CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc Europe

DOI: 10.1002/chem.201200831

Rapid and Efficient Access to Secondary Arylmethylamines

Nicolas Fleury-Brégeot,[a] Jessica Raushel,[a] Deidre L. Sandrock,[a] Spencer D. Dreher,*[b] and Gary A. Molander*[a]

Abstract: Ammoniomethyl trifluoroborates are very powerful reagents that can be used to access biologically relevant aryl- and heteroaryl-methylamine motifs via Suzuki–Miyaura cross-couplings. Until now, this method was limited to the production of tertiary and primary amines. The synthesis of a large array of secondary ammoniomethyltrifluoroborates has been achieved through a one step nucleophilic substitution reaction on the potassium bromomethyltrifluoroborate. Smooth cross-coupling conditions have been designed, based on the use of an aminobiphenyl palladium precatalyst, to couple these trifluoroborates efficiently with aryl bromides. This strategy offers a new way to access biologically relevant motifs and allows, with the previously developed methods, access to all three classes of aminomethylarenes.

Keywords: cross-coupling · palladium · secondary aminomethylarenes · Suzuki–Miyaura reaction · trifluoroborates

Introduction

Nitrogen-containing molecules are among the most important classes of organic molecules because of the tremendous array of applications in which they can be used.[1] Among them, the aminomethylarene moiety is quite well represented. A basic search in the literature generates thousands of hits of bioactive molecules containing this motif. The aminomethyl-containing molecules displayed below include molecules exhibiting activity against cancer and malaria, in addition to compounds that are candidates or approved drugs for the treatment of hypertension and obesity (Figure 1).[2]

Existing methods to introduce such relevant motifs require, in many cases, the employment of harsh reaction conditions that are not always suitable for use in molecules containing sensitive functional groups. Therefore, access to those target molecules often involves longer synthetic routes, including protection/deprotection steps or further functionalization. The main disconnections that can be envisioned for the construction of this structural motif are summarized in Scheme 1. The most commonly used reaction by far is the reductive amination, employing reducing agents such as sodium triacetoxyborohydride or amine-boranes to reduce the in situ generated imine from the reaction between an aldehyde and an amine (routes a and b, Scheme 1).[3] Other routes include nucleophilic substitution on the primary arylmethanamine moiety[4] or longer, similar sequences starting from the corresponding aryl nitrile or

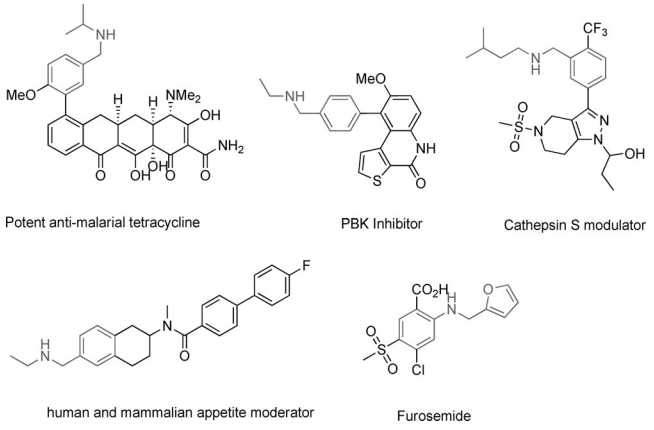
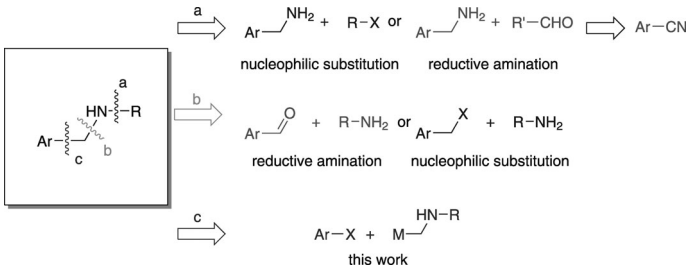


Figure 1. Examples of bioactive molecules containing the aminomethyl moiety.



Scheme 1. Possible disconnections to access the aminomethylarene moiety.

