A Suzuki Coupling Method for Directly Introducing a Protected β-Aminoethyl Group into Arenes and Alkenes. Convenient Synthesis of Phenethyl and Homoallylic Amines

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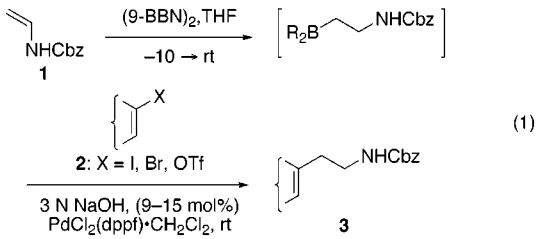
Aminoethyl groups are important structural features of a wide variety of organic molecules. Exemplary are phenethylamines, which exhibit a diversity of pharmacological activities and also serve as key building blocks in the synthesis of numerous nitrogen heterocycles and alkaloid natural products.[1] Multistep procedures are almost always employed to introduce an aminoethyl group into an arene or alkene. For example, a widely used sequence for preparing phenethylamines involves Friedel−Crafts acylation of activated arenes with *N*-protected amino acid chlorides followed by reduction of the ketone carbonyl group.[2,3] Metal-assisted coupling reactions, on the other hand, could introduce a β-aminoethyl group in as little as one step. Earlier investigations of this approach include the direct coupling of β-(*N*-benzoyl-*N*-lithio)ethyllithium with aryl and alkenyl halides,[4] ring-opening of *N*-sulfonylaziridines with aryl and alkenyl Grignard reagents,[5] and Heck arylation of *N*-vinyloxazolone followed by hydrogenation.[6] Herein, we disclose a convenient one-step Suzuki coupling method[7] for introducing alkoxycarbonyl-protected β-aminoethyl groups into arenes and alkenes.



(1)

The one-pot reaction sequence (eq 1) starts with hydroboration of benzyl vinylcarbamate **1**[8] (1.1−1.5 equiv) with $(9\text{-BBN})_2$ in THF.[9] The crude organoborane complex is then coupled at room temperature with 1 equiv of an aryl iodide, aryl bromide, alkenyl iodide, or enol triflate in the presence of a catalytic amount of $PdCl_2(dppf)\cdot CH_2Cl_2$ [dppf = 1,1′-bis(diphenylphosphino)-ferrocene] and excess 3 M aqueous NaOH. Aryl and vinyl iodides and enol triflates coupled efficiently within 1 h with the intermediate organoborane derived from 1.1 equiv of **1** using 9 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ (Table 1). In the aryl iodide series, no significant reactivity differences were observed between the substrates having electron-withdrawing (**2b**,**c**) or electron-donating (**2d**) substituents. Suzuki coupling was slower for aryl bromide **2e**,**f**, yet could still be accomplished at room temperature within 24 h if 15 mol % of $PdCl_2(dppf)$ was utilized. For aryl bromides, yields were higher if 1.5 equiv of the organoboron was employed.

In summary, the method described here is the most convenient reported to date for introducing β-aminoethyl groups into arenes and alkenes. The reaction conditions of this one-pot β-aminoethylation procedure are sufficiently mild that it should be applicable to a variety of substrates. Since vinylcarbamates containing most carbamate nitrogen protecting groups are available from Curtius rearrangement of acryloyl chloride,[10] the method illustrated here in the Cbz series should be easily adapted to prepare β-aminoethyl products containing other nitrogen protecting groups.

Experimental Section

General Details. Benzyl vinyl carbamate was prepared from acryloyl chloride using a slight modification of a literature procedure;[8] details are provided in Supporting Information. Triflate **2g**[11] and vinyl iodides **2h**−**j**[12] were prepared by standard procedures. General experimental details have been described.[13]

General Coupling Procedure. Preparation of Benzyl Phenethylcarbamate (3a). Following a modification of the procedure by Suzuki,[9] a solution of $(9\text{-BBN})_2$ (0.55 mmol) and THF (4 mL) was added dropwise to a stirring solution of benzyl vinylcarbamate **1**[8] (1.1 mmol) and THF (1 mL) at −10 °C. The resulting suspension was stirred at room temperature for 4 h, during which time the mixture became homogeneous. Aqueous 3 M NaOH (1 mL) was added, and the resulting suspension was stirred for 10 min. This mixture was transferred by cannula into a light brown solution of **2a** (204 mg, 1.00 mmol), $PdCl_2(dppf)\cdot CH_2Cl_2$ (0.09 mmol), and THF (3 mL). The resulting dark suspension was stirred at room temperature for 1 h and diluted with hexanes (10 mL). A 2:1 (v/v) mixture of pH 7 aqueous buffer (KH_2PO_4−NaOH)

