

Palladium-Catalyzed Amination of *N*-Free 2-Chloro-7-azaindole

Aurélie Plas, Camille Martin, Nicolas Joubert, and Marie-Claude Viaud-Massuard*

GICC UMR 7292 CNRS-Université de Tours, Equipe 4 Innovation Moléculaire et Thérapeutique, UFR Sciences Pharmaceutiques, 31 avenue Monge, 37200 Tours, France

S Supporting Information

ABSTRACT: A simple and efficient procedure for the Pd-catalyzed amination of *N*-free 2-chloro-7-azaindole is described, using either primary or secondary amines. An optimized combination of Brettphos, a Brettphos precatalyst, and LiHMDS in THF led us to a novel methodology, applied to various functionalized amines to study the scope of the reaction. This is the first report of cross-coupling amination on *N*-free 2-chloro-7-azaindole.



Azaindoles have prompted growing pharmacological interest due to their broad spectrum activities, including anti-inflammatory¹ or antitumor properties (Figure 1).² The

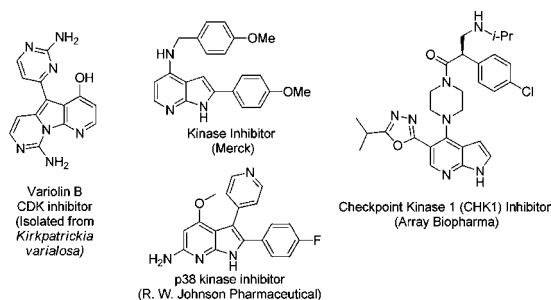


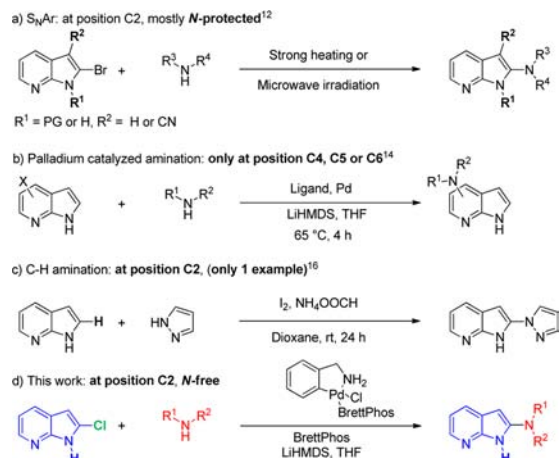
Figure 1. Aminated 7-azaindoles as potent inhibitors.

replacement of a carbon atom by nitrogen at position 7 in the indole skeleton provides the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine), a molecular architecture naturally occurring in variolin B,³ an alkaloid isolated from the marine sponge *Kirkpatrickia variolosa* and known to be a potent CDK inhibitor. The proximity of two nitrogen atoms, in this bioisostere of an indole or purine base, induces altered electronic properties due to both the neighboring hydrogen-bond donor and acceptor, a special feature explored in medicinal chemistry^{1,2} as well as in organic synthesis^{4,5} and fluorescence spectroscopy.⁶

To study 7-azaindole reactivity, Pd-catalyzed functionalizations at all positions of 7-azaindole have been successfully achieved in recent years.⁷ Nevertheless, Pd-catalyzed C–C bond formations, i.e. arylation through Suzuki cross-coupling reactions⁸ or alternate direct C–H activation,⁹ alkenylation,¹⁰ (Heck or Stille) and Sonogashira alkynylation,¹¹ seem to require *N*-alkyl or *N*-sulfonyl protection.^{7–11} C–N bond formation performed on 7-azaindole appears to be even more challenging. *S_NAr* displacement reactions have been performed mostly on *N*-protected azaindoles, but required strong heating or microwave activation on either 2-halo-7-azaindoles¹² or 4-halo-7-azaindoles.¹³ Pd-catalyzed cross-coupling of primary and secondary amines with halo-7-azaindoles have been reported but were

restricted on the pyridine ring.¹⁴ Alternatively on position 2, only metal-free iodine-promoted amination using a *N*-sulfonyl amine¹⁵ or direct C–H azolation¹⁶ were successfully achieved, but in each case with a very limited scope (one amine) (Scheme 1). Therefore, a more general and suitable method is needed to

