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Enantioselective Allylation of β,γ-Unsaturated Aldehydes Generated via Lewis Acid Induced Rearrangement of 2-Vinyloxiranes

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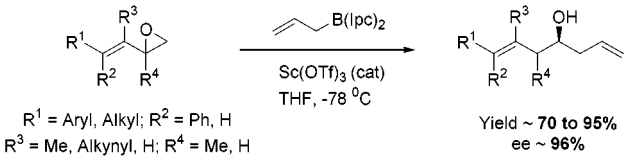
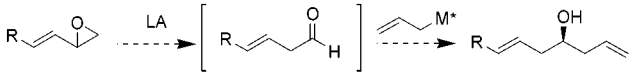
ABSTRACT



2-Vinyloxiranes have been found to be excellent surrogates to β,γ-unsaturated aldehydes. These valuable electrophiles, generated in situ by treatment of a 2-vinyloxirane with a catalytic amount of $Sc(OTf)_3$, are effectively trapped by the chiral allylating agents based on α-pinene, affording bishomoallylic alcohols in high yield and excellent selectivity.

β,γ-Unsaturated aldehydes have rarely been used as building blocks in synthetic organic chemistry, presumably due to their very low stability with respect to olefin isomerization.[1,2] As such, the potential utility of these substrates as electrophiles remains largely unexplored. One practical solution to this instability is to form and react the β,γ-unsaturated aldehyde in situ; a few strategies have been reported along these lines.[3,4] We recently disclosed[5] a high-yielding protocol for the allylation or crotylation of various β,γ-unsaturated aldehydes, generated by the treatment of 2-vinyloxiranes with a Lewis acid (LA). To extend the synthetic utility of this methodology, we sought to develop an asymmetric version of this transformation (Scheme 1). In this report we describe the successful realization of this objective, allowing ready access to enantiomerically enriched bishomoallylic alcohols.

Scheme 1. Enantio-Strategy for Preparation of Chiral Bishomoallylic Alcohols



We initiated our studies by examining the use of chiral allylboron compounds[6] as nucleophiles. This approach

(1) For examples, see: (a) Saha, G.; Basu, M. K.; Kim, S.; Jung, Y.; Adiyaman, Y.; Powell, W. S.; FitzGerald, G. A.; Rokach, J. *Tetrahedron Lett.* **1999**, *40*, 7179. (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (c) Paquette, L. A.; Braun, A. *Tetrahedron Lett.* **1997**, *38*, 5119. (d) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (e) Ahmar, M.; Bloch, R.; Mandville, G.; Romain, I. *Tetrahedron Lett.* **1992**, *33*, 2501.

(2) (a) Bachmann, W. E.; Horwitz, J. P.; Warzynshi, R. J.*J. Am. Chem. Soc.* **1953**, *75*, 3268. (b) Serramedan, D.; Marc, F.; Pereyre, M.; Filliatre, C.; Chabardes, P.; Delmond, B. *Tetrahedron Lett.* **1992**, *33*, 4457. (c) Marc, F.; Soulet, B.; Serramedan, D.; Delmond, B. *Tetrahedron* **1994**, *50*, 3381.

(3) (a) Hertweck, C.; Boland, W. *J. Org. Chem.* **2000**, *65*, 2458. (b) Bideau, F. L.; Gilloir, F.; Nilsson, Y.; Aubert, C.; Malacria, M. *Tetrahedron* **1996**, *52*, 7487.; (c) Wipf, P.; Xu, W. *J. Org. Chem.* **1993**, *53*, 825.

(4) For an alternative to the use of β,γ-unsaturated aldehydes, see: Hughes, G.; Lautens, M.; Wen, C. *Org. Lett.* **2000**, *2*, 107.

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

(6) Roush, W. R. *Methods of Organic Chemistry (Houben-Weyl) 4th Edition*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag Stuttgart; New York; 1995; Vol. E21b, pp 1410−1486.

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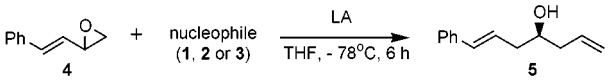
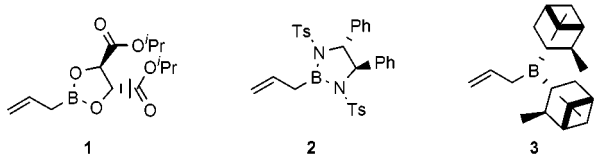
seemed especially promising since as a result of the empty p-orbital at the boron atom, these species are also Lewis acidic. We reasoned this feature could remove the need for an external LA since the nucleophile could play the dual role of ring opening the oxirane *and* effecting allylation. The reagents developed by Roush[7] (**1**), Corey[8] (**2**), and Brown[9] (**3** produced from (*R*)-(+)-α-pinene, or ***ent*-3** from (*S*)-(−)-α-pinene), were prepared according to literature procedures and reacted with our test substrate, 2-styryl-oxirane (**4**). A summary of the results is presented in Table 1.

