JOC Article

Scope of the Suzuki−Miyaura Aminoethylation Reaction Using Organotrifluoroborates

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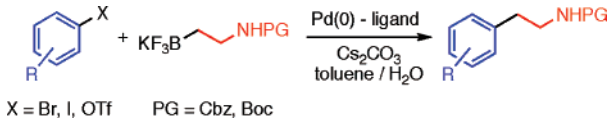

Potassium β-aminoethyltrifluoroborates were prepared in good yields via hydroboration of the corresponding enecarbamates using the Snieckus hydroborating reagent. A wide variety of phenethylamines containing a potentially free primary amine after appropriate deprotection have been successfully prepared in good yield using these organotrifluoroborates as partners in Suzuki−Miyaura coupling with aryl bromides, iodides, and triflates.

Introduction

Aminoethyl groups, and particularly phenethylamines, are of great interest because they are incorporated within a number of natural and synthetic compounds that exhibit important biological activities, and they are also important synthetic intermediates for the construction of these types of molecules. Examples include the erythrina and indole classes of alkaloids (Figure 1).

Prior to the development of transition-metal-catalyzed processes, the phenethylamine unit was normally installed by multistep sequences involving, for example, Friedel−Crafts acylation of activated arenes with *N*-protected amino acid chlorides followed by reduction of the ketone carbonyl group[1] or a sequence of three steps involving a chloromethylation of the aryl core followed by conversion to a nitrile group and subsequent reduction.[2] In certain cases, β-aminoethyl organolithiums could be directly coupled with aryl halides.[3] With the advent of metal-catalyzed coupling reactions, new avenues for preparing β-aminoethyl aromatics became available. For instance, aminoethylating strategies such as the Heck arylation of *N*-vinyloxazolone followed by hydrogenation[4] were reported. Additionally, nucleophilic aminoethylating reagents were developed such as β-amino organozinc reagents utilized in Negishi cross-coupling reactions.[5]

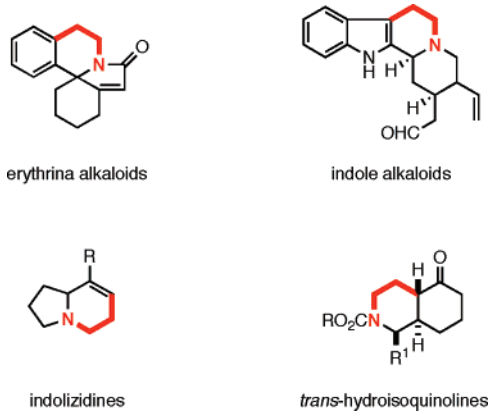

FIGURE 1. Nitrogen heterocycles containing aminoethyl groups.

The use of the Suzuki−Miyaura cross-coupling reaction for β-aminoethylation was first reported by Overman[6] and has been utilized in the synthesis of a variety of complex organic molecules.[7] This method possesses several distinct advantages. In addition to being performed at room temperature, the reaction is reported to have a wide substrate scope and

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(2) Ladd, D. L.; Weinstock, J.; Wise, M.; Gessner, G. W.; Sawyer, J. L.; Flaim, K. E. *J. Med. Chem.* **1986**, *29*, 1904−1912.
(3) Barluenga, J.; Montserrat, J. M.; Florez, J. *J. Org. Chem.* **1993**, *58*, 5976−5980.
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(6) Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743−8744.
(7) (a) Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1229−1232. (b) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186−10187. (c) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677−680.

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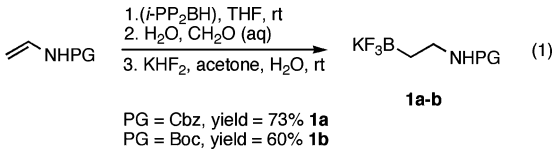
moreover can be executed in a one-pot fashion. However, it has some limitations as well. The procedure works well with aryl and alkenyl iodides, but the corresponding bromides generally require 1.5 equiv of the organoborane reagent. In addition, the aminoethylating reagent prepared in situ by hydroboration of the corresponding vinyl carbamate is air-sensitive and cannot be conveniently isolated and stored. While highly desirable within the context of a total synthesis, this in situ strategy is perhaps not ideal for reaction optimization on novel substrates and is not readily applicable to diversity-oriented synthesis or efforts in parallel synthesis.

