ORGANIC LETTERS

2010
Vol. 12, No. 21
4892−4895

Allyl Transfer to Aldehydes and Ketones by Brønsted Acid Activation of Allyl and Crotyl 1,3,2-Dioxazaborolidines

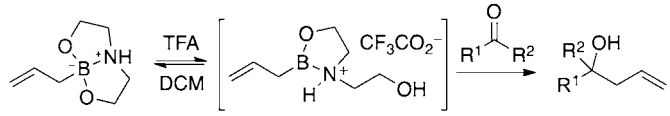
Maureen K. Reilly and Scott D. Rychnovsky*

Department of Chemistry, 1102 Natural Sciences II, University of California—Irvine, Irvine, California 92697, United States

srychnov@uci.edu

Received August 29, 2010

ABSTRACT



Alkyl dioxazaborolidines are air-stable and often crystalline organoboranes. A variety of Brønsted acids activate allyl dioxazaborolidines to generate reactive allyl-transfer reagents in situ. These reagents add to aldehydes and ketones to generate the corresponding alcohols in good yields under mild conditions. The *E*- and *Z*-crotyl reagents react diastereoselectively with aldehydes and ketones to produce *anti* and *syn* adducts, respectively, a result consistent with a cyclic transition state (type I mechanism).

The allylation of aldehydes and ketones to afford synthetically versatile homoallylic alcohols constitutes an important class of carbon−carbon bond forming reactions.[1] Many allyl transfer reagents have been reported, including allylstannanes,[2] allylsilanes,[3] and allylboranes,[4−6] among others.[1] Recent catalytic methods are particularly exciting.[7] Despite the variety of allyl transfer methods, many of them require stoichiometric amounts of toxic metal,[2,8] expensive chiral reagents[3,9,10] or catalysts,[4f,7,9] or preparation of reagents from expensive starting materials.[3] Therefore, we sought to design an inexpensive allyl transfer reagent with a practical balance of stability and reactivity.

This project was inspired by research exploring the activation of organoborane reagents. Studies conducted by Hall[5] demonstrated that the addition of 2-alkoxycarbonyl allylboronates to carbonyl compounds could be promoted by Lewis or Brønsted acid activation to provide the cyclized α-*exo*-methylene γ-lactones. In a related strategy, Corey demonstrated that chiral oxazaborolidines could be protonated with very strong acids to produce exceptionally reactive Lewis acids that were highly effective catalysts for Diels−Alder reactions.[11] By adding triflic acid at low temperatures, they were able to observe the

(1) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2794. (b) Hatano, M.; Ishihara, K. *Synthesis* **2008**, *11*, 1647–1675. (c) Lachance, H.; Hall, D. G. *Org. React.* **2008**, *73*, 1–554.

(2) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468. (b) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743–2745.

(3) (a) Kinnaird, J. W.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920–7921. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946–948. (c) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375–4377.

(4) (a) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (c) Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495–5496. (d) Burgos, C. H.; Canales, E.; Matos, K.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8044–8049. (e) Canales, E.; Prasad, K. G.; Soderquist, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573. (f) Kanai, M.; Wada, R.; Shibuguchi, T.; Shibasaki, M. *Pure Appl. Chem.* **2008**, *80*, 1055–1062. (g) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661. (h) Barnett, D. S.; Moquist, P. N.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 8679–8682.

(5) (a) Kennedy, J. W. J.; Hall, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587. (b) Yu, S. H.; Ferguson, M. J.; McDonald, R.; Hall, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 12808–12809. (c) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518–2519. (d) Hall, D. G. *Pure Appl. Chem.* **2008**, *80*, 913–927. (e) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481–8490.

(6) (a) Nowrouzi, F.; Thadani, A. N.; Batey, R. A. *Org. Lett.* **2009**, *11*, 2631–2634. (b) Matsuoka, H.; Kondo, K. *Tetrahedron Lett.* **2009**, *50*, 2320–2321. (c) Batey, R. A.; Thadani, A. N.; Smil, D. V.; Lough, A. J. *Synthesis* **2000**, 990–998. (d) Batey, R. A.; Thadani, A. N.; Smil, D. V. *Tetrahedron Lett.* **1999**, *40*, 4289–4292.

