Organic LETTERS

Letter

pubs.acs.org/OrgLett

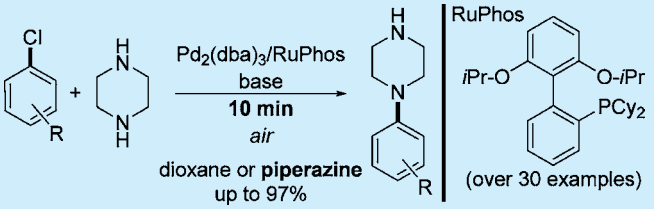
Pd-Catalyzed Synthesis of Piperazine Scaffolds Under Aerobic and Solvent-Free Conditions

Sean W. Reilly and Robert H. Mach*

Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104, United States

Supporting Information

ABSTRACT: A facile Pd-catalyzed methodology providing an efficient synthetic route to biologically relevant arylpiperazines under aerobic conditions is reported. Electron donating and sterically hindered aryl chlorides were aminated to afford yields up to 97%, with examples using piperazine as solvent, illustrating an ecofriendly, cost-effective synthesis of these privileged structures.



N-Arylpiperazine moieties are prevalent in a vast amount of biologically active compounds,[1] which display various pharmacological activities such as antiproliferative,[2] antidepressant,[3] antiretroviral therapy of human immunodeficiency virus (HIV),[4] antimalarial,[5] anti-Parkinsons,[6] antianxiety,[7] and dopamine selective properties,[8] and represent a potential gateway in combating substance abuse and dementia (Figure 1).[9] In 2001 alone, the MDL Drug Data Report (MDDR) contained 2271 phenyl-piperazines, with 16 accounting for marketed drugs, while 23 were in phase II/III clinical trials across 18 therapeutic areas.[10]

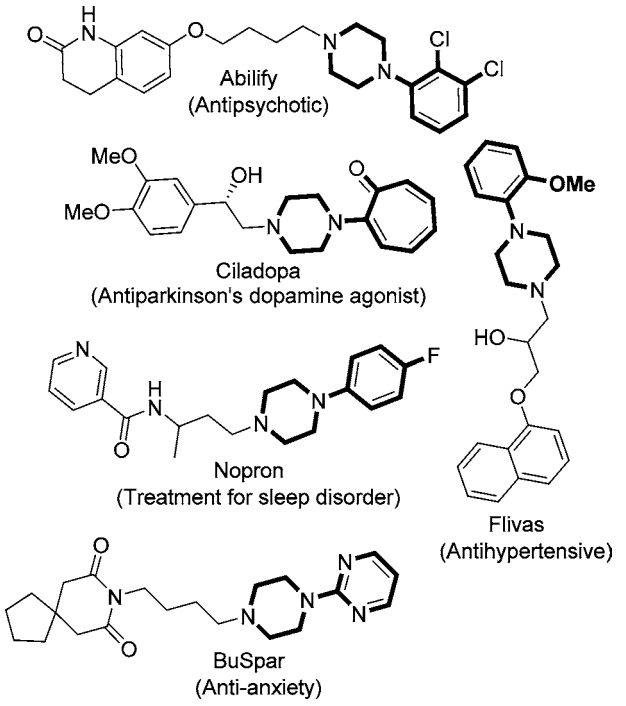


Figure 1. Bioactive compounds containing cyclic and arylpiperazine scaffolds.

Furthermore, aripiprazole (Ablify) earned more than $7.9 billion in 2015, making it the second highest selling medication after holding the top spot in 2014.[11] Therefore, synthesis and implementation of this privileged structure continue to play a vital role in drug development.

Traditional synthesis of *N*-arylpiperazines requires the appropriate aniline precursor and bis(2-chloroethyl)amine hydrochloride.[12] However, this synthetic method involves elevated temperatures, extended reaction times up to 24 h, and is hampered by costly substituted anilines. Piperazine arlyation with aryl halides using phase transfer catalysts has been documented as well; however, 12−24 h reaction times were also required.[13] Examples of microwave-assisted synthesis of *N*-arylpiperazines have been reported, but they too require substituted anilines.[14] The Buchwald−Hartwig amination provides an attractive alternative via Pd-catalyzed C−N bond formation of aryl halides and amines.[15] This catalysis has been applied to development of many bioactive compounds and is currently the only reported methodology to facilitate a key step in the synthesis of the lung cancer drug Zykadia.[16] In 2008, Buchwald and co-workers reported 10 min C−N cross coupling reactions with aryl chlorides using air- and moisture-stable Pd-precatalysts (Figure 2).[17] To our knowledge, there have been no reports extending this 10 min catalysis to a broad scope synthesis of *N*-arylpiperazines.