The development of a new Suzuki−Miyaura approach that makes use of the more stable organotrifluoroborates would be a good complement to the strategy pioneered and developed by Overman. The nature of these boron reagents also makes them an attractive alternative to the classical boronic acids or boronate esters. The organotrifluoroborates are crystalline compounds that are indefinitely stable to moisture and air.[8] Their monomeric form, coupled with their lower tendency to protodeboronate as compared to boronic acids,[9] permits the use of stoichiometric amounts of these nucleophiles. We recently reported an efficient and convenient synthesis of an important class of tertiary phenethylamines through the Suzuki−Miyaura cross-coupling reaction using β-aminoethyltrifluoroborates.[10] To expand the scope of this procedure, it appeared desirable to be able to prepare phenethylamines containing the equivalent of a primary amine. Herein, we disclose the results obtained from the preparation of several potassium β-aminoethyltrifluoroborates and their coupling with a wide variety of aryl halides and triflates.

Results and Discussion

The current study began with the preparation of potassium β-aminoethyltrifluoroborates using an adaptation of Overman's procedure.[6,7] Thus, the desired *N*-vinyl carbamates[6] were hydroborated using the Snieckus hydroborating reagent (*i*-PP_2-BH),[11] and the resulting organoborane intermediates were treated with an aqueous solution of KHF_2 (eq 1). The potassium β-aminoethyltrifluoroborates produced in this way were isolated in good yields and can be stored on the benchtop indefinitely without any detectable degradation.



(1)

After optimization, the reaction could reliably be used to prepare at least 5 g of the organotrifluoroborate without compromising the yield of the reaction. The preparation of a broader variety of these potassium β-aminoethyltrifluoroborates can be envisioned because many vinylcarbamates containing various protecting groups are available.[12]

With these compounds in hand, Suzuki cross-coupling reactions with a variety of aryl electrophiles were attempted. The first halide partner studied was the electron-poor 4-bromobenzonitrile **2a**. On the basis of the optimized conditions reported for the cross-coupling of the 9-vinylcarbazole-derived potassium aminoethyltrifluoroborate and aryl bromides,[10] we first conducted the reaction in the presence of $PdCl_2(dppf)\cdot CH_2Cl_2$ (5 mol %) using Cs_2CO_3 as a base and a mixture of toluene/H_2O as the solvent system. Under these conditions, a heterogeneous mixture was formed that, over time, eventually gave rise to two homogeneous phases. These conditions allowed the formation of the cross-coupled product **3a** in a yield of 75%. This promising result led us to test the generality of the method by attempting the reaction on various electron-poor aryl bromides containing diverse functional groups. The results obtained are summarized in Table 1.

All electron-poor aryl electrophiles gave rise to the corresponding cross-coupled products in good to excellent yields. The use of the aryl bromides, iodides, or triflates (entry 7) did not affect the efficiency of the reaction. As expected, the coupling reaction tolerates a wide variety of functional groups such as nitrile, halide, aldehyde, ketone, and ester and also permits the use of nitro-containing derivatives. This last result underscores an advantage of organotrifluoroborates over classical organoboron reagents such as alkyl 9-BBNs, where some reduction of the nitro group can be observed during the cross-coupling process.[13] Reaction of the Cbz-protected organotrifluoroborate with electron-poor aryl electrophiles was proven efficient even when only a slight excess of the organoboron substrate is used (entry 7). The reaction also scaled up efficiently to 3.5 mmol of potassium β-aminoethyltrifluoroborate, providing nearly identical yields.

We next expanded the scope of this method using the Cbz-protected trifluoroborate with various electron-rich aryl bromides. Initial experiments (Table 2, entries 1 and 2) showed that the conditions previously developed failed to give the desired coupled compounds in satisfactory yields. These results prompted us to choose another protocol. On the basis of a successful procedure utilizing the Buchwald ligands,[10,14] the combination of 5 mol % of $Pd(OAc)_2$ and 10 mol % of RuPhos (Figure 2) was chosen as the catalytic system, and this offered greatly improved yields for the coupling of 1-bromo-2,4-dimethoxybenzene **4a** (entry 1). These reactions generally proceeded more efficiently if they were conducted at 95 °C. Several electron-rich aryl electrophiles were coupled in good yields using this procedure, and even the use of sterically hindered electrophiles such as 2-bromomesitylene **4h** did not affect the efficiency of the reaction. However, when an aryl bromide containing an amino group was used, only a moderate yield (46%) was obtained (entry 7). Under the standard conditions utilized, the reaction was incomplete, and several byproducts were formed as well.

To investigate the method further, the array of electrophiles was expanded to heteroaromatic bromides (Table 3).