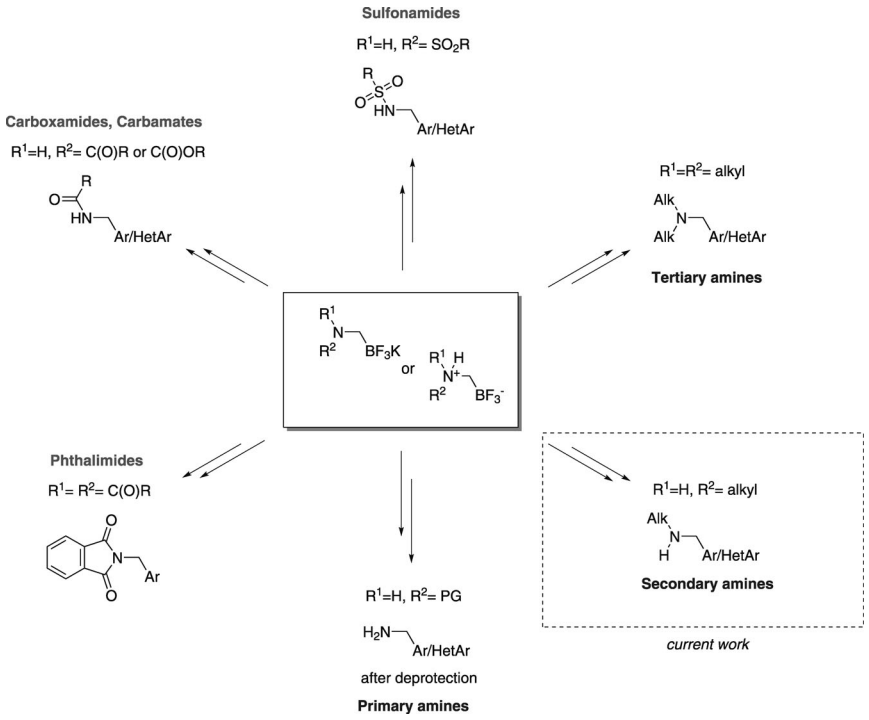
[a] Dr. N. Fleury-Brégeot, Dr. J. Raushel, Dr. D. L. Sandrock, Prof. G. A. Molander
Roy and Diana Vagelos Laboratories
Department of Chemistry, University of Pennsylvania
Philadelphia, PA 19104-6323 (USA)
E-mail: gmolandr@sas.upenn.edu

[b] Dr. S. D. Dreher
Department of Process Chemistry
Merck Research Laboratories
P.O. Box 2000, Rahway, NJ, 07065 (USA)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200831.

imine to introduce the desired methylamine group.[5] The reduction of carboxamides has also been reported.[6] These routes may also be limited by the relative lack of available starting materials (e.g., arylmethanamines or benzylic-type halides).

At the outset of our initial studies, there was no literature precedent for a disconnection involving the use of aryl halides and a methylamino carbanion equivalent (Scheme 1, route c). Our research group has focused on developing a cross-coupling strategy employing air and moisture stable ammoniomethyltrifluoroborate salts to create a versatile, complementary, and convenient method to access the aryl/heteroarylammoniomethyl moiety (Scheme 2). This new approach represents the most straightforward route to access the secondary aminomethylarene moiety starting from an aryl halide.



Scheme 2. Scope of amino and ammoniomethyltrifluoroborates.

The protocol envisioned would also represent the first example of direct introduction of the secondary aminomethyl moiety based on a cross-coupling approach, made feasible by the unique features offered by organotrifluoroborates. Organotrifluoroborates are very useful nucleophilic partners in the Suzuki–Miyaura cross-coupling reaction, overcoming some drawbacks of other boron-containing reagents, thus providing unprecedented and suitable synthetic routes to a variety of interesting substructures.[7] Concerning the ammoniomethyl moiety, Molander and co-workers have demonstrated that the corresponding trifluoroborates can be accessed successfully either by direct nucleophilic substitution on the halogenomethyltrifluoroborate (dialkylamines)[8] or using Matteson's alpha transfer route (e.g., carboxamides, carbamates, sulfonamides).[9] The different coupling partners can be used efficiently in cross-coupling reactions with various electrophilic partners such as aryl/hetaryl halides and more recently mesylates.[10]

Following this strategy, tertiary methylamine groups can be installed starting from the corresponding ammoniomethyl trifluoroborate salts. The introduction of primary methylamine groups has been recently achieved through the use of the Boc-protected aminomethyltrifluoroborate followed by a deprotection step.[11] Diverse functionalized aminomethyl groups such as carboxamides, sulfonamides, and very recently phthalimides can also be prepared and cross-coupled.[12] Surprisingly, access to secondary alkylaminomethyl groups, the last structural unit needed to fill a useful gap in our approach, has been a difficult transformation to achieve.

We report herein the synthesis and cross-coupling of secondary ammoniomethyltrifluoroborates with a large array of aryl bromides as an effective and straightforward route to obtain secondary aminomethylarenes.

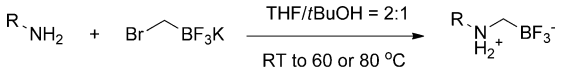
Results and Discussion

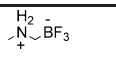
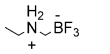
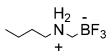
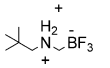
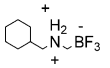
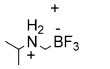
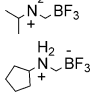
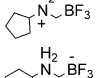
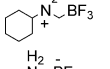
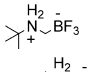
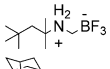
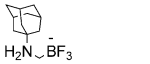
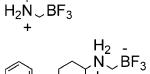
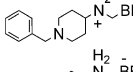
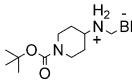
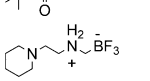
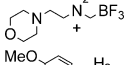
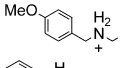
After reporting that aminomethyl based trifluoroborates exist as the ammoniomethyl internal salt,[8d] an imperative need arose for us to design a reliable method to access the desired secondary aminomethyl-containing trifluoroborates. We based our synthetic route on the direct nucleophilic substitution of potassium halogenomethyltrifluoroborates, in a mixture of THF/*t*BuOH, similar to the method already used to obtain other ammoniomethyl salts. Unfortunately, the synthesis starting from the chloromethyltrifluoroborate did not work efficiently even at high temperatures. Better results were obtained using the bromomethyltrifluoroborate and a gradual increase to the final oil bath temperature. Usually, nucleophilic substitutions on the halogenomethyltrifluoroborates are conducted at high temperatures,[8a] but when using primary amines, decomposition products of the trifluoroborate and unidentified polymeric mixtures were often recovered. Lowering the temperature helped reduce the amount of side products generated but also hampered the conversion, making the isolation of the desired secondary ammoniomethyltrifluoroborate problematic, owing to large amounts of unreacted bromomethyltrifluoroborate. The problem was

