Published in final edited form as:

Chemistry. 2015 July 27; 21(31): 11010–11013. doi:10.1002/chem.201502017.

Palladium-Catalyzed C(sp³)–H Arylation of *N*-Boc Benzylalkylamines via a Deprotonative Cross-Coupling Process

Nusrah Hussain, Byeong-Seon Kim, and Patrick J. Walsh^{a,*}

^aDepartment of Chemistry, University of Pennsylvania, 231 S, 34th St. Philadelphia, PA 19104 (USA)

Abstract

Diarylmethylamines are key intermediates and products in the pharmaceutical industry. Herein we disclose a novel method toward the synthesis of these important compounds via C–H functionalization. Presented is a reversible deprotonation of *N*-Boc benzylalkylamines at the benzylic C–H with in situ arylation by a NiXant-Phos-based palladium catalyst (50–93% yield, 29 examples). The method is also successful with *N*-Boc-tetrahydroisoquinolines. The advantages of this method are it avoids strong bases, low temperatures, and the need to transmetallate to main group metals for the coupling.

Keywords

C–H functionalization; cross-coupling; diarylmethylamines; NiXantPhos ligand; palladium

Diarylmethylamines are an important class of compounds that have had a significant impact in pharmaceutical sciences. For example, diarylmethylamines are core structures of Zyrtec,^[1] Levocetirizine,^[2] Meclizine,^[3] and Solifenacin.^[4] As such, their synthesis has attracted much attention. Generally, diarylmethylamines are prepared by nucleophilic addition of organometallic reagents to imines.^[5] More recently, functionalization of sp³-hybridized C–H bonds adjacent to nitrogen has emerged as a powerful method for the formation of C–C bonds.^[6]

Direct deprotonation and functionalization of the benzylic C–H bonds in secondary benzylamine derivatives under catalytic conditions is an attractive approach to elaborate amines, but remains challenging. The difficulty arises from the low acidity of sp³-hybridized benzylic C–H bonds adjacent to amino groups,^[7] which usually require alkyl lithiums for deprotonation.^[8] The resulting lithiated benzylic amines are quite versatile and can be captured with a variety of electrophiles.^[8, 9] The strong bases used in these deprotonations, however, are incompatible with the vast majority of cross-coupling catalysts. To circumvent this incompatibility, Baudoin,^[10] Knochel,^[11] Campos,^[12] and Dieter^[13] have established two-step methods that commence with direct lithiation of secondary amines with strong bases, such as *s*BuLi, followed by in situ transmetalation to zinc, boron, or copper and

pwalsh@sas.upenn.edu Homepage: <http://titanium.chem.upenn.edu/walsh/index.html>.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201502017>.

subsequent coupling with aryl halides. The practicality of these approaches is diminished by the use of strong bases, low temperatures (-78°C), and the need to transmetallate to main group metals.

Our approach to arylation adjacent to amino groups focuses on reversible in situ C–H deprotonations of benzylic amines under catalytic conditions. To circumvent the low acidity of benzylic amine C–H groups, we initially employed $(\eta^6\text{-C}_6\text{H}_5\text{-CH}_2\text{NR}_2)\text{Cr}(\text{CO})_3$ activation to decrease the pK_a of benzylic C–H bonds (Scheme 1a).^[14] The corresponding diarylmethylamines were obtained in excellent yields and enantioselectivities. To avoid the stoichiometric use of chromium, we employed a direct arylation of benzylic $\text{C}(\text{sp}^3)\text{-H}$ bonds using 2-azaallyl anions.^[15] This strategy, introduced by Oshima and co-workers^[16] and rendered synthetically useful by Buchwald's group^[17] and by us,^[18] takes advantage of the stability of 2-azaallyl anions (Scheme 1b).

Considering the importance of diarylmethylamines in medicinal chemistry,^[19] we envisioned a reversible deprotonation/functionalization of *N*-Boc benzylalkylamines at the benzylic C–H bonds under catalytic conditions. The Boc group is known to be useful in synthesis and was chosen for its ability to increase the acidity of the benzylic C–H bonds and to direct the base to facilitate deprotonation. Herein we report the first direct arylation of *N*-Boc-protected benzylalkylamines with aryl halides to provide *N*-Boc-diarylmethylamines (Scheme 2).