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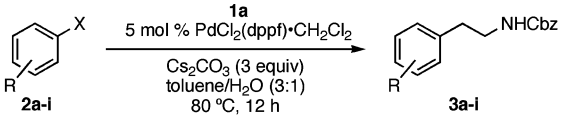
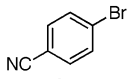
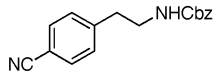
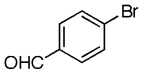
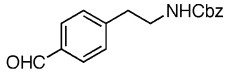
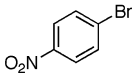
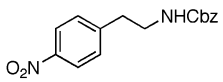
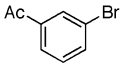
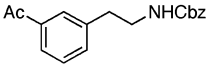
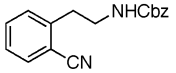
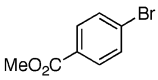
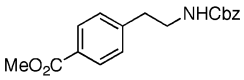
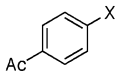
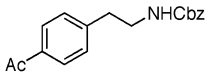
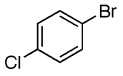
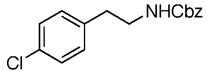
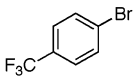
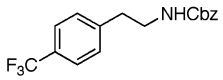
TABLE 1. Cross-Coupling of the Cbz-Protected Potassium β-Aminoethyltrifluoroborate 1a with Various Electron-Poor Aryl Electrophiles[a]

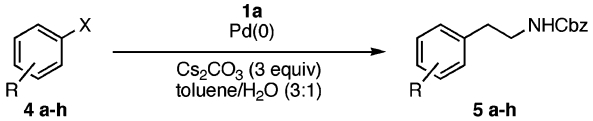


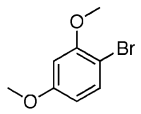
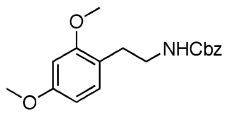
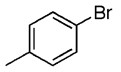
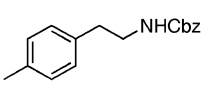
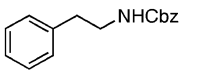
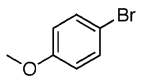
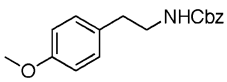
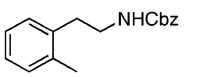
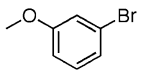
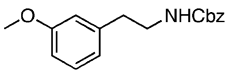
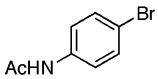
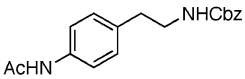
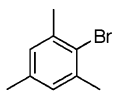
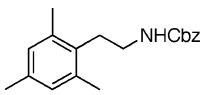
entry	aryl halide	product	% isolated yield
1	 **2a**	 **3a**	75
2	 **2b**	 **3b**	87
3	 **2c**	 **3c**	84
4	 **2d**	 **3d**	91
5	 **2e**	 **3e**	70
6	 **2f**	 **3f**	86
7	 **2g**	 **3g**	X = Br 89 (85[b]) X = I 60 X = OTf 82[c]
8	 **2h**	 **3h**	70
9	 **2i**	 **3i**	88

[a] Regarding the previously described conditions, all reactions, unless indicated, were carried out using 1.1 equiv of potassium β-aminoethyltrifluoroborate (0.26 mmol). During the course of this study, we observed that only 1.01 equiv was necessary. [b] This reaction was performed on a 3.5 mmol scale using only 1.01 equiv of potassium β-aminoethyltrifluoroborate. [c] This reaction was performed using only 1.01 equiv of potassium β-aminoethyltrifluoroborate.

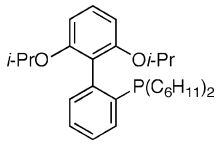
Different heteroaryl bromides, such as thiophene, pyrimidine, isoquinoline, and indole derivatives, were successfully coupled to the trifluoroborate **1a** under our previously described conditions [$Pd(OAc)_2$ (5 mol %), RuPhos (10 mol %), Cs_2CO_3 (3.0 equiv) in toluene/H_2O at 95 °C] to give rise to the desired compounds in very good yields. Interestingly, the isoquinoline (**6a**) and indole (**6e**) derivatives underwent coupling with the greatest efficiency to afford the aminoethylated products in excellent yields.

