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A Mild Protocol for Allylation and Highly Diastereoselective Syn or Anti Crotylation of Aldehydes in Biphasic and Aqueous Media Utilizing Potassium Allyl- and Crotyltrifluoroborates

Avinash N. Thadani and Robert A. Batey*

Department of Chemistry, University of Toronto, Toronto, ON, Canada M5S 3H6

rbatey@chem.utoronto.ca

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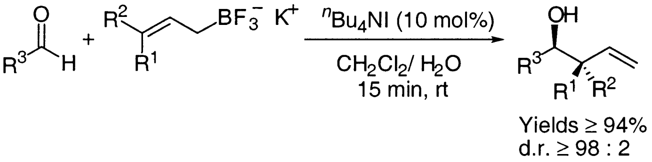
ABSTRACT



Potassium allyl- and crotyltrifluoroborates undergo addition to aldehydes in biphasic media as well as water to provide the corresponding homoallylic alcohols in high yields (≥94%), excellent diastereoselectivity (dr ≥ 98:2), and without the necessity of any subsequent purification. The presence of a phase transfer catalyst (e.g., ^{n}Bu$_4$NI) significantly accelerates the rate of reaction, whereas added fluoride ion retards the reaction.

The addition of crotyl and allylorganometallics to carbonyl compounds is of considerable importance in organic[1] and combinatorial[2] synthesis. The utility of many of these organometallics, though, is limited by their susceptibility to air and/or moisture. In recent years, numerous protocols have been developed to enable allylation of carbonyl compounds in aqueous media,[3,4] including the use of In,[5] Sn,[6] Zn,[7] and Mg[8] derived reagents. As a class of allylorganometallics, allyl/crotylboron compounds are very useful because of the high yields and excellent stereocontrol they provide in reactions with carbonyl compounds.[9] Many of these boron compounds, however, suffer from the limitations described above, and to the best of our knowledge there are no reported uses of these compounds in aqueous media.

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(1) (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 2, pp 1−53 and references therein.

(2) (a) Curran, D. P.; Luo, Z. Y.; Degenkolb, P. *Biorg. Med. Chem. Lett.* **1998**, *8*, 2403−2408. (b) Curran, D. P.; Hadida, S.; Mu, H. *J. Org. Chem.* **1997**, *62*, 6714−6715. (c) For a review on solution-phase combinatorial chemistry, see: An, H. Y.; Cook, P. D. *Chem. Rev.* **2000**, *100*, 3311−3340.

(3) (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751−2772. (b) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley & Sons: New York, 1997.

(4) For recent reviews, see: (a) Li, C. J. *Tetrahedron* **1996**, *52*, 5643−5668. (b) Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741−760.

(5) For recent examples, see: (a) Lu, W.; Chan, T. K. *J. Org. Chem.* **2001**, *66*, 3467−3473. (b) Loh, T.-P.; Zhou, J. R.; Yin, Z. *Org Lett.* **1999**, *1*, 1855−1857. (c) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217−224. (d) Paquette, L. A.; Mitzel, T. M. *J. Org. Chem.* **1996**, *61*, 8799−8804. (e) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228−3229.

(6) For recent examples, see: (a) Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *41*, 5261−5264. (b) Loh, T.-P.; Xu, J.; Hu, Q.-Y.; Vittal, J. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1565−1569. (c) Chan, T. H.; Yang, Y.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 4452−4455. (d) Ito, A.; Kishida, M.; Kurusu, Y.; Masuyama, Y. *J. Org. Chem.* **2000**, *65*, 494−498.

(7) For recent examples, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Rodríguez-Acebes, R. *J. Org. Chem.* **2001**, *66*, 5208−5216. (b) Márquez, F.; Llebaria, A.; Delgado, A. *Org. Lett.* **2000**, *2*, 547−549. (c) Marton, D.; Stivanello, D.; Tagliavini, G. *J. Org. Chem.* **1996**, *61*, 2731−2737.

