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Preparation of Homoallylic Homopropargylic Alcohols from 2-Vinyloxiranes

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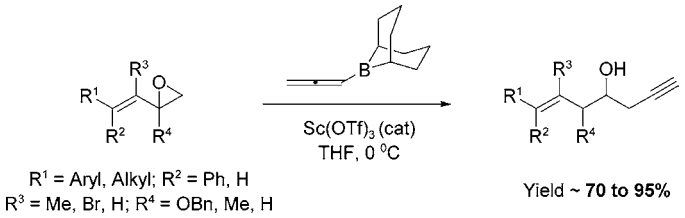
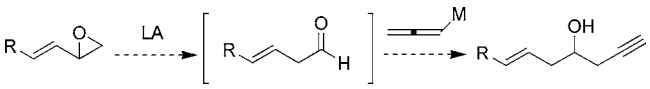
ABSTRACT



***β,γ*-Unsaturated aldehydes generated in situ by treatment of 2-vinyloxiranes with a catalytic amount of $Sc(OTf)_3$ or $BF{\cdot}OEt_2$ are effectively trapped by *B*-allenyl-9-BBN to afford homoallylic homopropargylic alcohols in high yield. An enantioselective version has been demonstrated, and a convenient synthesis of 9-allenyl-9-BBN is described.**

1,5-Enynes are valuable substrates for a variety of powerful reactions that afford useful structural motifs.[1] As a subset of this general class of molecules, homoallylic homopropargylic alcohols (Scheme 1) are interesting in that the intervening hydroxyl group can be used as a handle for further functionalization or as a stereochemical control element.[2] Such products have most often been prepared by ring opening of homoallylic epoxides with metalated alkyne nucleophiles.[3] An alternative approach, based on the addition of a propargyl fragment to β,γ-unsaturated aldehydes, has received little attention, presumably due to difficulties associated with their preparation.[4]

Scheme 1. General Approach to the Synthesis of Homoallylic Homopropargylic Alcohols



We have previously disclosed a high-yielding racemic protocol for the allylation or crotylation of various β,γ-unsaturated aldehydes generated by the treatment of 2-vinyloxiranes with a Lewis acid (LA).[4] Extension of this methodology to an asymmetric version in the case of

(1) For a general review, see: (a) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. For three typical applications, see: (b) Pauson−Khand reaction: Blanco-Urgoiti, J.; Anorbe, L.; Perez-Serrano, L.; Dominquez, G.; Perez-Castalls, J. *Chem. Soc. Rev.* **2004**, *33*, 6285. (c) Enyne metathesis: Driver, S. T.; Giessert, J. *Chem. Rev.* **2004**, *104*, 1317. (d) [4 + 2 + 2] cycloadditions: Evans, P. A.; Baum, E. W.; Fazal, A. N.; Pink, M. *Chem. Commun.* **2005**, 63 and references therein.

(2) For examples see: (a) Sato, F.; Urabe, H. *Tetrahedron Lett.* **1998**, *39*, 7329. (b) Casalnuovo, J. A.; Scott, R. W.; Harwood, E. A.; Schore, N. E. *Tetrahedron Lett.* **1994**, *35*, 1153. (c) Pagenkopf, B. L.; Lund, E. C.; Livinghouse, T. *Tetrahedron* **1995**, *51*, 4421. (d) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317.

(3) For examples, see: (a) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495. (b) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976. (c) Kim, H.; Choi, W. J.; Jung, J.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2003**, *125*, 10238. (d) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679. For alternative methods, see: (e) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2093. (f) Zacuto, M. J.; O'Malley, S. J.; Leighton, J. L. *Tetrahedron* **2003**, *59*, 8889. (g) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (h) Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819.

(4) Lautens, M.; Ouellet, S. G.; Raeppel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 4079.

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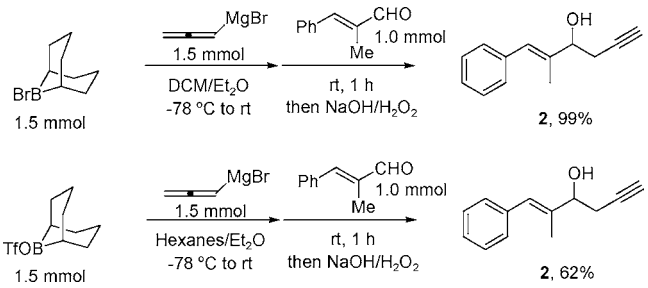
Published on Web 07/06/2005