TABLE 2. Cross-Coupling of the Cbz-Protected Potassium β-Aminoethyltrifluoroborate 1a with Various Electron-Rich Aryl Electrophiles[a]



entry	aryl halide	product	% isolated yield
1	 **4a**	 **5a**	55[b] 79[c]
2	 **4b**	 **5b**	71[b] 75[c]
3	 **4c**	 **5c**	X = Br 86[c] X = OTf 85[c,d]
4	 **4d**	 **5d**	80[c]
5	 **4e**	 **5e**	82[c]
6	 **4f**	 **5f**	86[c]
7	 **4g**	 **5g**	46[c]
8	 **4h**	 **5h**	85[c]

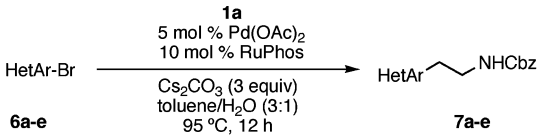
[a] All reactions were carried out using 0.24 mmol of aryl bromide and 0.26 mmol of potassium β-aminoethyltrifluoroborate. [b] Conditions: method A, $PdCl_2(dppf)•CH_2Cl_2$ (5 mol %), Cs_2CO_3 (3 equiv), toluene/H_2O (3:1), 80 °C, 12 h. [c] Conditions: method B, $Pd(OAc)_2$ (5 mol %), RuPhos (10 mol %), Cs_2CO_3 (3 equiv), toluene/H_2O (3:1), 95 °C, 12 h. [d] This reaction was performed using 1.01 equiv of potassium β-aminoethyltrifluoroborate.



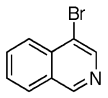
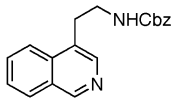
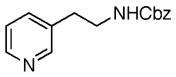
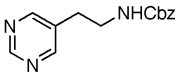
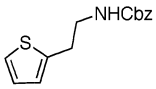
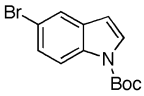
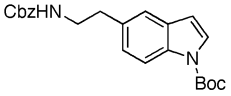
RuPhos

FIGURE 2. RuPhos ligand.

TABLE 3. Cross-Coupling of the Cbz-Protected Potassium β-Aminoethyltrifluoroborate 1a with Various Heteroaryl Bromides[a]



6a-e 7a-e

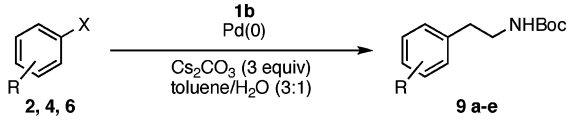
entry	bromide	product	% isolated yield
1	 **6a**	 **7a**	84 (74[b])
2	 **6b**	 **7b**	81
3	 **6c**	 **7c**	80
4	 **6d**	 **7d**	79
5	 **6e**	 **7e**	89

[a] All reactions were carried out using 0.24 mmol of aryl bromide and 0.26 mmol of potassium β-aminoethyltrifluoroborate. [b] Using 5 mol % of $PdCl_2(dppf)\cdot CH_2Cl_2$ as the catalyst.

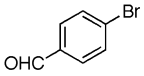
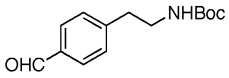
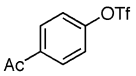
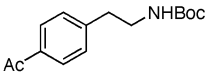
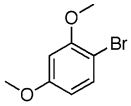
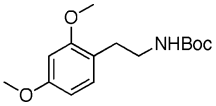
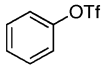
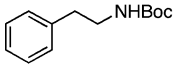
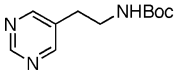
We next examined the efficiency of potassium 2-(*tert*-butoxycarbonylamino)ethyltrifluoroborate **1b** using our previously developed conditions (Table 4). Expanding the reaction to this organotrifluoroborate is particularly relevant, as it enables the introduction of either the Boc- or the Cbz-functionalized amino moiety, depending on the nature of the protection scheme desired within the target molecule.

Under the conditions previously developed, the Boc-protected trifluoroborate coupled as efficiently as the Cbz-protected organoboron with electron-poor or electron-rich aryl electrophiles (entries 1−4). Heteroaryl bromides such as 5-bromopyrimidine **8e** were also successfully reacted to afford the title compound in a yield of 83%.

TABLE 4. Cross-Coupling of the Boc-Protected Potassium β-Aminoethyltrifluoroborate 1b with Various Aryl Electrophiles[a]



2, 4, 6 9 a-e

entry	bromide	product	% isolated yield
1	 **2b**	 **9a**	79[b]
2	 **2g**	 **9b**	72[b]
3	 **4a**	 **9c**	86[c]
4	 **4c**	 **9d**	78[c]
5	 **6c**	 **9e**	83[c]

[a] All reactions were carried out using 0.24 mmol of aryl bromide and 0.242 mmol of potassium β-aminoethyltrifluoroborate (1.01 equiv). [b] Conditions: method A, $PdCl_2(dppf)\cdot CH_2Cl_2$ (5 mol %), Cs_2CO_3 (3 equiv), toluene/H_2O (3:1), 80 °C, 12 h. [c] Conditions: method B, $Pd(OAc)_2$ (5 mol %), RuPhos (10 mol %), Cs_2CO_3 (3 equiv), toluene/H_2O (3:1), 95 °C, 12 h.