(8) Zhang, W. C.; Li, C. J. *J. Org. Chem.* **1999**, *64*, 3230−3236.

(9) Roush, W. R. In *Houben-Weyl, Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, Germany, 1995; Vol. E21b, pp 1410−1486 and references therein. (b) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995.

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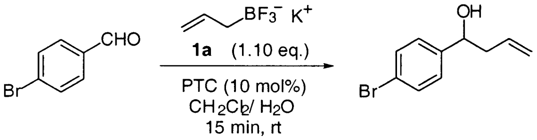
As part of ongoing studies on the synthesis and reactivity of organotrifluoroborate salts,[10] we have recently developed a new class of allyl/crotylboron reagents, potassium allyl- and crotyltrifluoroborates **1a**−**c**, and reported their Lewis acid-promoted additions to carbonyl compounds.[10a,b] In the course of developing milder reaction conditions, we discovered that **1a** undergoes facile addition to aldehydes **2** in a biphasic medium containing a phase transfer catalyst (PTC). A variety of PTCs (10 mol %) promote the allylation of 4-bromobenzaldehyde (1.0 equiv) by potassium allyltrifluoroborate **1a** (1.1 equiv) in a biphasic reaction medium (CH_2Cl_2/H_2O, 15 min at rt),[11] including quaternary ammonium and phosphonium halide salts (Table 1). In the absence of a PTC, the reaction was found to be rather sluggish (15% yield after 15 min at rt) and was incomplete after 15 min if less than 10 mol % PTC was used.

Table 1. Comparative Efficiency of Various Phase Transfer Catalysts (PTCs) (10 mol %) in the Addition of Potassium Allyltrifluoroborate **1a** (1.10 equiv) to 4-Bromobenzaldehyde

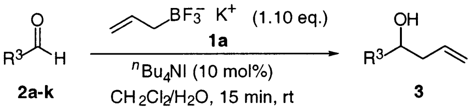


entry	PTC[a]	yield[a] [%]
1	none	15
2	$^nBu_4NI$	99
3	$^nBu_4NBr$	98
4	$BnEt_3NCl$	97
5	Ph_3MePCl	97

[a] Isolated yields. See ref 11.

The scope of the transformation was established with a variety of different aldehydes using $^nBu_4NI$ as the PTC (Table 2). Aliphatic, aromatic, α,*β*-unsaturated, and heterocyclic aldehydes were efficiently allylated in very high yields (≥94%), tolerating nitro, ester, and cyano groups, aromatic halides, and an unprotected phenol. In the case of cinnamaldehyde, only 1,2-addition was observed. Non-chlorinated organic solvents (e.g., toluene or diethyl ether) can also be used under the biphasic conditions without affecting the product yield. The additions can also be accomplished within 15 min *in water alone* as long as a PTC (10 mol %) is present. If a water-soluble aldehyde (such as **2k**) is used, then the PTC is unnecessary. The presumed role of the phase transfer catalyst in these reactions is to transport the allyltrifluoroborate anion from the aqueous phase into the organic phase with reaction presumably occurring at the interface of the aqueous and organic phases.[12]

Table 2. Allylation of Aldehydes **2a**−**k** by Potassium Allyltrifluoroborate **1a** in a Biphasic Medium Containing $^nBu_4NI$ (10 mol %)



entry	R^3	homoallylic alcohol	yield[a] [%]
1	$4\text{-}BrC_6H_4$	**3a**	99
2	$(CH_3)_3C$	**3b**	95
3	C_7H_{15}	**3c**	94
4	Chx	**3d**	97
5	$2\text{-}O_2NC_6H_4$	**3e**	99
6	$4\text{-}MeOC_6H_4$	**3f**	98
7	$3\text{-}HOC_6H_4$	**3g**	99
8	$4\text{-}MeO_2CC_6H_4$	**3h**	97
9	$4\text{-}NCC_6H_4$	**3i**	98
10	(*E*)-PhHC=CH	**3j**	95
11	2-furanyl	**3k**	95

[a] Isolated yields. See ref 11.