Table 1. Effect of the Nucleophile[a]



entry	nucleophile (equiv)	LA (mol %)	yield (%)	ee (%)[e]
1	**1** (1.5)		40	27
2	**1** (1.5)	$BF_3{\cdot}OEt_2$ (30)	70	47
3	**2** (1.5)	$BF_3{\cdot}OEt_2$ (30)	33[b]	37
4	**3** (2.3)	$BF_3{\cdot}OEt_2$ (20)	48[b,c]	93
5	**3** (2.3)	$BF_3{\cdot}OEt_2$ (20)	80[b,d]	96

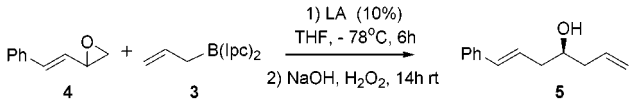
[a] All reactions performed by slow addition of the oxirane over 1 h. [b] HPLC yield. [c] NH_4Cl workup. [d] $NaOH/H_2O_2$ workup. [e] Determined by HPLC.



Roush's reagent (**1**) was studied extensively, and the results reported are the best following optimization studies. Of the three boron-based allylating agents, **1** was the only one to effect ring opening without the addition of an external LA (Table 1, entry 1). However, both the yield and selectivity of the bishomoallylic alcohol **5** were improved by the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 2). Corey's allylating reagent (**2**) was briefly examined, but provided inferior results for our system (Table 1, entry 3) and was significantly more difficult to prepare then the tartrate-based allylboron compound **1**. Consequently, our focus shifted to Brown's reagent (**3**), and initial studies were performed using the commercially available precursors $(MeO)B(Ipc)_2$ or DIPCl (Aldrich) to prepare the active trialkyl reagent (either **3** or ***ent*-3**) in situ. When combined with a LA and treated with the vinyloxirane (**4**), the reaction originating from $(MeO)B(Ipc)_2$ failed to give any product whatsoever and primarily starting material was recovered. Alternatively, reactions that employed Brown's reagent (**3**) prepared from DIPCl were very promising, but surprisingly inconsistent. In both cases the presence of the magnesium salts significantly complicated the reaction mixture, and notably (MeO)MgBr has been previously reported to retard the reaction rate and lower the ee.[9] Thus, Brown's reagent (**3**) was prepared salt free according to a published report[9] from basic starting materials. Although this procedure requires careful manipulation, once prepared **3** may be stored for more than 1 month as a solution in THF.[10] The initial results were very satisfying, and the observed selectivity was excellent (Table 1, entries 4 and 5).

A variety of Lewis acids were examined (Table 2), and

Table 2. Effect of the Lewis Acid[a]



entry	LA	yield (%)[b]	ee (%)[b]	note
1	$Sm(OTf)_3$	28	96	incomplete
2	$SnCl_4$	18	83	
3	Ag(OTf)	33	94	incomplete
4	$Y(OTf)_3$	65	96	incomplete
5	$Sc(OTf)_3$	92	96	
6	$BF_3{\cdot}OEt_2$	59	96	incomplete

[a] All reactions performed by slow addition of the oxirane over 1 h to a solution of **3** (2.3 equiv) and LA (10%) in THF at −78 °C (0.34 mmol scale). [b] Yield and ee determined by HPLC. Absolute configuration predicted by analogy.[12]

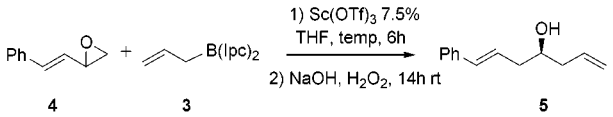
all gave the desired product (**5**) with comparable levels of induction with the exception of $SnCl_4$ (Table 2, entry 2) where a slightly reduced ee was observed. By far, the cleanest and highest yielding reaction was obtained with $Sc(OTf)_3$ (Table 2, entry 5). The majority of the other Lewis acids suffered from incomplete conversion (Table 2, entries 1, 3, 4, and 6) or caused decomposition of the vinyloxirane. Although the use of $BF_3{\cdot}OEt_2$ is economically attractive for large-scale work, decomposition (Table 1, entry 5) or incomplete conversion (Table 2, entry 6) resulted in lower isolated yields. As a control experiment, (MeO)MgBr[11] (2.3 equiv) was added to "salt free" **3** along with $Sc(OTf)_3$ (7.5 mol %). In analogy with the failure of the one-pot reaction from commercially available $(MeO)B(Ipc)_2$, only starting material (**4**) was recovered.

