Published in final edited form as:

Org Lett. 2015 December 4; 17(23): 5788–5791. doi:10.1021/acs.orglett.5b02898.

Palladium-Catalyzed Benzylic C–H Arylation of Azaarylmethylamines

Byeong-Seon Kim^{#†}, Jacqueline Jiménez^{#†,‡}, Feng Gao^{†,§}, and Patrick J. Walsh^{*†}

[†]Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323, United States

[‡]Facultad de Ciencias Químicas, Benemérita Universidad Autónoma de Puebla, Puebla 72570, Mexico

[§]Department of Medicinal Plants, Agronomy College, Sichuan Agricultural University, 211 Huimin Road, Wenjiang Region, Chengdu 611130, PR China

[#] These authors contributed equally to this work.

Abstract

A direct C–H functionalization approach to produce aryl(azaaryl)methylamines from azaarylmethylamines without directing groups is described. Under conditions where the azaarylmethylamines' C–H is reversibly deprotonated, a Pd(OAc)₂/NIXANTPHOS-based catalyst couples the resulting carbanions with various aryl halides to provide aryl(azaaryl)methylamines. This umpolung strategy directly provides tertiary amines without protecting or activating groups.

Pyridine and quinoline derivatives are important heterocycles that are present in a broad range of biologically active natural products and pharmaceutically relevant compounds.¹ Aryl(azaaryl)methylamines are prominent in biologically active small molecules, exhibiting antitumor,² anti-virus,³ anti-HIV,⁴ and antihistamine activities⁵ (Figure 1). Furthermore, recent statistical studies indicate that the prominence of heteroaromatic rings in marketed oral drugs is increasing.⁶

Conventional approaches to the synthesis of 1,1-diarylmethylamine derivatives⁷ include substitution reactions with amine nucleophiles, addition of aryl or azaaryl organometallic

*Corresponding Author, ; Email: pwalsh@sas.upenn.edu.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02898.

Spectroscopic characterization data and procedures for preparation of all new compounds (PDF)

Notes

The authors declare no competing financial interest.

reagents to imines, and reduction of imines.⁸ Despite the popularity of these methods, they involve prefunctionalized electrophiles or nucleophiles. Transition-metal-catalyzed cross-coupling reactions also represent an attractive approach.^{7d} The direct C–H functionalization of amino alkyl moieties ($R'CH_2NR_2$), however, is challenging⁹. Therefore, activated substrates, such as Boc-protected amines, ketimines, and (η^6 -benzylamine)Cr(CO)₃ complexes, have been employed to facilitate deprotonation of C–H bonds adjacent to nitrogen (Figure 2).¹⁰ The activating groups necessary in Figure 2 to increase reactivity are often subsequently transformed into the desired functional groups or excised from the product entirely, decreasing the synthetic efficiency.

Considering the importance of aryl(azaaryl)methylamines, the development of in situ deprotonation/arylation strategies for their synthesis that do not employ activating groups would be valuable. Based on our experience in deprotonative cross-coupling reactions^{10c–f,11} with weakly acidic substrates, we hypothesized that the reversible deprotonation of (aminomethyl)pyridines in the presence of a palladium catalyst should be possible.

Herein, we report a practical method to prepare aryl(azaaryl)methylamines from (aminomethyl)pyridines and aryl halides using a Pd–NIXANTPHOS-based catalyst (Scheme 1). This approach affords single-step access to aryl(azaaryl)methylamines from simple starting materials. Notably, to the best of our knowledge, the direct functionalization of aminomethyl azaarenes has not been successfully achieved prior to this work.