Scheme 1. Various Aminations on 7-Azaindole



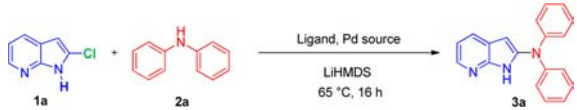
give access to original aminated 7-azaindoles, which are also important scaffolds in medicinal chemistry (Figure 1). Herein, we wish to report a Pd-catalyzed cross-coupling amination on *N*-free 2-chloro-7-azaindole with various primary and secondary amines.

Our initial efforts to find suitable conditions toward pallado-catalyzed amination were pursued using 2-chloro-7-azaindole **1a**, prepared in three steps from commercially available 7-azaindole (see Supporting Information (SI)),^{17,18} and diphenylamine **2a** as coupling partners, in the presence of different catalyst/ligand systems (Table 1, entries 1–5). Unfortunately in all cases, no reaction occurred. Similar findings were reported, with unsuccessful Buchwald–Hartwig amination on *N*-free 2-

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Table 1. Optimization of Ligand/Pd Catalysts for C2 Amination of 2-Chloro-7-azaindole 1a with Diphenylamine 2a^a



entry	catalyst	(equiv)	ligand	(equiv)	yield ^b (%)
1	Pd ₂ dba ₃	(0.1)	PPh ₃	(0.1)	n.r. ^c
2	Pd ₂ dba ₃	(0.1)	XantPhos	(0.1)	n.r.
3	Pd ₂ dba ₃	(0.1)	bdCyp ^d	(0.1)	n.r.
4	Pd(OAc) ₂	(0.1)	Binap-rac	(0.1)	n.r.
5	Pd(OAc) ₂	(0.1)	CyPF-tBu ^e	(0.1)	n.r.
6	Pd(OAc) ₂	(0.1)	RuPhos	(0.1)	n.r.
7	Pd(OAc) ₂	(0.1)	BrettPhos ^f	(0.1)	30
8	Pd ₂ dba ₃	(0.1)	BrettPhos	(0.1)	20
9	BPPC ^g	(0.1)	BrettPhos	(0.1)	70
10	BPPC	(0.05)	BrettPhos	(0.05)	70
11	BPPC	(0.04)	BrettPhos	(0.04)	50
12	BPPC	(0.025)	BrettPhos	(0.025)	n.r.

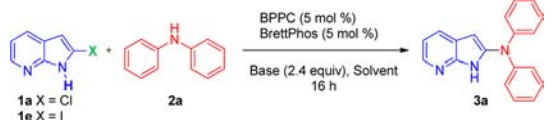
^aReaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), LiHMDS (1.2 mmol, 1 M in THF), 65 °C, 16 h. ^bIsolated yield. ^cn.r. = no reaction. ^dbdCyp = (2-biphenyl)dicyclohexylphosphine. ^eCyPF-tBu = Josiphos ligand. ^f2-(Dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl. ^gBrettPhos Precatalyst = Chloro[2-(dicyclohexylphosphino)-3,6-dimethoxy-2',4',6'-triisopropyl-1,1'-biphenyl] [2-(2-aminoethyl)phenyl] palladium(II).

bromo-indole.¹⁹ Indeed, *N*-free heterocycles or five-membered heterocyclic halide electrophiles, like 2- or 3-bromopyrrole, are known to be notoriously difficult partners in cross-coupling aminations.²⁰