More significantly, crotylations of aliphatic, aromatic, and α,*β*-unsaturated aldehydes could also be accomplished using the same reaction conditions, occurring with excellent diastereoselectivities and high yields (Table 3). The use of potassium (*Z*)-crotyltrifluoroborate **1b** led to the formation of syn homoallylic alcohols (dr ≥ 98:2), while the (*E*)-crotyl reagent **1c** afforded anti adducts (dr ≥ 98:2). To the best of our knowledge, this represents the first general method for the selective generation of either syn or anti homoallylic alcohols **4** in biphasic or aqueous media.[13]

The simplicity, high diastereoselectivity, and simple workup protocol should render this protocol attractive for parallel/combinatorial synthesis or for reactions where enantioselectivity[14] is not important. For large-scale reactions, or reactions where removal of the PTC may be problematic, reaction of aldehydes with **1** in biphasic media can be carried out in the absence of the PTC, but the reaction times are significantly lengthened. We found that all of the aldehydes tested reacted completely within 16 h to furnish the corresponding homoallylic alcohols in high yields and diastereoselectivity, without the necessity of further purification.

A number of experiments were conducted in order to deduce the mode of reactivity of **1**. The allylation of **2a** (1

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(10) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990−998. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289−4292. (c) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099−9103. (d) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Org. Lett.* **1999**, *1*, 1683−1686.

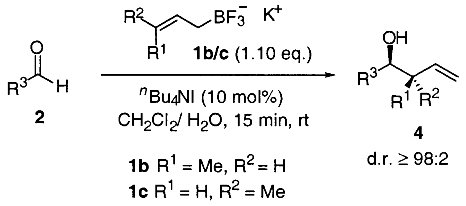
(11) Isolated yields reported after separation of the layers, extraction (3 × 5 mL, CH_2Cl_2), removal of the solvent, and passage of the resulting crude reaction mixture through a short plug of silica gel (EtOAc as the eluent) in order to remove the PTC.

(12) For a recent monograph on phase transfer catalysis, see: *Handbook of Phase Transfer Catalysis*; Sasson, Y., Neumann, R. Eds.; Blackie Academic & Professional: London, 1997.

(13) Reaction of specific indium reagents derived from functionalized allyl bromides with aldehydes proceeds in some cases with high diastereoselectivity, see: (a) Li, X.-R.; Loh, T.-P. *Tetrahedron: Asymmetry* **1996**, *7*, 1535−1538. (b) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333−5338. (c) Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893−1899. (d) Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206−3210.

(14) Not surprisingly, the use of chiral PTCs did not result in enantioselective addition. For leading references on chiral PTCs, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748.

Table 3. Crotylations of Aldehyde **2** by Potassium (*Z*)- and (*E*)-Crotyltrifluoroborate **1b**/**c** in a Biphasic Medium Containing $^{n}Bu_4NI$ (10 mol %)



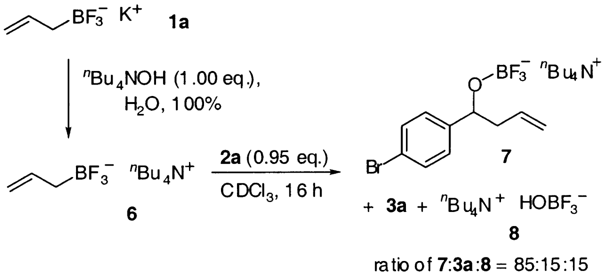
entry	R^1	R^2	R^3	yield[a] [%]
1	Me	H	$(CH_3)_3C$	96 (**4a**)
2	H	Me	$(CH_3)_3C$	95 (**4b**)
3	Me	H	C_7H_{15}	94 (**4c**)
4	H	Me	C_7H_{15}	96 (**4d**)
5	Me	H	Ph	96 (**4e**)
6	H	Me	Ph	95 (**4f**)
7	Me	H	4-$MeOC_6H_4$	98 (**4g**)
8	H	Me	4-$MeOC_6H_4$	98 (**4h**)
9	Me	H	(*E*)-PhHC=CH	99 (**4i**)
10	H	Me	(*E*)-PhHC=CH	99 (**4j**)

