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Preparation and Wittig Reactions of Organotrifluoroborato Phosphonium Ylides

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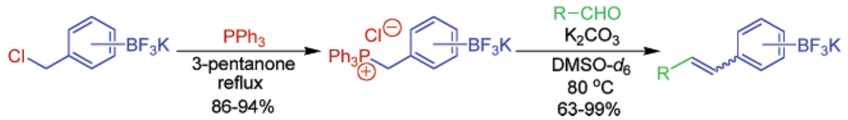
ABSTRACT



Potassium [(trifluoroboratophenyl)methyl]triphenylphosphonium chlorides have been prepared from the corresponding benzyl chlorides and PPh$_3$. In the presence of 1.2 equiv of K$_2$CO$_3$ and various aldehydes, these mixed salts are easily converted to the corresponding unsaturated organotrifluoroborates via the intermediate phosphorus ylides. A protocol for a one-pot transformation has also been developed.

The Suzuki−Miyaura cross-coupling reaction is an effective method for the formation of new carbon−carbon bonds under mild reaction conditions.[1] Although they have become the standards by which all other cross-coupling reagents are measured, the boronic acids and boronate esters used in these transformations still exhibit several limitations. Because many boronic acids are waxy solids, they are difficult to purify. Furthermore, at equilibrium, boronic acids form trimeric, cyclic anhydrides (boroxines), and these are not easily distinguished from the boronic acids, which themselves are not readily assayed.[2] This equilibrium has no direct bearing on the cross-coupling process itself but does influence the mass of material required for stoichiometric reactions with organic halide electrophiles. Consequently, for this reason and to overcome loss of the coupling partner as a result of protodeboronation, practitioners often utilize excess boronic acid to ensure an adequate amount of this nucleophile is available.

Most importantly, trivalent organoboron species undergo competitive, undesirable reactions with many classes of reagents commonly used in organic synthesis, including oxidants, bases, and nucleophiles. Because of this reactivity, boronic acids and boronate esters are normally either purchased or prepared and then coupled immediately. These boron reagents are not typically carried through further synthetic sequences prior to coupling, making them less attractive for early incorporation into synthetic schemes in which the carbon skeleton and functional groups might be elaborated while leaving the valuable carbon−boron bond intact for subsequent processing.[3] An organoboron reagent capable of withstanding extensive manipulation would address these issues and expand the range of imaginable retrosynthetic strategies in which Suzuki−Miyaura coupling could play an integral role.

For all of these reasons, there has been an increasing interest in the use of potassium organotrifluoroborates as

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(2) (a) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 137. (b) Hall, D. G., Ed. *Boronic Acids*; Wiley-VCH: Weinheim, 2005. (b) Onak, T. *Organoborane Chemistry*; Academic Press: New York, 1975.

(3) Jin, B.; Liu, Q.; Sulikowski, G. A. *Tetrahedron* **2005**, *61*, 401.

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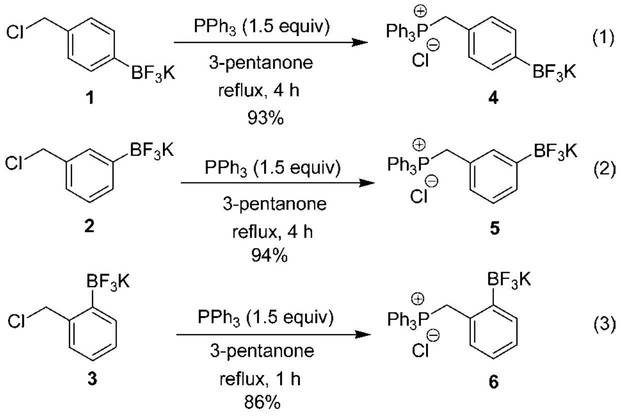
useful coupling partners for the Suzuki−Miyaura reaction.[4] The inherent air and moisture stability of these monomeric, tetracoordinate boron species, combined with their ease of preparation as white crystalline solids, makes them an excellent alternative to boronic acids and boronate esters. Taking advantage of their inherent stability, we have generated various useful organotrifluoroborate derivatives through direct epoxidation,[5] *cis*-dihydroxylation,[6] nucleophilic substitution,[7] 1,3-dipolar cycloaddition,[8] alcohol oxidation,[9] and halogen−lithium exchange reactions.[10]