Scheme 2. In Situ Generation and Reaction of *B*-Allenyl-9-BBN



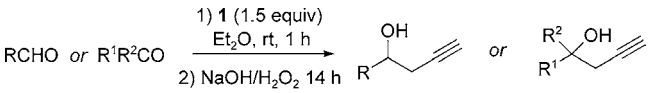
allylation afforded bishomoallylic alcohols as either antipode in excellent yield.[5] We speculated that this approach might be modified to allow for propargylation of the in situ-generated electrophiles (Scheme 1).[6] This would improve the general utility of employing 2-vinyloxiranes as surrogates to β,γ-unsaturated aldehydes and afford a versatile route to an important class of substrates due to the ready availability of the starting materials. Moreover, compared to our earlier accounts on allylation,[4,5] the products would have clearly differentiated π-systems useful for further elaboration. In this report, we describe the successful realization of this objective, allowing efficient access to homoallylic homopropargylic alcohols.

There are numerous methods to effect the propargylation of aldehydes that utilize various allenyl- or propargylorgano-metallics.[7] Our previous success of boron-based allylation and crotylation[4,5] protocols suggested that *B*-allenyl-9-BBN[7a,b] (**1**) might offer the most promise to effect the desired transformation (Scheme 1). This reagent (**1**) is known[7a,b] to be highly reactive and importantly exhibits excellent selectivity in favor of the homopropargylic product.

B-Allenyl-9-BBN is synthesized[7b] in high yield from *B*-chloro-9-BBN[8] and allenylmagnesium bromide.[9] However, in our hands, *B*-chloro-9-BBN proved to be inconvenient to synthesize due to the numerous manipulations of very sensitive compounds required. We speculated that either the commercially available (Aldrich) *B*-bromo-9-BBN or 9-BBN triflate might be a suitable substitute and allow for an expedient synthesis of this reagent (**1**).

Solutions of *B*-bromo-9-BBN (1 M in CH_2Cl_2) or 9-BBN triflate (0.5 M in hexanes) were treated with 1 equiv of freshly prepared allenylmagnesium bromide (~0.8 M in Et_2O) and stirred for 2 h at −78 °C. After warming to room temperature, analysis by ^{11}B NMR indicated formation of **1** (δ 79 ppm, >90% purity by ^{11}B NMR) in both cases. Addition of α-methyl-*trans*-cinnamaldehyde to the heterogeneous mixtures gave the desired propargylated product **2** in good yield (Scheme 2). In particular, this was especially true for *B*-allenyl-9-BBN derived from *B*-bromo-9-BBN. We note that none of the corresponding allenic alcohol was observed in the ^1H NMR spectrum of the crude reaction mixture.

Table 1. Propargylation of Representative Carbonyl Compound[a]



2 - 10

entry	substrate	no.	yield (%)[b]
1	α-methyl-*trans*-cinnamaldehyde	2	99
2	PhCHO	3	96
3	CyCHO	4	91
4	4-methoxybenzaldehyde	5	99
5	4-nitrobenzaldehyde	6	94
6	acetophenone	7	97
7	cyclopentanone	8	88
8	cyclohexanone	9	94
9	pinacolone	10	88

[a] All reactions were performed on a 1.6 mmol scale. [b] Isolated yield.

Neat *B*-allenyl-9-BBN, free from magnesium salts, is easily prepared on a large scale from *B*-bromo-9-BBN by drying crude **1** under high vacuum, filtration under nitrogen using pentane, followed by removal of the solvent. Addition of ether affords solutions that can be utilized directly to effect propargylation of a wide variety of aldehydes (Table 1, entries 1−5) and ketones (Table 1, entries 6−9) in excellent yield. Distillation of **1** is not required, and in no cases (Table 1, entries 1−9), even with pinacolone (Table 1, entry 9), were any of the corresponding allenic alcohols observed. These results are fully consistent with those previously reported with purified *B*-allenyl-9-BBN synthesized from *B*-chloro-9-BBN.[7a,b]

Attention was then focused on finding suitable conditions compatible with the rearrangement of 2-vinyloxiranes to β,γ-unsaturated aldehydes. Optimization studies were performed using the vinyl epoxide derived from α-methyl-*trans*-cinnamaldehyde (**11**). Attempts to apply the in situ developed conditions (Scheme 2) failed under all circumstances, which was consistent with prior results where magnesium salts were observed to interfere.[5,10] However, salt-free etheral solutions of **1** gave the desired product (**12**) in reasonable yields (55%) with $Sc(OTf)_3$ (7.5 mol %). We were unable to improve the yield by modification of any of the reaction parameters in this solvent. THF solutions of **1** displayed an ^{11}B NMR resonance at δ 16 ppm, suggesting that *B*-allenyl-9-BBN exists predominantly as a THF adduct. Whereas coordination

(5) Lautens, M.; Maddess, M. L.; Sauer, E. L. O.; Ouellet, S. G. *Org. Lett.* **2002**, *4*, 83.

