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Synthesis and Reactivity of Solid-Supported Organotrifluoroborates in Suzuki Cross-Coupling

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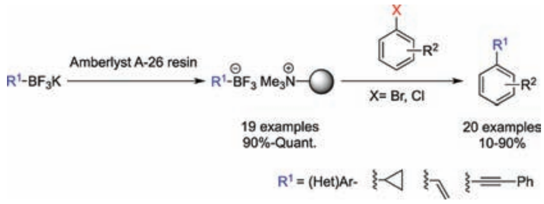
ABSTRACT



Solid-supported organotrifluoroborates were prepared in high yields by ion exchange with Amberlyst resins. The reactivity of solid supported aryltrifluoroborates was evaluated in Suzuki–Miyaura couplings with numerous aryl bromide partners. Electron-rich and -poor substituents were tolerated on both substrates, providing yields up to 90%. Examples of alkyl-, alkenyl-, alkynyl-, and heteroaryltrifluoborates were also successfully cross-coupled to aryl halides.

In conjunction with the increased use of organoboron compounds in the Suzuki–Miyaura cross-coupling, their use in solid-phase chemistry has received attention in the past decade for both purification and synthesis purposes. Arylboronic acids have been captured as alkyl- or arylboronate species. Previous work described three types of alkyl diol resins. One type is a macroporous polymer-supported 1,3-diol, but its application requires high temperature and an excess of boronic acid to optimize the catch phase.[1] Alternatively, a fluorinated 1,2-diol resin[2] as well as a DiEthanolAminoMethyl polystyrene (DEAM-PS) resin can be used, providing immobilization under milder conditions.[3] In all cases, the release procedure can provide access not only to the free and pure arylboronic acids but also to the corresponding arenes or phenol derivatives. Finally, boronic acids can be caught as catecholborane derivatives using the Merrifield resin.[4]

An alternative method for the formation of solid-supported pinacolboronate ester derivatives starts directly from the free boronate esters. Wilson and co-workers applied this strategy with the MBHA resin in a solid-supported boronic acid synthesis.[5]

Solid-phase aryl–aryl Suzuki–Miyaura cross-couplings are usually performed between a boronic acid and a resin-bound aryl halide.[6] Aryl bromides[7] and iodides[8] are the most utilized electrophiles, but aryl triflates can also be used.[9] However, only a few examples describe the reaction

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[1] (a) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H.; Maillard, B. *Tetrahedron Lett.* **1999**, *40*, 7979–7983. (b) Carboni, B.; Pourbaix, C.; Carreaux, F.; Deleuze, H. *Chem. Commun.* **2000**, 1275–1276.

[2] Chen, D.; Qing, F.-L; Huang, Y. *Org. Lett.* **2002**, *4*, 1003–1005.

[3] (a) Hall, D. G.; Tailor, J.; Gravel, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3064–3067. (b) Gravel, M.; Thompson, K. A.; Zak, M.; Bérubé, C.; Hall, D. G. *J. Org. Chem.* **2002**, *67*, 3–15. (c) Arimori, S.; Hartley, J. H.; Bell, M. L.; Oh, C. S.; James, T. D. *Tetrahedron Lett.* **2000**, *41*, 10291–10294.

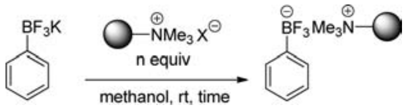
[4] Yang, W.; Gao, X.; Springsteen, G.; Wang, B. *Tetrahedron Lett.* **2002**, *43*, 6339–6342.

[5] MHBA Resin: 4-Methylbenzhydrylamine Hydrochloride Salt Resin. Dunsdon, R. M.; Greening, J. R.; Jones, P. S.; Jordan, S.; Wilson, F. X. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1577–1579.

[6] Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219–8222.

10.1021/ol300215p

Table 1. Optimization of Solid-Supported Phenyltrifluoroborate Formation



entry	X	equivalents	time (h)	conversion (%)[a]
1	F	1.1	0.5	100
2	Cl	4	4	100
3	Br	8	24	100

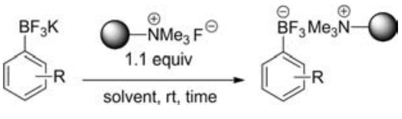
[a] Conversion determined by LCMS analysis using mesitylene or toluene as an internal standard.