Although Wittig and Horner−Wadsworth−Emmons reactions have been carried out on aldehyde derivatives of boronate esters,[11,12] to the best of our knowledge similar reactions using functionalized boronic acids have not been reported in the literature, presumably because of the presence of acidic protons on the boron species. Recently, our group revealed the synthesis of unsaturated potassium organotrifluoroborates via the Wittig and Horner−Wadsworth−Emmons reaction of the corresponding trifluoroborato-substituted benzaldehydes.[13]

The complementary process, i.e., generation and reaction of boron-functionalized phosphorus ylides with aldehydes, has apparently never been observed for any organoboron species. Herein, we report the preparation of potassium [(trifluoroboratophenyl)methyl]triphenylphosphonium chlorides, followed by the novel synthesis of unsaturated organotrifluoroborates via the direct Wittig reaction of these salts with various aldehydes in the presence of a base.

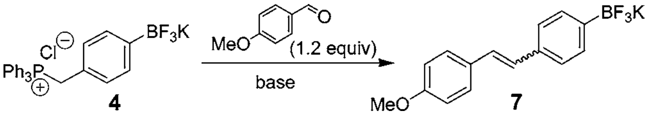
Initially, we prepared potassium [(trifluoroboratophenyl)-methyl]triphenylphosphonium chlorides from the corresponding potassium 2-, 3-, and 4-(chloromethyl)phenyltrifluoroborates in the presence of 1.5 equiv of triphenylphosphine (PPh_3) in 3-pentanone at reflux (eqs 1−3).



In the first attempts (eqs 1−3), the potassium [(trifluoroboratophenyl)methyl]triphenylphosphonium chlorides were isolated as white solids in 93%, 94%, and 86% yields, respectively. The excess PPh_3 was removed from the products by trituration with ether. All of the products are stable under normal atmospheric conditions.

Subsequently, we optimized the Wittig reaction of the ylides derived from these salts using *p*-anisaldehyde and organotrifluoroborate **4**. The reaction conditions explored are summarized in Table 1.

Table 1. Optimization of Wittig Reaction Conditions[a]



entry	solvent	base (1.2 equiv)	temp (°C)/5 h	conversion[b] (%, *E*/*Z*)
1	THF	*n*-BuLi	−78 to rt	48 (1.6:1)
2	THF	NaH	0 to rt	46 (2.8:1)
3	DMSO-d_6	NaH	0 to rt	53 (2.3:1)
4	DMSO-d_6	K_2CO_3	rt	16 (2.2:1)
5	DMSO-d_6	K_2CO_3	rt to 80	84 (2.5:1)[c]

[a] All reactions were carried out on a 0.1 mmol scale in 4 mL of THF in a 10 mL round-bottom flask or in 800 μL of DMSO-d_6 in an NMR tube and sonicated for 20 min. [b] Percent conversion was calculated by ^1H NMR. The *E*/*Z* ratio was based on the integration of peaks at 6.91 (*E*) ppm and 6.78 (*Z*) ppm, respectively. [c] Yield is given for the isolated products.

When the reaction was performed with *n*-BuLi or NaH in THF, the Wittig reactions did not completely generate **7** due to the poor solubility of **4** in THF (Table 1, entries 1 and 2). However, the yield of **7** slightly increased to 53% when the reaction was repeated with DMSO-d_6 in an NMR tube (Table 1, entry 3). When K_2CO_3 was used, although the conversion rate was lower at room temperature, a good isolated yield (84%) was obtained when the reaction temperature was increased to 80 °C (Table 1, entries 4 and 5).

With the optimized conditions for the formation of **7** (Table 1, entry 5) in hand, we examined the scope of the Wittig reaction for the synthesis of olefin-functionalized organotrifluoroborates using various aryl aldehydes. The results are summarized in Table 2.

In the study of the steric effect of the trifluoroborate unit using the ylides generated from the corresponding organotrifluoroborates **4**−**6**, there was little difference in the product yields (82−85%). The *E*/*Z* ratio and the reaction times increased according to the order of the *ortho*>*meta*>*para*-positioned trifluoroborate unit in the aromatic ring (Table 2, entries 1−3).

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(12) Horner−Wittig−Emmons: (a) Schmidt, U.; Leitenberger, V.; Griesser, H.; Schmidt, J.; Meyer, R. *Synthesis* **1992**, 1248. (b) Park, K. C.; Yoshino, K.; Tomiyasu, H. *Synthesis* **1999**, 2041. (c) Busnel, O.; Carreaux, F.; Carboni, B.; Pethe, S.; Goff, S. V.-L.; Mansuy, D.; Boucher, J.-L. *Bioorg. Med. Chem.* **2005**, *13*, 2373. (d) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7.

