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β-Aminoethyltrifluoroborates: Efficient Aminoethylations via Suzuki-Miyaura Cross-Coupling

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Abstract

A set of phenethylamines has been successfully prepared via Suzuki-Miyaura cross-coupling of diverse potassium β-aminoethyltrifluoroborates with aryl halides. The potassium *β*-aminoethyltrifluoroborates were easily prepared via hydroboration of enamine and enamide precursors.

Phenethylamines and their structural analogues comprise important substructures of a variety of biologically important compounds including dopamine, tyrosine, amphetamine, and adrenaline. These privileged scaffolds are also widely found as components of alkaloid natural products[1] and often serve as key building blocks in the synthesis of numerous nitrogen-containing complex molecules. Previous methods to introduce an aminoethyl group into an arene have employed the Friedel-Crafts acylation of activated arenes with *N*-protected amino acid chlorides,[2] Heck arylation of *N*-vinyloxazolone followed by hydrogenation,[3] and cross-coupling reactions involving *β*-amino organozinc reagents, which are somewhat unstable to β-elimination.[4] Earlier investigations to access these important units also include the direct coupling of *β*-aminoethyl organolithiums with aryl- and alkenyl halides.[5] A more broadly applicable Suzuki cross-coupling[6] approach to this interesting class of compounds has been developed by Overman.[7] However, although there are distinct advantages of this one-pot *β*-aminoethylation procedure in cross-coupling reactions and total synthesis (e.g., the reactions can be performed at room temperature),[8] there are some limitations as well. In particular, the organoborane reagents prepared *in situ* via hydroboration of benzyl vinyl carbamate cannot be easily isolated and stored, but must be prepared and utilized on a reaction-by-reaction basis.

By contrast, potassium organotrifluoroborates have been shown to overcome this particular limitation. These salts are unique organoboron compounds, notable for their stability to moisture and air.[9] They are powders or crystalline solids that are easy to access and handle, and these properties have made them attractive synthetic intermediates. Herein we describe our initial efforts to develop a convenient and practical access to phenethylamines via Suzuki cross-coupling of potassium *β*-aminoethyltrifluoroborates with aryl electrophiles.

To initiate studies on the aminoethylation reactions, a hydroboration protocol was employed that mimicked procedures reported by Overman.[8] Thus, the respective *N*-vinyl substrates[10] were hydroborated using Snieckus' di(isopropylprenyl)borane (i-PP$_2$BH),[11] and the resulting organoborane intermediates were treated with an aqueous solution of KHF$_2$ to afford the desired *β*-aminoethyltrifluoroborates **1a-e** as depicted in Table 1.

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Although organotrifluoroborate **1a** has been obtained in excellent yield (Table 1, entry 1), the organotrifluoroborates containing a 7-membered and 5-membered lactam **1b** and **1c** (Table 1, entries 2–3) were obtained in lower yields. The Snieckus hydroboration protocol also tolerates nitrogen protecting groups as Boc and Cbz. However, the desired salts **1d** and **1e** were obtained in moderate yields (Table 1, entries 4–5). All of the new potassium β-aminoethyltrifluoroborates were obtained as powders or crystalline white solids that were stored on the benchtop without detectable degradation.

Initially, we focused on optimization of the reaction conditions for the Suzuki cross-coupling of β-aminoethyltrifluoroborates and aryl electrophiles (Table 2). Thus, **1a** and 4-bromobenzonitrile were chosen as representative coupling partners. Based on the optimized cross-coupling reaction conditions reported between alkyltrifluoroborates and aryl bromides,[12] we first conducted the reaction in the presence of different loadings of $PdCl_2(dppf)\cdot CH_2Cl_2$ using Cs_2CO_3 (3 equiv) as base, in a mixture of toluene/H_2O (3:1) as solvent (Table 2, entries 1–3). It was observed that using 5 mol % of the catalyst, the desired phenethylamine **2a** was obtained in 90% yield (Table 2, entry 2). Subsequently, systems were tested using 5 mol % of different palladium sources and ligands (Table 2, entries 4–7), but the desired product was formed in lower yields. The efficiency of $PdCl_2(dppf)\cdot CH_2Cl_2$ was also evaluated in the presence of different inorganic bases and Et_3N, as well as in a different solvent [THF/H_2O (10:1)]. However, in all cases no improvement could be observed (Table 2, entries 8–11).