To overcome these limitations, we turned our attention to Buchwald's recent work dealing with RuPhos and BrettPhos,¹⁹ well-known to be key dialkylbiaryl phosphine ligands for coupling heteroaryl halides with secondary or functionalized amines.²¹ Surprisingly, no reaction took place in the presence of Pd(OAc)₂ and RuPhos (Table 1, entry 6), whereas the combination of Pd(OAc)₂ and BrettPhos enabled the amination with 30% yield (Table 1, entry 7). Interestingly, Pd₂dba₃ can also be employed with BrettPhos, but gave a lower yield (Table 1, entry 8). Finally, the combination of a BrettPhos precatalyst (BPPC) and BrettPhos is the most effective system, providing the desired product in 70% yield after 16 h (Table 1, entry 9). This result confirmed the synergy between BrettPhos and BPPC already mentioned in recent literature.²² Then, we studied catalyst and precatalyst loadings (Table 1, entries 9–12), and we found that the optimal quantity of the ligand and palladium source was 5 mol % (Table 1, entry 10). Indeed, a further decrease of catalyst and precatalyst loadings led only to a lower yield (Table 2, entry 11) or even to no reaction (Table 1, entry 12). Finally, a quick kinetic study showed that the optimal reaction time was 16 h for C2 amination of **1a** with diphenylamine **2a** (see SI).

Alternative combinations of solvents and bases were studied (Table 2, entries 2–5),^{14b,23} but unfortunately no reaction occurred in any new cases and starting material **1a** was recovered. In our study, first LiHMDS was confirmed to be the best base of choice for cross-coupling amination of a *N*-free haloheterocycle.²⁴ Second, a smaller quantity of base led only to recovered starting material (data not shown); thus, at least 2.4 equiv are necessary for amination, as previously reported in a similar

Table 2. Optimization of the Reaction Conditions^a



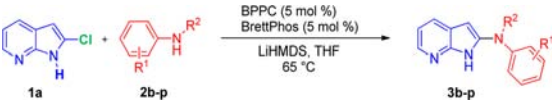
entry	X	base	solvent	temp (°C)	yield (%)
1	Cl	LiHMDS	THF	65	70
2	Cl	K ₂ CO ₃	<i>t</i> -BuOH	110	n.r.
3	Cl	<i>t</i> -BuONa	PhMe	110	n.r.
4	Cl	K ₃ PO ₄	DME	110	n.r.
5	Cl	Cs ₂ CO ₃	<i>t</i> -BuOH	110	n.r.
6	Cl	LiHMDS	THF	rt	n.r.
7	I	LiHMDS	THF	65	30 (45) ^b

^aReaction conditions: 2-halogeno-7-azaindole (0.5 mmol), **2a** (0.5 mmol), BrettPhos (5 mol %), BPPC (5 mol %), base (2.4 equiv), solvent (1 mL). ^bIsolated yield in parentheses of C2–C2 dimer of azaindole.

work.²⁵ We also observed that cross-coupling amination did not proceed at room temperature (Table 2, entry 6). Finally, C2 amination of 2-iodo-7-azaindole **1e** afforded **3a** with only a 30% yield, along with the C2–C2 dimer of 7-azaindole as a byproduct with a 45% yield. As expected, while the conversion rate is better, iodinated starting material is too reactive²⁶ and thus inappropriate for performing optimized amination. Therefore, the best conditions for performing cross-coupling amination of *N*-free 2-chloro-7-azaindole **1a** with diphenylamine **2a** were 1 equiv of **1a** with 1 equiv of **2a** in the presence of 2.4 equiv of LiHMDS (1 M THF), 5 mol % of BrettPhos, and 5 mol % of BPPC, with stirring for 16 h at 65 °C.

With optimized conditions in hand, we first investigated the challenging reactivity of *N*-free 2-chloro-7-azaindole **1a** toward a wide range of substituted primary anilines (Table 3, entries 1–12). First, amination of **1a** in the presence of aniline **2b** afforded

Table 3. Cross-Coupling Aminations of 2-Chloro-7-azaindole 1a with Various Substituted Anilines^a



entry	R ¹	R ²	reaction time (h)	product	conversion rate (%) ^b	yield (%)
1	H	H	4	3b	100	60
2	<i>o</i> -OMe	H	4	3c	100	72
3	<i>m</i> -OMe	H	4	3d	100	60
4	<i>p</i> -OMe	H	4	3e	70	25
5	<i>o</i> -OH	H	4	3f	100	50
6	<i>o</i> -Me	H	4	3g	100	40
7	<i>m</i> -Me	H	4	3h	100	16
8	<i>p</i> -Me	H	4	3i	100	11
9	<i>p</i> -NO ₂	H	16	3j	0	0
10	<i>p</i> -NH ₂	H	16	3k	50	22
11	H	Et	4	3l	100	60
12	<i>o</i> -OMe	Et	16	3m	0	0
13	<i>m</i> -OMe	Et	4	3n	100	60
14	<i>p</i> -OMe	Et	4	3o	100	67
15	<i>p</i> -NO ₂	Et	16	3p	0	0