We anticipated two challenges to advancing a successful deprotonative cross-coupling process (DCCP) with (aminomethyl)pyridine derivatives: (1) introduction of conditions for the in situ deprotonation of the weakly acidic C–H's of the substrate and (2) identification of a catalyst capable of promoting coupling of the resulting organolithium, -sodium, or -potassium derivatives with aryl halides. In the latter case, we have found that palladium complexes of van Leeuwen's NIXANTPHOS ligand¹² outperform other Pd–phosphine complexes in this class of reactions. As such, it has become our “go to” ligand for new substrate classes. Concerning the deprotonation step, the pK_a of the sp^3 -hybridized C–H's of 2-(aminomethyl)pyridines are unknown, although that of 2-methylpyridine has been determined to be 34 in THF.¹³ The high pK_a value of these substrates suggests that alkoxide and silylamide bases are good starting points. Additionally, palladium-catalyzed benzylic arylations of pyridine derivatives have become a powerful method to construct aryl(azaaryl)methane derivatives.¹⁴

We initially tested the reactions of 2-(morpholinomethyl)pyridine (**1a**) with 1-bromo-4-*tert*-butylbenzene using Pd-(OAc)₂ (5 mol %) and NIXANTPHOS (7.5 mol %) in THF at 65 °C. Six bases [LiO-*t*-Bu, NaO-*t*-Bu, KO-*t*-Bu, LiN(SiMe₃)₂, NaN(SiMe₃)₂, and KN(SiMe₃)₂] were employed, and the results are displayed in entries 1–6 of Table 1.

Although MO-*t*-Bu bases [M = Li, Na, K] did not generate the desired product **3a** (entries 1–3), MN(SiMe₃)₂ bases (M = Li, Na, K) were all very promising, affording 80–87% assay yield (AY) of the cross-coupling product **3a** (entries 4–6). The most promising result was obtained with LiN(SiMe₃)₂ (87% AY as determined by ¹H NMR, entry 4). We next screened other ethereal solvents (DME, CPME, 1,4-dioxane) (entries 7–9). Of these, 1,4-dioxane led

to 90% AY of the desired product (entry 9). Examination of the stoichiometry indicated use of a 1:1.2:2 ratio of pyridylmethylamine (**1a**)/1-bromo-4-*tert*-butylbenzene (**2a**)/LiN(SiMe₃)₂ rendered 98% AY of **3a**, leading to 92% isolated yield (entry 11). Use of a stoichiometric amount of 1-bromo-4-*tert*-butylbenzene (**2a**) or lower catalyst loading [2.5 mol % Pd(OAc)₂ and 3.75 mol % of NIXANTPHOS] resulted in incomplete conversion at 65 °C after 12 h (entries 12–13). The optimized conditions (entry 11, Table 1) were then used to define the substrate scope.

The scope of the arylation was initially explored with 2-(cyclic amino)methylpyridines (**1**) using aryl bromides (Scheme 2). Morpholine, pyrrolidine, and *N*-methylpiperazine were coupled with aryl bromides bearing various substituents, generating aryl(2-pyridyl)methylamines in good to excellent isolated yields (65–98%). The arylated products **3b–d** were obtained in 78–83% yield with bromobenzene and 1-bromonaphthalene. Under the same reaction conditions, chlorobenzene was also a suitable coupling partner, providing **3b** in 78% yield. Aryl bromides bearing electron-donating 4-NMe₂ and 4-OMe resulted in coupling products **3e–h** in 71–94% yield. Aryl bromides with electron-withdrawing 4-F and 3-CF₃ groups were well tolerated and provided aryl(2-pyridyl)methylamines **3i–k** in 71–94% yield. Heterocyclic 3-bromopyridine was also a suitable coupling partner to generate dipyridylmethyl morpholine **3l** in 65% yield. The reactions with 1 mol % of catalyst generally occurred in good yields (71–75% yield, **3d**, **3g**, and **3i**). To illustrate the scalability of our method, we conducted coupling of 2-(morpholinomethyl)pyridine (**1a**, 10 mmol) with 1-bromo-4-fluorobenzene using 4 mol % of catalyst. The coupling product **3m** was isolated in 96% yield (2.61 g).