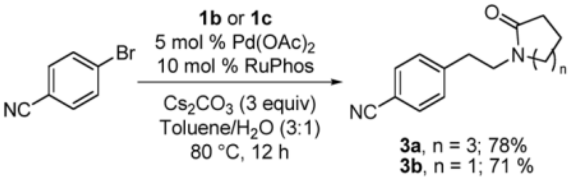
The optimized conditions were subsequently applied to cross-coupling reactions with electron-poor electrophiles, as depicted in Table 3. The reaction proceeds with comparable yields when different leaving groups attached to *p*-AcPhX (X = Br, I, OTf) were tested in the cross-coupling reaction (Table 3, entry 2). All of the desired phenethylamines were obtained with good to excellent yields (73–90%) in the presence of a wide variety of functional groups including nitriles, ketones, esters, aldehydes, halides, and nitro groups in the *para* position. The cross-coupling reaction also tolerates bromides with substituents in the *ortho* and *meta* positions, as the corresponding products were afforded in uniform yields (Table 3, entries 9–10).

The introduction of an ethylamine moiety was also evaluated under the same reaction conditions using electron-rich bromides, as shown in Table 4. The coupling products were synthesized in moderate to good yields in the presence of functionalized bromides. Interestingly, comparable yields for the corresponding phenethylamines were obtained when a non-substituted bromide and a sterically hindered bromide were used as coupling partners (Table 4, compare entries 1 and 2). As observed with the electron-poor bromides, substituents located at different positions about the aromatic ring do not seem to show a strong influence in terms of yield for the respective phenethylamines (Table 4, entries 6 and 7).

Next, the scope of the cross-coupling reaction was explored using heteroaryl bromides as coupling partners, as outlined in Table 5. The optimized conditions are quite general, as the present reaction provides the desired products in acceptable yields (Table 5, entries 1–3) and also tolerates different functional groups attached to furan, pyridine, and indole moieties. However, when a thiophene derivative was used, no coupling was observed. This unsatisfactory result prompted us to screen different coupling conditions as well as alternative ligands such as SPhos, XPhos and RuPhos (Figure 1).[13]

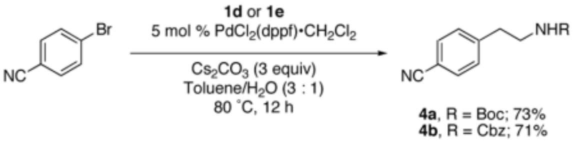
After investigating several conditions, 2 mol % of $Pd(OAc)_2$ and 4 mol % of RuPhos (Table 5, entry 4) showed the best catalytic performance, affording the product in 71% yield.

Having demonstrated the efficiency of organotrifluoroborate **1a** as a convenient aminoethylating agent for aryl- and heteroaryl bromides, we investigated the scope of the method using the β-aminoethyltrifluoroborates **1b** and **1 c.** We initially conducted the reaction using 5 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$, but the desired products were not obtained. Based on the successful procedure with the thiophene derivative, we used the RuPhos catalytic system, and in this case the phenethylamines **3a** and **3b** were obtained in 78% and 71% yields, respectively, as displayed in eq 1.



(1)

The organotrifluoroborates **1d** and **1 e** were also employed as coupling partners in the cross-coupling reaction. The previously optimized conditions were used to couple the corresponding *β*-aminoethyltrifluoroborates with 4-bromobenzonitrile, affording the corresponding phenethylamines **4a** and **4b** in good yields as outlined in eq 2. This coupling is particularly relevant because it provides an easy and efficient alternative to prepare phenethylamines containing free amino groups after appropriate deprotection of the respective Boc and Cbz protecting groups.