^aReaction conditions: **1a** (0.5 mmol), amine (0.5 mmol), BrettPhos (5 mol %), BPPC (5 mol %), LiHMDS (1.2 mmol, 1 M in THF), 65 °C, 4–16 h. ^bEstimated conversion rate according to TLC monitoring.

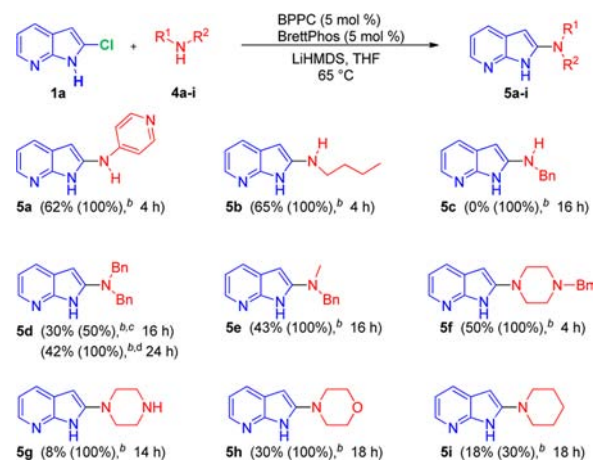
in such conditions the desired product **3b** in 60% yield. We were satisfied to observe that aniline **2b**, and also primary amines **2c–i**, required a reaction time of only 4 h to observe complete disappearance of the starting material (monitored by TLC). Importantly, it is noteworthy that no degradation was observable after treatment of the crude product just before purification. Therefore, differences between conversion rates and yields are only due to degradation during column chromatography.²⁷ Thus, we were able to perform aminations of **1a** with various anilines bearing EDG (Table 3, entries 2–8) with good to excellent yields in most cases. As expected, the best yields were observed with anilines **2c–f** containing substituents with an attractive inductive and mesomeric donor effect (Table 3, entries 2–5), while anilines **2g–i** presenting substituents with only an inductive donor effect gave moderate yields (Table 3, entries 6–8). Reaction with *ortho*-aminophenol **2f** in our conditions allowed C–N bond formation selectivity over C–O with an average yield of 50%. Despite complete disappearance of the starting material, we were surprised to observe low yields for anilines **2e**, **2h**, and **2i**, whose substituents are *p*-OMe, *m*-Me, and *p*-Me, respectively. While all compounds are purified by flash chromatography on previously neutralized silica gel, it appeared that the aminated derivatives (**3e**, **3h**, and **3i**) were even less stable than the other compounds.

Unfortunately, even after 16 h of reaction time, we were not able to perform Buchwald–Hartwig cross-coupling reactions with primary anilines bearing, in the *para* position, an electron-withdrawing group (EWG) such as nitro (Table 3, entry 9), cyano, or ethyl ester (data not shown), and **1a** was totally recovered.²⁸ Our optimized conditions also confirmed the selectivity of BrettPhos between primary and secondary amines, using aniline bearing a secondary amine in the *para* position (Table 3, entry 10), by giving a selective coupling with the primary amine, though with a moderate yield of 22% due to the instability of **3k**.²²