Our general approach to deprotonative cross-coupling processes (DCCP) involves initial identification of a base for reversible deprotonation and an arylation catalyst that is compatible with the basic reaction conditions.^[20] From our experience with DCCP of weakly acidic substrates (pK_a 25–35), we chose van Leeuwen's NiXantPhos ligand (Scheme 2) as a starting point.^[21] We have recently demonstrated that NiXantPhos is deprotonated under basic reaction conditions, leading significantly enhanced catalyst reactivity.^[21c] To identify a suitable base for the reversible deprotonation of the weakly acidic sp^3 -hybridized C–H bond adjacent to nitrogen, we screened six bases [$\text{LiN}(\text{-SiMe}_3)_2$, $\text{NaN}(\text{SiMe}_3)_2$, $\text{KN}(\text{SiMe}_3)_2$, LiOtBu , NaOtBu , and KOtBu] with the $\text{Pd}(\text{OAc})_2/\text{NiXantPhos}$ system at 85°C in cyclopentylmethyl ether (CPME) for 24 h. As illustrated in Table 1, the bases leading to arylation products were $\text{MN}(\text{SiMe}_3)_2$ ($\text{M}=\text{Li, Na, K}$), affording 10–40% assay yields (AY, determined by ^1H NMR spectroscopy of the crude products) of the diarylmethylamines in CPME (entries 1–3). None of the MOtBu ($\text{M}=\text{Li, Na, K}$) bases generated detectable amounts of arylated products (entries 4–6). Examination of four ethereal solvents [THF, DME, dioxane, and CPME] indicated that THF was an excellent choice (entry 9; 99% assay yield). To optimize the reaction conditions with the $\text{NiXantPhos}/\text{Pd}(\text{OAc})_2$ system, we examined different ratios of the benzylmethylamine pro-nucleophile, 4-bromotoluene, and $\text{LiN}(\text{SiMe}_3)_2$ at 50 and 85°C . When 3 equiv of *N*-Boc benzylmethylamine (**1a**), 3 equiv of $\text{LiN}(\text{SiMe}_3)_2$ or $\text{NaN}(\text{SiMe}_3)_2$, and 1 equiv of 4-Tol-Br were used in THF, the desired arylated product was obtained in quantitative yield (entries 9 and 10). $\text{KN}(\text{SiMe}_3)_2$, on the other hand, gave the product **4a** in only 21% yield (entry 11). Furthermore, decreasing the reaction temperature from 85 to 50°C had a detrimental effect on the yield (20 %, entry 12).

Although the combination of Pd(OAc)₂ and NiXant-Phos as precatalyst afforded the diarylmethylamine product **4a** in excellent yield, the use of 3 equiv of *N*-Boc benzylmethylamine (entries 9 and 10) required further attention. Reducing the equivalents of the benzylmethylamine pro-nucleophile from 3 to 1 equiv in THF at 85°C resulted in a drop in yield of **4a** from >95 to 61% yield, along with 30% unreacted *N*-Boc benzylmethylamine **1a** (entry 13). Changing base from LiN(SiMe₃)₂ to NaN(SiMe₃)₂ also resulted in a drop in yield of **4a** to 57% (entry 15). The best result was obtained when 1.1 equiv of *N*-Boc benzylmethylamine, 1 equiv of 4-bromotoluene **3a**, and 4 equiv of LiN(SiMe₃)₂ at 85°C were used in THF for 24 h, producing the product **4a** in 99% AY and 88% isolated yield (entry 16).