(2)

In summary, we have been described an efficient and convenient synthesis of an important class of compounds through the Suzuki-Miyaura cross-coupling reaction. The potassium *β*-aminoethyltrifluoroborates, readily obtained as stable crystalline solids in moderate to excellent yields via Snieckus hydroboration with *i*-PP$_2$BH, have successfully proven their utility and versatility as useful aminoethylating reagents in the synthesis of a series of phenethylamines. The *β*-aminoethylation procedure tolerates diverse functional groups in the organotrifluoroborates as well as in the respective aryl-and heteroaryl electrophiles, affording the desired products in good to excellent yields. The stability of the β-aminoethyltrifluoroborates recommends them to diversity oriented synthesis, as a variety of these reagents can be prepared and stored indefinitely, awaiting coupling to diverse electrophiles. In this regard, studies directed toward a general method to prepare a wider range of potassium *β*-aminoethyltrifluoroborates are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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9. For the synthesis of organotrifluoroborates see: (a) Vedejs E, Chapman RW, Fields SC, Liu S, Schrimpf MR. J Org Chem 1999;60:3020. (b) Vedejs E, Fields SC, Hayashi R, Hitchcock SR, Powell DR, Schrimpf MR. J Am Chem Soc 1999;121:2460. For reviews of organotrifluoroborate salts, see: (c) Molander GA, Figueroa R. Aldrichimica Acta 2005;38:49. (d) Darses S, Genêt JP. Eur J Org Chem 2003:4313. (e) Molander GA, Ellis N. Acc Chem Res. in press
10. 9-Vinylcarbazole, *N* -vinylcaprolactam and *N* -vinyl-2-pyrrolidone are commercially available; *N*-Boc vinyl carbamate and *N*-Cbz vinyl carbamate were prepared according to the procedures described in the literature (See Supporting Information).
11. Kalinin AV, Scherer S, Snieckus V. Angew Chem Int Ed 2003;42:3399.
12. (a) Molander GA, Ito T. Org Lett 2001;3:393. [PubMed: 11428022] (b) Molander GA, Yun CS, Ribagorda M, Biolatto B. J Org Chem 2003;68:5534. [PubMed: 12839444]
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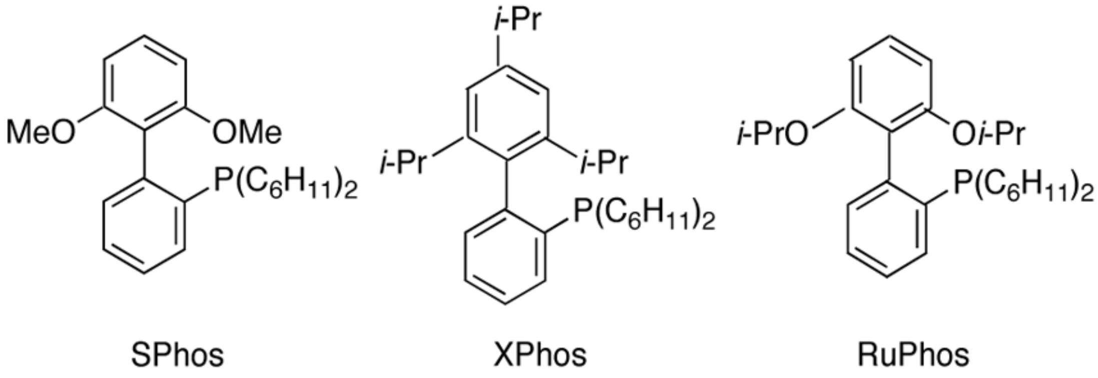
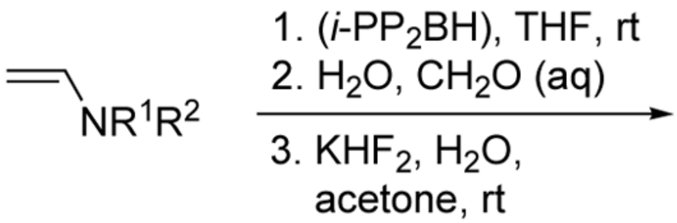