[a] Isolated yields after removal of the PTC. See ref 11.

equiv) by **1a** (1 equiv) in a 1:1 mixture of $CDCl_3/D_2O$ containing 10 mol % $^{n}Bu_4NI$ was monitored by multinuclear NMR. As the reaction progressed, the ^{11}B NMR (δ 4.68, q, J = 60.0 Hz) and ^{19}F NMR (δ −138.1, q, J = 60.0 Hz) signals of allyltrifluoroborate anion in the D_2O layer gradually disappeared. In the organic layer, ^{19}F NMR showed the appearance and subsequent disappearance of both allyltrifluoroborate anion and deuterioxytrifluoroborate anion ($DOBF_3^-$) as the reaction proceeded. At the end of the reaction, new signals corresponding to potassium deuterioxytrifluroborate (K^+ BF_3OD^-) **5** were evident in both the ^{11}B NMR (δ 0.02, q, J = 14.5 Hz) and ^{19}F NMR (δ −144.2, q, J = 14.5 Hz) spectra of the aqueous (D_2O) layer, whereas ^1H NMR of the organic ($CDCl_3$) layer showed full conversion of aldehyde **2a** to homoallylic alcohol **3a**. The partitioning of the allyltrifluoroborate and deuterioxytrifluoroborate anions over the course of the reaction suggests that the allylation reaction is occurring on the organic side of the solvent interphase.

To simplify the mechanistic analysis, the tetra-*n*-butylammonium salt **6**, which is soluble in organic solvents, was also studied. Compound **6** was synthesized by a counterion exchange method[10c] and is soluble in organic solvents.[15] Reaction of **6** with aldehyde **2a** over 16 h in $CDCl_3$ formed compound **7** in situ, which was characterized by ^1H, ^{13}C, ^{19}F, and ^{11}B NMR (Scheme 1). In the ^{13}C NMR of the reaction mixture, the benzylic carbon atom of **7** (δ 71.58, q, J = 3.5 Hz) appears as a quartet due to splitting by the adjacent fluorine atoms on boron. The trace amounts of water present in the reaction mixture presumably cause the hydrolysis of **7** to the corresponding homoallylic alcohol **3a** and tetra-*n*-butylammonium hydroxytrifluoroborate **8** (Scheme 1). Upon passage of the crude reaction mixture through a plug of silica gel, pure **3a** was obtained (98% yield based on **2a**).

Scheme 1



Most allylboron compounds are believed to react via tricoordinate species.[9] However, Yamamoto has reported that tetracoordinate trialkylcrotylborate reagents also readily add to aldehydes to generate the corresponding homoallylic alcohols at low temperatures.[16] We have previously proposed that the Lewis acid-promoted addition of the tetracoordinate reagents **1** to aldehydes in CH_2Cl_2 may proceed through the intermediacy of tricoordinate allyl/crotyldifluoroborane species.[10a,b] For PTC-promoted reactions of **1**, it is conceivable that reaction may proceed through tri- or tetracoordinate species. On the assumption that addition occurs via a tricoordinate boron species, a key step in the reaction must involve dissociation of fluoride from **1** to form allyl/crotyldifluoroborane. Although we have not detected the presence of allyl/crotyldifluoroborane or a discrete complexed intermediate between it and the aldehyde, under the reaction conditions, such species would reasonably be expected to give rise to products via a Zimmerman−Traxler transition state (TS).[17] The excellent diastereocontrol shown in the crotylation reactions is consistent with this hypothesis, and in any event, the diastereospecific nature of the process clearly reflects the remarkable configurational stability of (*Z*)- and (*E*)-crotyltrifluoroborates in both aqueous and organic solvents. If a dissociative mechanism is operative, the addition of fluoride ions would presumably suppress the dissociation of **1** into the reactive allyl/crotyldifluoroborane species and lead to a slower rate of reaction via the common ion effect.[18] This hypothesis was confirmed in the reaction of **6** (1.10 equiv) and **2a** (1.00 equiv) in CD_2Cl_2, for which added tetra-*n*-butylammomium fluoride hydrate (TBAF·H_2O, 0.01 equiv) had a significant inhibitory effect (<1% of the aldehyde was allylated after 16 h). Similarly, when KF (5 equiv) was added to a mixture of **1a** (1.10 equiv), **2a** (1.00 equiv), and $^{n}Bu_4NI$ (0.10 equiv) in a biphasic medium