Then, we investigated the reactivity of a wide range of substituted secondary amines (Table 3, entries 11–15). Although secondary amines are known to be challenging partners for Pd-catalyzed amination,²⁹ performing cross-coupling aminations with secondary aliphatic-aromatic amines gratifyingly gave results consistent with those obtained previously with primary anilines. Indeed, coupling with *N*-ethylaniline **2l** (Table 3, entry 11) gave a similar result to aniline **2b** and afforded the desired compound **3l** in 60% yield. Coupling with *meta* **2n** and *para* methoxy-*N*-ethylaniline **2o** provided the desired compounds **3n** and **3o** in 60% and 67% yields respectively (Table 3, entries 13 and 14). In contrast, no reaction occurred between **1a** and *ortho* methoxy-*N*-ethylaniline **2m** (Table 3, entry 12). The hydrogen of the amine and oxygen of the methoxy group may interact through hydrogen bonding, forming a stable five-membered ring. Consequently, the deprotonation step is no longer feasible, as suggested by Buchwald for the coupling of secondary hindered amines and *ortho*-substituted aryl halides.³⁰ As expected, no reaction was possible using *para* nitro-*N*-ethylaniline **2p** as a coupling partner containing an EWG (Table 3, entry 15).

We studied the scope of the reaction with various primary and secondary amines (Scheme 2). We noted with satisfaction that coupling *para* aminopyridine **4a** with **1a** was successfully achieved to give **5a** with 62% yield. Indeed, couplings of heteroarylamines on heteroaryl halides are challenging due to their low nucleophilicity and their difficulty to undergo reductive elimination, and they usually required higher catalyst loadings²¹

Scheme 2. Scope of Cross-Coupling Amination of **1a** with Various Primary and Secondary Amines^a



^aReaction conditions: **1a** (0.5 mmol), amine (0.5 mmol), BrettPhos (5 mol %), BPPC (5 mol %), LiHMDS (1.2 mmol, 1 M in THF), 65 °C, 4–16 h. ^bBetween parentheses, estimated conversion rate according to TLC monitoring. ^c50% of **1a** was recovered after column chromatography. ^d20 mol % of BPPC and BrettPhos were used for 24 h.

and protection of the heterocyclic NH.³¹ It is noteworthy to report that we were able to couple chlorinated azaindole **1a** with aliphatic amines. These amines are known to be difficult partners requiring high catalyst loadings.³² Butylamine **4b** and *N*-benzylpiperazine **4f** gave **5b** and **5f** with 65% and 50% yields, respectively. Under these conditions piperazine **4g** and morpholine **4h** only gave the desired compounds **5g** and **5h** respectively in 8% and 30% yield, even if TLC monitoring indicated complete conversion of the starting material. Unfortunately, degradation occurred during coupling of piperidine **4i**, explaining the moderate yield of 18%. No product of coupling **5c** was isolated with benzylamine; however, **1a** was completely converted after 16 h of reaction time (TLC monitoring) into a new product unstable during purification by flash chromatography. We must emphasize that coupling bulky dibenzylamine **4d** gave **5d** in 30% yield, using the classical conditions (and 50% of **1a** was recovered), and in 42% yield, using a higher catalyst loading (20 mol %) allowing complete disappearance of **1a**. *N*-Methylbenzylamine **4e** was successfully coupled to **1a** to give **5e** in 43% yield. Bulky amines **4d** and **4e** required a prolonged reaction time to observe the complete disappearance of **1a** (monitored by TLC), due to steric hindrance that slows the binding of the obtained species after the oxidative addition. The use of **1a** can therefore be regarded as providing 2-amino-7-azaindole as a key scaffold. However, the preliminary attempts of debenzylation have been at this time unsuccessful (see SI).

In conclusion, we explored the scope and the limitations of an efficient palladium-catalyzed amination of *N*-free 2-chloro-7-azaindole, easily available in three steps. This methodology provides quite efficient access to a large variety of 2-amino-7-azaindoles with a wide primary and secondary amine scope. These conditions provided selectivity on one hand for C–N bond over C–O bond formation and on the other hand for coupling a primary over a secondary amine. We were able to access new 2-substituted amino-7-azaindole scaffolds, and further insight into biological evaluations of these analogs is being pursued.

■ ASSOCIATED CONTENT**■ Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.5b02173](https://doi.org/10.1021/acs.orglett.5b02173).