Compared to other examples of Pd-catalyzed *N*-arylpiperazine synthesis,[18] this methodology would not require anhydrous solvents, an inert atmosphere, and would be applicable to notoriously unreactive, electron-rich and sterically congested aryl chlorides. In this report, we provide a 10 min, benchtop synthesis demonstrating a wide scope with readily available aryl and *N*-heterocyclic chlorides. We also include ecofriendly examples of using piperazine as solvent, affording modest to good yields. This methodology will assist in the development of structurally

Received: August 29, 2016
Published: October 13, 2016

DOI: 10.1021/acs.orglett.6b02591
Org. Lett. 2016, 18, 5272−5275

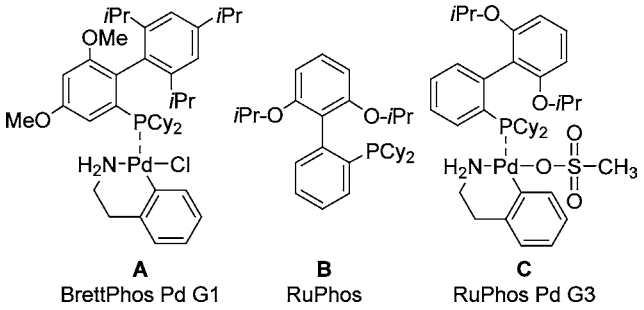


Figure 2. Pd-precatalysts examined.

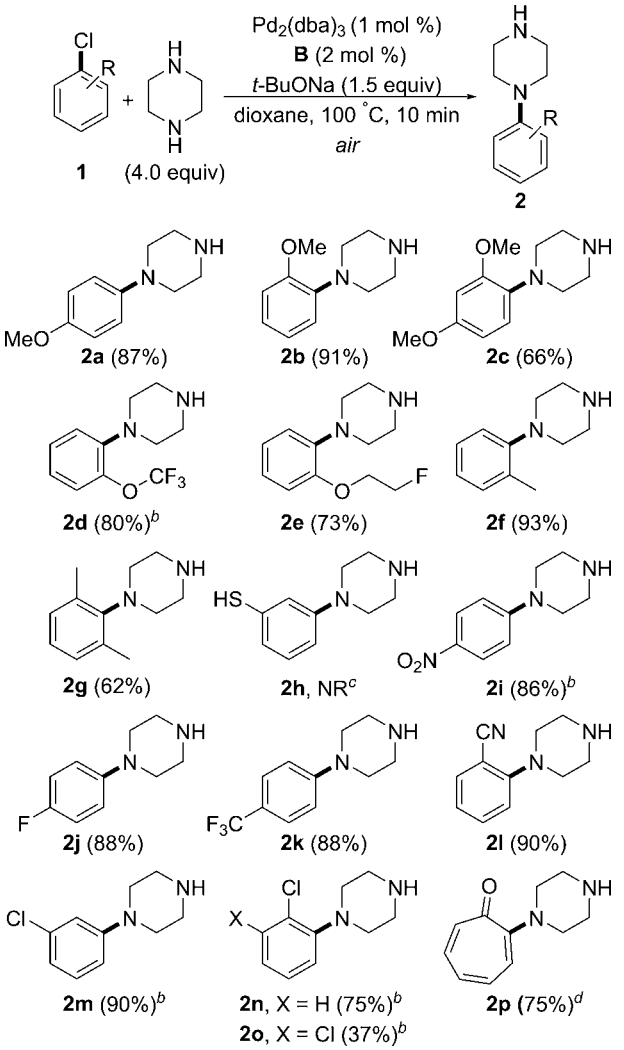
diverse and sterically demanding, *N*-arylpiperazine compounds having a wide range of biological activity.