Conclusion

We have extended the method of β-aminoethylation previously developed toward the preparation of phenethylamines that would possess free primary amines after appropriate deprotection of the respective Boc or Cbz protecting groups. The strategy consists of a Suzuki−Miyaura cross-coupling reaction of aryl electrophiles with potassium β-aminoethyltrifluoroborates prepared via Snieckus hydroboration. A number of electron-poor, electron-rich, and heteroaryl electrophiles containing various functional groups (carbonyl, nitro, ester, etc.) and various substitution patterns were evaluated, demonstrating the efficiency of this strategy. These results should permit easy access to other nitrogen-containing materials incorporating the phenethylamine group. Efforts toward the extension of this strategy to the cross-coupling with alkenyl bromides are currently underway.

Experimental Section

METHOD A. Preparation of Benzyl 4-Acetylphenethylcarbamate (3g). To a mixture of potassium β-aminoethyltrifluoroborate (**1a**) (1.0 g, 3.5 mmol), 4-bromoacetophenone (691.5 mg, 3.47

mmol), Cs_2CO_3 (3.39 g, 10.41 mmol), and $PdCl_2(dppf)\cdot CH_2Cl_2$ (141.7 mg, 0.17 mmol) under nitrogen was added toluene/H_2O (3:1, 22 mL). The reaction was heated at 80 °C with stirring under a nitrogen atmosphere in a sealed tube for 12 h and then cooled to rt. A saturated aqueous solution of NH_4Cl (10 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried ($MgSO_4$) and then filtered. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (elution with EtOAc/hexane 3:7) to afford the product as a white solid (mp 84−85 °C, lit. 85−87 °C[6]) in 85% yield (876 mg, 2.95 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, 2H, J = 8.0 Hz), 7.36−7.26 (m, 7H), 5.09 (s, 2H), 4.82 (br s, 1H), 3.50−3.46 (m, 2H), 2.88 (app t, 2H, J = 6.6 Hz), 2.57 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.8, 156.3, 144.6, 136.5, 135.6, 129.1, 128.7, 128.6, 128.2, 128.1, 66.7, 41.9, 36.2, 26.6. The spectroscopic data correspond to those reported in the literature.[6]

METHOD B. Preparation of Benzyl 2,4-Dimethoxyphenethylcarbamate (5a). To a mixture of potassium β-aminoethyltrifluoroborate (**1a**) (69.1 mg, 0.242 mmol), 1-bromo-2,4-dimethoxybenzene (46.0 mg, 0.24 mmol), Cs_2CO_3 (234.6 mg, 0.72 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol), and RuPhos (11.2 mg, 0.024 mmol) under nitrogen was added toluene/H_2O (3:1, 1.5 mL). The reaction was heated at 95 °C with stirring under a nitrogen atmosphere in a sealed tube for 12 h and then cooled to rt. A saturated aqueous solution of NH_4Cl (4 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried ($MgSO_4$) and then filtered. The solvent was removed in vacuo, and the crude product was purified by silica gel chromatography (elution with EtOAc/hexane 3:7) to afford the product as a white solid in 79% yield (59.5 mg, 0.19 mmol). mp = 91−92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 6.99 (d, 1H, J = 8.1 Hz), 6.42−6.39 (m, 2H), 5.07 (s, 2H), 4.88 (br s, 1H), 3.77 (s, 6H), 3.40−3.36 (m, 2H), 2.75 (app t, 2H, J = 6.7 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 159.8, 158.5, 156.5, 136.9, 130.9, 128.5, 128.11, 128.07, 119.6, 104.1, 98.7, 66.5, 55.4, 55.3, 41.4, 30.1; IR (KBr) 3341, 1697, 1546, 1465, 1260, 1133 cm^{-1}; HRMS (ES+) m/z calcd for $C_{18}H_{21}NO_4Na^+$ ($M+Na^+$) 338.1368, found 338.1369.

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Supporting Information Available: Experimental procedures, spectral characterization, and copies of ^{1}H, ^{13}C, ^{11}B, and ^{19}F spectra for all compounds prepared by the method described. This material is available free of charge via the Internet at http://pubs.acs.org.

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