A brief examination of reaction stoichiometry showed that the ee remained constant but the best yield was obtained with 2.3 equiv of the allylation agent (**3**) and 7.5−10 mol % of $Sc(OTf)_3$. Examination of the effect of varying the temperature (Table 3) indicated that the ee remained above 90% (Table 3, entries 1−3) as long as the reaction was kept < -50 °C. Even at room temperature the level of selectivity was good (ee = 86%) (Table 3, entry 5).

(7) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.
(8) Corey, E. J.; Yu, C.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.
(9) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

(10) Solution stored in a Wheaton bottle at −20 °C to ensure consistency. It is highly recommended that the methanol be freshly distilled from magnesium and iodine.
(11) This magnesium salt was obtained from drying the filtrate from the synthesis of **3** under high vacuum for 12 h.

Table 3. Effect of Temperature[a]

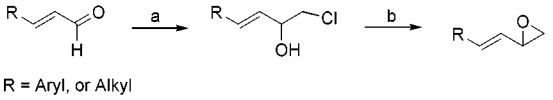


entry	temp (°C)	yield (%)[a]	ee (%)[a]
1	−96	94	>98
2	−78	96	97
3	−50	100	95
4	0	100	89
5	20	100	86

[a] All reactions performed by slow addition of the oxirane over 1 h to a solution of **3** (2.3 equiv) and LA (7.5%) in THF (0.34 mmol scale). [b] Yield and ee determined by HPLC. Absolute configuration predicted by analogy.[12]

We next prepared a series of 2-vinyloxiranes through the two-step sequence described by Matteson[13] (Scheme 2). In most cases, careful purification of the chlorohydrin intermediates allowed the desired epoxides to be isolated in high yield and purity after a simple aqueous wash. This approach was advantageous, as purification of these often-sensitive epoxides could be avoided. When purification was required,[14] the isolated chemical yield was typically sacrificed in order to obtain the desired 2-vinyloxiranes free from the original impurities and decomposition products that arise during their purification.

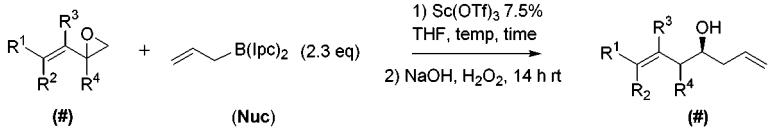
Scheme 2. Approach to Synthesis of 2-Vinyloxiranes[a]



[a] (a) $ClCH_2I$ (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C, ∼1 h; (b) NaH (95%, 1.1 equiv), NaI (10%), THF, 0 °C, ∼1 h.

In general, both the yield and enantiomeric excess for most of the substrates were excellent (Table 4). Either antipode[12] of the desired bishomoallylic alcohols is readily available (Table 4, entries 1 versus 2) depending on whether Brown's reagent was synthesized from (*R*)-(+)- or (*S*)-(−)-α-pinene (i.e., use of **3** versus ***ent*-3**). 2-Vinyloxiranes of moderate reactivity (Table 4, entries 1−3, 8−10, and 11) gave the best yields with no appreciable difference between aryl or alkyl substituents. It appears that a balance between stabilization of the proposed carbocation intermediate and the propensity for the requisite 1,2-hydride shift to occur is responsible. Electron rich substrates (Table 4, entry 5) were very reactive toward ring opening but gave lower yields in the carbonyl addition with the remainder of the mass balance being decomposition products. This is potentially explained as a consequence of an increased lifetime for the carbocation intermediate. On the other hand, electron poor substrates (Table 4, entries 4, 6, and 7) were much more sluggish to react. However, with extended reaction times the *o*-nitro product (***ent*-13**) was available in high yield and excellent enantioselectivity (Table 4, entry 7 versus 6). A vinyloxirane with a bromo substituent α to the epoxide (**8**) failed to react (Table 4, entry 4) except when $BF_3{\cdot}OEt_2$ at significantly higher loadings of the LA (1.1 equiv versus 7.5%) was employed. The ee of **9** was high (90%), but the yield was poor (17%) due to significant decomposition under these

