Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 7899–7903

Tetrahedron Letters

Deprotection of pinacolyl boronate esters via hydrolysis of intermediate potassium trifluoroborates

Alexander K. L. Yuen[a] and Craig A. Hutton[a,b,c,*]

[a]School of Chemistry, The University of Sydney, NSW 2006, Australia
[b]School of Chemistry, The University of Melbourne VIC 3010, Australia
[c]Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne VIC 3010, Australia

Received 28 July 2005; revised 6 September 2005; accepted 16 September 2005

Abstract—An efficient two-step procedure for the deprotection of pinacolyl organoboronate esters is described. Reaction with excess potassium hydrogen fluoride produces the corresponding stable, crystalline potassium organotrifluoroborate salts. Treatment of the trifluoroborates with either inorganic base or trimethylsilyl chloride and water affords the corresponding organoboronic acid in high yield.

The utility of organoboronic acids in organic synthesis has flourished in recent years, particularly through developments in the Miyaura–Suzuki coupling,[1] allylboration,[2,3] copper-catalysed arylboronic acid–heteroatom coupling[4] and the Petasis reaction.[5,6] Miyaura's protocol[7] for the palladium-catalysed boronation of aryl and vinyl halides with bis(pinacolato)diboron has become one of the most popular methods for incorporating boron into functionalised substrates under mild conditions. The resultant pinacolyl boronate esters have the advantage of being stable compounds, which generally can be purified by chromatography.

Although pinacolyl boronate esters are useful substrates for cross-coupling chemistry in their own right, many procedures are more efficient with or have an absolute requirement for free boronic acids in order to proceed. The arylation of phenols and a variety of nitrogen nucleophiles in the presence of arylboronic acids and Cu(I) or Cu(II) catalysts has been fine-tuned over recent years to represent one of the best methods for heteroatom arylation.[4] However, these reactions proceed in very low yields with pinacolyl boronate esters.[8,9] Similarly, the three-component coupling of an aldehyde, amine and organoboron species (Petasis reaction) can proceed with a pinacolyl boronate ester in some circumstances, but is higher yielding and more general with boronic acid substrates.[10] Hence, the conversion of pinacolyl organoboronate esters to the corresponding organoboronic acids is of much interest.

Methods currently available for the deprotection of pinacolyl esters include destructive procedures such as the use of periodate to cleave the protecting diol oxidatively,[11] or hydrolytic protocols, for example, displacement of the diol with diethanolamine to form an intermediate 'ate complex', which is then hydrolysed under acidic or basic conditions.[12] Transesterification of pinacolyl esters to yield the free boronic acids has been achieved previously using mild conditions under phase-transfer[13] or homogeneous conditions,[9] but such methods normally suffer from incomplete reaction or problems in separating the desired boronic acid from a large excess of the transesterification partner. We recently developed an improved transesterification procedure, which employs excess polymer-supported boronic acid to deprotect a variety of arylboronic pinacolyl esters in good to excellent yields. Ease of purification and the ability to regenerate the solid-supported reagent were also advantages of this approach.[14] The only current limitation of this procedure, however, remains the inconsistent commercial availability of the polymer-supported boronic acid.

We report herein an alternative method for pinacolyl ester deprotection using a two-step process that

---

* Corresponding author. Tel.: +61 3 8344 2393; fax: +61 3 9347 8124; e-mail: chutton@unimelb.edu.au

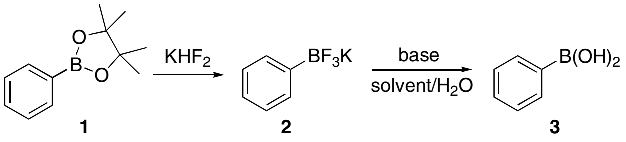
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.09.101

proceeds via a readily isolable potassium trifluoroborate. Aryl trifluoroborate salts are readily prepared from the corresponding boronate esters and are crystalline, air and moisture stable, and can be stored indefinitely without oligomerisation.[15] Liberation of the desired free boronic acid can be achieved effectively using either basic hydrolysis with a variety of alkali metal salts or using trimethylsilyl chloride as an effective fluorophile.