Next, we turned our attention to acyclic amines. The optimized arylation conditions employed with cyclic amines were easily transferable to *N,N*-dimethyl- or -diethylamine derivatives with a variety of aryl bromides. Thus, aryl bromides with neutral (4-*t*-Bu, 3-Me), electron-donating (4-OMe, 4-NMe₂), or electron-withdrawing (4-F, 4-Cl, 3-OMe, 3-CF₃) substituents coupled with 2-(*N,N*-dialkylaminomethyl)pyridine, providing the cross-coupling products **4a–o** in 60–98% yield (Scheme 3). The yields with *N,N*-dimethylamine derivatives are slightly higher than those with cyclic amines. Several relatively challenging substrates (1-bromo-4-trifluoromethylbenzene and 5-bromobenzofuran) were also competent coupling partners, albeit in reduced yields (**4i,j**, 60–66% yield). While 1-bromonaphthylene furnished coupling product **4k** in 69% yield, the sterically more hindered 2-bromotoluene failed to provide the desired product (<2% yield). 2-(3-Bromophenyl)-1,3-dioxolane generated acetal-protected aldehyde product **4l** in 60% yield. When the same conditions were applied to 2-(*N,N*-diethylaminomethyl)pyridine, the desired products **4m–o** were isolated in 66–69% yield. Sterically more hindered 2-(*N*-benzyl-*N*-methylaminomethyl)pyridine did not react (<2% yield). Similar results were observed in related reactions by Baudoin and our groups with bulkier substituents on nitrogen.^{11o,15}

The above results led us to wonder if this method would be limited to 2-pyridyl derivatives because it requires a directed metalation for the deprotonation. To answer this question, other heterocyclic substrates were tested. Although the p*K*_a's of 4-pyridylmethylamines are not reported, 4-methylpyridine has a p*K*_a of 32.2 in THF.¹³ As shown in Scheme 4, 4-pyridylmethylamine derivatives were excellent substrates, providing coupling products in

55–92% yield (**5a–h**) with 1 mol % catalyst loading. These results indicate that chelation of the base to the 2-pyridyl group is not necessary for the reversible deprotonation step of this DCCP.

Additional heterocycles were also amenable to the DCCP. Under the conditions used for 2-pyridylamines, a 2-(aminomethyl)quinoline derivative underwent a direct arylation reaction in 52% yield (**5i**). The least acidic substrate tested in this study was the 3-pyridylmethylamine derivative. The pK_a of 3-methylpyridine is 37.7 in THF.¹³ After extensive optimization of bases, solvents, and temperature, we were able to achieve coupling in the presence of 2 equiv of $KN(SiMe_3)_2$ in THF at 110 °C, resulting in arylation product **5j** in 65% yield.

In summary, we report the first direct palladium-catalyzed *benzylic C(sp³)-H* arylation of cyclic and acyclic aminomethyl-substituted azaarenes with aryl bromides. A variety of aryl(azaaryl)methylamines were prepared in good to excellent yields from readily accessible tertiary aminomethyl azaarenes. It is noteworthy that addition and removal of directing groups was not necessary with these substrates, facilitating their streamlined synthesis. This new method enables the rapid preparation of druglike molecules using straightforward techniques that are ideal for applications in medicinal chemistry.¹⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Financial support for this work was provided by NIH/NIGMS (GM 104349). J.J. thanks CONACyT (México) for fellowships. F.G. thanks the China Scholarship Counsel for fellowships.