solved by initiating the reaction in a room temperature oil bath and heating it gradually to the desired temperature over 40 min. These conditions allowed access to a large array of diversely substituted secondary ammoniomethyltrifluoroborates. The final temperature as well as the reaction time varied on a case by case basis, depending on the substrate. The various secondary ammoniomethyltrifluoroborates synthesized (**1a–s**) are summarized in Table 1.

Linear alkyl chains of different lengths were tolerated (Table 1, entries 1–3) in very disparate yields. Although the 29% yield for the methylammoniomethyltrifluoroborate **1a** can be explained by the volatility of the starting methylamine, the low yield obtained with *n*-butylamine (Table 1, entry 3) remains unclear. The reaction conditions are very specific to each substrate as illustrated by entries 4, 8, and 18, which exhibit no illuminating trend. Secondary alkylamines proved to react very well with the bromomethyltrifluoroborate, yielding the desired ammonio salts with good to excellent yields (Table 1, entries 6–8). Cyclohexylammoniomethyltrifluoroborate was obtained in 90% yield on a 10 mmol scale. More hindered alkylamines, such as *tert*-butylamine, *tert*-octylamine, and even adamantylamine reacted to afford the desired ammonio salts in very good yields (Table 1, entries 9–11). Of note, the salt **1k** derived from adamantylamine is so insoluble and hydrophobic that it had to be purified with water.[14]

Table 1. Preparation of secondary ammoniomethyltrifluoroborates.



Entry	Product		Method	Yield [%][a]
1		**1a**	A	29
2		**1b**	A	81
3		**1c**	B	15
4		**1d**	A B	85 58
5		**1e**	B	81
6		**1f**	A	92
7		**1g**	A	87
8		**1h**	A B	90[b] 67
9		**1i**	A	74
10		**1j**	A	83
11		**1k**	B	89
12		**1l**	B	67
13		**1m**	A	90
14		**1n**	B	9
15		**1o**	B	30
16		**1p**	B	35
17		**1q**	A	85
18		**1r**	A B	54 69
19		**1s**	A	44

Method A: 60 °C for 4–16 h; Method B: 80 °C for 2–24 h. [a] Yield of isolated product. [b] Reaction performed on a 10 mmol scale.

Amines bearing a second heteroatom were more difficult to react in good yields and often required the use of method B to afford the expected trifluoroborate salts (Table 1, entries 12–16 and 19). The presence of tertiary amine moieties, which could also compete with the desired nucleophilic substitution, can account for the lower yields observed. The success of the reaction might be directly related to the steric bulk on the ancillary group on the amine. For example, in entry 12, the 4-amino-*N*-benzylpiperidine ammonio salt **1l** was obtained in a 67% yield, which increased to 90% when the piperidine moiety was protected by a bulkier Boc group (**1m**; Table 1, entry 13). However, basicity might also play a role, as the more basic the second nitrogen atom is, the more likely it will react, leading to undesired side reactions. Unhindered diamines provided very low yields (Table 1, entries 14, 15). The 35% yield obtained for **1p** can be explained by the low nucleophilicity of the corresponding *para*-methoxyaniline compared to alkylamines. On the other hand, diphenylmethanamine was able to react well, affording **1q** in 85% yield (Table 1, entry 17). Of note, tryptamine, even with the unprotected indole, led to the formation of the desired ammonio salt **1s** in 44% yield (Table 1, entry 19). In all cases, the secondary ammoniomethyltrifluoroborates were obtained as air and moisture stable solids that were stored on the bench for weeks without any observed decomposition.

As the substitution reactions were performed on bromomethyltrifluoroborate, we were concerned by possible contamination of the final internal salts by KBr.[8d] To prevent this possible issue, work-up conditions were designed using hot filtration in acetonitrile and/or Soxhlet extraction using isopropyl acetate, as it was found that KBr has a very low solubility in those solvents. However, to prevent any problems, it was decided to use a small excess of the ammonio salt when performing the cross-coupling reactions to ensure that enough of the trifluoroborate was still engaged in the reaction even in the case of trace contamination. We were also able to grow crystals of two of the secondary ammoniomethyl trifluoroborates (**1h** and **1j**), and their structures were elucidated by X-ray crystallography (Figure 2).

