a]



1a-b 2a 3a

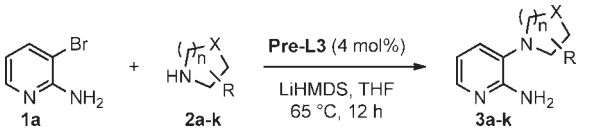
entry	X	catalyst	temp [°C]	solvent	yield[b]
1	Br	Pd_2dba_3/**L3**	65	THF	71
2	Br	**Pre-L3**	65	THF	83 (85)[c]
3	Br	Pd_2dba_3/**L9**	65	THF	71
4	Br	**Pre-L3**	rt	THF	68
5	Br	Pd_2dba_3/**L9**	rt	THF	11
6	Cl	**Pre-L3**	65	THF	76
7	Cl	Pd_2dba_3/**L9**	65	THF	0
8	Br	Pd_2dba_3/**L3**	90	dioxane	82
9	Br	Pd_2dba_3/**L3**	90	toluene	0
10	Br	$Pd(OAc)_2$/**L3**[d]	65	THF	51

[a] Reaction conditions: 3-halo-2-aminopyridine (1 mmol), morpholine (1.5 mmol), Pd_2dba_3 (2 mol %)/ligand (8 mol %), LiHMDS (2.5 mmol), solvent (2.5 mL) or 3-halo-2-aminopyridine (1 mmol), morpholine (1.5 mmol), **Pre-L3** (4 mol %), LiHMDS (2.5 mmol), solvent (2.5 mL). [b] Yields [%] were determined by GC analysis using dodecane as an internal standard. [c] Reaction was analyzed after 5 h reaction time. [d] $Pd(OAc)_2$ (4 mol %) was used.

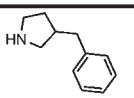
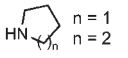
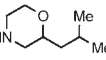
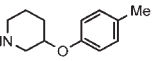
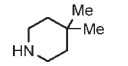
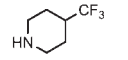
at 65 °C. Replacing THF with dioxane and increasing the reaction temperature from 65 to 90 °C delivered comparable results (Table 1, entries 1 and 8), though no product formation was observed in toluene (Table 1, entry 9). When initiating the reaction with a Pd-source in a higher oxidation state, only 51% yield was obtained [$Pd(OAc)_2$, Table 1, entry 10].[17] Alternative bases, such as NaO*t*Bu, K_3PO_4, Cs_2CO_3, K_2CO_3, or Na_2CO_3 proved to be ineffective in the coupling reaction and 2.5 equiv of LiHMDS were determined to be optimal.[18]

With these optimized reaction conditions in hand we set out to investigate the scope of the reaction with regard to the secondary cyclic amine coupling partner. High yields were obtained for a range of substituted morpholines (Table 2, entries 1−4) and piperidines (Table 2, entries 8−11); pyrrolidines were coupled in moderate yields (Table 2, entries 6−7). The ability to perform the reaction at room temperature proved important in the case of the Boc-protected piperazine as the yield was increased from 39 to 65% by lowering the reaction temperature (Table 2, entry 5). Substituents in positions 5 and 6 on the 3-bromo-2-aminopyridine were well tolerated, whereas substitution in position 4 was deleterious (Figure 2).

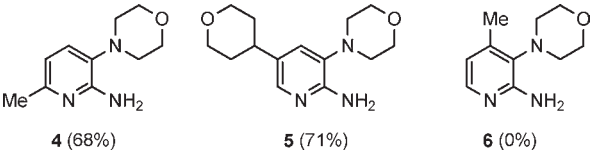
Table 2. Cross-Coupling of 3-Bromo-2-aminopyridine with Secondary Cyclic Amines[a]



