Fluoride-Mediated Boronic Acid Coupling Reactions

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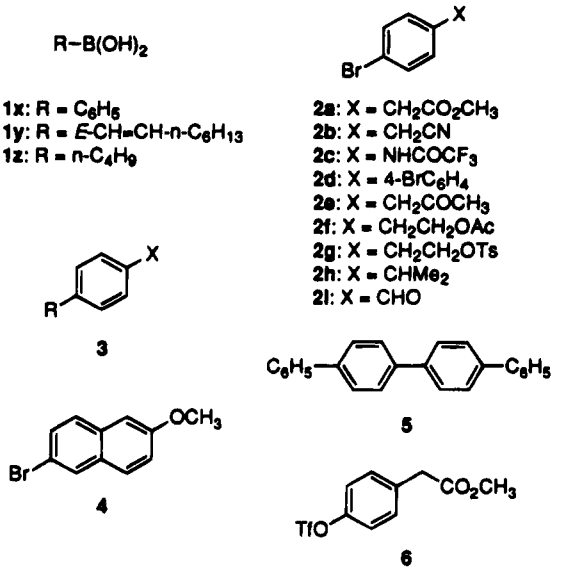
The palladium-catalyzed coupling of aryl-, vinyl-, and alkylboronic acids with aryl and vinyl bromides, iodides, and triflates is a powerful and popular method for the formation of carbon–carbon bonds.[1] The ready availability of the necessary reactants, the mild reaction conditions, and the lack of toxic byproducts all contribute to the versatility of this reaction. These reactions are selective and proceed in the presence of a variety of functional groups. However, no generally applicable set of reaction conditions has yet been found to effect this reaction. In many cases the reaction conditions, and in particular the base that is necessary, are not entirely compatible with the functional groups present in the desired reactants. Aqueous carbonate is the most frequently used base, with hydroxide or bicarbonate also employed in certain cases.[2] Recent efforts to circumvent this difficulty have focused on the use of less basic reagents, such as tripotassium phosphate, in hydrocarbon solvents.[3]

Because the function of the base in the coupling reaction is thought to be to form a boronate anion that is capable of effecting boron to palladium transmetalation,[4] we reasoned that fluorides should be especially suitable for this purpose, given the high affinity of fluoride ion for boron and the considerable stability of the product fluoroborate ion.[5] Additionally, the relatively weak basicity and poor nucleophilicity of the fluoride ion, and the weakness of the palladium–fluorine bond, all suggested that fluorides could be of particular value in boronic acid coupling reactions.

Discussion

For our initial studies, we examined the reaction of phenylboric acid (**1x**) with methyl 4-bromophenylacetate (**2a**). These reactants had provided only the saponified product 4-phenylphenylacetic acid when subjected to the palladium-catalyzed boronic acid coupling reaction in the presence of either sodium bicarbonate or sodium carbonate and had failed to afford any biaryl products with triethylamine as the base under aprotic conditions (DMF).[6] Indeed, we found that in a 1:2 methanol–DME solvent mixture, in which all the reactants were soluble, the coupling went to completion with the formation of the desired ester **3ax** in good yields with either tetraethylammonium, tetrabutylammonium,[7] cesium, or potassium fluoride (Table 1, entries 1–4). Only sodium fluoride, which was insoluble in the reaction mixture, failed to give the desired product (entry 5).[8]



We then examined the effect of various aprotic solvents upon the course of the reaction (entries 6–13), using 2-bromo-6-methoxynaphthalene (**4**) as a model aryl bromide. Despite the fact that the fluoride salts were insoluble in these solvents (except DMSO), it was found that the coupling reactions generally proceeded more quickly in aprotic solvents, particularly DME. Potassium fluoride was somewhat inferior to cesium fluoride in these solvents, even when potassium fluoride was taken in excess (entries 7 and 8). It was also observed that reaction mixtures containing either cesium fluoride or tetraethylammonium fluoride became briefly homogeneous upon heating, after which a water-soluble precipitate formed.[9] On the basis of the results of these experiments, we determined that cesium fluoride represented the best fluoride source for this transformation

(1) (a) Suzuki, A.; Yanagi, T.; Miyaura, N. *Synth. Commun.* **1981**, *11*, 513–519. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321. (c) Hoshino, Y.; Miyaura, N.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3008–3010.