With the optimized conditions (entry 16, Table 1), we sought to evaluate the substrate scope of the arylation of *N*-Boc benzylmethylamine (Table 2). Overall, the DCCP showed good to excellent reactivity with a variety of aryl electrophiles. For example, the arylated products were obtained in 50–91% yields for *para*, *meta*, and *ortho* alkyl-substituted aryl bromides, chlorides, an aryl iodide, and an aryl triflate (**4a**, **4c–4e**, Table 2). Sterically hindered 2-bromotoluene proved to be a more challenging substrate, furnishing the product **4e** in 50% yield. On the other hand, 1-bromonaphthalene resulted in **4f** in 78% yield. Aryl halides bearing 3-methoxy and 3-*N,N*-dimethylamino groups led to coupling products **4g** and **4h** in 64 and 93% yields, respectively. Electron-rich 4-bromo- and 4-chloroanisole yielded the coupling product **4i** in 87 and 85% yield, respectively. The reactivity with 1-bromo- and 1-chloro-4-fluorobenzene was lower, giving **4j** in 70 and 60% yield, respectively. Acetals are known to undergo C–O bond cleavage with reactive organometallic reagents,^[22] however, the C–H functionalization product **4k** was isolated in 68% yield. With heterocyclic 4-chlorophenyl pyrrole, the arylated product **4l** was obtained in 93% yield. *N*-TBS 5-bromoindole furnished the heterocyclic product **4m** in 50% yield.

We next turned our attention to the scope of *N*-Boc benzylmethylamine derivatives (Table 3). Heterocyclic *N*-Boc methyl(-pyridin-3-methyl)amine exhibited good reactivity with alkylsubstituted, electron-donating and electron-deficient aryl bromides (**4n–4p**, 72–98% yield). The benzylmethylamine bearing a 3-OMe substituent furnished the desired products in 57–90% yield (**4g**, **4q**, and **4r**). The *tert*-butyl methyl(naphthalen-1-ylmethyl) carbamate also afforded products in 57–80% yield (**4s**, **4t**, and **4u**). *N*-Boc 4-fluorobenzylmethylamine coupled with bromobenzene and 4-bromoanisole in 76 and 73% yields (**4j** and **4v**), respectively. When the methyl group on *N*-Boc benzylmethylamine was changed to *N*-ethyl group, the arylated products with 4-bromotoluene and 4-bromoanisole were obtained in 75 and 60% yield, respectively (**4w** and **4x**).

Unfortunately, reactions with 2-thiophenyl, 2-furyl, 2- and 4-pyridyl-derived benzylmethylamines did not yield any detectable amounts of coupling products under these conditions. These substrates are significantly more acidic than *N*-Boc benzylmethylamine and will require different conditions to form the desired products.

The Boc-protected **4c** was treated with hydrochloric acid followed by basic work up to provide the secondary amine **5c** in 75% yield (Scheme 3).

We next desired to expand our method to the synthesis of 1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5aa**, Scheme 4), a key intermediate in the antimuscarinic agent Solifenacin (Vesicare).^[23] 1-Arylated tetrahydroisoquinolines have also been studied for their anti-HIV activities.^[24]

Under our DCCP conditions, the cross-coupling of **1aa** took place smoothly to provide **4aa** in 81% isolated yield (Scheme 4). The arylated tetrahydroisoquinoline products derived from 4-bromoanisole and 1-bromo-4-fluorobenzene were obtained in 76 and 65% yields, respectively (**4ab** and **4ac**, Scheme 4). Toward the synthesis of the key intermediate (**5aa**), the arylated product (**4aa**) was deprotected with HCl followed by basic workup to provide 1-phenyl-1,2,3,4-tetrahydroisoquinoline **5aa** in 95% yield. Racemic **5aa** has been used in the synthesis of Solifenacin (**6**, Scheme 4).^[25]

In summary, we have developed the first direct α -arylation of *N*-Boc benzylalkylamines with aryl electrophiles by using deprotonative cross-coupling processes. This method avoids two-step procedures involving low temperature deprotonation with very strong bases and transmetallation to main group intermediates previously used. Key to success of this approach are the development of conditions for the reversible in situ C–H deprotonation of the substrates and the application of a Pd(NiXantPhos)-based catalyst that enables the arylation to be conducted under mild conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

P.J.W acknowledges the NIH (National Institute of General Medical Sciences GM 104349) and the NSF (CHE-1152488).