We initially investigated the conversion of phenyl pinacolylboronate **1** to the corresponding boronic acid **3** via potassium phenyltrifluoroborate **2**. The pinacolyl boronate was converted to the trifluoroborate by treatment with aqueous potassium hydrogen fluoride according to Genêt's[16] modification of Vedejs'[17] procedure (Scheme 1). The resultant crude potassium trifluoroborate was recrystallised from acetone/diethyl ether to afford the pure product, free of pinacol.

Hydrolysis of phenyl trifluoroborate was then investigated with a range of aqueous alkali metal hydroxides and carbonates in mixtures of aqueous acetone or acetonitrile (Table 1). Solvent choice was limited by the solubility of the trifluoroborate, with DMSO being avoided for ease of work-up and alcohols being incompatible due to the subsequent formation of boronate esters.

Comparison of entries 1–3 in Table 1 clearly indicates that lithium hydroxide is much more effective than either potassium or sodium hydroxide in converting the trifluoroborate to the boronic acid. The efficacy of lithium hydroxide at hydrolysing the trifluoroborate may be in part due to the large lattice enthalpy of the lithium fluoride formed (1047 kJ mol^{-1})[18] and its low solubility in water (ca. 1.3 mg/mL at 25 °C),[19] compared with either sodium or potassium fluoride. Vedejs et al.[17] noted in their work concerning aryltrifluoroborates that the counter-ion present is largely responsible for the stability of the complex. While potassium, and to a lesser extent sodium, led to the most stable trifluoroborates, lithium and magnesium counterions caused trifluoroborate decomposition in solution due to their fluorophilic natures.



Scheme 1.

Table 1. Hydrolysis of potassium phenyltrifluoroborate **2** to phenylboronic acid **3**

Entry	Base	Equiv	% Conversion	
			CH_3CN/H_2O[a]	Acetone/H_2O[b]
1	LiOH	3.0	100	—
2	NaOH	3.0	84	—
3	KOH	3.0	74	—
4	Li_2CO_3	1.5	100	80
5	Na_2CO_3	1.5	100	—
6	K_2CO_3	1.5	100	84
7	$NaHCO_3$	3.0	—	84
8	$KHCO_3$	3.0	—	74
9	$KHCO_3$	5.0	—	74

[a] $PhBF_3K$ (1 mmol) in acetonitrile (10 mL) and water (9 mL), 4–9 h.
[b] $PhBF_3K$ (1 mmol) in acetone (5 mL) and water (5 mL), 7–24 h.

Despite the difference in reactivities between lithium, sodium and potassium hydroxides, the corresponding carbonates were all effective bases in the hydrolysis of the phenyl trifluoroborate (entries 4–6). Additionally, sodium bicarbonate was found to be a reasonably effective base, with potassium bicarbonate being less effective (entries 7–9). Thus, while generally basic conditions lead to hydrolysis, it is important that the cation be chosen to ensure completion, with lithium being slightly more effective than sodium, and potassium being the least effective. Acetonitrile was found to be a better co-solvent than acetone, despite the increased solubility of the substrates in the latter (entries 4 and 6).

The hydrolysis of phenyltrifluoroborate **2** presumably proceeds via the hydroxydifluoro **4** and dihydroxyfluoro **5** borate species, as outlined in Scheme 2. Previous work by the Molander[20,21] and Batey[22,23] groups sought to identify the nature of hydrolytic intermediates of aryltrifluoroborates, as part of research into their utility in palladium-catalysed cross-coupling reactions. Although unable to reveal the identities of the hydrolytic intermediates unequivocally, NMR studies[20–22] and model couplings of trifluoroborates, with and without added base,[23] led both groups to conclude that exchange of fluoride for hydroxide ligands occurred and was necessary for successful cross-coupling. We conducted ^{19}F NMR studies of the hydrolysis of potassium phenyltrifluoroborate, which supports these suggestions (Figs. 1