Having synthesized a large array of secondary ammoniomethyltrifluoroborates through a very direct and effective

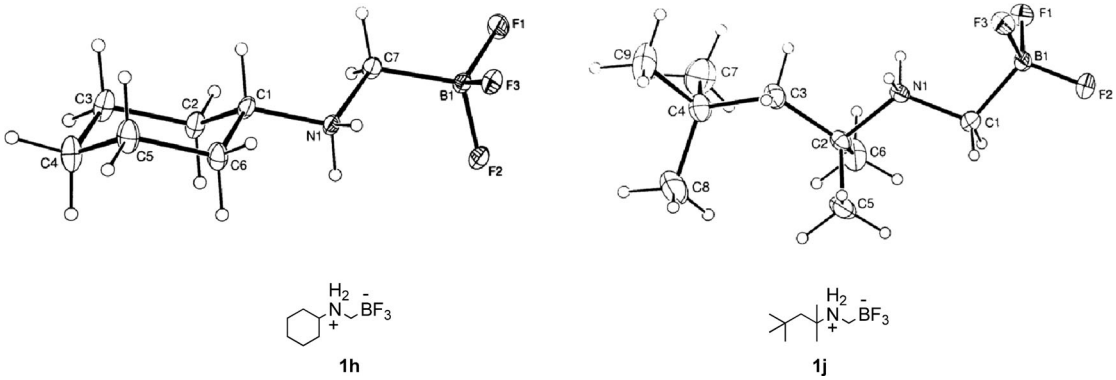
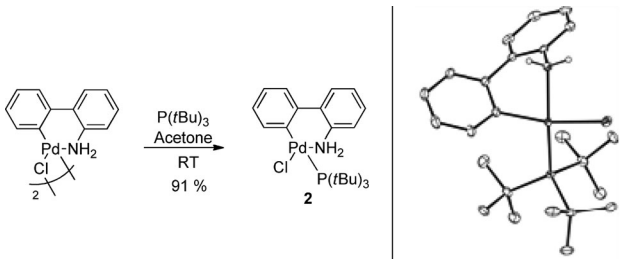


Figure 2. X-ray structures of ammoniomethyltrifluoroborates **1h** and **1j**.

nucleophilic substitution pathway, we then explored their behavior in the Suzuki–Miyaura cross-coupling reaction to afford arenemethylamine products. This reaction proved to be much more difficult than expected and very extensive screening was required to find suitable and reproducible conditions. None of the previously reported cross-coupling conditions with the other ammoniomethyltrifluoroborates provided a trace of the expected product. Indeed, being able to perform a cross-coupling on those internal salts bearing a free amine moiety requires a very effective catalytic system. Specifically, after the transmetalation step, the amine moiety could possibly bind intra- or intermolecularly to the metal, creating aggregates, thus deactivating the catalyst and preventing completion of the catalytic cycle. Moreover, the free amine can also coordinate to the metal as the reagent or as the product and prevent the reaction. This transformation is challenging, and those factors could explain why finding the right catalytic system required such extensive exploratory investigation. The use of the recently reported aminobiphenyl precatalysts developed by Buchwald et al. proved to be crucial.[15] This precatalyst system allows rapid formation of the desired active Pd^0 species in the presence of a weak base. After much screening of ligands, we determined that the classic Buchwald phosphines were not suitable for this reaction. The best ligand was found to be the bulky and electron rich tri-*tert*-butylphosphine.[16] The synthesis of the precatalyst **2** is shown in Scheme 3.

The reaction conditions were optimized using the cyclohexylammoniomethyltrifluoroborate **1h** and *para*-halogeno

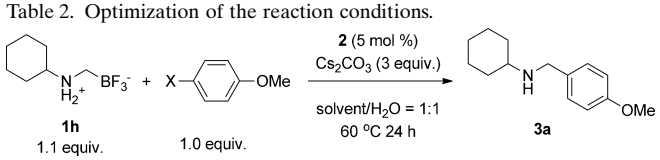


Scheme 3. Synthesis and X-ray stucture of the palladium biphenyl tri-*tert*-butylphosphine precatalyst 2.[17]

anisole electrophiles in the presence of catalyst (5 mol%), and the results are summarized in Table 2.

The best solvent system was found to be a 1:1 mixture of THF/H_2O at a concentration of 0.05 M at 60 °C, yielding **3a** in 83% isolated yield. When the reaction temperature was increased to 80 °C, irreproducible results were obtained with an average 66% isolated yield (Table 2, entry 2). The very dilute conditions required can be explained by a possible coordination of the nitrogen of either the boron-containing amino reagent or the amine product to the palladium that can lead to its deactivation when the reaction is run at higher concentration. A solution to overcome this drawback could be envisioned by using continuous flow technology.[18]

Table 2. Optimization of the reaction conditions.



Entry	X	Solvent[a]	Conc. [M]	Yield [%][b]
1	Br	CPME	0.05	38
2	Br	THF	0.05	83 (66)[c]
3	Br	THF	0.10	42
4	Br	THF	0.50	34
5	Cl	THF	0.05	50
6	I	THF	0.05	30

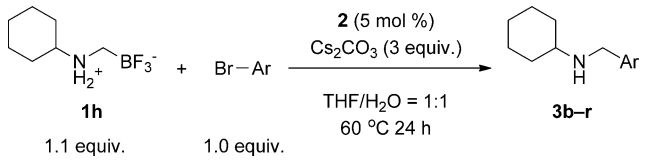
[a] CPME = cyclopentyl methyl ether. [b] Yields of isolated product. [c] Reaction performed at 80 °C.