References

1. Li, J.J.; Johnson, D.S.; Sliskovic, D.R.; Roth, B. Contemporary Drug Synthesis. Wiley-Interscience; 2004.
2. Grant JA, Riethuisen J-M, Moulart B, DeVos C. Ann. Allergy Asthma Immunol. 2002; 88:190–197. [PubMed: 11868924]
3. Fuhrhop, J-H.; Li, G. Organic Synthesis: Concepts and Methods. 3rd. Wiley; 2003. p. 237
4. Ko Y, Malone DC, Armstrong EP. Pharmacotherapy. 2006; 26:1694–1702. [PubMed: 17125433]
5. a) Silverio DL, Torker S, Pilyugina T, Vieira EM, Snapper ML, Haeffner F, Hoveyda AH. Nature. 2013; 494:216–221. [PubMed: 23407537] b) Xu H-C, Chowdhury S, Ellman JA. Nat. Protoc. 2013; 8:2271–2280. [PubMed: 24157547] c) Kobayashi S, Mori Y, Fossey JS, Salter MM. Chem. Rev. 2011; 111:2626–2704. [PubMed: 21405021] d) Zuend SJ, Coughlin MP, Lalonde MP, Jacobsen EN. Nature. 2009; 461:968–970. [PubMed: 19829379] e) Yamada, K-i; Tomioka, K. Chem. Rev. 2008; 108:2874–2886. [PubMed: 18652515]
6. a) Li Z, Li C-J. J. Am. Chem. Soc. 2005; 127:6968–6969. [PubMed: 15884937] b) Li Z, Li C-J. Org. Lett. 2004; 6:4997–4999. [PubMed: 15606119] c) Li Z, Li C-J. J. Am. Chem. Soc. 2004; 126:11810–11811. [PubMed: 15382913]
7. a) Beak P, Basu A, Gallagher DJ, Park YS, Thayumanavan S. Acc. Chem. Res. 1996; 29:552–560. b) Meyers AI. Aldrichimica Acta. 1985; 18:59–68.