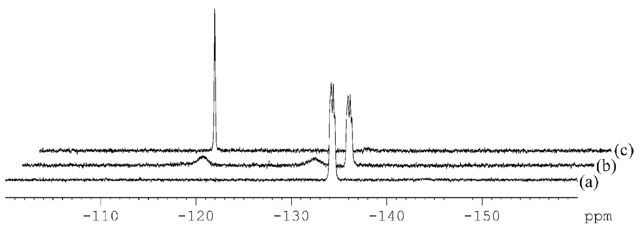
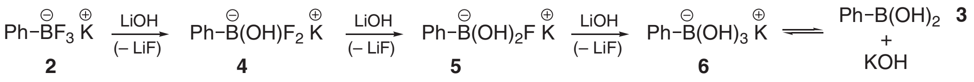


Figure 1. ^{19}F NMR spectra of $PhBF_3K$ **2** in D_2O (a), and after addition of 1.0 (b) and 2.0 (c) equivalents of LiOH.



$$\underset{\mathbf{2}}{\text{Ph-}\overset{\ominus}{\text{B}}\text{F}_3\ \overset{\oplus}{\text{K}}} \xrightarrow[(-\text{ LiF})]{\text{LiOH}} \underset{\mathbf{4}}{\text{Ph-}\overset{\ominus}{\text{B}}\text{(OH)F}_2\ \overset{\oplus}{\text{K}}} \xrightarrow[(-\text{ LiF})]{\text{LiOH}} \underset{\mathbf{5}}{\text{Ph-}\overset{\ominus}{\text{B}}\text{(OH)}_2\text{F}\ \overset{\oplus}{\text{K}}} \xrightarrow[(-\text{ LiF})]{\text{LiOH}} \underset{\mathbf{6}}{\text{Ph-}\overset{\ominus}{\text{B}}\text{(OH)}_3\ \overset{\oplus}{\text{K}}} \rightleftharpoons \begin{array}{c}\text{Ph-B(OH)}_2\ \mathbf{3}\\+\\\text{KOH}\end{array}$$

Scheme 2. Presumed potassium phenyltrifluoroborate hydrolysis pathway.

and 2). The first NMR experiment was conducted by the sequential addition of aqueous lithium hydroxide to a solution of potassium phenyltrifluoroborate in D_2O (Fig. 1). The phenyltrifluoroborate anion gives rise to a multiplet (arising from B–F coupling) at δ -135 ppm. After addition of 1 equiv of lithium hydroxide two new broad peaks were observed at δ -119 and -132 ppm. After the addition of 2 equiv of LiOH, only fluoride was observed as a sharp singlet at δ -119 ppm, and phenylboronic acid was observed by ^{1}H and ^{11}B NMR.

In contrast to the above experiment, addition of 3 equiv of $KHCO_3$ over a 10 h time-period failed to effect complete hydrolysis of potassium phenyltrifluoroborate, but rather, an equilibrium was reached in which all three species are present, with the formation of the boronic acid favoured (Fig. 2).

Under both sets of conditions, a broad peak at δ -132 ppm was observed in the ^{19}F NMR spectra, presumably attributable to intermediate **4** or **5**. Neither ^{19}F nor ^{11}B NMR were able to identify the nature of the intermediate, but ESI mass spectrometry was able to identify the presence of difluorohydroxy species **4** under similar conditions: a solution of potassium phenyltrifluoroborate in methanol was treated with 1 equiv of lithium hydroxide, and the solution analysed by negative ion electrospray ionisation (ESI) mass spectrometry (Fig. 3). The three main species present were identified as the trifluoroborate **2**, which gave rise to a peak at *m*/*z* 145, the difluorohydroxy species **4**, which gave rise to a peak at *m*/*z* 143, and the difluoromethoxy species (*m*/*z* 157), which arises from exchange of –OH for –OMe. The peaks at *m*/*z* 325–353 correspond to potassium-linked homo- and hetero-dimers of these anions. These results indicate that the difluorohydroxy species **4** is stable enough to be observed by mass spectrometry and is presumably the species that gives rise to the signal at δ -132 ppm in the ^{19}F spectra in Figures 1 and 2. It cannot be ruled out however that the broadness of these signals is due to ligand exchange and that both **4** and **5** exist in equilibrium in solution, with **4** being the only species stable enough to withstand ESI conditions.

