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Allylation and Crotylation of Ketones and Aldehydes Using Potassium Organotrifluoroborate Salts under Lewis Acid and Montmorillonite K10 Catalyzed Conditions

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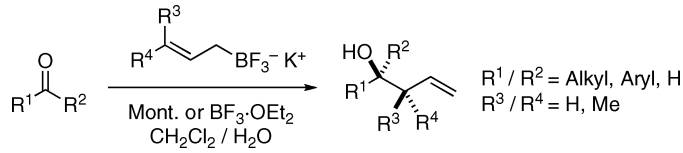
ABSTRACT



Two convenient highly diastereoselective protocols for the allylation and crotylation of ketones using practical, air- and water-stable potassium allyl and crotyltrifluoroborate salts have been developed. BF_3·OEt_2 and montmorillonite clay are used as catalysts to promote additions. The montmorillonite-catalyzed method in particular is very robust, providing a straightforward and scalable method for the allylation and crotylation of a range of ketones and aldehydes.

The allylation and crotylation of carbonyl compounds is one of the most important C−C bond formation methods in organic synthesis.[1] The resulting homoallylic alcohol products are versatile synthetic intermediates, as exemplified by their application toward the synthesis of numerous natural products.[2] Classical methods that have been employed for these transformations include reactions of allylic halides with stoichiometric metals (e.g., Mg, Cr, Zn, In) under Barbier-type conditions[3] or the use of various allyl or crotyl organometalloid derivatives (e.g., B, Si, Sn).[4] Asymmetric variants of the reaction have also been accomplished with either chiral reagents or chiral catalysts.[5] However, whereas reactions of aldehydes are well established, the allylation and

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(1) For reviews on allylations in general, see: (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. (c) Matteson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer-Verlag: Berlin, 1995. (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739. (e) Denmark, S. E.; Fu, J. P. *Chem. Rev.* **2003**, *103*, 2763–2793.

(2) See for example: (a) Nicolaou, K. C.; Kim, D. W.; Baati, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3701–3704. (b) Felpin, F. X.; Lebreton, J. *J. Org. Chem.* **2002**, *67*, 9192–9199. (c) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894–12895.

(3) For selected recent examples of allylations of ketones under Barbier-like conditions, see: (a) Zhao, L.; Burnell, D. J. *Tetrahedron Lett.* **2006**, *47*, 3291–3294. (b) Preite, M. D.; Perez-Carvajal, A. *Synlett* **2006**, 3337–3339. (c) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753.

(4) Using allylsilanes, see: (a) Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 676–677. (b) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557. Using allylstannanes, see: (c) Waltz, K. M.; Gavenonis, J.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3697–3699. (d) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, 4217–4218. (e) Gu, Y.; Ogawa, C.; Kobayashi, J.; Mori, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7217–7220. (f) Wooten, A. J.; Kim, J. G.; Walsh, P. J. *Org. Lett.* **2007**, *9*, 381–384.

(5) See for example: (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490. (b) Wu, T. R.; Shen, L.; Chong, J. M. *Org. Lett.* **2004**, *6*, 2701–2704. (c) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160–10161. (d) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290–1302.

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crotylation reactions of ketones are more challenging because of their lower reactivity and the difficulty in achieving stereoselective additions. Recently the allylation of ketones has been the focus of renewed attention using organoboron compounds.[6] We now report two convenient ambient temperature protocols for the allylation and crotylation of ketones using practical, air- and water-stable potassium allyl and crotyltrifluoroborate salts **1a**−**c** (Figure 1).

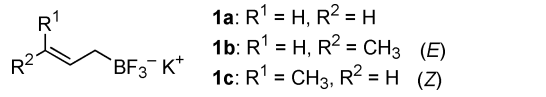
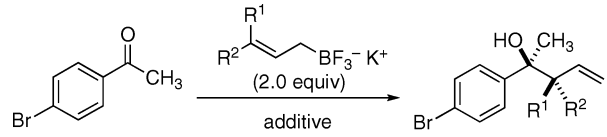


Figure 1. Potassium allyl and crotyltrifluoroborate salts **1a**−**c**.

