Article

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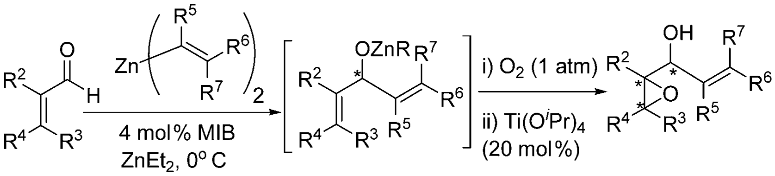

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Highly Enantio- and Diastereoselective One-Pot Synthesis of Acyclic Epoxy Alcohols and Allylic Epoxy Alcohols

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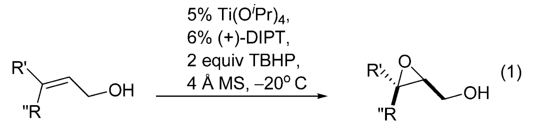
Abstract: In this report, we outline a highly enantio- and diastereoselective one-pot method for the efficient synthesis of synthetically useful acyclic epoxy alcohols and allylic epoxy alcohols. Our method takes advantage of a highly enantioselective C−C bond-forming reaction to set the initial chirality. The resulting allylic zinc alkoxide intermediate is then epoxidized in situ using either dioxygen or TBHP in the presence of a titanium tetraalkoxide. Epoxy alcohols with up to three contiguous stereocenters are formed in one pot with excellent enantio- and diastereoselectivity. In cases where the zinc alkoxide intermediates contain two different allylic olefins, the more electron-rich double bond is chemoselectively epoxidized to afford an allylic epoxy alcohol. This method represents a highly efficient, stereoselective, and chemoselective approach to the synthesis of a wide range of useful epoxy alcohol and allylic epoxy alcohol products that were previously difficult to access.

Introduction

Enantioenriched epoxy alcohols are among the most versatile and utile intermediates in asymmetric organic synthesis. These substrates readily undergo regio- and stereoselective ring-opening reactions with a wide array of nucleophiles. As a result, they have been employed frequently in the synthesis of natural and non-natural products. Much interest has been shown, therefore, in developing regio- and stereoselective synthetic methods for this class of compounds.[1,2]

Currently, the asymmetric epoxidation introduced by Sharpless and Katsuki, is the foremost method for synthesizing epoxy alcohols from prochiral allylic alcohols (eq 1).[3−7] The Sharpless−Katsuki asymmetric epoxidation employs catalytic titanium tetraisopropoxide, tartrate ester ligands, 4 Å molecular sieves, and *tert*-butyl hydroperoxide (TBHP) in the construction of enantioenriched epoxy alcohols. The ability to efficiently synthesize these useful chiral building blocks led to new synthetic disconnections and, thereby, transformed the approaches taken to synthesize natural products, making it one of the most useful reactions in organic synthesis.



In contrast to the synthesis of epoxy alcohols from prochiral allylic alcohols (eq 1), the synthesis of epoxy alcohols containing a stereogenic center at the carbinol carbon from achiral materials requires that three contiguous stereocenters be generated diastereo- and enantioselectively. An alternative approach is, therefore, required to achieve this challenging goal. This transformation is currently performed in a two-step process involving synthesis, isolation, and purification of the enantioenriched allylic alcohol, followed by a directed epoxidation.[8]

A widely used method for the synthesis of enantioenriched epoxy alcohols with three contiguous stereocenters is the Sharpless kinetic resolution (KR) (eq 2); however, this method has significant limitations.[9−11] As with all kinetic resolutions, the isolated yield of the epoxy alcohol product can be no greater than 50%, and in most cases, it is significantly less.[12] This transformation is performed on a racemic allylic alcohol, and the resulting enantioenriched starting material and the epoxy alcohol product must be separated by column chromatography. To obtain the epoxy alcohol with high ee, the reaction must be quenched at low conversion, because the ee of the epoxy alcohol decreases over the course of the KR.[13] The epoxy alcohol is, therefore, not usually obtained directly from the Sharpless KR; rather, the enatioenriched allylic alcohol is first isolated.[1] After purification, the allylic alcohol is subjected to a directed

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(1) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993.
(2) Helmchen, G., Hoffmann, R. W., Muler, J., Schaumann, E., Eds. *Methods of Organic Chemistry*; Thieme: New York, 1995; Vol. E.
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(9) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem.* Soc. **1987**, *109*, 5765−5780.
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(11) McKee, B. H.; Kalantar, T. H.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 6966−6968.
(12) Katsuki, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, NY, 2000, pp 287−325.
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Scheme 1. Diasteromeric Epoxidation Transition States for the Titanium-Peroxide Catalyst