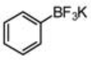
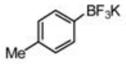
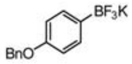
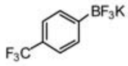
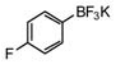
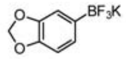
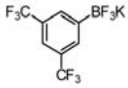
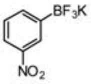
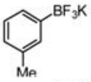
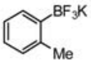
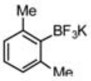
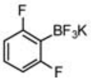
between solid-phase boronate esters and aryl halides. Suzuki–Miyaura cross-couplings have been achieved between polystyrene-supported arylboronic acids [PS-R-B$(OH)_2$] and iodo- or bromoarenes in good yields,[10] as well as solid-phase boronate esters [R-B(OR)OR′-PS] and iodoaryls.[2,11]

Arylboronic acids have also been captured as ammonium trihydroxyborate salts on ammonium hydroxide form Dowex ion exchange resins and directly cross-coupled under palladium-catalyzed Suzuki–Miyaura conditions to form biaryls as well as macroheterocycles.[12]

Because of their increased stability, organotrifluoroborates represent an attractive alternative to boronic acids in these contexts.[13] Over the past 10 years, potassium aryltrifluoroborates have been shown to be very efficient partners in Suzuki–Miyaura cross-couplings[14] with various aryl halides.[15]

Table 2. Scope of Solid-Supported Aryltrifluoroborates[a]



entry	R-BF_3K	product	time (h)	yield (%)
1		**1a**	0.5[b]	93
2		**1b**	0.5[c]	quant
3		**1c**	0.5[d]	91
4		**1d**	0.5[b]	93
5		**1e**	0.5[b]	94
6		**1f**	0.5[c]	99
7		**1g**	1[b]	93
8		**1h**	2[c]	96
9		**1i**	0.5[c]	99
10		**1j**	1[b]	98
11		**1k**	2[b]	90
12		**1l**	1.5[c]	quant

[a] Conditions: Potassium aryltrifluoroborate (1.0 mmol), resin (1.1 mmol), solvent, 20 °C, time. [b] Reaction performed in MeOH. [c] Reaction performed in acetone. [d] Reaction performed in a mixture of MeOH/MeCN (1:1).

In addition to the more common potassium salts, ammonium[16] organotrifluoroborates can also be synthesized.[17] Batey et al. initially investigated the cross-coupling between *n*-tetrabutylammonium phenyltrifluoroborate and iodo- or bromoarenes.[17] Recently, our group has also reported cross-coupling reactions using *n*-tetrabutylammonium[18] or

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(7) (a) Lago, M. A.; Nguyen, T. T.; Bhatnagar, P. *Tetrahedron Lett.* **1998**, *39*, 3885–3888. (b) Chamoin, S.; Houldsworth, S.; Kruse, C. G.; Kruse, C. G.; Bakker, W. I.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 4179–4182. (c) Xiong, Y.; Klopp, J.; Chapman, K. T. *Tetrahedron Lett.* **2001**, *42*, 8423–8427. (d) Chhabra, S. R.; Mahajan, A.; Chan, W. C. *J. Org. Chem.* **2002**, *67*, 4017–4029. (e) Ohnmacht, S. A.; Brenstrum, T.; Bleicher, K. H.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2004**, *45*, 5661–5663. (f) Zhu, J.; Pottorf, R. S.; Player, M. R. *Tetrahedron Lett.* **2006**, *47*, 7267–7270. (g) Cousaert, N.; Willand, N.; Gesquière, J.-C.; Tartar, A.; Déprez, B.; Deprez-Poulain, R. *Tetrahedron Lett.* **2008**, *49*, 2743–2747.