Initial efforts to optimize piperazine *N*-arylation were conducted using a 1:1 ratio of **A** and **B** following previously reported conditions with 1.5 equiv of piperazine.[19] Although minimal aryl chloride was detected by LCMS after 10 min, a significant amount of the undesirable bis-arylated piperazine was observed. After exhausting other solvents and catalyst loading options, a 2:1 ratio of RuPhos/$Pd_2(dba)_3$ consistently provided moderate to high yields of the monoarylated piperazine in 10 min. With optimized conditions in hand, a broad range of electron rich and deficient aryl chlorides were investigated (Scheme 1). Screening was limited to chloride substrates due to the economic value of these commercially available reagents, compared to bromides and iodides. It is worth noting, no additional product formation was observed beyond the 10 min reaction time, unless otherwise noted. Milder base (Cs_2CO_3) was examined throughout the aryl chloride scope (Scheme 1); however, lower yields were obtained compared to trials conducted with *t*-BuONa.

Investigation began with a series of anisoles, affording the desired products **2a**−**b** in good yield; and a modest 66% yield with strongly deactivated **1c**. Substrate **1a** was also investigated with well-defined RuPhos complex **C** (Figure 2) at 1 mol %; however, only a 21% yield of **2a** was afforded. The base sensitivity of the trifluoromethyl ether substituent on **1d** required reducing the *t*-BuONa to 1.1 equiv to obtain a good yield of **2d**. The reaction conditions were also applied to synthesize **2e**, a key intermediate in the development of fluorinated D_3 dopamine receptor ligands for positron emission tomography (PET) imaging studies,[20] currently ongoing in our lab. Catalytic activity was impeded with sterically crowded **1g**; yielding 62% of **2g** in 10 min.

Functional group compatibility was further explored to determine the tolerance of these substituents in the outlined reaction conditions. No product formation was observed with **1h**, potentially due to coordination of the thiol substituent to the Pd-center, thus inhibiting catalytic activity. When using 1.1 equiv of the alkoxide base, nitro arene **2i** was isolated in 86% yield, while other electron-poor aryl chlorides **1j**−**l** provided excellent yields as well. As expected, an increase of the bis-arylated side-product was observed by LCMS with electron deficient aryl chlorides **1i**−**1l**, compared to electron rich substrates **1a**−**1g** in which unreacted arene was observed after 10 min reaction trials. It is worth mentioning control reactions were also performed for electron-poor aryl chlorides without the catalyst system to ensure the yields obtained were not a result of S_NAr chemistry. The reaction conditions also provided access to chloro *N*-arylpiperazine motifs **2m**−**n**, found in many antipsychotics[21] in good yield. However, only a 37% yield of **2o** was recovered due to

Scheme 1. Piperazine Arylation Scope with Aryl Chlorides[a]



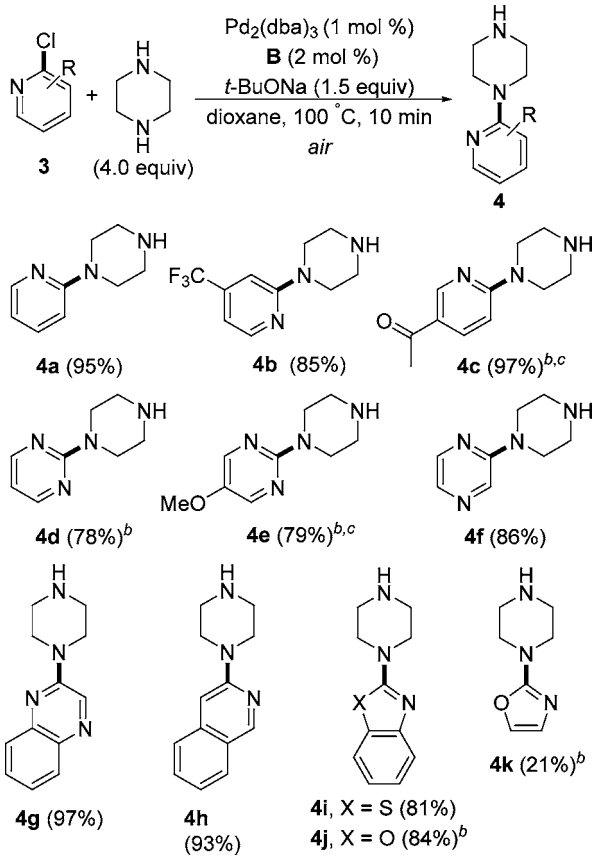
[a]Conditions: $Pd_2(dba)_3$ (1 mol %), **B** (2 mol %), substrate (2 mmol), piperazine (4.0 equiv), *t*-BuONa (1.5 equiv), and dioxane (7.0 mL), 10 min. Isolated yields. Reaction monitored by LCMS. [b]1.2 equiv of *t*-BuONa used. [c]Substrate was still observed by LCMS after 10 min reaction time. [d]1.5 equiv of Cs_2CO_3 used as base.