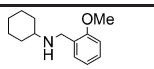
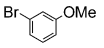
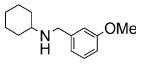
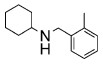
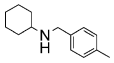
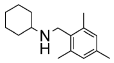
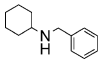
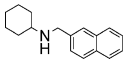
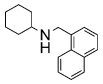
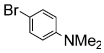
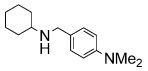
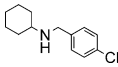
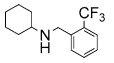
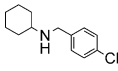
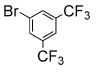
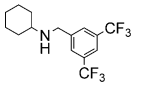
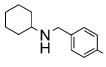
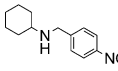
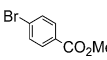
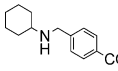
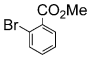
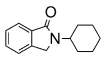
para-Bromoanisole provided the best results, while chloro- and iodo-derivatives only afforded the desired product **3a** in 50 and 30% yields, respectively (Table 2 entries 2, 5, 6).

Once the conditions were optimized, and to investigate the method further, various electron rich (Table 3, entries 1–9) and electron poor (Table 3, entries 10–17) aryl bromides were examined as electrophiles in the reaction (Table 3).

All the bromides tested afforded the cross-coupled products with yields ranging from 45 to 95%. Interestingly, when the *ortho*-bromomethylbenzoate (Table 3 entry 17) was used, the *iso*-indolinone **3r** was isolated in a 48% yield. This

Table 3. Scope of the reaction with aryl bromides.



Entry	Electrophile	Product		Yield [%][a]
1			**3b**	53
2			**3c**	77
3			**3d**	90
4			**3e**	82
5			**3f**	42
6			**3g**	85
7			**3h**	95
8			**3i**	90
9			**3j**	52
10			**3k**	81
11			**3l**	24
12			**3m**	85
13			**3n**	45
14			**3o**	80
15			**3p**	86
16			**3q**	53
17			**3r**	48

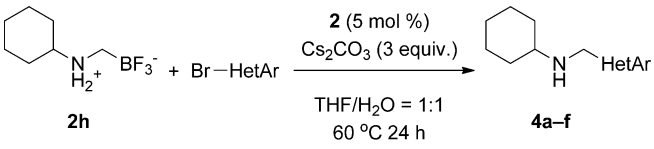
[a] Yield of product isolated after purification, product can contain up to 5% of phosphine oxide.

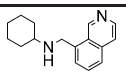
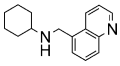
product corresponds to the intramolecular cyclization of the amine onto the ester group under basic conditions. Electron rich bromides provided good to excellent yields. The effect of steric hindrance was tested with several mono and di *ortho*-substituted bromides (Table 3 entries 1, 3, 5, 11, 17).

Depending on the nature of the ortho substituent, the outcome of the reaction was very different. Although chemically inert groups (Table 3 entries 1, 3) did not really have an influence on the yields, other functional groups had a negative effect (Table 3, entry 11) or even participated in the formation of the observed product **3r** (Table 3, entry 17). A very hindered system (Table 3, entry 5) still proceeded to react, albeit without total conversion, giving a lower yield. Naphthalene bromides (Table 3, entries 7, 8) cross-coupled very efficiently, affording **3h** and **3i** in 95 and 90% yield, respectively. The designed method allows the presence of functional groups such as ethers, amines, nitriles, esters, and nitro groups. Fluoro- and trifluoromethyl containing aryl bromides were also well tolerated (Table 3, entries 12–14). As a general rule, heteroatom-containing aryl bromides gave diminished yields, but still reacted efficiently.

To expand the scope of the reaction, the cyclohexylammoniomethyl trifluoroborate salt **3h** was also reacted with heteroaryl bromides under the same conditions with much less success (Table 4).

Table 4. Scope of the cross-coupling reaction between **1h** and various heteroaryl bromides.



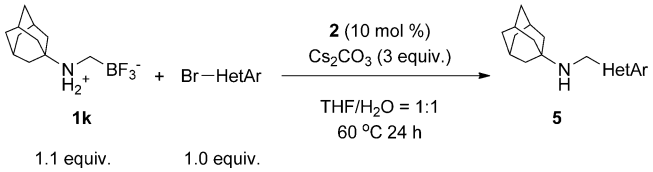
Entry	Electrophile	Product		Yield [%][a]
1			**4a**	36 34[b]
2			**4b**	61[b] 57[b,c]
3			**4c**	38
4			**4d**	31[b]
5			**4e**	32[d]
6			**4f**	34[d]

[a] Yield of isolated products, which might be contaminated with up to 10 mol% of phosphine oxide. [b] 10 mol% of catalyst was used. [c] Reaction time of 48 h. [d] Reaction ran at 75 °C.