Experimental procedures and spectral data of all products (PDF)

■ AUTHOR INFORMATION**Corresponding Author**

*E-mail: mcviaud@univ-tours.fr

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Chaulet, C.; Croix, C.; Alagille, A.; Normand, S.; Delwail, A.; Favot, L.; Lecron, J.-C.; Viaud-Massuard, M.-C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1019–1022. (b) Sandham, D. A.; Adcock, C.; Bala, K.; Barker, L.; Brown, Z.; Dubois, G.; Budd, D.; Cox, B.; Fairhurst, R. A.; Furegati, M.; Leblanc, C.; Manini, J.; Proft, R.; Reilly, J.; Stringer, R.; Schmidt, A.; Turner, K. L.; Watson, S. J.; Willis, J.; Williams, G.; Wilson, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4794–4798. (c) Henry, J. R.; Rupert, K. C.; Dodd, J. H.; Turchi, I. J.; Wadsworth, S. A.; Cavender, D. E.; Fahmy, B.; Olini, G. C.; Davis, J. E.; Pellegrino-Gensey, J. L.; Schafer, P. H.; Siekierka, J. J. *J. Med. Chem.* **1998**, *41*, 4196–4198.
- (2) Recent selected papers: (a) Carbone, A.; Pennati, M.; Parrino, B.; Loperogo, A.; Barraja, P.; Montalbano, A.; Spano, V.; Sbarra, S.; Doldi, V.; De Cesare, M.; Cirrincione, G.; Diana, P.; Zaffaroni, N. *J. Med. Chem.* **2013**, *56*, 7060–7072. (b) Starha, P.; Travnické, Z.; Popa, A.; Popa, L.; Muchova, T.; Brabec, V. *J. Inorg. Biochem.* **2012**, *115*, 57–63. (c) Tung, Y.-S.; Coumar, M. S.; Wu, Y.-S.; Shiao, H.-Y.; Chang, J.-Y.; Liou, J.-P.; Shukla, P.; Chang, C.-W.; Chang, C.-Y.; Kuo, C.-C.; Yeh, T.-K.; Lin, C.-Y.; Wu, J.-S.; Wu, S.-Y.; Liao, C.-C.; Hsieh, H.-P. *J. Med. Chem.* **2011**, *54*, 3076–3080.
- (3) Walker, S. R.; Carter, E. J.; Huff, B. C.; Morris, J. C. *Chem. Rev.* **2009**, *109*, 3080–3098.
- (4) Reviews: (a) Ila, H.; Markiewicz, J. T.; Malakhov, V.; Knochel, P. *Synthesis* **2013**, *45*, 2343–2371. (b) Merour, J. Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471–506.
- (5) (a) Larraya, C.; Guillard, J.; Renard, P.; Audinot, V.; Boutin, J.; Delagrangé, P.; Bennejean, C.; Viaud-Massuard, M.-C. *Eur. J. Med. Chem.* **2004**, *39*, 515–526. (b) Guillard, J.; Larraya, C.; Viaud-Massuard, M.-C. *Heterocycles* **2003**, *60*, 865–877.
- (6) Hsieh, C.-C.; Jiang, C.-M.; Chou, P.-T. *Acc. Chem. Res.* **2010**, *43*, 1364–1374.
- (7) Reviews: (a) Merour, J. Y.; Routier, S.; Suzenet, F.; Joseph, B. *Tetrahedron* **2013**, *69*, 4767–4834. (b) Popowycz, F.; Routier, S.; Joseph, B.; Merour, J. Y. *Tetrahedron* **2007**, *63*, 1031–1064.
- (8) (a) Adams, N. D.; Adams, J. L.; Burgess, J. L.; Chaudhari, A. M.; Copeland, R. A.; Donatelli, C. A.; Drewry, D. H.; Fisher, K. E.; Hamajima, T.; Hardwicke, M. A.; Huffman, W. F.; Koretke-Brown, K. K.; Lai, Z. V.; McDonald, O. B.; Nakamura, H.; Newlander, K. A.; Oleykowski, C. A.; Parrish, C. A.; Patrick, D. R.; Plant, R.; Sarpong, M. A.; Sasaki, K.; Schmidt, S. J.; Silva, D. J.; Sutton, D.; Tang, J.; Thompson, C. S.; Tummino, P. J.; Wang, J. C.; Xiang, H.; Yang, J.; Dhanak, D. *J. Med. Chem.* **2010**, *53*, 3973–4001. (b) Medina, J. R.; Grant, S. W.; Axtén, J. M.; Miller, W. H.; Donatelli, C. A.; Hardwicke, M. A.; Oleykowski, C. A.; Liao, Q.; Plant, R.; Xiang, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2552–2555.