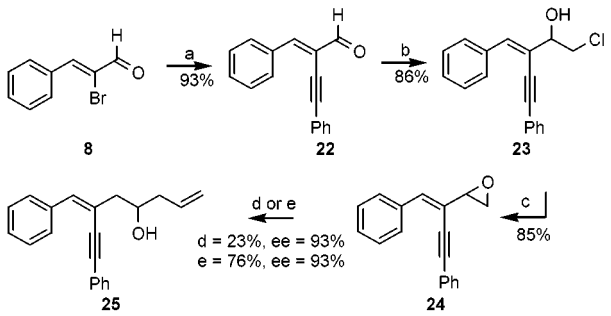
Table 4. Substrate Scope[a]



	substrate								product		
entry	no.	R^1	R^2	R^3	R^4	**Nuc**	temp (°C)	time (h)	no.	yield (%)[b]	ee (%)[c]
1	**4**	Ph	H	H	H	**3**	−78	6	**5**	88 (92)[d]	96
2	**4**	Ph	H	H	H	***ent*-3**	−78	6	***ent*-5**	96[d]	96
3	**6**	Ph	H	Me	H	**3**	−78	6	**7**	83	96
4	**8**	Ph	H	Br	H	**3**	−78	6	**9**	SM	
5	**10**	*o*-(MeO)C_6H_4	H	H	H	**3**	−78	6	**11**	68	96
6	**12**	*o*-(NO_2)C_6H_4	H	H	H	**3**	−78	6	**13**	35	96
7	**12**	*o*-(NO_2)C_6H_4	H	H	H	***ent*-3**	−78, then −70	4, then 36	***ent*-13**	88	96
8	**14**	Ph	Ph	H	H	**3**	−78	6	**15**	94	95
9	**16**[15]	Ph	H	H	Me	**3**	−78	6	**17**	92	>95,[e] de ∼0
10	**18**	$CH_3(CH_2)_4$	H	H	H	**3**	−78	6	**19**	80	97[f]
11	**20**	R^1 to $R^3 = (CH_2)_4$, R^2 and R^4 = H				**3**	−78	6	**21**	92	96[f]

[a] All reactions performed by the slow addition of the oxirane over 1 h on a 0.34−0.68 mmol scale. [b] Yields are isolated yields. [c] ee determined by chiral HPLC against racemic material.[5] [d] HPLC yield. [e] ee of both diastereomers greater than 95, inseparable. [f] ee determined by chiral GC. Absolute configuration predicted by analogy.[12]

Scheme 3. Palladium-Catalyzed Cross Coupling−Allylation Sequence[a]



[a] $Pd(PPh_3)_4$ (5%), CuI (10%), THF/Et_3N (1:1), rt, 3 h. [b] $ClCH_2I$ (1.5 equiv), *n*-BuLi (1.5 equiv), THF, −78 °C, 1 h. [c] NaH (95%, 1.1 equiv), NaI (10%), THF, 0 °C, 2 h. [d] (1) ***ent*-3** (2.3 equiv), $Sc(OTf)_3$ (7.5%), THF, −78 °C, 6 h; (2) 3 N NaOH, 30% H_2O_2, rt, 14 h. [e] (1) ***ent*-3** (2.3 equiv), $Sc(OTf)_3$ (7.5%), THF, −78 °C, 4 h, −70 °C 36 h; (2) 3 N NaOH, 30% H_2O_2, rt, 14 h.

conditions. It is possible to perform a palladium cross coupling reaction as a first step and subsequently carry the intermediate on to a bishomoallylic alcohol (**25**) (Scheme 3).

Finally, a 2-vinyloxirane substituted at the 2-position (**16**) performed very well, giving the desired products in high yield and excellent selectivity (Table 4, entry 9). No control over the α-methyl stereocenter was observed, and a nearly 1:1 mixture of diastereomers (inseparable) was isolated (**17**). Our current studies are focused on addressing this issue.

In conclusion, we have shown that 2-vinyloxiranes are excellent surrogates for β,γ-unsaturated aldehydes in the preparation of bishomoallylic alcohols. These valuable electrophiles, generated in situ by treatment of a 2-vinyloxirane with a catalytic amount of $Sc(OTf)_3$, are effectively trapped by chiral allylating agents based on α-pinene, affording the products in high yield and excellent selectivity. The reaction is highly versatile and allows access to a useful class of products that would be difficult to synthesize by other means. Mechanistic details, further examples, and applications will be reported in due course.

Acknowledgment. We thank Merck Frosst Canada, the Ontario Research and Development Challenge Fund (ORDCF), NSERC (Canada), and the University of Toronto for financial support of this work. M.M. thanks NSERC (Canada) for financial support in the form of a postgraduate fellowship.

Supporting Information Available: Representative experimental procedures, and full characterization of all novel compounds within **4**−**25** as well as related intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The absolute configuration may be predicted from analogy with previous results. **3** is known to give si face attack while ***ent*-3** provides the enantiomer. See: (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092; (b) Vulpetti, A.; Gardner, M.; Gennari, C.; Bernardi, A.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1993**, *58*, 1711.

(13) Sadhu, K. M.; Matteson, D. S. *Tetrahedron Lett.* **1986**, *27*, 795.

(14) When necessary the 2-vinyloxiranes may be purified by distillation or in some cases flash chromatography (5% Et_3N, EtOAc/Hex).