Organotrifluoroborate salts are air- and moisture-stable compounds that are readily formed by the reaction of boronic acids with KHF_2[7] and are now widely used as equivalents to the corresponding organoboronic acids.[8] We have previously demonstrated the synthesis and use of **1a**−**c** as mild allylation/crotylation reagents for aldehydes in the presence of Lewis acids (e.g., $BF_3{\cdot}OEt_2$) in organic solvents or in the presence of phase-transfer catalysts (i.e., Bu_4NI in CH_2Cl_2/H_2O).[9] The salts **1a**−**c** avoid some of the problems typically associated with tricoordinate allyl- and crotylboron compounds, which can be sensitive to air and/or moisture and have poor storage properties. Further to these studies we were interested in expanding the scope of these reactions to include other carbonyl compounds such as ketones and pyruvates. Initial experiments revealed that the reaction of potassium allyl- and crotyltrifluoroborates with ketones was much slower than with aldehydes. For example, the only substrates that would react completely with **1a** using the previously reported phase-transfer catalyzed conditions (CH_2Cl_2/H_2O with 1.0 equiv of $^nBu_4NI$ for 16 h)[9c] were the more reactive cyclic ketones such as cyclohexanone. Noncyclic ketones such as acetophenone gave only a moderate yield (30%) of the corresponding homoallylic alcohol product under these conditions even when an excess of **1a** (5 equiv) was used.

The inapplicability of the previously developed phase-transfer catalyzed conditions toward ketones prompted us to consider alternative protocols. The use of Lewis acid activation using $BF_3{\cdot}OEt_2$ could be accomplished. Thus, reaction of 4-bromoacetophenone with **1a** (2.0 equiv) using catalytic $BF_3{\cdot}OEt_2$ (5 mol %) in CH_2Cl_2 at room temperature for 24 h afforded homoallylic alcohol **2a** in 98% yield (Method A, Table 1, entry 1). Reaction using catalytic $BF_3{\cdot}OEt_2$ for a shorter time (3 h) gave a much lower yield of **2a** (Table 1, entry 2). The reaction rate was much slower than for aldehydes, which typically react within 3 h using catalytic conditions or within 15 min using stoichiometric $BF_3{\cdot}OEt_2$ at −78 °C.[9a,b]

Table 1. Optimization of Reaction Conditions for Allylation and Crotylation of 4-Bromoacetophenone using Potassium Allyltrifluoroborate **1a** and Crotyltrifluoroborate Salts **1b** and **1c**



2a: R^1 = H, R^2 = H
2b: R^1 = H, R^2 = CH_3
2c: R^1 = CH_3, R^2 = H

entry	RBF_3K	additive[a]	solvent (mL)	yield[b,c]
1	**1a**	$BF_3{\cdot}OEt_2$	CD_2Cl_2	98
2	**1a**	$BF_3{\cdot}OEt_2$	CD_2Cl_2	28
3	**1a**	montmorillonite	D_2O (0.1)/$CDCl_3$ (1.4)	96
4	**1a**	montmorillonite	$CDCl_3$ (1.5)	66
5	**1a**	alumina(N)	D_2O (0.1)/$CDCl_3$ (1.4)	quant
6	**1a**	charcoal	D_2O (0.1)/$CDCl_3$ (1.4)	11
7	**1a**	silica gel	D_2O (0.1)/$CDCl_3$ (1.4)	37
8	**1b**	montmorillonite	D_2O (0.1)/$CDCl_3$ (1.4)	98
9	**1b**	alumina(N)	D_2O (0.1)/$CDCl_3$ (1.4)	98
10	**1c**	montmorillonite	D_2O (0.1)/$CDCl_3$ (1.4)	73
11	**1c**	alumina(N)	D_2O (0.1)/$CDCl_3$ (1.4)	5
12	**1c**	montmorillonite	D_2O (0.1)/CD_2Cl_2 (1.4)	98

[a] 0.1 g of solid additives were used, with reaction times of 3 h, except for entries 1 and 2 where 5 mol % of $BF_3{\cdot}OEt_2$ was used for 24 h and 3 h, respectively. [b] Yield of the product determined by ^1H NMR using an internal standard. [c] Entries 1−7 gave product **2a**, entries 8 and 9 gave **2b** (dr ≥98:2), and entries 10−12 gave **2c** (dr ≥95:5).

Although the use of $BF_3{\cdot}OEt_2$ was successful, a more experimentally convenient protocol that would achieve faster additions and higher yields was desirable. A screen of a variety of other solid reagents (Table 1, entries 3−7) revealed that montmorillonite K10[10] and neutral alumina had the most beneficial effect on reactivity using a water/chloroform solvent system. The most effective additives were applied for the crotylation using **1b** under identical conditions. Reactions using montmorillonite K10 and neutral alumina were effective, giving **2b** in excellent diastereoselectivity (Table 1, entries 8 and 9). However, only montmorillonite K10 gave satisfactory results with the more sensitive (*Z*)-

(6) For selected recent examples of allylborations of ketones, see: (a) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911. (b) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573. (c) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. (d) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909–5912. (e) Carosi, L.; Hall, D. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913–5915. (f) Schneider, U.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13824–13825.

(7) Vedejs, E.; Fields, S. C.; Shrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *117*, 11612–11613.

(8) For reviews of organotrifluoroborates and other leading references, see: (a) Darses, S.; Genêt, J. P. *Eur. J. Org. Chem.* **2003**, 4313–4327. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (d) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325.