REFERENCES

- (1) (a). Henry GD. Tetrahedron. 2004; 60:6043. (b) Michael JP. Nat. Prod. Rep. 2005; 22:627. [PubMed: 16193160] (c) Laird T. Org. Process Res. Dev. 2006; 10:851. (d) Joule, JA.; Mills, K. Heterocyclic Chemistry. 5th ed. John Wiley & Sons; Chichester, U.K.: 2010. (e) Alexander, F.; Pozharskii, AS.; Katritzky, AR. Heterocycles in Life and Society: An Introduction to Heterocyclic Chemistry, Biochemistry and Applications. 2nd ed. John Wiley & Sons; Chichester, U.K.: 2011. (f) Baumann M, Baxendale IR. Beilstein J. Org. Chem. 2013; 9:2265. [PubMed: 24204439]
- (2). Liu M, Bryant MS, Chen J, Lee S, Yaremko B, Li Z, Dell J, Lipari P, Malkowski M, Prioli N, Rossman RR, Korfmacher WA, Nomeir AA, Lin CC, Mallams AK, Doll RJ, Catino JJ, Girijavallabhan VM, Kirschmeier P, Bishop WR. Cancer Chemother. Pharmacol. 1998; 43:50. [PubMed: 9923541]
- (3). Chern J-H, Shia K-S, Hsu T-A, Tai C-L, Lee C-C, Lee Y-C, Chang C-S, Tseng S-N, Shih S-R. Bioorg. Med. Chem. Lett. 2004; 14:2519. [PubMed: 15109643]
- (4). Summa V, Petrocchi A, Matassa VG, Gardelli C, Muraglia E, Rowley M, Paz OG, Laufer R, Monteagudo E, Pace P. J. Med. Chem. 2006; 49:6646. [PubMed: 17154493]
- (5). Anagnostopoulos H, Bartlett RR, Elben U, Stoll P. Eur. J. Med. Chem. 1989; 24:227.
- (6). Ritchie TJ, Macdonald SJF, Young RJ, Pickett SD. Drug Discovery Today. 2011; 16:164. [PubMed: 21129497]
- (7) (a). Doggrell SA, Liang LC. Naunyn-Schmiedeberg's Arch. Pharmacol. 1998; 357:126. [PubMed: 9521485] (b) Plobeck N, Delorme D, Wei Z-Y, Yang H, Zhou F, Schwarz P, Gawell L, Gagnon