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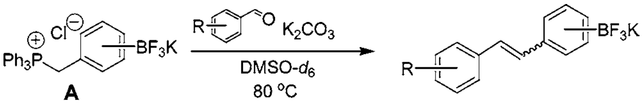
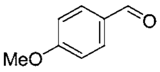
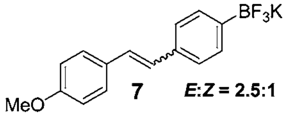
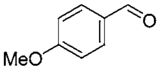
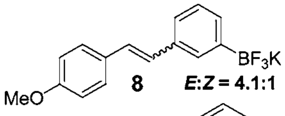
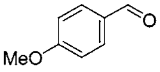
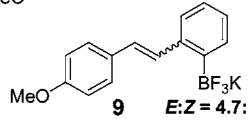
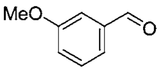
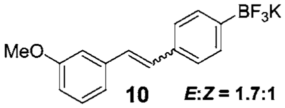
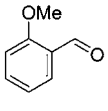
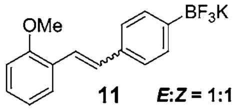
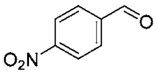
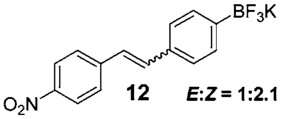
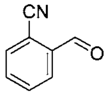
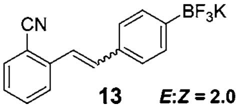
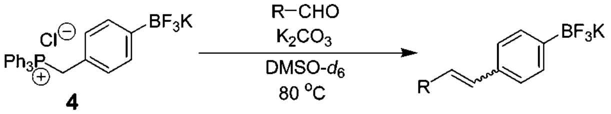
Table 2. Wittig Reaction of Potassium [(Trifluoroboratophenyl)methyl]triphenylphosphonium Chlorides with Various *o*-, *m*-, and *p*-Substituted Aryl Aldehydes[a]

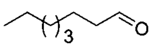
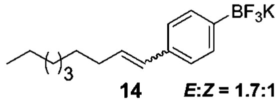
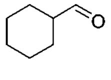
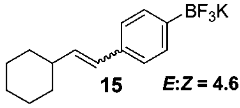
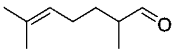
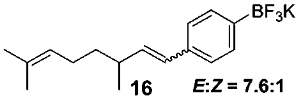
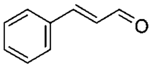
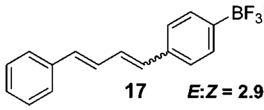
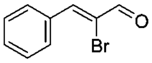
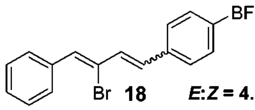
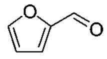
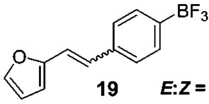
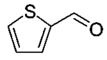
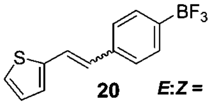
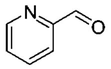
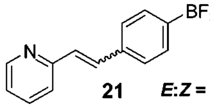


entry	A	aldehyde	reaction time (h)	product	yield (%)^b
1	**4**		5	 **7** *E*:*Z* = 2.5:1	84
2	**5**		6	 **8** *E*:*Z* = 4.1:1	85
3	**6**		24	 **9** *E*:*Z* = 4.7:1	(82)^c
4	**4**		4	 **10** *E*:*Z* = 1.7:1	99 (94)^d
5	**4**		3	 **11** *E*:*Z* = 1:1.2	97
6	**4**		1	 **12** *E*:*Z* = 1:2.1	87
7	**4**		1	 **13** *E*:*Z* = 2.0:1	97

[a] All reactions were carried out on a 0.1 mmol scale in 800 μL of DMSO-d_6 and sonicated for 20 min. [b] Yield is given for the isolated products, and the *E*/*Z* ratios were determined by ^{1}H NMR. [c] Product was contaminated with 2.6% of the starting potassium [(2-trifluoroboratophenyl)methyl]triphenylphosphonium chloride (**6**). [d] Reaction was performed on a 1 mmol scale in 3 mL of DMF.