Figure 1.
Buchwald Ligands

Table 1

Preparation of Potassium β-Aminoethyltrifluoroborates



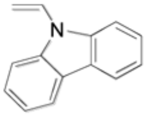
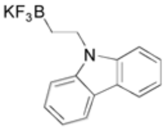
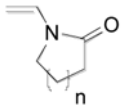
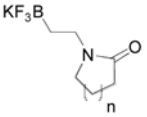
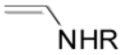
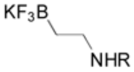
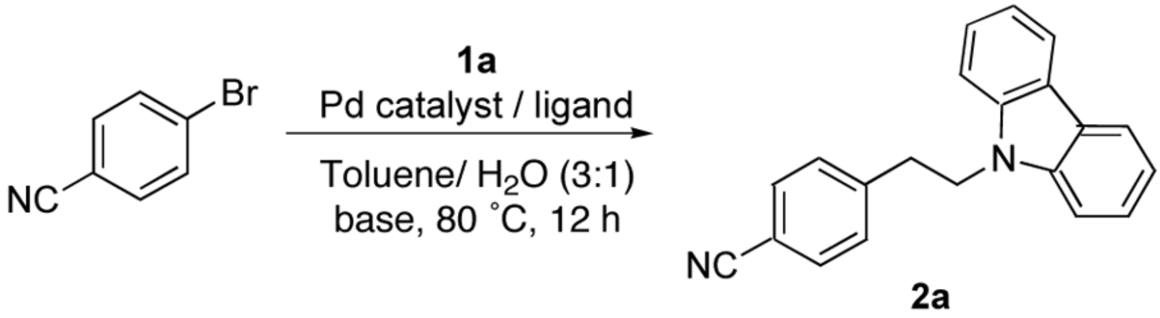
entry	substrate	product	1, % isolated yield
1			**1a**, 94
2 3			**1b**, n = 3; 76 **1c**, n = 1; 68
4 5			**1d**, R = Boc; 52 **1e**, R = Cbz; 50

Table 2

Optimization of Cross-Coupling Reaction for the Synthesis of **2a**



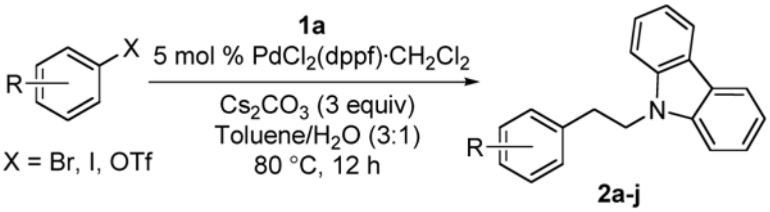
entry	catalyst/ligand (mol %)	base[a]	% isolated yield
1	$PdCl_2(dppf)\cdot CH_2Cl_2$ (10)	Cs_2CO_3	84
2	$PdCl_2(dppf)\cdot CH_2Cl_2$ (5)	Cs_2CO_3	90
3	$PdCl_2(dppf)\cdot CH_2Cl_2$ (2)	Cs_2CO_3	68
4	$Pd(OAc)_2/2\ PPh_3$ (5)	Cs_2CO_3	78
5	$PdCl_2/2\ PPh_3$ (5)	Cs_2CO_3	56
6	$PdCl_2(PPh_3)_2$ (5)	Cs_2CO_3	72
7	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	51
8	$PdCl_2(dppf)\cdot CH_2Cl_2$ (5)	K_2CO_3	69
9	$PdCl_2(dppf)\cdot CH_2Cl_2$ (5)	K_3PO_4	77
10	$PdCl_2(dppf)\cdot CH_2Cl_2$ (5)	Et_3N	73
11	$PdCl_2(dppf)\cdot CH_2Cl_2$ (5)	Cs_2CO_3	75[b]

[a] 3 equiv

[b] A mixture of THF/H_2O (10:1) was used as the solvent.