- H, Pelcman B, Schmidt R, Yue SY, Walpole C, Brown W, Zhou E, Labarre M, Payza K, St-Onge S, Kamassah A, Morin P-E, Projean D, Ducharme J, Roberts E. *J. Med. Chem.* 2000; 43:3878. [PubMed: 11052793] (c) Ko Y, Malone DC, Armstrong EP. *Pharmacotherapy.* 2006; 26:1694. [PubMed: 17125433] (d) Ameen D, Snape TJ. *MedChemComm.* 2013; 4:893.
- (8) (a). Kobayashi S, Ishitani H. *Chem. Rev.* 1999; 99:1069. [PubMed: 11749440] (b) Carey, FA.; Sundberg, R.J. *Advanced Organic Chemistry: Part B: Reaction and Synthesis.* 5th ed. Springer; New York: 2007. (c) Kobayashi S, Mori Y, Fossey JS, Salter MM. *Chem. Rev.* 2011; 111:2626. [PubMed: 21405021] (d) Smith, MB.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure.* 7th ed. John Wiley & Sons, Inc.; Hoboken: 2013.
- (9). Dastbaravardeh N, Schnuerch M, Mihovilovic MD. *Org. Lett.* 2012; 14:1930. [PubMed: 22449256]
- (10) (a). Niwa T, Yorimitsu H, Oshima K. *Org. Lett.* 2008; 10:4689. [PubMed: 18808130] (b) Niwa T, Suehiro T, Yorimitsu H, Oshima K. *Tetrahedron.* 2009; 65:5125. (c) McGrew GI, Temaismithi J, Carroll PJ, Walsh PJ. *Angew. Chem., Int. Ed.* 2010; 49:5541. (d) McGrew GI, Stanciu C, Zhang J, Carroll PJ, Dreher SD, Walsh PJ. *Angew. Chem., Int. Ed.* 2012; 51:11510. (e) Li M, Yücel B, Adrio J, Bellomo A, Walsh PJ. *Chem. Sci.* 2014; 5:2383. [PubMed: 25396041] (f) Li M, Berritt S, Walsh PJ. *Org. Lett.* 2014; 16:4312. [PubMed: 25093713] (g) Fernandez-Salas JA, Marelli E, Nolan SP. *Chem. Sci.* 2015; 6:4973. [PubMed: 27019690]
- (11) (a). Zhang J, Bellomo A, Creamer AD, Dreher SD, Walsh PJ. *J. Am. Chem. Soc.* 2012; 134:13765. [PubMed: 22816972] (b) Jia T, Bellomo A, El Baina K, Dreher SD, Walsh PJ. *J. Am. Chem. Soc.* 2013; 135:3740. [PubMed: 23419158] (c) Montel S, Jia T, Walsh PJ. *Org. Lett.* 2014; 16:130. [PubMed: 24295336] (d) Zheng B, Jia T, Walsh PJ. *Org. Lett.* 2013; 15:1690. [PubMed: 23517309] (e) Zheng B, Jia TZ, Walsh PJ. *Org. Lett.* 2013; 15:4190. [PubMed: 23909856] (f) Frensch G, Hussain N, Marques FA, Walsh PJ. *Adv. Synth. Catal.* 2014; 356:2517. [PubMed: 25685127] (g) Gao F, Kim B-S, Walsh PJ. *Chem. Commun.* 2014; 50:10661. (h) Hussain N, Frensch G, Zhang J, Walsh PJ. *Angew. Chem., Int. Ed.* 2014; 53:3693. (i) Montel S, Raffier L, He Y, Walsh PJ. *Org. Lett.* 2014; 16:1446. [PubMed: 24520897] (j) Yücel B, Walsh PJ. *Adv. Synth. Catal.* 2014; 356:3659. [PubMed: 26185491] (k) Zheng B, Jia T, Walsh PJ. *Adv. Synth. Catal.* 2014; 356:165. [PubMed: 24765060] (l) Zhang J, Bellomo A, Trongsirawat N, Jia T, Carroll PJ, Dreher SD, Tudge MT, Yin H, Robinson JR, Schelter EJ, Walsh PJ. *J. Am. Chem. Soc.* 2014; 136:6276. [PubMed: 24745758] (m) Mao J, Eberle K, Zhang J, Rodríguez-Escrich C, Xi Z, Pericàs MA, Walsh PJ. *Tetrahedron Lett.* 2015; 56:3604. [PubMed: 26034337] (n) Sha S-C, Zhang J, Walsh PJ. *Org. Lett.* 2015; 17:410. [PubMed: 25582024] (o) Hussain N, Kim B-S, Walsh PJ. *Chem. - Eur. J.* 2015; 21:11010. [PubMed: 26129922]
- (12) (a). van der Veen LA, Keeven PH, Schoemaker GC, Reek JNH, Kamer PCJ, van Leeuwen PWNM, Lutz M, Spek AL. *Organometallics.* 2000; 19:872. (b) Kamer PCJ, van Leeuwen PWNM, Reek JNH. *Acc. Chem. Res.* 2001; 34:895. [PubMed: 11714261]
- (13). Fraser RR, Mansour TS, Savard S. *J. Org. Chem.* 1985; 50:3232.
- (14) (a). Niwa T, Yorimitsu H, Oshima K. *Angew. Chem., Int. Ed.* 2007; 46:2643. (b) Niwa T, Yorimitsu H, Oshima K. *Org. Lett.* 2007; 9:2373. [PubMed: 17497870] (c) Hlavinka ML, Hagadorn JR. *Organometallics.* 2007; 26:4105. (d) Campeau L-C, Schipper DJ, Fagnou K. *J. Am. Chem. Soc.* 2008; 130:3266. [PubMed: 18293986] (e) Mousseau JJ, Larivée A, Charette AB. *Org. Lett.* 2008; 10:1641. [PubMed: 18358041] (f) Schipper DJ, Campeau L-C, Fagnou K. *Tetrahedron.* 2009; 65:3155. (g) Burton PM, Morris JA. *Org. Lett.* 2010; 12:5359. [PubMed: 21043493] (h) Shang R, Yang Z-W, Wang Y, Zhang S-L, Liu L. *J. Am. Chem. Soc.* 2010; 132:14391. [PubMed: 20873805] (i) Duez S, Steib AK, Manolikakes SM, Knochel P. *Angew. Chem., Int. Ed.* 2011; 50:7686. (j) Song G, Su Y, Gong X, Han K, Li X. *Org. Lett.* 2011; 13:1968. [PubMed: 21405051] (k) Zhao D, Zhu M-X, Wang Y, Shen Q, Li J-X. *Org. Biomol. Chem.* 2013; 11:6246. [PubMed: 23959586]
- (15). Millet A, Dailier D, Larini P, Baudoin O. *Angew. Chem., Int. Ed.* 2014; 53:2678.
- (16). From preliminary experiments screening 37 different Ni(phosphine)-based catalysts in the coupling of **1a** with bromobenzene, it was found that the Ni(NIXANTPHOS)-based catalyst gave the highest product/internal standard ratio; see: Cao X, Sha S-C, Li M, Kim B-S, Morgan C, Huang R, Yang X, Walsh PJ. *Chem. Sci.* 2016 DOI: 10.1039/C5SC03704B.