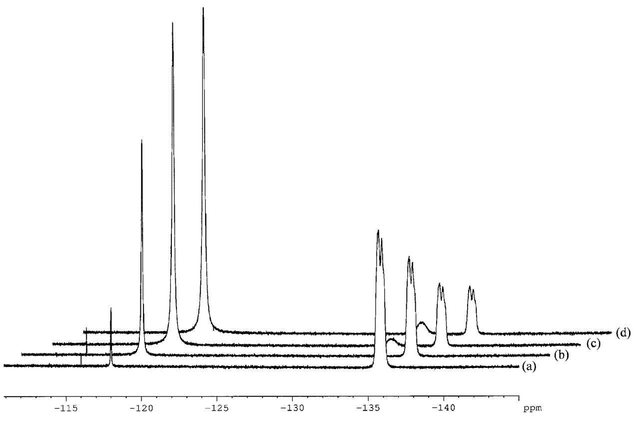


Figure 2. ^{19}F NMR of $PhBF_3K$ **2** + 3 equiv of $KHCO_3$; (a) $t = 10$ min; (b) $t = 2$ h; (c) $t = 6$ h; (d) $t = 10$ h.

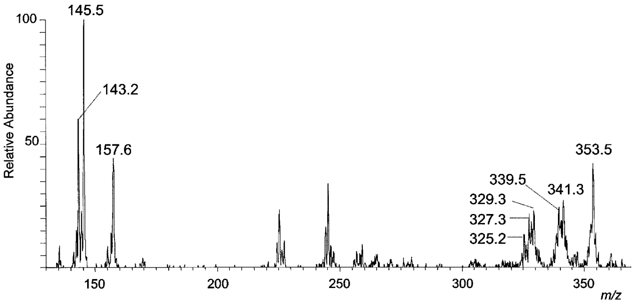


Figure 3. ESI MS of potassium phenyltrifluoroborate treated with 1.0 equiv of LiOH.

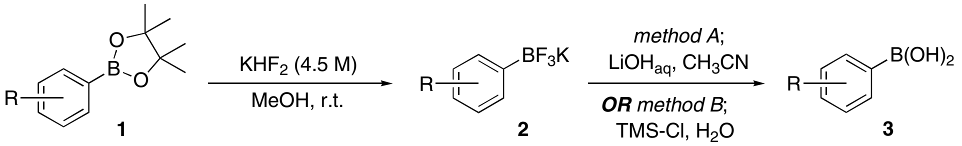
Having established that lithium bases were well suited to the task of trifluoroborate hydrolysis, various aryl pinacolyl boronate substrates were first converted to the corresponding trifluoroborates and then subjected to basic hydrolysis with lithium hydroxide in acetonitrile/water (Table 2).

Conversion of the pinacolyl boronates to the trifluoroborates proceeded in good to excellent yields under the same conditions described previously.[24] Hydrolysis of the trifluoroborates to the boronic acids proceeded well in most cases; however, mixed results were obtained for 2-substituted aryltrifluoroborates. While both the 2-tosylate and 2-formyl derivatives (entries 7 and 8) were hydrolysed completely, hydrolysis of the 2-hydroxy derivative resulted in decomposition of the starting material to a dark polymeric mixture (entry 4) and in the case of the 2-methoxy derivative only a low yield of the boronic acid was obtained (entry 5).