(2) Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y. *J. Heterocycl. Chem.* **1989**, *26*, 865–868.

(3) Suzuki, A.; Miyaura, N.; Oh-e, T. *Synlett* **1990**, 221–223. Strong bases, such as hydroxide or alkoxide, frequently give diminished yields even when the reactants are compatible with these reagents (see ref 1).

(4) Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178–184.

(5) The fluorooxyborate ion, $BF_2(OH)_2^-$, which is the putative byproduct of this reaction has been described; see: Maya, L. *Inorg. Chem.* **1976**, *15*, 2179–2184. However, it is recognized that this ion may either not be the first borate anion formed or may disproportionate under the conditions of the boronic acid coupling. The identity of the boron-containing residues formed in these reactions was not determined.

(6) The use of Et_3N in DMF as a base/solvent system for boronic acid coupling reactions has been reported: Thompson, W. J.; Gaudino, J. *J. Org. Chem.* **1984**, *49*, 5237–5243. Under the conditions (B) reported we observed no reaction between **1x** and **2a**; the bromide **2a** was recovered unchanged.

(7) Tetrabutylammonium fluoride was used in the form of its crystalline hydrate.

(8) The use fluoride ion was essential for coupling to occur. Attempts to substitute other halides, such as Et_4NCl or CsCl, for Et_4NF and CsF were unsuccessful.

(9) Analysis of these reaction mixtures by GC–MS at this point indicated that the coupling reaction was only about 30% to 50% complete, suggesting that the solution of the fluoride salt is due to the formation of a (possibly complex) phenylfluoroborate anion. This is supported by the observation of a peak in the GC–MS of $m/z = 312$, which corresponds to the (possibly cyclic) trimeric ion $FB(Ph)OB(Ph)OB(Ph)^+$. This peak increased in intensity until the reaction mixture became homogeneous and then subsequently decreased in intensity similarly to the **1a** peak until it was not detected at the completion of the reaction. These mixtures only became homogeneous when the boronic acid was present; in control experiments in the absence of boronic acid the fluoride salts remained undissolved upon heating.

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Table 1. Results of Fluoride-Mediated Boronic Acid Coupling Reactions

entry	boronic acid	halide	fluoride (equiv)[a]	solvent	time (h)	product (yield, %)[b]
1	**1x**	**2a**	Et_4NF (2)	MeOH:DME	8	**3ax**[c] (86)
2	**1x**	**2a**	Bu_4NF (2)	MeOH:DME	8	**3ax** (80)
3	**1x**	**2a**	CsF (2)	MeOH:DME	8	**3ax** (95)
4	**1x**	**2a**	KF (2)	MeOH:DME	8	**3ax** (91)
5	**1x**	**2a**	NaF (2)	MeOH:DME	8	**3ax** (0)
6	**1x**	**4**	Et_4NF (2)	MeCN	3	**7**[d] (78)
7	**1x**	**4**	KF (2)	MeCN	18	**7** (59)
8	**1x**	**4**	KF (4)	MeCN	6	**7** (73)
9	**1x**	**4**	KF (2)	DMSO	18	**7** (57)
10	**1x**	**4**	CsF (2)	MeCN	6	**7** (91)
11	**1x**	**4**	CsF (2)	DMSO	18	**7** (72)
12	**1x**	**4**	CsF (2)	DME	3	**7** (95)
13	**1x**	**4**	CsF (2)	PhMe	1	**7** (72)
14	**1x**	**2a**	CsF (2)	DME	2	**3ax** (100)
15	**1x**	**2b**	CsF (2)	DME	2	**3bx**[e] (92)
16	**1x**	**2c**	CsF (2)	DME	2	**3cx**[f] (92)
17	**1x**	**2d**	CsF (2)	DMSO	18	**5**[g] (45)
18	**1x**	**2e**	CsF (2)	DME	3	**3ex**[h] (85)
19	**1x**	**2f**	CsF (2)	DME	3	**3fx**[i] (78)
20	**1x**	**2g**	CsF (2)	DME	3	**3gx**[j] (63)
21	**1x**	**6**	CsF (2)	DME	18	**3ax** (64)
22	**1y**	**2a**	CsF (2)	DME	18	**3ay**[k] (81)
23	**1y**	**2h**	CsF (2)	DME	18	**3hy**[l] (83)
24	**1y**	**2i**	CsF (2)	DME	18	**3iy**[m] (81)
25	**1y**	**2c**	CsF (2)	DME	18	**3cy**[n] (77)
26	**1z**	**2a**	CsF (2)	DME	48	**3az**[o] (22)[p]
27	**1y**	**2a**	CsF (3)	DME	6	**3ay** (83)
28	**1z**	**2a**	CsF (3)	DME	48	**3az** (27)[p]
29	**1y**	**2a**	CsF (4)	DME	6	**3ay** (85)
30	**1x**	**2a**	KF (2)	H_2O:MeOH:DME[q]	4	**3ax** (68)
31	**1x**	**2a**	KF (2)	H_2O:DME[r]	3	**3ax** (78)
32	**1x**	**2a**	KF (2)	H_2O:PhMe[s]	6	**3ax** (98)