(7) (a) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340–6341. (b) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899.

(8) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017–7020.

(9) Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752–2753.

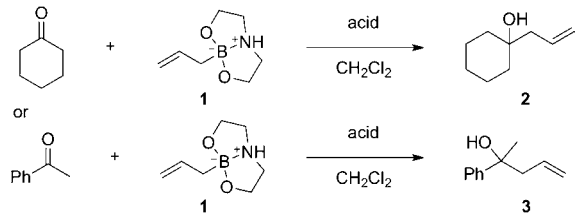
(10) Tietze, L. F.; Kinzel, T.; Brazel, C. C. *Acc. Chem. Res.* **2009**, *42*, 367–378.

10.1021/ol1020515
Published on Web 10/13/2010

N-protonated species by NMR spectroscopy.[11a] We sought to apply the activation modes developed by Hall and Corey to enhance the reactivity of allyloxazaborolidines.[5,12] Batey and Kondo have used a similar strategy to activate allyltrifluoroborates.[6] With an eye toward developing bench-stable reagents, we investigated allyldioxazaborolidines, which were first reported by Roush.[13] Allyldioxazaborolidine **1** is a white, crystalline solid that can be stored in the freezer for months with no noticeable decomposition[14] and appeared to be a promising precursor for an allyl transfer reagent.

Although at room temperature dioxazaborolidine **1** does not react with ketones, a variety of protic acids were found to activate this complex (Table 1). Triflic acid primarily led to the decomposition of reagent **1** (entry 1). Methanesulfonic acid aided the allylation of cyclohexanone but not acetophenone, possibly because acetophenone is less reactive toward allylation and the rate of allylation is slower than that of decomposition of **1**. Trifluoroacetic acid (TFA) provided both homoallylic alcohols **2** and **3** in excellent yields (entry 3). Weaker acids such as phenol and acetic acid also promoted the allylation of cyclohexanone, but with lower efficiency (entries 7 and 6). TFA was the most active promoter and was used for subsequent allylation reactions.

Table 1. Acid-Promoted Allyl Transfer with Allyl Dioxazaborolidine **1**



entry	acid[a,e]	pK_a[b]	yield of **2** (%)[c]	yield of **3** (%)[c]
1	TfOH	−15	0	0
2	CH_3SO_3H	−5.0	88	0
3	CF_3CO_2H	−0.25	95	98
4	BINPA	1.3	68	40[d]
5	$ClCH_2CO_2H$	2.9	70	38
6	CH_3CO_2H	4.8	85	28
7	PhOH	10	50	0

[a] Standard conditions: reaction scale, 1.0 mmol ketone. Concentration of **1** in CH_2Cl_2 was 0.5 M. Unreacted ketone was detected for low yielding reactions. Reactions were conducted at room temperature and were worked up after 6 h. Either 1.3 or 1.7 equiv of the acid and **1** were used for the reactions to form **2** and **3**, respectively. [b] Reported pK_a values were in water. [c] Isolated yield. [d] No enantioselectivity was observed. [e] TfOH = triflic acid. BINPA = (*S*)-(−)-1,1′binaphthyl-2,2′diyl hydrogenphosphate.

Kinetic studies were conducted to determine the influence of acid on the rate of allylation by monitoring reaction progress using ^{1}H NMR spectroscopy. The formation of **4** was observed under pseudofirst-order conditions to provide reaction rates as a function of TFA concentration (Figure 1). A plot of these rates against the concentration of TFA demonstrates that the reaction rate is first-order in TFA. The first-order dependence on TFA concentration is consistent with a simple protonation to activate dioxazaborolidine **1**.