When 8-bromo-isoquinoline was employed in the reaction under the conditions described (Table 4, entry 1), the desired amine **4a** was isolated in 36% yield. Increasing the catalyst loading to 10 mol% did not improve the yield. The 5-bromoquinoline proved to be a better substrate, affording **4b** in 61% yield. Extending the reaction time from 24 to 48 h did not impact the yield of the reaction (Table 4, entry 2). Indole, pyridine, and thiophene derivatives cross-coupled with yields ranging from 31 to 38% (Table 4, entries 3–6). Harsher reactions conditions (75 °C) did not improve the outcome of the reaction.

The presence of an extra heteroatom that can interact with the catalyst in a bidentate fashion prevents the reaction from working well.[19] To avoid this issue, or at least to lower its impact, we tried performing the cross coupling with the

sterically hindered ammoniomethyl salt **1k**. We were hoping that the steric bulk of the adamantyl moiety would prevent the nitrogen of the ammonio salt from interacting with the palladium, thus avoiding deactivation. Unfortunately, when using the 5-bromoquinoline, the desired product **5** was only retrieved in 44% yield (Scheme 4), lower than the one ob-



Scheme 4. Attempts of cross-coupling **1k** and 5-bromoquinoline.

tained when using the cyclohexyltrifluoroborate **1h**. The 3-bromopyridine and thiophene did not provide any of the cross-coupled products. The adamantyl group might be too bulky, and in addition to surrounding the nitrogen of the ammoniomethyl, it might also slow down the cross-coupling reaction. Another hypothesis to explain this lack of reactivity could also be the very low solubility of this trifluoroborate salt, with subsequent slow conversion into the active boron species required for the cross-coupling reaction.[20]

To demonstrate the scope of the method on aryl bromides, a variety of ammoniomethyl salts were used in the cross-coupling reaction using *para*-bromoanisole under the previously defined conditions (Table 5). In some cases, for ease of purification, the products were isolated as their HCl salt.

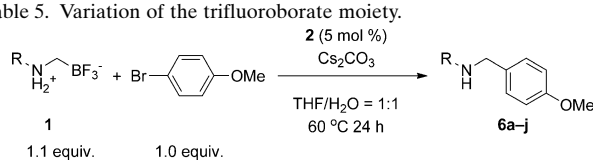
The ten different ammoniomethyl salts cross-coupled with yields ranging from 30 to 83%. Alkylamine-based trifluoroborates (Table 5, entries 1–8) proved to be efficient coupling partners in the reaction. The adamantylammoniomethyltrifluoroborate **1k** provided the best result with an 83% yield. The presence of an additional nitrogen (e.g., an NBoc group) on the nucleophilic partner **1m** did not hamper the outcome of the reaction, as the desired coupled product **6i** bearing two amino groups was obtained in 81% yield. Interestingly, the 2-(2-chlorophenyl)ethylaminomethyltrifluoroborate **1r** afforded the expected secondary amine **6j** in 59% yield, which could be increased to 64% when using NaO*t*Bu as the base. Thus, the presence of another halogen did significantly inhibit the reaction.

This product could be used for further functionalization and even other cross-coupling reactions. For instance, we were able to use it to perform an intramolecular amination reaction to yield the corresponding *para*-methoxybenzylindoline **7a** in 73% isolated yield, providing an efficient and short reaction sequence to create this unit (Scheme 5).[21]

Conclusions

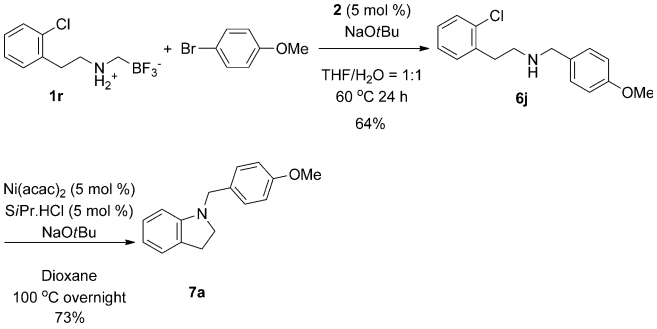
In conclusion, a straightforward and efficient synthesis of secondary ammoniomethyltrifluoroborate salts has been developed. Their suitability as coupling partners in the

Table 5. Variation of the trifluoroborate moiety.



Entry	R	BF_3K	Product		Yield [%][a]
1	*t*Bu	**1i**		**6a**	30[b]
2	*i*Pr	**1f**		**6b**	53[b]
3		**1e**		**6c**	69
4	cyclopentyl	**1g**		**6d**	72[b]
5	adamantyl	**1k**		**6e**	83[b]
6	*neo*-pentyl	**1d**		**6f**	54[b]
7	*tert*-octyl	**1j**		**6g**	81[b]
8		**1q**		**6h**	74[c]
9		**1m**		**6i**	81
10		**1r**		**6j**	59 64[d]

[a] Yield of isolated products, which might contain up to 5% of phosphine oxide. [b] Products isolated as the HCl salt. [c] Contaminated with 5% carbazole. [d] NaO*t*Bu used instead of Cs_2CO_3.



Scheme 5. Rapid synthesis of indoline derivative **7a** from trifluoroborate **1r** in two metal-catalyzed reactions.