[a] Equivalents of fluoride salt to boronic acid. [b] Isolated yield of purified product. All products were homogeneous by GC and gave satisfactory ^1H NMR, IR, and MS data. [c] Mp 19–21 °C (see ref 17a). [d] 2-Methoxy-6-phenylnaphthalene, mp 146–147 °C (lit.[17b] mp 148 °C). [e] Mp 94–95 °C (lit.[17c] mp 95 °C). [f] Mp 198–200 °C (lit.[17d] mp 197 °C). [g] Mp 314–316 °C (lit.[17e] mp 320 °C). [h] Oil, oxime mp 150–152 °C (oxime lit.[17f] mp 152 °C). [i] Oil. [j] Mp 92–94 °C (lit.[17g] mp 94–95 °C). [k] Oil. [l] Oil. [m] Oil. [n] Mp 107–110 °C. [o] Oil. [p] Unreacted **2a** was recovered as the major product. [q] 1:1:2 by volume. [r] 1:2 by volume. [s] 5 mL of each liquid was used.

in terms of cost per mole, reaction time, reaction yield, solvent choice, and ease of drying.[10]

We then examined the cesium fluoride promoted coupling of **1x** with a variety of base- and nucleophile-sensitive aryl bromides (entries 14–27). It may be seen that an aliphatic acid methyl ester (entry 14), aliphatic nitrile (entry 15), trifluoroacetamide (entry 16), and β-phenethyl acetate (entry 19) all survive the reaction. Furthermore, no condensation products were detected in the reaction of the phenylacetone derivative **2e** (entry 18). The β-phenethyl tosylate **2g** did not undergo elimination to the corresponding styrene by GC–MS analysis, nor was the displacement of tosylate by fluoride observed (entry 20). Not surprisingly, the major byproduct in this case (25%) was 1-bromo-2-(4-phenylphenyl)ethane resulting from displacement of the tosylate group in the product (**3gx**) by the bromide ion generated during the course of the reaction. While yields are somewhat lesser in DMSO than in DME (entry 11 vs 12), the possibility of using neat DMSO as a solvent for these reactions allows the use of, or preparation of, compounds of poor solubility. For example, the extremely insoluble 4,4′-quaterphenyl (**5**) could be prepared using this method (entry 17). The reaction was also successfully carried out on an aryl triflate (**6**, entry 21). In this case, 3 equiv of cesium bromide were added to the reaction mixture.[11] The extension of this methodology to a model vinylboronic acid ((*E*)-1-octenyl-1-boronic acid, **1y**) and a model alkylboronic acid (butylboronic acid, **1z**) was then examined. These coupling reactions proceeded in good yields with **1y**, albeit with longer reaction times, and in much poorer yields with **1z** (entries 22–26). However, even with an 18 h reaction time the methyl ester survives (entries 22, 26), as does the trifluoroacetamide (entry 25). No products of Cannizzarro disproportionation were noted by GC–MS with the aldehyde **2i** (entry 24). The time required for complete reaction of the alkenylboronic acid was considerably reduced upon the addition of 3 equiv of cesium fluoride, rather than the stochiometric 2 equiv (entries 27, 28). No further enhancement of reaction rate was noted when 4 equiv of cesium fluoride was used (entry 29).[12]