1a 2a-k 3a-k

entry	HNR^1R^2	yield[b]	entry	HNR^1R^2	yield[b]
1		79 (76)[c] **3a**	6		53 **3f**
2		76 **3b**	7	 n = 1	53 (**3g**)
3		85 **3c**	8	n = 2	79 (**3h**)
4		70 **3d**	9		65 **3i**
5		65[d] (39) **3e**	10		65 **3j**
			11		81 **3k**

[a] Reaction conditions: 3- bromo-2-amino pyridine (1 mmol), amine (1.5 mmol), **Pre-L3** (4 mol %), LiHMDS (2.5 mmol, 1 M in THF), 65 °C, 12 h. [b] Isolated yields [%] are an average of two runs. [c] 3-Chloro-2-aminopyridine was used. [d] Reaction was run at room temperature.



4 (68%) **5** (71%) **6** (0%)

Figure 2. Amination of substituted 2-amino-3-bromopyridines; for reaction conditions see Table 2.

In contrast to the cross-coupling of secondary amines, BrettPhos-precatalyst (**Pre-L8**) outperformed RuPhos-precatalyst (**Pre-L3**) and Pd_2dba_3/BrettPhos (**L8**) in the coupling of 3-bromo-2-aminopyridine with a branched primary amine such as cyclopentylamine, yielding **8a** in 78% (Table 3, entry 1), compared to only 47 and 66%, respectively. Benzylamine and linear primary amines also proved to be competent under these reaction conditions yielding the corresponding products in moderate to good yields (Table 3, entries 3−5).

As mentioned above no synthesis of N^3-arylated 2,3-diaminopyridines has been described to date. A new screen of catalysts revealed again BrettPhos-precatalyst (**Pre-L8**) as the best system delivering **8f** up to 66% yield versus 42% when using Pd_2dba_3/BrettPhos (**L8**) (Table 3, entry 6). Electron-rich anilines were coupled in comparably high yields (Table 3, entries 7 and 8), electron-withdrawing groups were tolerated and in the case

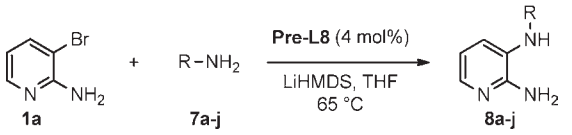
(13) Buckley, R. B.; Christie, S. D. R.; Elsegood, M. R. J.; Gillings, C. M.; Page, P. C. B.; Pardoe, W. J. M. *Synlett* **2010**, *6*, 939.

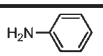
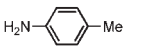
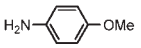
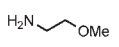
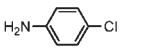
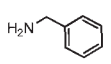
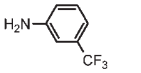
(14) Anderson, K. W.; Tundel, R. E.; Ikawa, T; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523.

(17) No product formation was observed without ligand or without palladium source under the reaction conditions.

(18) For the role of LiHMDS as a base to enable Pd-catalyzed C,N-cross coupling reactions in the presence of functional groups with acidic protons, see: (a) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885. (b) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965.

Table 3. Cross-Coupling of 3-Bromo-2-aminopyridine with Primary Amines[a]



entry	RNH_2	yield[b]	entry	RNH_2	yield[b]
1		78 (69)[c] **8a**	6		66 (61)[d] **8f**
2		70 **8b**	7		73 **8g**
3	H_2N-*n*-Hex	58 **8c**	8		75 **8h**
4		48 **8d**	9		66 **8i**
5		70 **8e**	10		63 **8j**

[a] Reaction conditions: 3-bromo-2-aminopyridine (1 mmol), amine (1.5 mmol), **Pre-L8** (4 mol %), LiHMDS (2.5 mmol, 1 M in THF), 65 °C, 12 h. [b] Isolated yields [%] are an average of two runs. [c] 3-Chloro-2-aminopyridine was used.

of *para*-chloroaniline no competitive coupling on the chloride was observed (Table 3, entries 9 and 10).