side-product formation with the trichloro substrate **1o**. Lastly, substrate **1p** was investigated using 1.5 equiv of milder base Cs_2CO_3 to determine if nonaryl substrates were compatible with the illustrated reaction conditions. Indeed, the desired piperazine motif **2p**, present in Ciladopa, was afforded at a 75% yield.

Nitrogen heterocycles were then investigated as these *N*-arylpiperazine scaffolds are commonly found in many biologically active compounds (Scheme 2).[13a,22] The high yields acquired with *N*-aryl chlorides matched previously reported trends of faster reductive elimination rates to form carbon−nitrogen bonds from Pd-complexes containing a heteroaromatic ring.[23] For example, a yield of 94% was obtained with **3a**, and excellent yields of **4c**−**e** were afforded with milder base Cs_2CO_3. The scope was expanded beyond six-membered heteroaromatic rings, **3g**−**h**, to include 2-chloroquinoline, affording the serotonin receptor agonist[3] quipazine, **4h**, in 93% yield. Excellent C−N cross-coupling activity continued with benzothiazole and benzoxazole chlorides, **3i**−**j**, compounds with anticancer[24] and antipsychotic[25] properties, respectively. However, sluggish

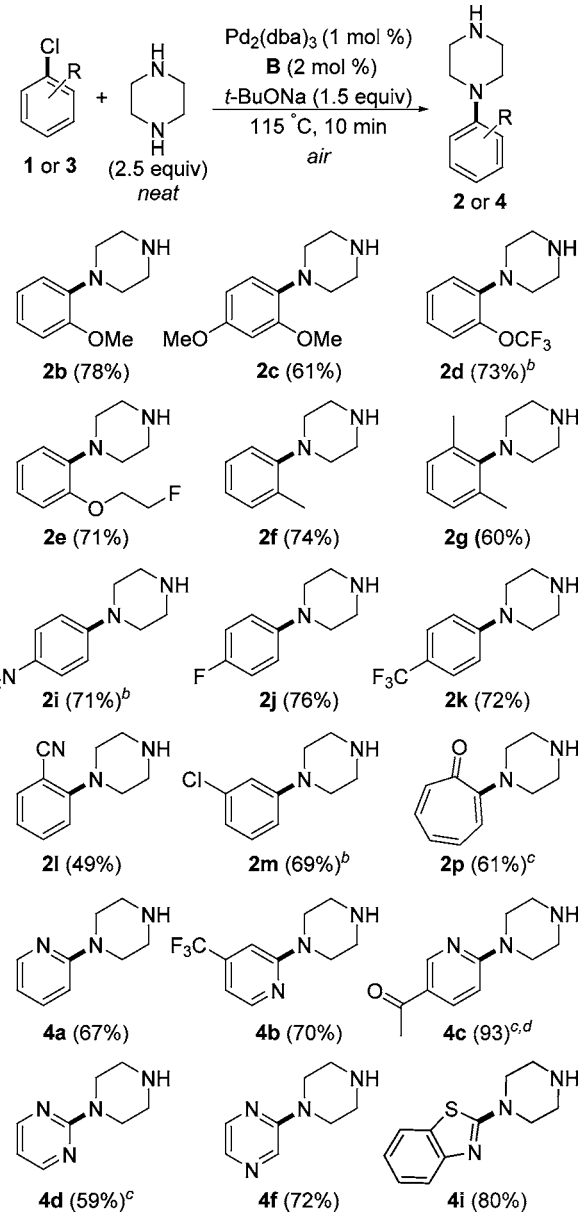
DOI: 10.1021/acs.orglett.6b02591
Org. Lett. 2016, 18, 5272−5275