8. a) Schlosser M, Limat D. J. Am. Chem. Soc. 1995; 117:12342–12343. b) Resek JE, Beak P. J. Am. Chem. Soc. 1994; 116:405–406.
9. a) Clayden J, Dufour J, Grainger DM, Helliwell M. J. Am. Chem. Soc. 2007; 129:7488–7489. [PubMed: 17521189] b) Fernández I, González J, López-Ortiz F. J. Am. Chem. Soc. 2004; 126:12551–12564. [PubMed: 15453788] c) Faibish NC, Park YS, Lee S, Beak P. J. Am. Chem. Soc. 1997; 119:11561–11570.
10. Millet A, Dailier D, Larini P, Baudoin O. Angew. Chem. Int. Ed. 2014; 53:2678–2682. *Angew. Chem.* **2014**, *126*, 2716–2720.
11. Seel S, Thaler T, Takatsu K, Zhang C, Zipse H, Straub BF, Mayer P, Knochel P. J. Am. Chem. Soc. 2011; 133:4774–4777. [PubMed: 21388211]
12. Campos KR, Klapars A, Waldman JH, Dormer PG, Chen C-y. J. Am. Chem. Soc. 2006; 128:3538–3539. [PubMed: 16536525]
13. Dieter RK, Li SJ. J. Org. Chem. 1997; 62:7726–7735.
14. a) McGrew GI, Stanciu C, Zhang J, Carroll PJ, Dreher SD, Walsh PJ. Angew. Chem. Int. Ed. 2012; 51:11510–11513. *Angew. Chem.* **2012**, *124*, 11678–11681. b) McGrew GI, Temaismithi J, Carroll PJ, Walsh PJ. Angew. Chem. Int. Ed. 2010; 49:5541–5544. *Angew. Chem.* **2010**, *122*, 5673–5676.
15. a) Li Z, Jiang Y-Y, Yeagley AA, Bour JP, Liu L, Chruma JJ, Fu Y. Chem. Eur. J. 2012; 18:14527–14538. [PubMed: 23002017] b) Weaver JD, Recio IIIA, Grenning AJ, Tunge JA. Chem. Rev. 2011; 111:1846–1913. [PubMed: 21235271] c) Grenning AJ, Tunge JA. J. Am. Chem. Soc. 2011; 133:14785–14794. [PubMed: 21830777] d) Fields WH, Chruma JJ. Org. Lett. 2010; 12:316–319. [PubMed: 20000671] e) Yeagley AA, Lowder MA, Chruma JJ. Org. Lett. 2009; 11:4022–4025. [PubMed: 19658425] f) Fields WH, Khan AK, Sabat M, Chruma JJ. Org. Lett. 2008; 10:5131–5134. [PubMed: 18956870] g) Yeagley AA, Chruma JJ. Org. Lett. 2007; 9:2879–2882. [PubMed: 17580888] h) Burger EC, Tunge JA. J. Am. Chem. Soc. 2006; 128:10002–10003. [PubMed: 16881615] i) Tunge JA, Burger EC. Eur. J. Org. Chem. 2005; 2005:1715–1726.
16. a) Niwa T, Suehiro T, Yorimitsu H, Oshima K. Tetrahedron. 2009; 65:5125–5131. b) Niwa T, Yorimitsu H, Oshima K. Org. Lett. 2008; 10:4689–4691. [PubMed: 18808130]
17. Zhu Y, Buchwald SL. J. Am. Chem. Soc. 2014; 136:4500–4503. [PubMed: 24621247]
18. a) Li M, Yücel B, Adrio J, Bellomo A, Walsh PJ. Chem. Sci. 2014; 5:2383–2391. [PubMed: 25396041] b) Li M, Berritt S, Walsh PJ. Org. Lett. 2014; 16:4312–4315. [PubMed: 25093713]
19. Ameen D, Snape TJ. Med. Chem. Commun. 2013; 4:893–907.
20. a) Gao F, Kim B-S, Walsh PJ. Chem. Commun. 2014; 50:10661–10664. b) Montel S, Jia T, Walsh PJ. Org. Lett. 2014; 16:130–133. [PubMed: 24295336] c) Frensch G, Hussain N, Marques FA, Walsh PJ. Adv. Synth. Catal. 2014; 356:2517–2524. [PubMed: 25685127] d) Hussain N, Frensch G, Zhang J, Walsh PJ. Angew. Chem. Int. Ed. 2014; 53:3693–3697. *Angew. Chem.* **2014**, *126*, 3767–3771. e) Zheng B, Jia T, Walsh PJ. Org. Lett. 2013; 15:1690–1693. [PubMed: 23517309] f) Zhang J, Bellomo A, Creamer AD, Dreher SD, Walsh PJ. J. Am. Chem. Soc. 2012; 134:13765–13772. [PubMed: 22816972]
21. a) van der Veen LA, Keeven PH, Schoemaker GC, Reek JNH, Kamer PCJ, van Leeuwen PWNM, Lutz M, Spek AL. Organometallics. 2000; 19:872–883. b) Kamer PCJ, van Leeuwen PWNM, Reek JNH. Acc. Chem. Res. 2001; 34:895–904. [PubMed: 11714261] c) 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; 136:6276–6287. [PubMed: 24745758]
22. Müller P, Nury P, Bernardinelli G. Eur. J. Org. Chem. 2001:4137–4147.
23. Bolchi C, Pallavicini M, Fumagalli L, Straniero V, Valoti E. Org. Process Res. Dev. 2013; 17:432–437.
24. Chen, K-x; Xie, H-y; Li, Z-g; Gao, J-r. Bioorg. Med. Chem. Lett. 2008; 18:5381–5386. [PubMed: 18835162]
25. a) Ye Z-S, Guo R-N, Cai X-F, Chen M-W, Shi L, Zhou Y-G. Angew. Chem. Int. Ed. 2013; 52:3685–3689. *Angew. Chem.* **2013**, *125*, 3773–3777. b) Niphade NC, Jagtap KM, Mali AC, Solanki PV, Jachak MN, Mathad VT. Monatsh. Chem. 2011; 142:1181–1186. c) Naito R, Yonetoku Y, Okamoto Y, Toyoshima A, Ikeda K, Takeuchi M. J. Med. Chem. 2005; 48:6597–6606. [PubMed: 16220976]

Scheme 1.

a) Synthesis of diarylmethylamines based on an η^6 -arene-activation strategy. b) Cross-coupling of *N*-benzyl benzophenone ketimines.