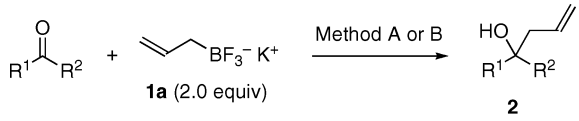
(9) (a) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289–4292. (b) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Synthesis* **2000**, 990–998. (c) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827–3830. (d) Thadani, A. N.; Batey, R. A. *Tetrahedron Lett.* **2003**, *44*, 8051–8055. (e) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382–1383.

(10) For reviews on the use of clay-catalyzed reactions, see: (a) Dasgupta, S.; Török, B. *Org. Prep. Proced. Int.* **2008**, *40*, 1–65. (b) Varma, R. S. *Tetrahedron* **2002**, *58*, 1235–1255. (c) Nikalje, M. D.; Phukan, P.; Sudalai, A. *Org. Prep. Proced. Int.* **2002**, *32*, 1–40.

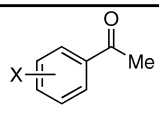
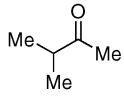
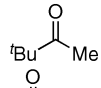
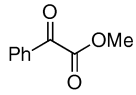
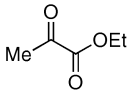
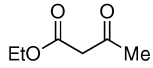
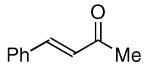
crotyltrifluoroborate **1c**, giving full conversion to **2c** in CD_2Cl_2 solvent (Table 1, entries 10−12).[11]

A series of ketones were then allylated under the two sets of conditions: BF_3•OEt_2 (5 mol %)/CH_2Cl_2/rt (Method A), and montmorillonite K10/CH_2Cl_2/H_2O/rt (Method B) (Table 2). Aromatic, aliphatic, and α,β-unsaturated ketones were

Table 2. Substrate Generality for the Lewis Acid and Montmorillonite K10 Catalyzed Allylation of Ketones with Potassium Allyltrifluoroborate **1a**



Method A: BF_3·OEt_2 (5 mol%), CH_2Cl_2, rt, 24 h
Method B: Montmorillonite (0.1 g), CH_2Cl_2:H_2O, rt, 3-5 h

entry	ketone	product	yield[a]/methods A : B
1		**2a**: X=Br	93:97
2		**2d**: X= 2-OMe	94:89
3		**2e**: X=3-NH_2	84:78
4		**2f**: X=4-NO_2	94:96
5		**2g**	82:94
6		**2h**	≤5:59
7		**2i**	92:98
8		**2j**	87:91
9		**2k**	91:98
10		**2l**	87:83

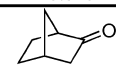
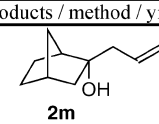
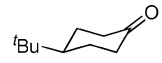
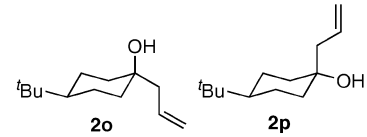
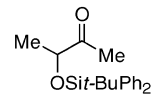
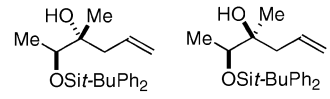
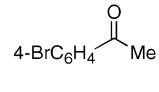
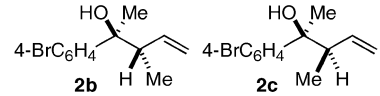
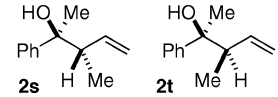
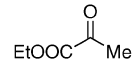
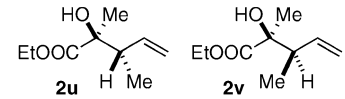
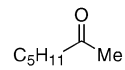
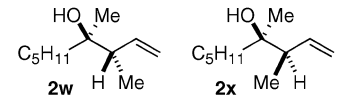
[a] Yield of product isolated after silica gel chromatography.

efficiently allylated using each of these methods. Overall, the use of montmorillonite K10 (Method B) was the most general, giving better results with more hindered ketones (Table 2, entry 6). In addition, reactions using Method B were faster than those of Method A. Purification was straightforward and avoided problems associated with the removal of phase transfer catalysts.[9c] Also, the use of an inert atmosphere or other special requirements were not necessary.[6] Moreover, Method B was more scaleable, as exemplified by the allylation of 4-bromoacetophenone to **2a** on a 20 mmol scale, which occurred without any changes in reaction time or yield.

(11) CH_2Cl_2 was used as solvent for both allylation and crotylation because the observed conversion or diastereoselectivity was lower using other solvents such as toluene, H_2O, THF, MeCN, $CHCl_3$, DMF, or MeOH.