An alternative approach to the conversion of the trifluoroborates to the corresponding boronic acids was then investigated, based on the work of Vedejs et al.[17] concerning the conversion of trifluoroborates to reactive difluoroborane species. Vedejs had shown that treatment of an aryl trifluoroborate with 1 equiv of trimethylsilyl chloride, under anhydrous conditions, led to the rapid formation of a difluoroborane, with concomitant formation of potassium chloride and trimethylsilyl fluoride. Matteson and Kim[27] were able to use a modified version of this approach with silicon tetrachloride to prepare cyclic, secondary amines from alkyltrifluoroborates via intramolecular cyclisation of the intermediate difluoroborane onto a pendant azido group. It was reasoned that treatment of aryltrifluoroborates with excess trimethylsilyl chloride in the presence of water would lead to initial formation of the difluoroborane **7**, which would react with water to give the hydroxydifluoroboronate species **4**. Sequential removal of the remaining fluorides by TMS-Cl and in situ trapping with water would lead to the boronic acid **3** (Scheme 3).

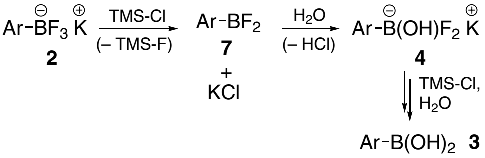
To our delight, treatment of the aryltrifluoroborates with 3 equiv of trimethylsilyl chloride and 3 equiv of water in acetonitrile resulted in rapid conversion to the boronic acid in all cases (Table 2, method B). Yields were good to excellent and the work-up procedure was simpler than for the corresponding reactions with

Table 2. Conversion of pinacolyl esters to boronic acids via the corresponding trifluoroborates



Entry	R	Yield of **2** (%)[24]	Yield of **3** (%) (% **2** remaining in brackets)	
			Method A[25]	Method B[26]
1	H	73	Quant.	—
2	2-Me	97	71 (18)	Quant.
3	4-Me	77	85 (10)	—
4	2-OH	87	0 (decomp.)	90
5	2-OMe	97	49 (12)	70
6	4-OMe	95	95 (2)	—
7	2-OTs	63	Quant.	Quant.
8	2-CHO	95	Quant.[a]	Quant.
9	2-Cl	95	21[a](75)	Quant.
10	4-F	80	Quant.	—
11	4-Br, 3-NHCbz	67	—	93
12	4-Br, 3-CO_2Me	94	—	Quant.

[a] 3.5 equiv of LiOH used.



Scheme 3.

lithium hydroxide. The only by-products were inorganic salts and the volatile trimethylsilyl fluoride. Noteworthy is the fact that these conditions are compatible with base sensitive substrates, such as the free phenol (compare methods A and B, entry 4) and that the procedure led to an improved isolated yield of difficult substrates such as those containing *ortho* electron-donating substituents (compare methods A and B, entry 5).

In conclusion, implementation of a practical two-step protocol for the mild deprotection of pinacolyl boronate esters has been demonstrated. Following conversion of the pinacolyl boronate to the corresponding trifluoroborate with potassium hydrogen fluoride, subsequent fluoride removal/hydroxylation was achieved with alkali metal bases or more effectively using trimethylsilyl chloride and water. These mild conditions tolerated a range of functional groups and were relatively unaffected by the steric or electronic properties of the aromatic ring.