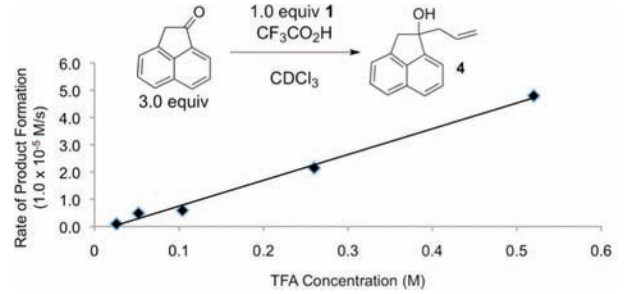
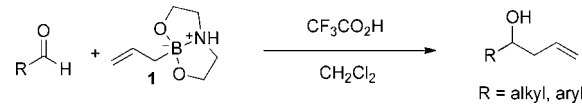
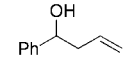
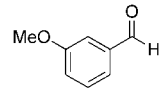
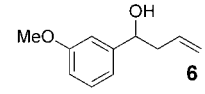
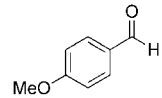
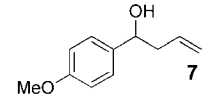
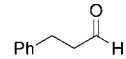
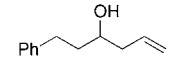
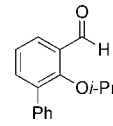
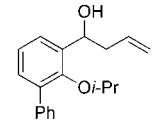


Figure 1. Relationship between rate of allylation and concentration of acid.

The activated reagent was first investigated with aldehydes. Allyl reagent **1**, when activated with TFA, affected the allylation of aldehydes to provide the corresponding secondary alcohols **5**−**9** in excellent yields (Table 2). The most efficient conditions required equal amounts of **1** and TFA.[15] The reaction with

Table 2. Allyl Transfer Reactions with Aldehydes



entry	aldehyde	equiv[a]	product	yield (%)[b]
1		1.1	 **5**	99
2		1.1	 **6**	95
3		1.5	 **7**	99
4		1.1	 **8**	91
5		1.5	 **9**	81

[a] Standard conditions: reaction scale, 1.0 mmol aldehyde. Concentration of **1** in CH_2Cl_2 was 0.5 M, and the ratio of TFA to **1** was 1:1. Reactions were conducted at room temperature and completed in 1−18 h. [b] Isolated yield.

(11) (a) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808–3809. (b) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388–6390. (c) Shibatomi, K.; Futatsugi, K.; Kobayashi, F.; Iwasa, S.; Yamamoto, H. *J. Am. Chem. Soc.* **2010**, *132*, 5625–5627.

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

(13) (a) Roush, W. R.; Grover, P. T. *J. Org. Chem.* **1995**, *60*, 3806–3813. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339–6348.

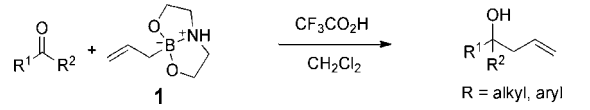
(14) Reagent **1** is stable for months in a −5 °C freezer. It can be weighed in air, but it will decompose into a yellow liquid if left open to the air for several days.

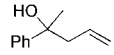
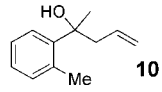
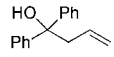
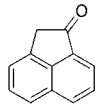
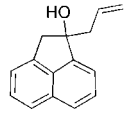
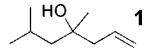
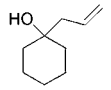
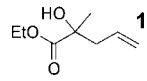
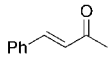
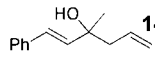
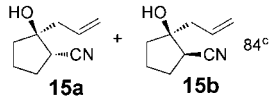
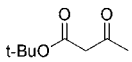
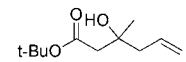
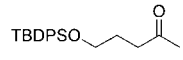
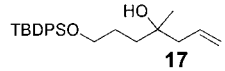
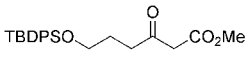
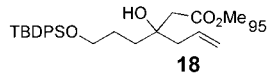
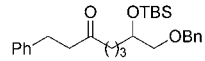
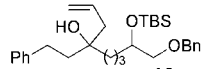
p-anisaldehyde (entry 3) was slower than with *m*-anisaldehyde (entry 2); this rate order disfavors a carbonyl protonation step in the reaction. Conveniently, all of the side products are water soluble, and a simple aqueous workup led to products with minimal impurities.