Lastly, a series of coupling reactions using fluoride salts in the aqueous solvent systems traditionally used for boronic acid coupling reactions were carried out (entries 30–32). All of the fluoride salts examined previously were readily soluble in these solvent systems, and therefore inexpensive potassium fluoride was used as the fluoride source in these reactions. The coupling reactions proceeded well in each case, and particularly so in the biphasic mixture of toluene and water (entry 32).[13] In this case, an essentially quantitative yield of the coupled ester **3ax** was obtained, in marked contrast to the results obtained with carbonate and bicarbonate bases in the same solvent system.

In summary, we have found that fluoride salts, and cesium fluoride in particular, allow boronic acid coupling reactions to occur rapidly and in good yields under essentially nonbasic conditions in a variety of solvents that are compatible with many sensitive functional groups. The use of fluoride salts to effect the boron to palladium transmetalation appears to represent one of the most generally applicable reaction conditions for aryl- and vinylboronic acid couplings described to date.

Experimental Section

All solutions were dried over anhydrous $MgSO_4$; all evaporations were carried out on a rotary evaporator at *ca.* 30 Torr. Commercial reagents were used as received without additional purification. The starting materials listed in Table 1 were either commercial products or prepared by standard methods,[14] except

(10) Commercially available tetraalkylammonium fluorides (Bu_4NF, Et_4NF, $BnMe_3NF$) are generally supplied as hydrates of indeterminate composition which often suffer decomposition upon drying and are considerably more expensive than CsF in a cost per mole comparison.

(11) The addition of halide ion to coupling reactions involving aryl triflates generally results in improved yields. This is thought to occur via greater stabilization of the arylpalladium species by halide ion than triflate ion; see: (a) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040. (b) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. Cesium bromide was used instead of the more customarily used lithium salts in order to prevent the formation of highly insoluble lithium fluoride by an exchange reaction.

(12) A possible explanation for this observation is that the species that actually undergoes transmetalation is the aryltrifluoroboronate $ArBF_3^-$. It is also possible that the fluoroxyboronates $ArBF_2(OH)^-$ and/or $ArBF(OH)_2^-$ formed with 2 equiv of CsF undergo transmetalation less readily than $ArBF_3^-$.

(13) The success of the reaction under these conditions is presumably due to distribution of the boronic acid into the aqueous phase, followed by formation of a fluoroboronate, which may partition back into the toluene phase.

(14) **2b**, **2d**, **2e**, **2h**, and **2i** were commercially available and used as received. **2a** was prepared by Fischer esterification of the corresponding acid (95%, bp 105 °C/2 Torr). **2c** was prepared by reaction of 4-bromoaniline with TFAA and pyridine in CH_2Cl_2 (93%, mp 124–126 °C). **2f** was prepared from 2-(4-bromophenyl)ethanol, Ac_2O, and pyridine in EtOAc (94%, oil). **2g** was prepared from 2-(4-bromophenyl)-ethanol, *p*-TsCl, and pyridine in CH_2Cl_2 (86%, mp 81–83 °C).

for (*E*)-1-octenyl-1-boronic acid which was prepared as described by Brown.[15] Solvents were commercial anhydrous grades and were used without further drying. $Pd(PPh_3)_4$ was prepared from $PdCl_2$, PPh_3, and hydrazine[16] and stored under argon in the freezer.