Scheme 2. Piperazine Arylation Scope with *N*-Aryl Chlorides[a]



[a]Conditions: $Pd_2(dba)_3$ (1 mol %), **B** (2 mol %), substrate (2 mmol), piperazine (4.0 equiv), *t*-BuONa (1.5 equiv), and dioxane (7.0 mL), 10 min. Isolated yields. Reaction monitored by LCMS. [b]1.5 equiv of Cs_2CO_3 used as base. [c]Reaction time extended to 30 min.

Scheme 3. Neat Piperazine Arylation[a]



[a]Conditions: $Pd_2(dba)_3$ (1 mol %), **B** (2 mol %), substrate (1 mmol), piperazine (2.5 equiv), *t*-BuONa (1.5 equiv), 10 min. Isolated yields. Reaction monitored by LCMS. [b]1.2 equiv of *t*-BuONa used as base. [c]1.5 equiv of Cs_2CO_3 used as base. [d]Reaction time extended to 30 min.

reactivity was observed with the five-membered heterocycle 2-chlorooxazole, **3k**, despite extending the reaction time beyond 10 min. Lower reactivity of five-membered heterocyclic electrophiles has previously been reported due to the electronic properties of certain ring positions that can be unfavorable for Pd-catalyzed coupling.[26]

Lastly, we wanted to investigate a solvent-free arylation of piperazine to demonstrate a "green" amination procedure (Scheme 3). While the Buchwald–Hartwig remains a dominant tool in C–N bond formation, reports illustrating solvent-free conditions are rare.[27] Of those reports, only one example of unprotected piperazine has been examined, resulting in a high yield of the bis-arylated product.[27g] After optimizing piperazine equivalents with **1b**, we were able to obtain modest yields of the desired monoarylated products with selected chloride substrates. Although the afforded isolated yields are lower than those listed in Schemes 1 and 2, mainly due to bis-arylation, this method provides a more ecofriendly alternative by eliminating the need for potentially hazardous solvents.

In conclusion, excellent yields of arylpiperazines were obtained in a one-pot, 10 min Buchwald–Hartwig amination, under aerobic conditions. Moderate to good yields were also obtained when conducting the reactions neat in piperazine, demonstrating an ecofriendly application to this catalysis. Finally, this procedure eliminates reaction times of many hours and provides an efficient and vastly synthetically useful methodology in developing complex piperazine scaffolds of biological and pharmaceutical interest.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02591.

Experimental procedure, NMR, and mass spectral data of the isolated products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rmach@mail.med.upenn.edu.

DOI: 10.1021/acs.orglett.6b02591
Org. Lett. 2016, 18, 5272–5275

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

National Institute on Drug Abuse [(R01 DA29840-07 to R.H.M.) and (R01 DA23957-06 to R. R. Luedtke, University of North Texas Health Science Center-Fort Worth)] is gratefully acknowledged for financial support.