Allyl transfer to a variety of ketones using reagent **1** proceeded in good to excellent yields (Table 3). Acetophenone and benzophenone (entries 1 and 3) were less reactive in this system and required excess **1** and TFA to provide high yields of **3** and **11**. In general, aliphatic ketones required fewer equivalents of reagents (1.1−1.5 equiv). Allyl transfer to an α-keto ester (entry 7) provided **13** in excellent yield. Only 1,2-addition products were observed with α,*β*-unsaturated ketones (entry 8).[16] The acidic nature of the reaction conditions allowed for allyl transfer to enolizable ketones to provide products **15a**/**15b** and **16** (entries 9 and 10) that are not accessible using basic allylating agents. Although acidic, the reaction conditions were tolerant to silyl ether protecting groups (entries 11−13), and no deprotection was observed. The activated reagent is a highly effective allyl transfer reagent with a variety of aldehydes and ketones.

The activation strategy is also effective with substituted allyldioxazaborolidines. Crotyl reagents **20** and **21** were obtained in gram quantities following a literature procedure.[13b] The *Z*- and *E*-crotylations provided the α-methylhomoallylic alcohols in good yields and diastereoselectivities (Table 4). *Z*-Crotyl reagent **20** provided the *syn* diastereomers as the major products, while *E*-crotyl reagent **21** led to *anti* diastereoselectivity. These diastereoselectivities are consistent with a type I mechanism, where the crotyl group transfer occurs through a closed, six-membered transition state.[1]

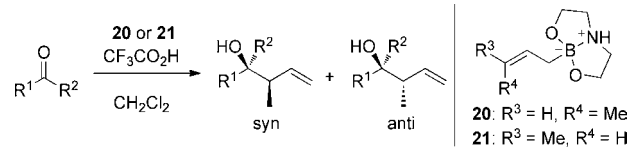
Table 3. Allyl Transfer Reactions with Ketones

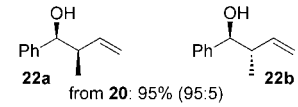
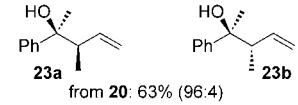
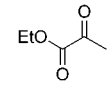
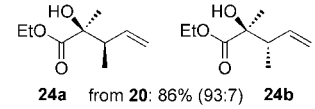


entry	ketone	equiv[a]	product	yield (%)[b]
1		1.7	 **3**	98
2		1.5	 **10**	99
3		2.0	 **11**	79
4		1.5	 **4**	99
5		1.5	 **12**	84
6		1.1	 **2**	99
7		1.1	 **13**	97
8		1.5	 **14**	86
9		1.5	 **15a** **15b**	84[c]
10		1.5	 **16**	99
11		1.5	 **17**	81
12		1.5	 **18**	95
13		1.5	 **19**	72[d]

[a] Standard conditions: reaction scale, 1.0 mmol ketone. Concentration of **1** in CH_2Cl_2 was 0.5 M, and the ratio of TFA to **1** was 1:1. Reactions were conducted at room temperature and completed in 12−18 h. [b] Isolated yield. [c] The dr of **15a**:**15b** was 1:1. [d] The diastereomers of **19** were formed in a 1:1 ratio.

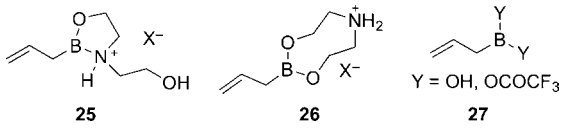
Table 4. Crotyl Tranfer to Aldehydes and Ketones Using Crotyl Dioxazaborolidine Reagents (*Z*)-**20** and (*E*)-**21**



entry	substrate	equiv[a]	products/yield[b] (dr)[c]
1		1.5	 **22a** **22b** from **20**: 95% (95:5) from **21**: 93% (5:95)
2		2.0	 **23a** **23b** from **20**: 63% (96:4) from **21**: 96% (3:97)
3		1.5	 **24a** from **20**: 86% (93:7) **24b** from **21**: 71% (2:98)

[a] Standard conditions: reaction scale, 1.0 mmol ketone. Concentration of **20** and **21** in CH_2Cl_2 was 0.5 M. The ratio of **20** or **21** and TFA was 1:1. Reactions were conducted at room temperature and completed in 16 h. [b] Isolated yield. [c] Diastereomeric ratios were determined by proton NMR of the crude reaction mixture.