Suzuki–Miyaura cross-coupling reaction has been demonstrated with a wide variety of aryl bromides. This new method readily allows access to secondary arylmethanamine moieties via a new disconnection, thus filling a void in the synthesis of aminomethyl substituted arenes based on the use of aminomethyltrifluoroborates to access all the different classes of arylmethylamines. The cross-coupling with heteroaryl electrophiles involving unprotected free amines creates some challenges, but further work is currently underway in our laboratory to overcome these issues.

Acknowledgements

This research was supported by a National Priorities Research Program (NRP) grant from the Qatar National Research Fund (Grant No. 08-035-1-008), the National Science Foundation (GOALI), and the NIH (R01GM-081376). AllyChem is acknowledged for the generous donation of bromomethyl potassium trifluoroborate. Dr. Matthew Tudge (Merck Research Laboratories) is acknowledged for preparing and donating the aminobiphenyl palladium μ-chloro dimer. Dr. Rakesh Kohli (University of Pennsylvania) is acknowledged for obtaining HRMS data. Dr. Patrick Caroll (University of Pennsylvania) is acknowledged for performing the X-ray analysis.

[1] a) C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26; b) G. F. Smith, *Prog. Med. Chem.* **2009**, *48*, 1–29; c) K. Grabowski, K.-H. Baringhaus, G. Schneider, *Nat. Prod. Rep.* **2008**, *25*, 892–904; d) F. E. Koehn, G. T. Carter, *Nat. Rev. Drug. Discov.* **2005**, *4*, 206–220; e) D. Lednicer, L. A. Mitscher, in *The Organic Chemistry of Drug Synthesis, Vol. 7*, Wiley, New York, **1997**; f) R. B. Silverman, in *The Organic Chemistry of Drug Design and Drug Action*, 2nd ed., Elsevier, Burlington, **2004**.

[2] a) M. Drapier, M. L. Nelson, Patent WO2004/038001; b) Y. Nakamura, Y. Matsuo, S. Hisada, F. Ahmed, R. Huntley, Z. Sajjadi-Hashemi, D. M. Jenkins, R. B. Kargbo, W. Cui, P. J. F. Guuan, J. R. Walker, Patent WO2011/123419; c) D. Allen, M. L. Ameriks, F. U. Axe, M. Burdett, H. Cai, I. Choong, J. P. Edwards, W. Lew, S. P. Meduna, Patent US2009/0118274; d) X. E. Hu, Patent WO2008/001160; e) H. Lüddens, H.-J. Lang, E. R. Korpi, *Euro. J. Pharmacol.* **1998**, *344*, 269–277.

[3] a) A. F. Abdel-Magid, S. J. Mehrman, *Org. Process Res. Dev.* **2006**, *10*, 971–1031; b) A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff, R. D. Shah, *J. Org. Chem.* **1996**, *61*, 3849–3862; c) E. W. Baxter, A. B. Reitz, *Organic Reactions, Vol. 59*, Wiley, New York, **2002**, pp. 1–714; d) S. Gomez, J. A. Peters, T. Maschemeyer, *Adv. Synth. Catal.* **2002**, *344*, 1037–1057; e) R. N. Salvatore, C. H. Yoon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785–7811; f) M. D. Bomann, I. C. Guch, M. DiMare, *J. Org. Chem.* **1995**, *60*, 5995–5996; g) W. Liao, Y. Chen, Y. Liu, H. Duan, J. L. Petersen, X. Shi, *Chem. Commun.* **2009**, 6436–6438; h) C. Wang, A. Pettman, J. Bacsa, J. Xiao, *Angew. Chem.* **2010**, *122*, 7710–7714; *Angew. Chem. Int. Ed.* **2010**, *49*, 7548–7552.

[4] a) A. Pinner, A. Franz, *Chem. Ber.* **1905**, *38*, 1539–1548; b) R. N. Salvatore, A. S. Nagle, S. E. Schmidt, K. W. Jung, *Org. Lett.* **1999**, *1*, 1893–1896; c) R. N. Salvatore, A. S. Nagle, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 674–683; d) C. Chiappe, D. Pieraccini, *Green Chem.* **2003**, *5*, 193–197; e) G. Guillena, D. J. Ramon, M. Yus, *Chem. Rev.* **2010**, *110*, 1611–1641.

[5] For recent examples, see: a) X. Cui, Y. Zhang, F. Shi, Y. Deng, *Chem. Eur. J.* **2011**, *17*, 2587–2591; b) C. Guérin, V. Bellosta, G. Guillamot, J. Cossy, *Org. Lett.* **2011**, *13*, 3534–3537; c) J. M. Farrell, Z. M. Heiden, D. W. Stephan, *Organometallics* **2011**, *30*, 4497–4500.

[6] For a metal-free protocol, see: a) G. Pelletier, W. S. Bechara, A. B. Charette, *J. Am. Chem. Soc.* **2010**, *132*, 12817–12919; for iron-catalyzed examples see: b) S. Zhou, K. Junge, D. Addis, S. Das, M. Beller, *Angew. Chem.* **2009**, *121*, 9671–9674; *Angew. Chem. Int. Ed.* **2009**, *48*, 9507–9510; c) Y. Sunada, H. Kawakami, T. Imaoka, Y. Motoyama, H. Nagashima, *Angew. Chem.* **2009**, *121*, 9675–9678; *Angew. Chem. Int. Ed.* **2009**, *48*, 9511–9514.