(8) (a) Guiles, J. W.; Johnson, S. G.; Murray, W. V. *J. Org. Chem.* **1996**, *61*, 5169–5171. (b) Ruhland, B.; Bombru, A.; Gallop, M. A. *J. Org. Chem.* **1997**, *62*, 7820–7826. (c) Wendeborn, S.; Berteina, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, 671–675. (d) Blettner, C. G.; König, W. A.; Rühter, G.; Stenzel, W.; Schotten, T. *Synlett* **1999**, 307–310. (e) Baudoin, O.; Cesario, M.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2002**, *67*, 1199–1207. (f) Revell, J. D.; Ganesan, A. *Org. Lett.* **2002**, *4*, 3071–3073. Lepore, S. D.; Wiley, M. R. *Org. Lett.* **2003**, *5*, 7–10. (g) Sunami, S.; Ohkudo, M. *Tetrahedron* **2009**, *65*, 638–643.

(9) Lutz, C.; Bleicher, K. H. *Tetrahedron Lett.* **2002**, *43*, 2211–2214.

(10) (a) Piettre, S. R.; Baltzer, S. *Tetrahedron Lett.* **1997**, *38*, 1197–1200. (b) Main, C. A.; Petersson, H. M.; Rahman, S. S.; Hartley, R. C. *Tetrahedron* **2008**, *64*, 901–914.

(11) (a) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527–6530. (b) Pourbaix, C.; Carreaux, F.; Carboni, B. *Org. Lett.* **2001**, *3*, 803–805.

(12) Lobrégat, V.; Alcaraz, G.; Bienaymé, H.; Vaultier, M. *Chem. Commun.* **2001**, 817–818.

(13) (a) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (c) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.

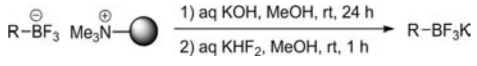
(14) (a) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156–5160. (b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem.—Eur. J.* **2011**, *17*, 2492–2503.

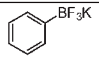
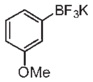
(15) (a) Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870. (b) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314. (c) Kabalka, G. W.; Al-Masum, M. *Tetrahedron Lett.* **2005**, *46*, 6329–6331. (d) Kim, D.-S.; Bolla, K.; Lee, S.; Ham, J. *Tetrahedron* **2011**, *67*, 1062–1070.

(16) (a) Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135–6140. (b) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558–3560. (c) Prakash, G. K. S.; Pertusati, F.; Olah, G. A. *Synthesis* **2011**, 292–302.

(17) Batey, R.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103.

Table 3. Release of Potassium Organotrifluoroborates[a]



entry	R-BF_3K	isolated yield (%)
1		30
2		16
3		71

[a] Solid-supported organotrifluoroborate (1.0 mmol), (1) aq 4.5 M KOH (5.0 mmol), MeOH, 20 °C, 24 h; (2) sat. aq KHF_2 (10.0 mmol), MeOH, rt, 1 h.

cesium[19] aryltrifluoroborates. In both cases, good yields were obtained, showing no difference in comparison with potassium salt analogs.

Herein, we report an efficient way to prepare solid-supported organotrifluoroborates using an ion exchange process with a quaternary ammonium salt functionalized resin. Additionally, we describe the release of pure potassium organotrifluoroborate salts and the first Suzuki–Miyaura cross-coupling involving solid-supported organotrifluoroborates.

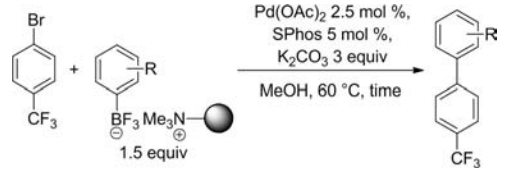
We began our investigations with the study of the catch phase. Because of the high stability of *n*-tetrabutylammonium organotrifluoroborates, we turned our attention to PS-trimethylammonium Amberlyst resins (Table 1).

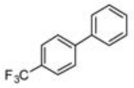
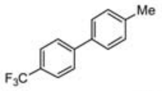
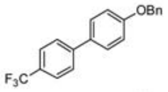
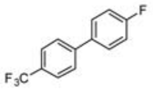
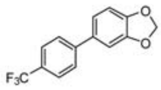
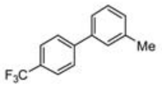
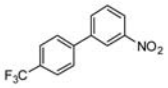
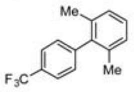
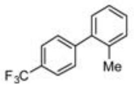
In all cases, a complete immobilization of phenyltrifluoroborate on the solid support could be achieved. The most efficient resin proved to be the one with a fluoride counterion, as only 1.1 equiv of resin were needed for complete conversion after 30 min.