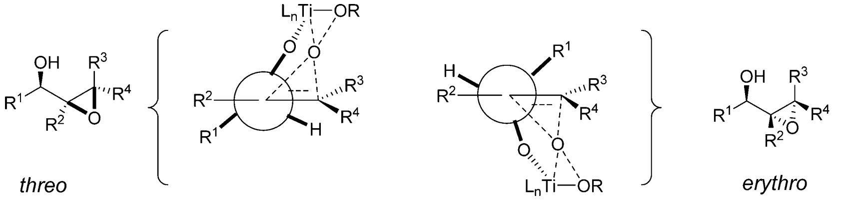
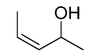
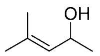
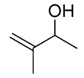
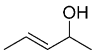
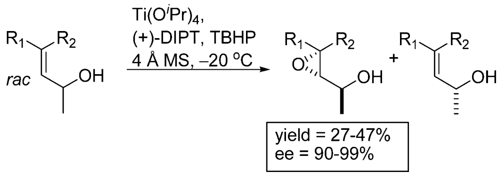


Table 1. Diastereomeric Ratios for the Directed Epoxidation of Chiral Secondary Allylic Alcohols with Various Oxidizing Agents[14]

		Diastereomeric Ratios (*erthyro : threo)*		
Entry	Substrate	$Ti(O^iPr)_4$ *t*-BuOOH	$VO(acac)_2$ *t*-BuOOH	*m*CPBA
1		1 : 10	1 : 2.4	1 : 19
2		1 : 19	1 : 6.1	1 : 19
3		3.5 : 1	19 : 1	1.2 : 1
4		1 : 1.9	2.4 : 1	1 : 1.8

epoxidation to yield the desired epoxy alcohol. The lack of efficient methods for the synthesis of this class of epoxy alcohols has prevented their widespread implementation as key intermediates in organic synthesis.



(2)

Epoxidation of the isolated enantioenriched secondary allylic alcohols is generally performed using an organic peracid, such as *meta*-chloroperbenzoic acid (*m*CPBA), or with a transition-metal catalyst in combination with a stoichiometric oxidant.[8] Good to excellent diastereoselectivities have been achieved with cyclic allylic alcohols using a wide range of oxidizing agents. Acyclic allylic alcohols have proven to be a more synthetically challenging class of chiral building blocks, because the increased conformational freedom permits directed epoxidation to occur at both diastereotopic faces of the olefin. Substitution on the olefin, such that significant $A^{1,2}$ or $A^{1,3}$ strain exists in one of the diastereomeric transition states, can lead to strong preference for formation of one diastereomer over the other; however, the degree of selectivity is dictated by the type of oxidant used (Table 1). In the case where $A^{1,3}$ strain exists in one of the diastereomeric transition states, the *threo* diastereomer predominates (Table 1, entries 1 and 2). On the other hand, the major diastereomer is the *erythro* in the case where $A^{1,2}$ strain is present in one of the diastereomeric transition states (Table 1, entry 3). With trans-disubstituted olefins, there is no significant source of allylic strain in either diastereomeric transition state. This leads to low diastereoselectivities, with neither the *erythro* nor the *threo* diastereomer consistently predominating (Table 1, entry 4).[14−19]

Differences in diastereoselectivity for a given allylic alcohol or allylic alkoxide substrate with different epoxidation methods can be explained by examination of the degree of allylic strain in the diastereomeric epoxidation transition states. The dihedral angle, C═C−C−O, of the substrate determines the spatial relationships between the substituents on the olefin (R^2, R^3, and R^4) and the substituent at the stereogenic center (R^1) in the transition states (Scheme 1). The two diastereomeric transition states for epoxidation with $Ti(O^iPr)_4$/TBHP are shown in Scheme 1. For that system, the titanium peroxide catalyst binds to the allylic alkoxide and delivers the oxidant with a dihedral angle of 70°−90°.[1,15] This leads to $Ti(O^iPr)_4$/TBHP being more diastereoselective in the case of $A^{1,3}$ strain (Table 1, entries 1, 2) than in the case of $A^{1,2}$ strain (entry 3).

Epoxy alcohols bearing additional functionality, such as allylic epoxy alcohols, are of interest for their increased synthetic potential in the construction of natural products. These compounds contain three different functional groups: an olefin, a carbinol, and the epoxide. This increased functionality makes them especially useful intermediates, but it also makes their synthesis more difficult. As in the case of the epoxy alcohol substrates discussed previously, the issues of enantio- and diastereoselectivity for the generation of three contiguous stereocenters must be addressed. In addition, there are chemoselectivity issues involving differentiation of the two allylic double bonds in the synthesis of allylic epoxy alcohols.