Table 3. Wittig Reaction of Various Aldehydes with **4**[a]



entry	aldehyde	reaction time (h)	product	yield (%)^b
1		4	 **14** *E*:*Z* = 1.7:1	82
2		12	 **15** *E*:*Z* = 4.6:1	87
3		10	 **16** *E*:*Z* = 7.6:1	63
4		7	 **17** *E*:*Z* = 2.9:1	72 (65)^c
5		5	 **18** *E*:*Z* = 4.0:1	76
6		11	 **19** *E*:*Z* = 1.5:1	98
7		1	 **20** *E*:*Z* = 2.8:1	92 (87)^c
8		2	 **21** *E*:*Z* = 1:1.7	83 (94)^c

[a] All reactions were carried out on a 0.1 mmol scale in 800 μL of DMSO-d_6 and sonicated for 20 min. [b] Yield is given for the isolated products, and the *E*/*Z* ratios were determined by ^{1}H NMR. [c] Reaction was performed on a 1 mmol scale in 3 mL of DMF.

Interestingly, when 3- and 2-anisaldehydes were used (Table 2, entries 4 and 5), the reaction rates, yields, and ratios of the *Z*-isomer were increased compared to the 4-anisaldehyde (Table 2, entry 1). Both 4-nitrobenzaldehyde- and 2-cyanobenzaldehyde-containing substrates were converted to the corresponding unsaturated organotrifluoroborates in high yields (Table 2, entries 6 and 7). The *Z*-isomer was predominant for compound **12**.

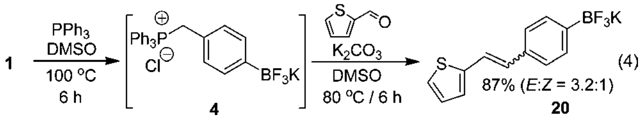
On the basis of the results in Table 2, we examined the Wittig reactions of potassium [(4-trifluoroboratophenyl)methyl]triphenylphosphonium chloride (**4**) with various aliphatic and heteroaryl aldehydes (Table 3).

In the reactivity test of various saturated alkyl aldehydes, the reaction with the linear alkyl aldehyde (Table 3, entry 1) proceeded faster than the reactions with cyclic or branched alkanals. Moreover, the stereoselectivity of the *E*-isomer of products **15** and **16** was significantly influenced by the sterically more hindered saturated alkyl aldehydes such as cyclohexanecarboxaldehyde and 2,6-dimethyl-5-heptenal (Table 3, entries 2 and 3). Furthermore, conjugated diene-functionalized organotrifluoroborates **17** and **18** were obtained successfully from *trans*-cinnamaldehyde and α-bromocinnamaldehyde in 72% and 76% yields, respectively (Table 3, entries 4 and 5).

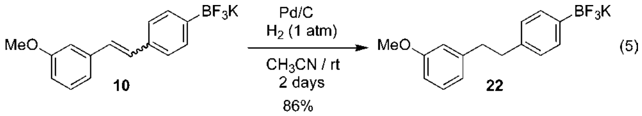
For the Wittig reaction of aryl aldehydes containing a heteroatom such as oxygen, sulfur, and nitrogen (Table 3, entries 6−8), the desired products were obtained in good yields. The reactivity of 2-thiophenecarboxaldehyde was higher when compared to that of other heterocyclic aldehydes (Table 3, entry 7).

The Wittig reactions could be scaled up to a 1 mmol scale (Table 3, entries 4, 7, and 8) yielding similar results.

Moreover, a one-pot Wittig reaction was developed. In this case, potassium [(4-trifluoroboratophenyl)methyl]triphenylphosphonium chloride (**4**), the intermediate generated by reaction of **1** with triphenylphosphine, was reacted directly with 2-thiophenecarboxaldehyde in the presence of a base, and the desired product was isolated in 87% overall yield (eq 4).



To demonstrate the viability and utility of this method further, we used a Pd/C-catalyzed hydrogenation to reduce the diastereomeric mixture of alkene isomers to a single compound. In the event, **10** was reduced to **22** in 86% yield using 20 wt % Pd/C in acetonitrile (eq 5).



In summary, we have successfully prepared potassium [(trifluoroboratophenyl)methyl]triphenylphosphonium chlorides in 86−94% yield using PPh_3 and the corresponding potassium (chloromethyl)phenyltrifluoroborates in 3-pentanone under refluxing conditions. We have developed a novel synthetic method for creating an alkene within potassium organotrifluoroborates via the Wittig reaction with various aldehydes in 63−99% yield. Additionally, these Wittig reactions can be performed via a one-pot process.

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

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