Table 3

Cross-Coupling of Potassium *β*-Aminoethyltrifluoroborate **1a** with Electron-Poor Aryl Bromides



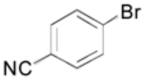
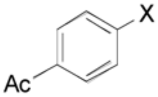
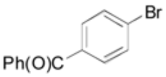
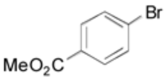
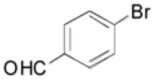
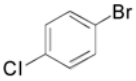
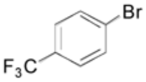
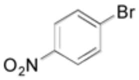
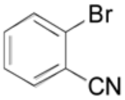
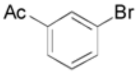
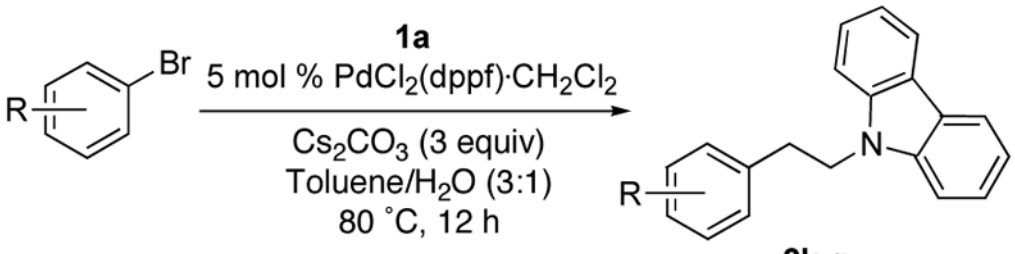
entry	Ar-X	% isolated yield
1		**2a**, 90
2		**2b**, X = Br, 82 X = I, 79 X = Otf, 77
3		**2c**, 79
4		**2d**, 84
5		**2e**, 84
6		**2f**, 73
7		**2g**, 74
8		**2h**, 79
9		**2i**, 85
10		**2j**, 79

Table 4

Cross-Coupling of Potassium β-Aminoethyltrifluoroborate **1a** with Electron-Rich Bromides



2k-q

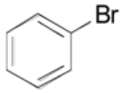
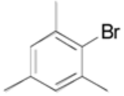
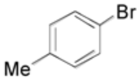
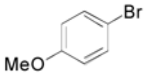
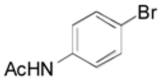
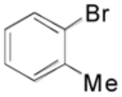
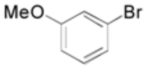
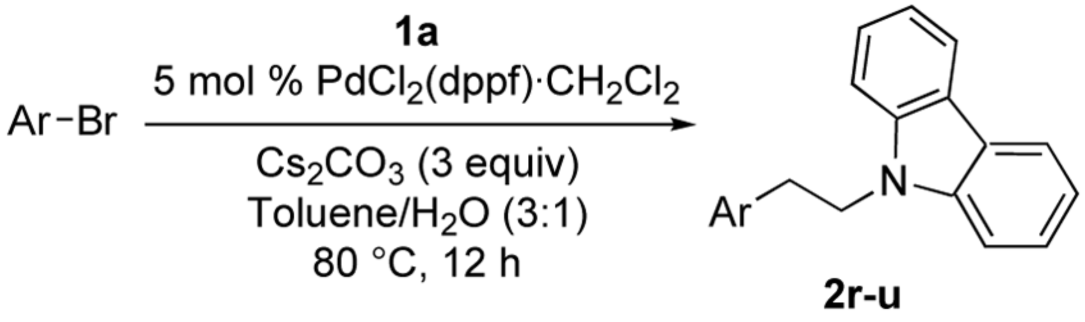
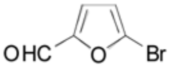
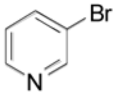
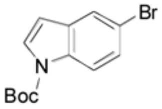
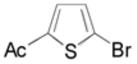
entry	Ar-Br	% isolated yield
1		**2k**, 89
2		**2l**, 88
3		**2m**, 81
4		**2n**, 70
5		**2o**, 73
6		**2p**, 79
7		**2q**, 68

Table 5

Cross-Coupling of Potassium β-Aminoethyltrifluoroborate **1a** with Heteroaryl Bromides



entry	bromide	% isolated yield
1		**2r**, 62
2		**2s**, 69
3		**2t**, 63
4		**2u**, 71[a]

[a] $Pd(OAc)_2$ (2 mol %) and RuPhos (4 mol %) were used in the catalytic system.