A wide range of potassium aryltrifluoroborates were immobilized in very good yields using fluoride on Amberlyst A-26 resin (Table 2). Indeed, both electron-rich (entries 2, 3, 6, 9–11) and electron-deficient (entries 4, 5, 7, 8, 12) solid-phase aryltrifluoroborates **1a**–**l** were obtained in less than 2 h. Methanol, acetone, or a mixture of MeOH/CH_3CN is alternatively used as a solvent, depending on the solubility of each potassium aryltrifluoroborate.

We then focused on the release phase to develop a purification method for organotrifluoroborates. In this case, the chloride form of the resin was chosen to make this operation more cost-effective.[20] Different potassium salts were surveyed to release the potassium organotrifluoroborate. The use of excess aqueous KOH in methanol allowed a quantitative release measured by ^1H NMR.

Table 4. Cross-Coupling of Solid-Supported Aryltrifluoroborates[a]



entry	R	product	time (h)	yield (%)
1		**2a**	10	83
2		**2b**	8	72
3		**2c**	20	84
4		**2d**	4	61
5		**2e**	10	87
6		**2f**	8	83
7		**2g**	15	31
8		**2h**	7	90
9		**2i**	30	80

[a] 4-Bromobenzotrifluoride (1.0 mmol), aryltrifluoroborate on resin (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), SPhos (0.05 mmol), MeOH (0.25 M), 60 °C, time.

However, the isolation of the desired products was more problematic than expected. We discovered that an additional acidic treatment was necessary following the basic release, but the overall yield strongly depended on the nature of the organotrifluoroborate (Table 3).

The second part of the study was focused on the cross-coupling of numerous solid-supported aryltrifluoroborates with 4-bromobenzotrifluoride. After optimizing the conditions for the cross-coupling, yields between 31 and 90% were obtained (Table 4). Various electron-donating groups are tolerated in the *para*, *meta* or *ortho* positions, affording the corresponding desired biaryls in good to very good yields (entries 2, 3, 5, 6, 8, and 9). The reaction is also compatible with sterically hindered substrates, as evidenced by the successful cross-coupling of 2,6-dimethylphenyltrifluoroborate (entry 8). Electron-deficient substituents

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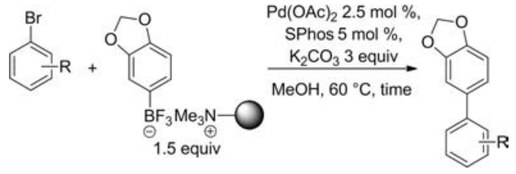
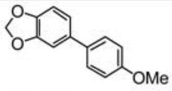
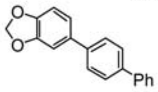
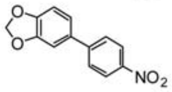
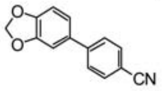
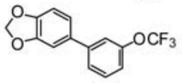
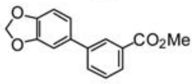
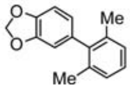
(18) Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634–9635.

(19) Molander, G. A.; Fleury-Brégot, N.; Hiebel, M.-A. *Org. Lett.* **2011**, *13*, 1694–1697.

(20) In Sigma-Aldrich catalog: Amberlyst A-26 (fluoride), CAS # 39339-85-0, \$445 for 50 g; Amberlite IRA-900 (chloride), CAS # 9050-97-9, \$60.80 for 500 g.