(6) A similar indium-mediated transformation has been developed by Pae that includes a few examples for synthesis of homoallylic homopropargylic alcohols, albeit as mixtures of addition products; see: Oh, B. K.; Cha, J. H.; Cho, Y. S.; Choi, K. I.; Koh, H. Y.; Chang, M. H.; Pae, A. N. *Tetrahedron Lett.* **2003**, *44*, 2911.

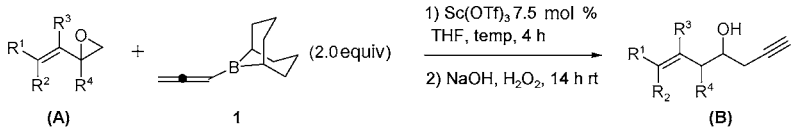
(7) See references cited in the following works: (a) Brown, H. C.; Khire, U. R.; Racherla, U. S. *Tetrahedron Lett.* **1993**, *34*, 15. (b) Brown, H. C.; Khire, U. R.; Narla, G.; Racherla, U. S. *J. Org. Chem.* **1995**, *60*, 544.

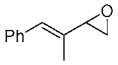
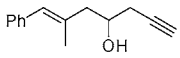
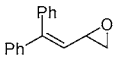
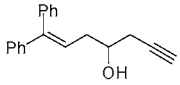
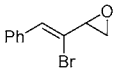
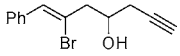
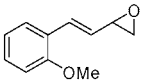
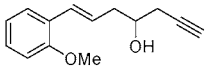
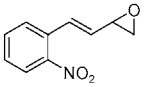
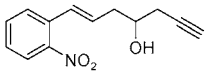
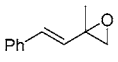
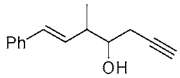
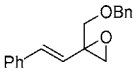
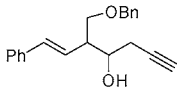
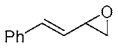
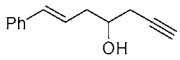
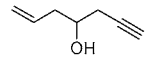
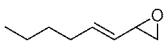
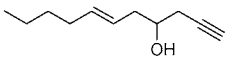
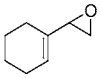
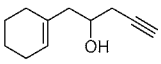
(8) (a) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (b) Brown, H. C.; Ravindran, N.; Kulkarni, S. U. *J. Org. Chem.* **1979**, *44*, 1979. (c) Kramer, G. W.; Brown, H. C. *J. Organomet. Chem.* **1974**, *73*, 1 (d) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *79*, 281.

(9) Hopf, H.; Bohm, I.; Kleinschroth, J. *Org. Synth.* **1982**, *60*, 41.

(10) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

Table 2. Substrate Scope[a]



entry	substrate		temp (°C)	product			
	A	structure		B	structure	Yield (%)[b]	dr
1	**11**		0 (20)[c]	**12**		77 (78)[c]	
2	**13**		0	**14**		93	
3	**15**		0 (20)[c]	**16**		83 (70)[c]	
4	**17**		0	**18**		77	
5	**19**		0 (20)[c]	**20**		98 (22)[c]	
6	**21**		0	**22**		70	~1.2:1
7	**23**		0	**24**		89	~1:1[e]
8	**25**		0 (20)[c]	**26**		73 (73)[c]	
9	**27**		0	**28**		62	
10	**29**		0	**30**		71[d]	
11	**31**		0	**32**		76[d]	

[a] All reactions were performed with the slow addition of the oxirane over 40 min on a 1.0 mmol scale unless otherwise noted. [b] Isolated yields. [c] $BF_3{\cdot}OEt_2$ (15 mol%) added to a mixture of vinyl oxirane and *B*-allenyl-9-BBN. [d] Minimum yield reported, product isolated as the TBS ether. [e] Diastereomers separable by flash chromatography.

of this type has been noted to significantly reduce the reactivity of similar reagents,[11] THF was found to give far superior results with regard to application to 2-vinyloxiranes.