The combination of the bench-stable allyl dioxazaborolidine **1** and TFA leads to a highly reactive allyl transfer reagent. The actual intermediate in the reaction has not been identified. The diastereoselective crotylations suggest a boron allyl transfer reagent with an open coordination site on the boron, and the reaction apparently proceeds through an organized six-membered ring transtion state. Figure 2 shows



25 **26** **27**

Figure 2. Possible allyl transfer reagent generated under the reaction conditions.

several possible trivalent boron reagents that might be responsible for the allyl transfer reaction. The first two reagents, **25** and **26**, would arise from protonation and decomplexation of an oxygen or a nitrogen from the boron center. The third class of reagent (**27**) would arise from decomplexation of the diethanolamine. Roush used the dioxazaborolidines to generate other boronate esters by exchange,[13] so this mode of activation is possible and perhaps likely with the less acidic promoters in Table 1 such as phenol. Allylboronic acid is a quite active allyl transfer reagent,[12] but it is unlikely to be responsible for most of the reactivity because the allylation reactions proceed equally well in the presence of 4 Å MS. Complexes **25**, **26**, and **27** are all plausible intermediates in the reaction.

Experiments to elucidate the mechanism of this system have been conducted, including monitoring reaction progress by ^{1}H, ^{11}B, and ^{13}C NMR spectroscopy. Unfortunately, only starting materials and products could be observed spectroscopically. The transition states for activated complexes **25** and **26** reacting with acetaldehyde were calculated using B3LYP/6-311G(d,p).[17] Computationally, oxazaborolidine **25** is predicted to be more reactive than dioxaborolane **26** by ca. 5.0 kcal/mol (Figure 3).[18] We will continue to evaluate the mechanism of the reaction.

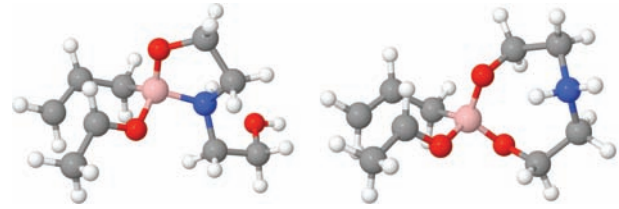


Figure 3. Calculated transitions states 1,3,2-oxazaborolidine from **25** (left) and 1,3,2,6-dioxazaborocane from **26** (right).[18]

This research has demonstrated the utility of allyldioxazaborolidine **1** as a stable, crystalline allyl transfer reagent for aldehydes and ketones. A variety of homoallylic alcohols were accessed in high yield with simple in situ activation by TFA. Crotylation reagents **20** and **21** provided the requisite α-methylhomoallylic alcohols in good yields and diastereoselectivities. Ongoing research is directed to developing enantioselective variants of this transformation.

Acknowledgment. This work was supported by the S. T. Li foundation and the Schering-Plough Research Institute.

Supporting Information Available: Characterization data and experimental procedures for all compounds described are included. Geometries for calculated TS are included. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1020515

(15) An excess of either allyl reagent **1** or TFA did not drive allylations to completion; an excess of both reagents was required to complete the reaction.

(16) Isomerization of the homoallylic alcohol to the more substituted olefin was observed in acid-sensitive products.

(17) Sakata, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 12519–12526.

(18) Calculated reaction profiles using the B3LYP/6-311G(d,p) level (ref 17) with Δ*G* (298 K) and unscaled ZPE. The 1,3,2-oxazaborolidine TS from **25** is about 5.0 kcal/mol lower in energy than the 1,3,6,2-dioxazaborocane TS from **26**.