High-yielding stereoselective allylations of cyclic and acyclic ketones were also accomplished using both allylation protocols (Table 3, entries 1−3). Diastereoselective crotylations of ketones are, in general, much more difficult than reactions with aldehydes. Nevertheless, crotylations of ac-

Table 3. Diastereoselective Allylation and Crotylation of Ketones using **1a**−**c** under Lewis Acid or Montmorillonite K10 Catalyzed Conditions[a]

entry	ketone	products / method / yield (%)[b] (dr)[c]
1		 **2m** **2n** Method **A**: 86 (≥95:5) Method **B**: 93 (≥95:5)
2		 **2o** **2p** Method **B**: 93 (82:18)
3		 **2q** **2r** Method **B**: 92 (78:22)
4		 **2b** **2c** from **1b**: Method **A**: 85 (92:8) Method **B**: 97 (98:2) from **1c**: Method **A**: 85 (5:95) Method **B**: 94 (5:95)
5		 **2s** **2t** from **1b**: Method **A**: 81 (95:5) Method **B**: 91 (98:2) from **1c**: Method **A**: 83 (5:95) Method **B**: 94 (5:95)
6		 **2u** **2v** from **1b**: Method **A**: 92 (95:5) Method **B**: 93 (98:2) from **1c**: Method **A**: 90 (5:95) Method **B**: 91 (5:95)
7		 **2w** **2x** from **1b**: Method **A**: 74 (58:42)[d] Method **B**: 97 (62:38) from **1c**: Method **A**: 53 (51:49)[d] Method **B**: 95 (53:47)

[a] Method A: BF_3•OEt_2 (5 mol %), CH_2Cl_2, rt, 24 h. Method B: Montmorillonite K10 (0.1 g), CH_2Cl_2/H_2O, rt, 3−5 h. [b] Yield of isolated product after silica gel chromatography. [c] Diastereomeric ratio determined by ^1H NMR or GC analysis of the crude products before column chromatography. [d] Crude conversion with **1b** and **1c** was 75% and 62%, respectively.

etophenone, 4-bromoacetophenone, and ethyl pyruvate by potassium crotyltrifluoroborates **1b,c** gave adducts in good yields and excellent diastereoselectivities (Table 3, entries 4−6). As anticipated from previous crotylation reactions of organometalloid reagents,[1] the reaction of a less sterically differentiated linear substrate, 2-heptanone, gave products with modest diasteroselectivy under both sets of conditions (Table 3, entry 7).

Method B was also applied toward the allylation and crotylation of various aldehydes (Figure 2). The much higher

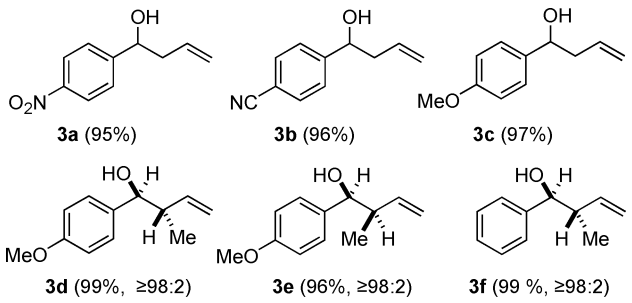


Figure 2. Examples of products of allylation and crotylation of aldehydes using montmorillonite K10 catalysis (Method B).

reactivity of aldehydes compared to that of ketones allowed the use of just 1.2 equiv of the trifluoroborate salts **1a−c**, rather than the 2.0 equiv necessary for the reactions with ketones. Under these conditions full conversions were achieved in less than 10 min to give the adducts **3a−f** in high yields. The diastereoselectivity of the crotylations was high (≥98:2), with **1b** giving the *anti*-adducts **3d,f**, and **1c** giving *syn*-adduct **3e**. This method thus provides one of the most operationally simple approaches to the allylation/crotylation of aldehydes.

The diastereospecific additions achieved with the (*E*)- and (*Z*)-crotyl reagents **1b** and **1c** afforded *anti* and *syn* diastereomeric adducts, respectively. This selectivity is consistent with reaction of tricoordinate allylboron species through cyclic Zimmerman−Traxler-like transition states.[9] The requisite tricoordinate allylboron species can be formed by fluoride ion abstraction from **1** under Lewis acidic or montmorillonite based conditions.

In summary, we have developed mild and practical methods for the allylation and crotylation of ketones and aldehydes using organotrifluoroborate salts, under either Lewis acidic or montmorillonite K10 catalysis. The latter method in particular is very robust, providing a remarkably straightforward and simple method for allylation and crotylation using an inexpensive and environmentally benign catalyst. Further applications of these methods and related chemistry will be reported in due course.

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Supporting Information Available: Spectroscopic data of all the new compounds and detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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