Finally, as N^3,N^5-disubsituted 2,3,5-triaminopyridines have been disclosed as important pharmacophores,[3] we set out to synthesize this scaffold using our methodology. First, 3,5-dibromo-2-aminopyridine (**9**) was reacted with morpholine following the general conditions (Scheme 2). Three different products (**10**–**12**) were formed, the major product being 2-morpholine-5-bromo-2-aminopyridine (**11**)[19] arising from preferred coupling in position 3.[20,21]

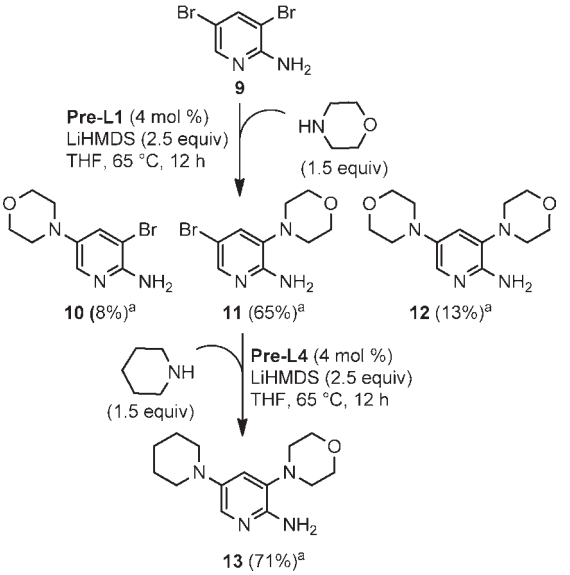
XPhos-precatalyst (**Pre-L1**) gave slightly better selectivity than RuPhos-precatalyst (**Pre-L3**) with respect to the desired product **11** (1:8:1.6, 86% total yield vs 1:8.5:3, 75% total yield). The ratio of the products was not altered by shortening the reaction time or by performing the reaction at room temperature. After isolating 2-morpholine-5-bromo-2-aminopyridine (**11**), a second Pd-catalyzed C,N-cross coupling reaction with piperidine was carried out. From all precatalysts tested SPhos-precatalyst (**Pre-L4**) performed best and provided product **13** in 71% yield.

(19) Product configuration was confirmed by NOE experiment.

(20) The prefered C,N-cross coupling in position 3 is in accordance with selectivities observed in C,C-cross coupling reactions: (a) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett*. **2007**, *48*, 6951. (b) Zhao, S.-B.; Cui, Q.; Wang, S.-N. *Organometallics* **2010**, *29*, 998.

(21) For the origin of regioselectivity in Pd-catalyzed cross-coupling reactions of polyhalogenated heterocycles, see: Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc*. **2007**, *129*, 12664.

Scheme 2. Sequential Pd-Catalyzed C,N-Cross Coupling of 3,5-Dibromo-2-aminopyridine



[a] Isolated yields.

In summary, we have identified reaction conditions for the efficient Pd-catalyzed C,N-cross coupling of unprotected 3-halo-2-aminopyridines with a range of primary and secondary amines. Additionally, the method described herein allowed for the synthesis of N^3-arylated 2,3-diaminopyridines, which had been unprecedented to date. The precatalysts derived from the ligands RuPhos and BrettPhos were identified as outstanding catalyst systems for secondary amines and primary amines, respectively, which is in accordance with recently identified trends.[22]

Acknowledgment. We thank Prof. Stephen L. Buchwald (Massachusetts Institute for Technology) and Dr. Nick A. Paras (Amgen Inc.) for insightful discussions. Felix Perez thanks the National Institutes of Health Chemistry Biology Interface Training program at UCLA for support.

Supporting Information Available. Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) (a) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci*. **2011**, *2*, 57. (b) Henderson, J. L.; McDermott, S. M.; Buchwald, S. L. *Org. Lett*. **2010**, *12*, 4438. (c) Henderson, J. L.; Buchwald, S. L. *Org. Lett*. **2010**, *12*, 4442.