Scheme 2.

Palladium-catalyzed DCCP of *N*-Boc benzylalkylamines followed by deprotection.

Scheme 3.
Deprotection of the Boc group to provide **5c** from **4c**.

Table 1Optimization of the DCCP of *N*-Boc benzylmethylamine with 4-bromotoluene.

Entry	Base	1a:2:3b	Solvent	Yield ^[a] [%]
1	LiN(SiMe ₃) ₂	3:3:1	CPME	40
2	NaN(SiMe ₃) ₂	3:3:1	CPME	30
3	KN(SiMe ₃) ₂	3:3:1	CPME	10
4	LiO <i>t</i> Bu	3:3:1	CPME	–
5	NaO <i>t</i> Bu	3:3:1	CPME	–
6	KO <i>t</i> Bu	3:3:1	CPME	–
7	LiN(SiMe ₃) ₂	3:3:1	dioxane	15
8	LiN(SiMe ₃) ₂	3:3:1	DME	10
9	LiN(SiMe ₃) ₂	3:3:1	THF	99
10	NaN(SiMe ₃) ₂	3:3:1	THF	99
11	KN(SiMe ₃) ₂	3:3:1	THF	21
12	LiN(SiMe ₃) ₂	3:3:1	THF	20 ^[b]
13	LiN(SiMe ₃) ₂	1:3:3	THF	61 ^[c]
14	LiN(SiMe ₃) ₂	1:3:1	THF	74 ^[d]
15	NaN(SiMe ₃) ₂	1:3:3	THF	57 ^[e]
16	LiN(SiMe ₃) ₂	1.1:4:1	THF	99 (88) ^[f]

^[a] Assay yield determined by ¹H NMR analysis of unpurified reaction mixture with internal standard CH₂Br₂.^[b] Reaction at 50 °C.^[c] 30% unreacted **1a**.^[d] 20% unreacted **1a**.^[e] 18%, unreacted **1a**.^[f] Isolated yield.

Table 2Cross-coupling of *N*-Boc benzylmethanamine with aryl electrophiles.^[a]

<p>4a 88 % (X = Br) 78 % (X = I)</p>	<p>4b 90 % (X = Br) 87 % (X = Cl)</p>	<p>4c 90 % (X = Br) 91 % (X = OTf)</p>
<p>4d 86 % (X = Br)</p>	<p>4e 50 % (X = Br)</p>	<p>4f 78 % (X = Br)</p>
<p>4g 64 % (X = Br)</p>	<p>4h 93 % (X = Br)</p>	<p>4i 87 % (X = Br) 85 % (X = Cl)</p>
<p>4j 70 % (X = Br) 60 % (X = Cl)</p>	<p>4k 68 % (X = Br)</p>	<p>4l 93 % (X = Cl)</p>
<p>4m 50 % (X = Br)</p>		

^[a] See the Supporting Information for experimental details.

Table 3Cross-coupling of *N*-Boc benzylalkylamines with aryl bromides.^[a]

<p>4n 98 %</p>	<p>4o 88 %</p>	<p>4p 72 %</p>
<p>4g 90 %</p>	<p>4q 87 %</p>	<p>4r 57 %</p>
<p>4s 70 %</p>	<p>4t 57 %</p>	<p>4u 80 %^[b]</p>
<p>4j 76 %</p>	<p>4v 73 %</p>	
<p>4w 75 %</p>	<p>4x 60 %</p>	

^[a] See the Supporting Information for experimental details.^[b] 10/20 mol % of Pd(OAc)₂ and NiXantPhos used.