■ REFERENCES

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.
(2) (a) Berardi, F.; Abate, C.; Ferorelli, S.; de Robertis, A. F.; Leopoldo, M.; Colabufo, N. A.; Niso, M.; Perrone, R. *J. Med. Chem.* **2008**, *51*, 7523. (b) Abate, C.; Niso, M.; Contino, M.; Colabufo, N. A.; Ferorelli, S.; Perrone, R.; Berardi, F. *ChemMedChem* **2011**, *6*, 73. (c) Mao, Z.-W.; Zheng, X.; Lin, Y.-P.; Hu, C.-Y.; Wang, X.-L.; Wan, C.-P.; Rao, G.-X. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3421. (d) Chen, H.; Xu, F.; Liang, X.; Xu, B.-B.; Yang, Z.-L.; He, X.-L.; Huang, B.-Y.; Yuan, M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 285. (e) Mao, Z.; Zheng, X.; Qi, Y.; Zhang, M.; Huang, Y.; Wan, C.; Rao, G. *RSC Adv.* **2016**, *6*, 7723.
(3) Cappelli, A.; Anzini, M.; Vomero, S.; Mennuni, L.; Makovec, F.; Doucet, E.; Hamon, M.; Bruni, G.; Romeo, M. R.; Menziani, M. C.; De Benedetti, P. G.; Langer, T. *J. Med. Chem.* **1998**, *41*, 728.
(4) Romero, D. L.; Morge, R. A.; Genin, M. J.; Biles, C.; Busso, M.; Resnick, L.; Althaus, I. W.; Reusser, F.; Thomas, R. C.; Tarpley, W. G. *J. Med. Chem.* **1993**, *36*, 1505.
(5) Mendoza, A.; Pérez-Silanes, S.; Quiliano, M.; Pabón, A.; Galiano, S.; González, G.; Garavito, G.; Zimic, M.; Vaisberg, A.; Aldana, I.; Monge, A.; Deharo, E. *Exp. Parasitol.* **2011**, *128*, 97.
(6) Koller, W. C.; Fields, J. Z.; Gordon, J. H.; Perlow, M. J. *Neuropharmacology* **1986**, *25*, 973.
(7) Loane, C.; Politis, M. *Brain Res.* **2012**, *1461*, 111.
(8) Audinot, V.; Newman-Tancredi, A.; Gobert, A.; Rivet, J.-M.; Brocco, M.; Lejeune, F.; Gluck, L.; Desposte, I.; Bervoets, K.; Dekeyne, A.; Millan, M. J. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 187.
(9) (a) Sokoloff, P.; Foll, B. L.; Perachon, S.; Bordet, R.; Ridray, S.; Schwartz, J.-C. *Neurotoxic. Res.* **2001**, *3*, 433. (b) Pilla, M.; Perachon, S.; Sautel, F.; Garrido, F.; Mann, A.; Wermuth, C. G.; Schwartz, J.-C.; Everitt, B. J.; Sokoloff, P. *Nature* **1999**, *400*, 371. (c) Khaled, M. A. T. M.; Farid Araki, K.; Li, B.; Coen, K. M.; Marinelli, P. W.; Varga, J.; Gaál, J.; Le Foll, B. *Int. J. Neuropsychopharmacol.* **2010**, *13*, 181. (d) Grundt, P.; Carlson, E. E.; Cao, J.; Bennett, C. J.; McElveen, E.; Taylor, M.; Luedtke, R. R.; Newman, A. H. *J. Med. Chem.* **2005**, *48*, 839. (e) Garcia-Ladona, F. J.; Cox, B. F. *CNS Drug Rev.* **2003**, *9*, 141.
(10) Nilsson, J. W.; Thorstensson, F.; Kvarnström, I.; Oprea, T.; Samuelsson, B.; Nilsson, I. *J. Comb. Chem.* **2001**, *3*, 546.
(11) Brown, T.; Medscape Medical News: WebMD, 2015.
(12) (a) Mishani, E.; Dence, C. S.; McCarthy, T. J.; Welch, M. J. *Tetrahedron Lett.* **1996**, *37*, 319. (b) Neuville, L.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 4091. (c) Ravilla, L.; Venkata Subba Naidu, N.; Nagarajan, K. *Tetrahedron Lett.* **2015**, *56*, 4541.
(13) (a) Hepperle, M.; Eckert, J.; Gala, D. *Tetrahedron Lett.* **1999**, *40*, 5655. (b) Eckert, J.; Chan, T.-M.; Osterman, R. M.; Lambert, J. B.; Gala, D. *Tetrahedron Lett.* **1999**, *40*, 5661. (c) Verma, S. K.; Ghorpade, R.; Kaushik, M. P. *Synth. Commun.* **2014**, *44*, 2645.
(14) (a) Jaisinghani, H. G.; Khadilkar, B. M. *Tetrahedron Lett.* **1997**, *38*, 6875. (b) Gao, R.; Canney, D. J. *J. Org. Chem.* **2010**, *75*, 7451.