Of the various Lewis acids screened, $Sc(OTf)_3$ and $BF_3{\cdot}OEt_2$ gave the highest and roughly equal yields of product, with the former reagent performing slightly better. In general, reaction was rapid at 0 °C and usually complete after 1 h.[12] To ensure complete conversion, reaction times of 4 h and 2 equiv[13] of *B*-allenyl-9-BBN were used. A slow addition of the 2-vinyloxirane was found to improve the yield by approximately 10%, and thus this protocol was used to examine the reaction scope (Table 2).

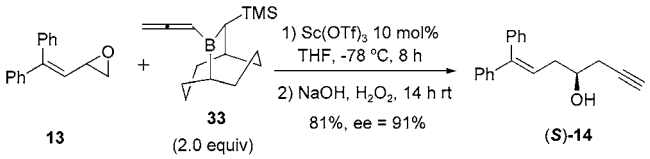
The optimized conditions for **11** translated very well for a variety of either aromatic or aliphatic substrates (Table 2). As seen for the model 2-vinyloxirane (**11**), the protocol employing $Sc(OTf)_3$ gave the highest yields. However, aside from the nitro-aromatic substrate (**19**), $BF_3{\cdot}OEt_2$ is a useful substitute (Table 2, entries 1, 3, 5, and 7). There was no noticeable difference in reactivity for electron-rich versus electron-poor systems, and we were particularly pleased to observe that even the vinyl bromide **15** gave a good yield

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

(12) It is not recommended that reaction times extend past 4 h since THF is observed to polymerize slowly under the reaction conditions, making workup problematic.

(13) THF solutions of **1** were estimated to be approximately 0.8 M after dilution with a volume calculated from the crude mass to afford a 1.0 M solution. There was no noticeable improvement in yield in the optimization studies between 1.5 and 2.0 equiv of **1**.

Scheme 3. Asymmetric Propargylation

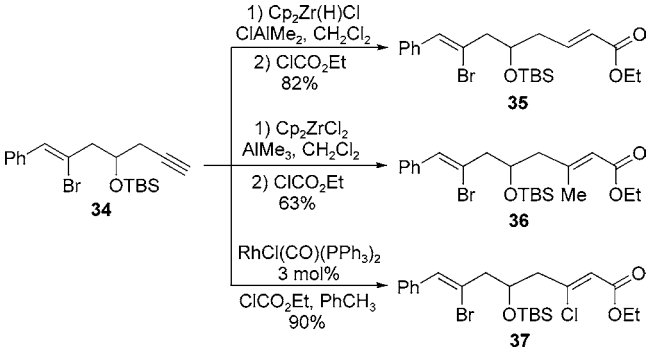


of the desired product **16** since this substrate had been previously unreactive in the allylation chemistry (Table 2, entry 3).[5] 2-Vinyloxiranes substituted at the 2-position also gave the desired products in high yield. However, no diastereoselectivity was observed even when an additional chelating moiety was present (Table 2, entries 6 and 7).

To extend the utility of this transformation by rendering it enantioselective, we selected the recently disclosed 10-TMS-9-borabicyclo[3.3.2]decanes (**33** and ***ent*33**) by Soderquist,[14] given the close analogy and success of the *B*-allenyl-9-BBN reagent in this system. With a representative 2-vinyloxirane (**13**), we observed that under slightly modified conditions **33** gave the desired homoallylic homopropargylic alcohol (**14**) in good yield and high enantioselectivity (Scheme 3). The absolute stereochemistry was assigned according to Soderquists' model,[14,15] and this was confirmed to be consistent with Browns' model for asymmetric allylation by partial reduction of (***S*)-14** to the corresponding bishomoallylic alcohol.[16] Both antipodes are conveniently available by suitable choice of the 10-TMS-9-borabicyclo-[3.3.2]decanes.[14]

We demonstrated the ability to differentiate the π-systems under a variety of conditions[17] (Scheme 4) to provide access to α,β-unsaturated esters (**35**−**37**). These enoates (**35**−**37**) are structurally similar to fragment A of the cryptophycins[18]

Scheme 4. Homologation of the Terminal π-System



and may be useful for the rapid construction of analogues of these interesting and pharmacologically active natural products.

In summary, a convenient synthesis of *B*-allenyl-9-BBN has been developed and applied to the propargylation of simple aldehydes and ketones. Extension to in situ-formed β,γ-unsaturated aldehydes affords homoallylic homopropargylic alcohols in good yield and is applicable to a wide variety of 2-vinyl epoxides. Such products have clearly differentiated π-systems for further structural elaboration and are available in enantiomerically enriched form. Application of this methodology to the synthesis of the cryptophycins is underway.

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Supporting Information Available: Representative experimental procedures, as well as full characterization of all novel compounds and related intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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