[7] For reviews on organotrifluoroborate salts, see: a) G. A. Molander, R. Figueroa, *Aldrichimica Acta* **2005**, *38*, 49–56; b) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286; c) H. A. Stefani, R. Cella, S. Adriano, *Tetrahedron* **2007**, *63*, 3623–3658; d) S. Darses, J.-P. Genêt, *Chem. Rev.* **2008**, *108*, 288–325; for mechanistic details on the advantages of trifluoroborates over other boron reagents in the Suzuki reaction, see: e) M. Butters, J. N. Harvey, J. Jover, A. J. J. Lennox, G. C. Lloyd-Jones, P. M. Murray, *Angew. Chem.* **2010**, *122*, 5282–5286; *Angew. Chem. Int. Ed.* **2010**, *49*, 5156–5160.

[8] For the first examples of ammoniomethyltrifluoroborate syntheses, see: a) G. A. Molander, J. Ham, *Org. Lett.* **2006**, *8*, 2031–2034; for more examples and their use in Suzuki–Miyaura cross-coupling, see: b) G. A. Molander, D. L. Sandrock, *Org. Lett.* **2007**, *9*, 1597–1600; c) G. A. Molander, P. E. Gormisky, D. L. Sandrock, *J. Org. Chem.* **2008**, *73*, 2052–2057; for a recent reinvestigation of the ammoniomethyltrifluoroborates, see: d) J. Raushel, D. L. Sandrock, K. V. Josyula, D. Pakyz, G. A. Molander, *J. Org. Chem.* **2011**, *76*, 2762–2769.

[9] a) G. A. Molander, M.-A. Hiebel, *Org. Lett.* **2010**, *12*, 4876–4879; b) G. A. Molander, N. Fleury-Brégeot, M.-A. Hiebel, *Org. Lett.* **2011**, *13*, 1694–1697.

[10] For aryl and heteroaryl halides, see Ref. [8b–d]; for aryl and heteroaryl mesylates, see: G. A. Molander, F, Beaumard, *Org. Lett.* **2011**, *13*, 1242–1245.

[11] G. A. Molander, I. Shin, *Org. Lett.* **2011**, *13*, 3956–3959.

[12] For carboxamides, see ref. [9a]; for sulfonamides, see Ref. [9b] and for phthalimides, see: R. Devulapally, N. Fleury-Brégeot, G. A. Molander, D. G. Seapy, *Tetrahedron Lett.* **2012**, *53*, 1051–1055.

[13] F. Brotzel, Y. C. Chu, H. Mayr, *J. Org. Chem.* **2007**, *72*, 3679–3688.

[14] See the Supporting Information for more details.

[15] T. Kinzel, Y. Zhang, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 14073–14075.

[16] a) G. C. Fu, *Acc. Chem. Res.* **2008**, *41*, 1555–1564; b) A. F. Littke, G. C. Fu, *Angew. Chem.* **1998**, *110*, 3586–3587; *Angew. Chem. Int. Ed.* **1998**, *37*, 3387–3388.

[17] For other references dealing with the synthesis of biphenyl precatalysts, see: a) J. Albert, J. Granell, J. Zafrilla, M. Font-Bardia, X. Solans, *J. Organomet. Chem.* **2005**, *690*, 422–429; b) J. Albert, J. Granell, A. Luque, J. Minguez, R. Moragas, M. Font-Bardia, X. Solans, *J. Organomet. Chem.* **1996**, *522*, 87–96.

[18] For a review on cross-coupling reactions in continuous flow, see: a) T. Noël, S. L. Buchwald, *Chem. Soc. Rev.* **2011**, *40*, 5010–5029; for recent articles using the biphenyl precatalyst in continuous flow see: b) T. Noël, A. J. Musacchio, *Org. Lett.* **2011**, *13*, 5180–5183; c) W. Shu, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 2321–2325; d) T. Noël, S. Kuhn, A. J. Musacchio, K. F. Jensen, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 5943–5946; e) P. Li, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 6396–6400; f) W. Shu, L. Pellegatti, M. A. Oberli, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2011**, *50*, 10665–10669.

[19] a) M. W. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861–2873; b) R. B. Bedford, C. S. J. Cazin, S. J. Coles, T. Gelbrich, M. B. Hurthouse, V. J. M. Scordia, *Dalton Trans.* **2003**, 3350–3356.

[20] See ref. [7a, 7e]; a) G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396; b) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870; c) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302–4314; d) A. J. J. Lennox, G. C. Lloyd-Jones, *J. Am. Chem. Soc.* **2012**, *134*, 7431–7441.

[21] a) R. Omar-Amrani, A. Thomas, E. Brenner, B. Schneider, Y. Fort, *Org. Lett.* **2003**, *5*, 2311–2314; b) R. Omar-Amrani, R. Schneider, Y. Fort, *Synthesis* **2004**, *15*, 2527–2534; c) C. A. Baxter, E. Cleator, M. Alam, A. J. Davies, A. Goodyear, M. O'Hagan, *Org. Lett.* **2010**, *12*, 668–671.

Received: March 12, 2012
Published online: July 5, 2012