Figure 1.
Selected pharmacologically active compounds containing aryl(azaaryl)methylamines.

Figure 2.
Representative synthetic intermediates with directing groups (A, B) and activating groups (C–F) employed in metal-catalyzed C–H functionalization adjacent to nitrogen.

Scheme 1.

Palladium-Catalyzed Benzylic C–H Arylation with Azaarylmethylamines

Scheme 2. Pd-Catalyzed C(*sp*³)-H Arylation of 2-Pyridylmethylamines **1 with Aryl Bromides **2**^a**

^aIsolated yields. ^bX = Br was used unless noted. ^c5 mol % of Pd(OAc)₂ and 7.5 mol % of NIXANTPHOS and the yields in parentheses with 1 mol % of Pd(OAc)₂ and 1.5 mol % of NIXANTPHOS. ^d4 mol % of Pd(OAc)₂ and 6 mol % of NIXANTPHOS.

Scheme 3. Benzylic Cross-Coupling of 2-(Dialkylaminomethyl)pyridine 1 with Aryl Bromides 2^a
^aIsolated yields.

Scheme 4. Benzylic Cross-Coupling of Azaarene Derivatives

^aIsolated yields. ^bX = Br unless noted. ^c1 mol % of Pd(OAc)₂ and 1.5 mol % of NIXANTPHOS and the yields in parentheses with 5 mol % of Pd(OAc)₂ and 7.5 mol % of NIXANTPHOS. ^d5 mol % of Pd(OAc)₂ and 10 mol % of NIXANTPHOS. ^eThe reaction was conducted in THF at 110 °C with KN(SiMe₃)₂ instead of LiN(SiMe₃)₂.

Table 1
Selected Optimization of Pd-Catalyzed C(*sp*³)-H Arylation of **1a with **2a****

entry	base	1a/2a/base	solvent ^a	yield ^b (%)
1	LiO- <i>t</i> -Bu	1:1.5:3	THF	0
2	NaO- <i>t</i> -Bu	1:1.5:3	THF	0
3	KO- <i>t</i> -Bu	1:1.5:3	THF	0
4	LiN(SiMe ₃) ₂	1:1.5:3	THF	87
5	NaN(SiMe ₃) ₂	1:1.5:3	THF	80
6	KN(SiMe ₃) ₂	1:1.5:3	THF	83
7	LiN(SiMe ₃) ₂	1:1.5:3	DME	82
8	LiN(SiMe ₃) ₂	1:1.5:3	CPME	85
9	LiN(SiMe ₃) ₂	1:1.5:3	1,4-dioxane	90
10	LiN(SiMe ₃) ₂	1:1.5:2	1,4-dioxane	92
11	LiN(SiMe ₃) ₂	1:1.2:2	1,4-dioxane	98 (92) ^c
12	LiN(SiMe ₃) ₂	1:1:1.5	1,4-dioxane	73 ^d
13	LiN(SiMe ₃) ₂	1:1.2:2	1,4-dioxane	64 ^e

^aTetrahydrofuran (THF), 1,2-dimethoxyethane (DME), cyclopentyl methyl ether (CPME), and 1,4-dioxane (dioxane).

^bYields were determined by ¹H NMR analysis of unpurified reaction mixtures with internal standard CH₂Br₂.

^cIsolated yield.

^d14% of **1a** remained.

^e2.5 mol % of Pd(OAc)₂ and 3.75 mol % of NIXANTPHOS.