References and notes

1. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
2. Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434.
3. Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644–13645.
4. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
5. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.
6. Petasis, N. A.; Yudin, A. K.; Zavialov, I. A.; Prakash, G. K. S.; Olah, G. A. *Synlett* **1997**, 606–608.
7. Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510.
8. Chan, D. M. T.; Monaco, K. L.; Li, R.; Bonne, D.; Clark, C. G.; Lam, P. Y. S. *Tetrahedron Lett.* **2003**, *44*, 3863–3865.
9. Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029–1032.
10. Koolmeister, T.; Sodergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5965–5968.
11. Nakamura, H.; Fujiwara, M.; Yamamoto, Y. J. *J. Org. Chem.* **1998**, *63*, 7529–7530.
12. Song, Y.-L.; Morin, C. *Synlett* **2001**, 266–268.
13. Coutts, S. J.; Adams, J.; Krolikowski, D.; Snow, R. *Tetrahedron Lett.* **1994**, *35*, 5109–5112.
14. Pennington, T. E.; Hardiman, C.; Hutton, C. A. *Tetrahedron Lett.* **2004**, *45*, 6657–6660.
15. Molander, G. A.; Rivero, M. R. *Org. Lett.* **2002**, *4*, 107–109.
16. Darses, S.; Genêt, J.-P. *Eur. J. Org. Chem.* **2003**, 4313–4327.
17. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.
18. Aylward, G.; Findlay, T. *SI Chemical Data*, 3rd ed.; Jacaranda Wiley Ltd: Berlin, 1994; p 125.
19. *The Merck Index of Chemicals and Drugs*; Stecher, P. G., Ed.; Merck & Co: Rahway, NJ, USA, 1960; p 613.
20. Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396.
21. Molander, G. A.; Biolatto, B. *Org. Lett.* **2002**, *4*, 1867–1870.
22. Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *2*, 3827–3830.
23. Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099–9103.
24. Representative procedure for preparation of potassium aryltrifluoroborates **2** (Table 2, entry 12): to a solution of 4-bromo-3-methoxycarbonylphenyl pinacolylboronate (814 mg, 2.39 mmol) in methanol (7 mL) was added aqueous potassium hydrogen fluoride (3.0 mL, 4.5 M, 13.5 mmol). The resulting white slurry was stirred at room temperature

for 15 min, concentrated in vacuo and dissolved in hot acetone. The mixture was filtered, the filtrate was concentrated in vacuo and the residue recrystallised from a minimal amount of hot acetone and ether (20 mL), to afford the corresponding potassium trifluoroborate as a crystalline solid (721 mg, 94%); mp 226–228 °C; Found: C, 28.78, H, 2.36; $C_8H_6BF_3BrO_2K{\cdot}H_2O$ requires C, 28.35, H, 2.38; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.87 (1H, d, $J = 1.1$ Hz), 7.49 (1H, dd, $J = 1.1$, 7.8 Hz), 7.42 (1H, d, $J = 7.8$ Hz), 3.84 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.4, 137.1, 135.2, 132.6, 131.6, 118.1, 52.1 (C *ipso* to B not observed); ^{19}F NMR (282 MHz, acetone-d_6) δ −142.9 (br m); MS (ESI, negative ion); found *m*/*z* 280.9619, $C_8H_6{}^{11}B^{79}BrF_3O_2$ requires *m*/*z* 280.9611.

25. Representative procedure for hydrolysis of aryltrifluoroborates **2** with LiOH (Table 2, entry 10): to a mixture of potassium 4-fluorophenyl trifluoroborate (202 mg, 1.00 mmol) and lithium hydroxide (84 mg, 3.50 mmol) was added water (5 mL) and acetonitrile (10 mL). The resulting solution was stirred at room temperature for 20 h, acidified with saturated aqueous ammonium chloride (8 mL) and 1 M hydrochloric acid (2 mL), then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated in vacuo to afford 4-fluorophenylboronic acid as a white solid (140 mg, 100%).
26. Representative procedure for hydrolysis of aryltrifluoroborates **2** with TMS-Cl/H_2O (Table 2 entry 12): to a solution of potassium 4-bromo-3-methoxycarbonyl-phenyltrifluoroborate (107 mg, 0.33 mmol) in acetonitrile (3 mL) and water (18 μL, 1.00 mmol), was added trimethylsilyl chloride (127 μL, 1.00 mmol). The resulting suspension was stirred for 1 h, quenched with saturated aqueous sodium hydrogencarbonate solution (0.5 mL) and dried over sodium sulfate. The mixture was filtered and the filtrate concentrated in vacuo to afford the corresponding boronic acid as a white solid (86 mg, 100%); ^{1}H NMR (400 MHz, acetone-d_6) δ 8.24 (1H, d, $J = 1.7$ Hz), 7.87 (1H, dd, $J = 1.7$, 8.0 Hz), 7.71 (1H, d, $J = 8.0$ Hz), 3.90 (3H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.3, 139.0, 137.4, 134.2, 132.9, 123.9, 52.6 (C *ipso* to B not observed); ^{11}B NMR (128 MHz, acetone-d_6) δ 26.2 (br s).
27. Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153–2155.