- (9) (a) Kannaboina, P.; Anilkumar, K.; Aravinda, S.; Vishwakarma, R. A.; Das, P. *Org. Lett.* **2013**, *15*, 5718–5721. (b) Huestis, M. P.; Fagnou, K. *Org. Lett.* **2009**, *11*, 1357–1360. (c) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897–2900.
- (10) Joseph, B.; Da Costa, H.; Merour, J. Y.; Léonce, S. *Tetrahedron* **2000**, *56*, 3189–3196.
- (11) Layek, M.; Gajare, V.; Kalita, D.; Islam, A.; Mukkanti, K.; Pal, M. *Tetrahedron* **2009**, *65*, 4814–4819.
- (12) (a) Apelqvist, T.; Cheng, A.; Rhönnsstad, P.; Hagberg, L.; Krüger, L. Patent WO 2011042474, 2011. (b) Wu, G.; Chan, K.; Ewing, T.; Ibrahim, P. N.; Lin, J.; Nespi, M.; Spevak, W.; Zhang, Y. Patent WO 2014100620, 2014.
- (13) Caldwell, J. J.; Cheung, K. M.; Collins, I. *Tetrahedron Lett.* **2007**, *48*, 1527–1529.
- (14) (a) Surasani, R.; Kalita, D.; Rao, A. V. D.; Chandrasekhar, K. B. *Beilstein J. Org. Chem.* **2012**, *8*, 2004–2018. (b) Henderson, J. L.; McDermott, S. M.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4438–4441. (c) Guillard, J.; Decrop, M.; Gallay, N.; Espanel, C.; Boissier, E.; Herault, O.; Viaud-Massuard, M.-C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1934–1937. (d) Henderson, J. L.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 4442–4445.
- (15) Prasad, B.; Sreenivas, B. Y.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Kumar, K. L.; Pal, M. *Chem. Commun.* **2013**, *49*, 3970–3972.
- (16) Wu, W. B.; Huang, J.-M. *Org. Lett.* **2012**, *14*, 5832–5835.
- (17) Sandham, D. A.; Adcock, C.; Bala, K.; Brown, Z.; Dubois, G.; Wilson, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4794–4798.
- (18) Chaulet, C.; Croix, C.; Basset, J.; Pujol, M.-D.; Viaud-Massuard, M.-C. *Synlett* **2010**, *2010*, 1481–1484.
- (19) Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861–2873.
- (20) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710–4713.
- (21) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57–68.
- (22) Fors, B. F.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552–13554.
- (23) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
- (24) (a) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527. (b) Perez, F.; Minatti, A. *Org. Lett.* **2011**, *13*, 1984–1987.
- (25) Harris, M. C.; Huang, X.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 2885–2888.
- (26) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755–2763.
- (27) Purification on column chromatography using alumina instead of previously neutralized silica did not improve the yield of the desired product (tested for **5d**).
- (28) No reaction was observed using primary anilines bearing a nitro group in either the *meta* or *ortho* position or a cyano or ethyl ester in the *para* position as a coupling partner.
- (29) (a) Bolm, C.; Frison, J. C.; Le Pailh, J.; Moessner, C.; Raabe, G. *J. Organomet. Chem.* **2004**, *689*, 3767–3777. (b) Patriciu, O. I.; Pillard, C.; Finaru, A. L.; Sandulescu, L.; Guillaumet, G. *Synthesis* **2007**, *2007*, 3868–3876.
- (30) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50.
- (31) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968.
- (32) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131–209.