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(3) Many multistep sequences have been employed for introducing β-aminoethyl units.[1b]

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(7) Review: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

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(10) Examples include: (a) *tert*-butoxycarbonyl: Hart, R. *Makromol. Chem.* **1959**, *32*, 51−56. (b) β-(trimethylsilyl)ethoxycarbonyl: Carpino, L. A.; Tsao, J.-H. *J. Chem. Soc., Chem. Commun.* **1978**, 358−359. (c) methoxycarbonyl: Hart, R. *Bull. Soc. Chim. Belg.* **1957**, *66*, 229−242.

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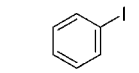
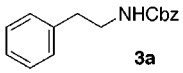
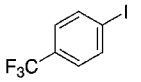
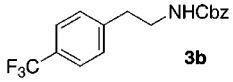
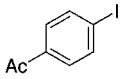
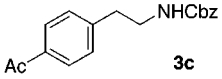
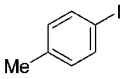
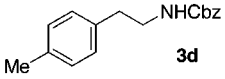
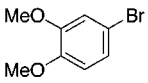
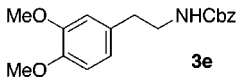
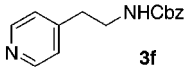
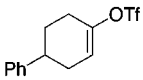
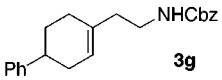
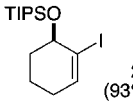
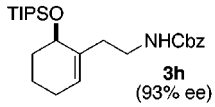
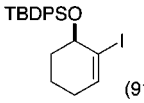
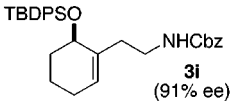
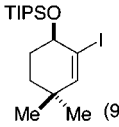
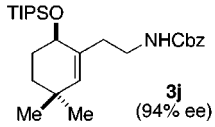
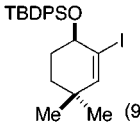
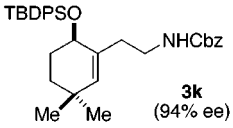
Table 1. Aminoethylation of Arenes and Alkenes

R–X	reaction conditions[a] 1 (equiv)	$PdCl_2$(dppf) (mol %)	time (h)	product	yield (%)
 **2a**	1.1	9	1	 **3a**	86
 **2b**	1.1	9	1	 **3b**	87
 **2c**	1.1	9	1	 **3c**	80
 **2d**	1.1	9	1	 **3d**	94
 **2e**	1.5	15	24	 **3e**	91
 **2f**	1.5	15	24	 **3f**	88
 **2g**	1.1	9	1	 **3g**	97
 **2h** (93% ee)	1.1	9	1	 **3h** (93% ee)	94
 **2i** (91% ee)	1.1	9	1	 **3i** (91% ee)	78
 **2j** (94% ee)	1.1	9	1	 **3j** (94% ee)	77
 **2k** (94% ee)	1.1	9	1	 **3k** (94% ee)	82

[a] The coupling step was conducted in THF at rt.

and 30% aqueous H_2O_2 (20 mL) was then added dropwise to the stirring reaction mixture at 0 °C. At this stage, precipitated palladium residues can be removed by filtration through Celite, if necessary. The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated. The resulting residue was purified on silica gel (4:1 hexanes−EtOAc) to give known[14] **3a** (220 mg, 86%) as a colorless solid: mp 62−64 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 70 °C) δ 7.17−7.36 (m, 10H, Ph), 7.25 (br s, 1H, NH), 5.01 (s, 2H, CH_2O), 3.23−3.28 (m, 2H, CH_2N), 2.74 (app t, J = 7.5 Hz, 2H, CH_2CH_2N); ^{13}C NMR (125 MHz, DMSO-d_6, 70 °C) δ 155.7, 139.0, 137.0, 128.2, 127.9, 127.3, 127.2, 125.6, 64.8, 41.6, 35.1; IR (film) 3327, 1694 cm^{-1}; MS (CI, isobutane) *m/e* 255.1262 (M, 255.1259 calcd for $C_{16}H_{17}NO_2$), 194, 181, 164, 146, 120. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.30; H, 6.75; N, 5.54.

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Supporting Information Available: Experimental procedure for preparation of **1**, and spectroscopic and analytical data for compounds **3b**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Tanaka, C.; Nasu, K.; Yamamoto, N.; Shibata, M. *Chem. Pharm. Bull.* **1982**, *30*, 4195−4198.