Table 5. Scope of Aryl Bromide Cross-Coupling[a]



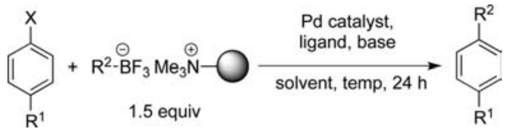
entry	product		time (h)	yield (%)
1		**3a**	7	76
2		**3b**	7	25
3		**3c**	6	10
4		**3d**	7	74
5		**3e**	5.5	72
6		**3f**	7	78
7		**3g**	10	61

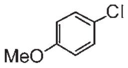
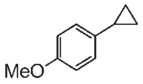
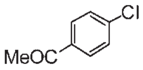
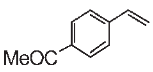
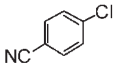
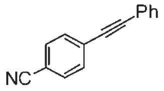
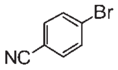
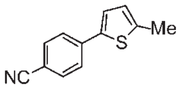
[a] Aryl bromide (1.0 mmol), solid-supported 2*H*-1,3-benzodioxol-5-yltrifluoroborate (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), SPhos (0.05 mmol), MeOH (0.25 M), 60 °C, time.

were also tolerated (entries 4, 7) even though a lower yield of 31% was obtained for the biaryl **2g** (entry 7).

The optimized conditions also proved to be efficient for a wide range of substituted aryl bromides (Table 5). The Suzuki cross-coupling was performed using solid-supported 2*H*-1,3-benzodioxol-5-yltrifluoroborate, resulting in yields between 10 and 78%. Aryl bromides presenting electron-rich (entries 1, 2, 5, and 7) and electron-withdrawing groups (entries 3, 4, and 6) were alternatively tested. As was the case in the synthesis of **2g** (Table 4, entry 7), a poor yield was obtained in the presence of a nitro substituent (entry 3), even though the analysis of the crude mixture showed complete conversion.

Table 6. Cross-Coupling of Solid-Supported Alkyl-, Alkenyl-, Alkynyl-, and Heteroaryltrifluoroborates[a]



entry	aryl halide	product		yield (%)
1			**4a**	54[b]
2			**4b**	54[c]
3			**4c**	55[d]
4			**4d**	55[e]

[a] All the reactions were performed on a 1.0 mmol scale of aryl halide. [b] $Pd(OAc)_2$ 3 mol %, XPhos 6 mol %, K_2CO_3 3 equiv, THF/H_2O (10:1), 100 °C. [c] $Pd(OAc)_2$ 1 mol %, RuPhos 2 mol %, Na_2CO_3 2 equiv, THF/H_2O (10:1), 100 °C. [d] $PdCl_2(dppf){\bullet}CH_2Cl_2$, Cs_2CO_3, THF/H_2O (20:1), 110 °C. [e] $Pd(OAc)_2$ 1 mol %, RuPhos 2 mol %, Na_2CO_3 2 equiv, EtOH, 85 °C.

The scope of solid-supported organotrifluoroborates was then explored with nonaromatic substrates (Table 6). To represent alkyl-, alkenyl-, alkynyl-, and heteroaryltrifluoroborates, solid-supported cyclopropyl-, vinyl-, phenylethynyl-, and 5-methyl-2-thienyltrifluoroborate, respectively, were selected. They all reacted according to the literature reported conditions,[21] giving unoptimized yields of around 55%.

In summary, we have developed a general procedure for the synthesis of solid-supported organotrifluoroborates. These compounds can be released from the solid support, providing a purification method for potassium organotrifluoroborates, or engaged in further reactions. We report the first solid-phase Suzuki cross-coupling involving immobilized aryltrifluoroborates. Numerous biaryls carrying both electron-donating and -withdrawing substituents were synthesized in yields up to 90%. The substrate scope was successfully extended to solid-supported alkyl-, alkenyl-, alkynyl-, and thienyltrifluoroborates.

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Supporting Information Available. Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For Suzuki couplings with potassium cyclopropyl-, vinyl-, alkynyl-, and thienyltrifluoroborate, respectively, see: (a) Molander, G. A.; Gormisky, P. E. *J. Org. Chem.* **2008**, *73*, 7481–7485. (b) Molander, G. A.; Brown, A. R. *J. Org. Chem.* **2006**, *71*, 9681–9686. (c) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416–8423. (d) Molander, G. A.; Canturk, B.; Kennedy, L. E. *J. Org. Chem.* **2009**, *74*, 973–980.

The authors declare no competing financial interest.