(15) (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (e) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23. (f) Johansson Seechurn, C. C. C.; DeAngelis, A.; Colacot, T. J. *New Trends in Cross-Coupling: Theory and Applications*; The Royal Society of Chemistry, 2015.
(16) Flick, A. C.; Ding, H. X.; Leverett, C. A.; Kyne, R. E., Jr; Liu, K. K. C.; Fink, S. J.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2016**, *24*, 1937.
(17) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.
(18) (a) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617. (b) Zhao, S.-H.; Miller, A. K.; Berger, J.; Flippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 4463. (c) Romero, M.; Harrak, Y.; Basset, J.; Ginet, L.; Constans, P.; Pujol, M. D. *Tetrahedron* **2006**, *62*, 9010. (d) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 9135. (e) Verma, S. K.; Acharya, B. N.; Kaushik, M. P. *Org. Biomol. Chem.* **2011**, *9*, 1324. (f) Hepperle, M.; Eckert, J.; Gala, D.; Shen, L.; Anderson Evans, C.; Goodman, A. *Tetrahedron Lett.* **2002**, *43*, 3359.
(19) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.
(20) (a) Tu, Z.; Li, S.; Cui, J.; Xu, J.; Taylor, M.; Ho, D.; Luedtke, R. R.; Mach, R. H. *J. Med. Chem.* **2011**, *54*, 1555. (b) Chu, W.; Tu, Z.; McElveen, E.; Xu, J.; Taylor, M.; Luedtke, R. R.; Mach, R. H. *Bioorg. Med. Chem.* **2005**, *13*, 77.
(21) (a) Lawler, C. P.; Prioleau, C.; Lewis, M. M.; Mak, C.; Jiang, D.; Schetz, J. A.; Gonzalez, A. M.; Sibley, D. R.; Mailman, R. B. *Neuropsychopharmacology* **1999**, *20*, 612. (b) Cusack, B.; Nelson, A.; Richelson, E. *Psychopharmacology* **1994**, *114*, 559.
(22) (a) Broekkamp, C. L. E.; Leysen, D.; Peeters, B. W. M. M.; Pinder, R. M. *J. Med. Chem.* **1995**, *38*, 4615. (b) Chen, Y.-L.; Fang, K.-C.; Sheu, J.-Y.; Hsu, S.-L.; Tzeng, C.-C. *J. Med. Chem.* **2001**, *44*, 2374. (c) Yan, X.; Mirzai, B.; Chackalamannil, S.; Czarniecki, M.; Wang, S.; Clemmons, A.; Ahn, H.-S.; Boykow, G. C. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 919.
(23) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534.
(24) (a) Gurdal, E.; Ebru, B.; Irem, D.; Rengul, C.-A.; Mine, Y. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 382. (b) Gurdal, E. E.; Durmaz, I.; Cetin-Atalay, R.; Yarim, M. *J. Enzyme Inhib. Med. Chem.* **2015**, *30*, 649.
(25) Huang, L.; Zhang, W.; Zhang, X.; Yin, L.; Chen, B.; Song, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5299.
(26) (a) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734. (b) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371. (c) Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 4710.
(27) (a) Artamkina, G. A.; Ermolina, M. V.; Beletskaya, I. P. *Mendeleev Commun.* **2003**, *13*, 158. (b) Basolo, L.; Bernasconi, A.; Broggini, G.; Gazzola, S.; Beccalli, E. M. *Synthesis* **2013**, *45*, 3151. (c) Basolo, L.; Bernasconi, A.; Borsini, E.; Broggini, G.; Beccalli, E. M. *ChemSusChem* **2011**, *4*, 1637. (d) Marelli, E.; Chartoire, A.; Le Duc, G.; Nolan, S. P. *ChemCatChem* **2015**, *7*, 4021. (e) Chartoire, A.; Boreux, A.; Martin, A. R.; Nolan, S. P. *RSC Adv.* **2013**, *3*, 3840. (f) Topchiy, M. A.; Dzhevakov, P. B.; Rubina, M. S.; Morozov, O. S.; Asachenko, A. F.; Nechaev, M. S. *Eur. J. Org. Chem.* **2016**, *2016*, 1908. (g) Topchiy, M. A.; Asachenko, A. F.; Nechaev, M. S. *Eur. J. Org. Chem.* **2014**, *2014*, 3319.

DOI: 10.1021/acs.orglett.6b02591
Org. Lett. 2016, 18, 5272−5275