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[15] Compound **6** was isolated as a clear, colorless solid contaminated with approximately 1% of tetra *n*-butylammonium tetrafluoroborate.

[16] Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969−1975 and references therein.

[17] Le Serre, S.; Guillemin, J. C. *Organometallics* **1997**, *16*, 5844−5848.

[18] For examples of the common ion effect, see: (a) Bolton, J. L.; McClelland, R. A. *Can. J. Chem.* **1989**, *67*, 1139−1143. (b) Gun'kin, I. F.; Butin, K. P.; Beletskaya, I. P.; Reutov, O. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1978**, 1297−1300. (c) Hughes, E. D.; Ingold, C. K.; Mok, S. F.; Pocker, Y. *J. Chem. Soc.* **1957**, 1238−1255.

($CDCl_3/D_2O$), the reaction rate was again retarded, albeit to a lesser extent (15% of the aldehyde was allylated after 15 min). In the absence of added fluoride ion, the slower rate of allylation of **2a** by **6** (16 h at rt) in CD_2Cl_2 solvent compared to the reaction of **1** under biphasic conditions is, presumably, a reflection of the decreased dissociation of fluoride ion in organic media rather than in aqueous (or biphasic) media.

Interestingly, Le Serre and Guillemin have reported that allyldifluoroborane, synthesized by transmetalation of allyltributylstannane by gaseous boron trifluoride, does not give homoallylic alcohol **3** (R^3 = Ph) upon reaction with benzaldehyde in dichloromethane. Conversely, Omoto and Fujimoto have calculated (MP2/6-31G**) that allyldifluoroborane should react spontaneously with aldehydes.[19] Finally, we note that Brown and co-workers have shown that allylboronic acid reacts with benzaldehyde instantaneously at 0 °C.[20] The much greater reactivity of allylboronic acid compared with allylboronates was rationalized by the presence of a +I effect from the alkyl groups in the latter reagents. Under our reaction conditions the replacement of fluoride by one or more OH group to form the active allylation agent could occur. While the exact nature of the reactive species in these reactions has not been definitively established, the remarkable common ion effect exhibited by fluoride ions on the reaction of **6** in CD_2Cl_2 solvent is *not* consistent with a mechanism involving direct addition of tetracoordinate trifluoroborate salts to aldehydes.

In conclusion, we have established efficient procedures for the generation of homoallylic alcohols in biphasic, aqueous, and organic media using allyl- and crotyltrifluoroborate salts **1**. Phase transfer catalysis is necessary to achieve rapid reactions under biphasic conditions. The reagents are stable to air and water and can be stored for extended periods. The homoallylic alcohol products are obtained in high yields and do not require further purification by chromatography. Significantly, diastereospecific crotylations can be achieved with high selectivity. Initial studies suggest a mechanism involving initial dissociation of fluoride, rather than direct addition of the tetracoordinate salts, as shown by a pronounced common ion effect. Further studies utilizing these reagents and other substituted variants of **1** are currently underway in our laboratory.

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Supporting Information Available: Preparation procedures and characterization data for **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Omoto, K.; Fujimoto, H. *J. Org. Chem.* **1998**, *63*, 8331−8336.

(20) Brown, H. C.; Racherla, U. S.; Pellechia, P. J. *J. Org. Chem.* **1990**, *55*, 1868−1874.