General Procedure for Coupling Reactions: Methyl 4-Phenylphenylacetate (3ax). The preparation of **3ax** is representative. To a magnetically stirred mixture of phenylboric acid (**1x**, 0.30 g, 2.50 mmol), methyl 4-bromophenylacetate (**2a**, 0.52 g, 2.25 mmol), and powdered CsF (0.76 g, 5.00 mmol) in 8 mL of DME was added 87 mg (75 μmol, 3 mol percent) of $Pd(PPh_3)_4$. The reaction mixture was flushed with argon and maintained under argon while being heated at reflux in a 100 °C oil bath. The reaction was monitored by GC–MS until no more bromide was detected. The reaction mixture was then cooled and diluted with EtOAc and H_2O, and the EtOAc layer was dried and concentrated. Chromatography of the residue on silica (5:1 hexanes:EtOAc) afforded 0.50 g (98%) of **3ax**, mp 19–21 °C. ^1H NMR ($CDCl_3$): 7.56 (m, 4 H); 7.43 (m, 2 H); 7.35 (m, 3 H); 3.71 (s, 3 H); 3.67 (s, 2 H). MS (EI): $m/z = 226$ (M^+, 100).

Methyl 4-Butylphenylacetate (3az). ^1H NMR ($CDCl_3$): δ = 7.17 (d, 2 H); 7.13 (d, 2 H); 3.68 (s, 3 H); 3.59 (s, 2 H); 2.58 (t, 2 H); 1.57 (m, 2 H); 1.35 (m, 2 H); 0.91 (t, 3 H). MS (EI): m/z = 206 (M^+, 50); 163 ($M^+ - C_3H_7$, 100). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.89; H, 8.83.

4-Oct-1-enylphenylacetic Acid Methyl Ester (3ay). ^1H NMR ($CDCl_3$): $\delta = 7.29$ (d, 2 H); 7.19 (d, 2 H); 6.35 (d, $J = 15.9$ Hz, 1 H); 6.22 (m, 1 H); 3.67 (s, 3 H); 3.59 (s, 2 H); 2.17 (m, 2 H); 1.45 (m, 2 H); 1.29 (m, 6 H); 0.88 (t, 3 H). MS (EI): $m/z = 260$ (M^+, 20); 176 ($M^+ - C_6H_{12}$).

1-Isopropyl-4-oct-1-enylbenzene (3hy). ^1H NMR ($CDCl_3$): $\delta = 7.27$ (d, 2 H); 7.15 (d, 2 H); 6.35 (d, $J = 15.9$ Hz, 1 H); 6.22 (m, 1 H); 2.88 (m, 1 H); 2.17 (m, 2 H); 1.45 (m, 2 H); 1.29 (m, 6 H); 1.24 (d, 6 H); 0.88 (t, 3 H). MS (EI): $m/z = 230$ (M^+, 30); 146 ($M^+ - C_6H_{12}$, 100).

4-Oct-1-enylbenzaldehyde (3iy). ^1H NMR ($CDCl_3$): δ = 9.95 (s, 1 H); 7.79 (d, 2 H); 7.46 (d, 2 H); 6.42 (m, 2 H); 2.23 (m, 2 H); 1.45 (m, 2 H); 1.29 (m, 6 H); 0.88 (t, 3 H). MS (EI): m/z = 216 (M^+, 20); 132 ($M^+ - C_6H_{12}$, 100).

2,2,2-Trifluoro-*N*-(4-oct-1-enylphenyl)acetamide (3cy). ^1H NMR ($CDCl_3$): $\delta = 7.79$ (br, 1 H); 7.47 (d, 2 H); 7.35 (d, 2 H); 6.35 (d, $J = 15.9$ Hz, 1 H); 6.22 (m, 1 H); 2.18 (m, 2 H); 1.45 (m, 2 H); 1.29 (m, 6 H); 0.88 (t, 3 H). MS (EI): $m/z = 299$ (M^+, 35); 215 ($M^+ - C_6H_{12}$, 100).

Acetic Acid 2-Biphenyl-4-ylethyl Ester (3fx). ^1H NMR ($CDCl_3$): $\delta = 7.57$–7.49 (m, 4 H); 7.41 (m, 2 H); 7.29 (m, 3 H); 4.30 (t, 2 H); 2.96 (t, 3 H); 2.04 (s, 3 H). MS (EI): $m/z = 240$ (M^+, 15); 180 ($M^+ - CH_3CO_2H$, 100). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.18; H, 6.60.

Supplementary Material Available: ^1H NMR spectra of **3ay**, **3cy**, **3hy**, and **3iy** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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