In our intial studies on the synthesis of epoxy alcohols with three contiguous stereocenters, we generated allylic alkoxides with substituents on the olefin that led to $A^{1,2}$ or $A^{1,3}$ strain in one of the diastereomeric transition states. The allylic zinc alkoxide was formed via enantioselective addition of an alkylzinc reagent to an α,*β*-unsaturated aldehyde (Scheme 2, Route A) or via an asymmetric vinyl addition with a preformed divinylzinc species to a simple aldehyde (Scheme 2, Route B). Subsequent epoxidation was performed using dioxygen and catalytic $Ti(O^iPr)_4$ to provide the desired product with high enantio- and diastereoselectivity.[20] In the absence of either $A^{1,2}$ or $A^{1,3}$ strain, moderate diastereoselectivities were obtained.[21]

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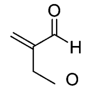
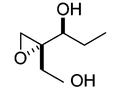
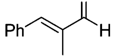
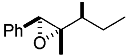
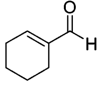
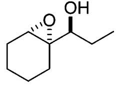
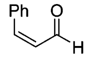
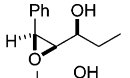
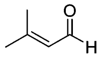
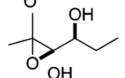
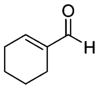
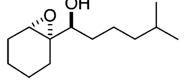
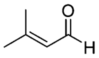
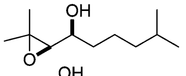
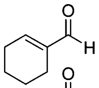
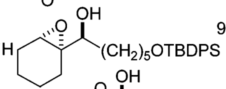
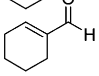
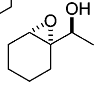
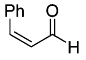
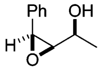
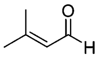
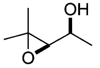
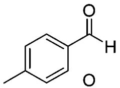
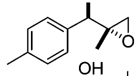
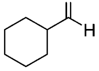
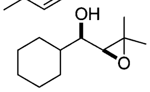
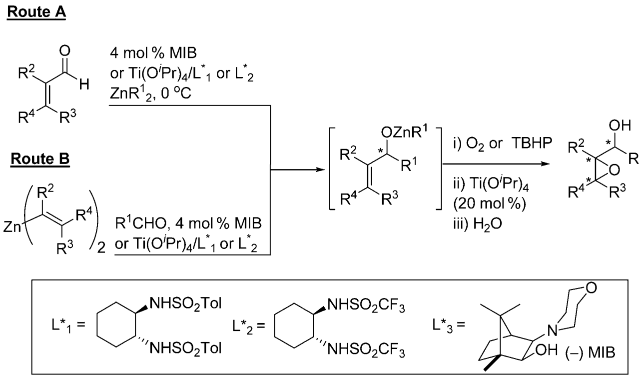
Table 2. Results for Synthesis of Epoxy Alcohols with Three Contiguous Stereocenters (Scheme 2, Routes A and B)

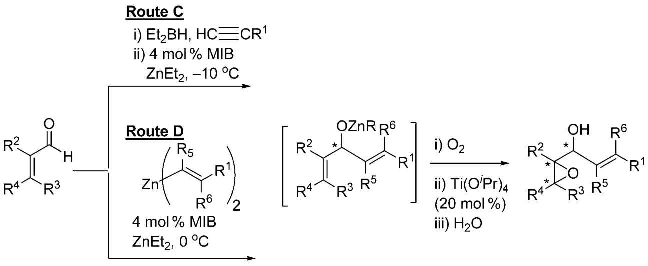
					Diastereomeric Ratios (*erythro* : *threo*)[c]			
entry	aldehyde	epoxy alcohol[a]	L*$_3$, $\mathrm{Ti(O^iPr)_4}$ and O_2 % ee[b] (% y)	[dr]	L*$_1$ or L*$_2$, $\mathrm{Ti(O^iPr)_4}$ or $\mathrm{Ti(O^tBu)_4}$ and O_2 % ee[b] (% y)	[dr]	L*$_2$ or L*$_3$, $\mathrm{Ti(O^iPr)_4}$ or $\mathrm{Ti(O^tBu)_4}$ and TBHP % ee[b] (% y)	[dr]
Scheme 2, Route A: Alkylzinc additions to enals								
1			93 (60)[f]	[17 : 1]	91 (89)[d]	[20 : 1]	93 (65)[f]	[20 : 1]
2			96 (65)[f]	[18 : 1]	92 (90)[d]	[20 : 1]	96 (79)[f]	[20 : 1]
3			99 (90)[f]	[20 : 1]	99 (91)[d]	[20 : 1]	99 (82)[f]	[10 : 1]
4			91 (96)[f]	[1 : 10]	96 (60)[d]	[1 : 10]	91 (60)[f]	[1 : 10]
5			95 (96)[f]	[1 : 20]	95 (93)[d]	[1 : 20]	95 (98)[f]	[1 : 20]
6			97 (62)[f]	[15 : 1]	97 (85)[d]	[20 : 1]	97 (74)[f]	[17 : 1]
7			96 (81)[f]	[1 : 20]	96 (86)[d]	[1 : 20]	96 (83)[f]	[1 : 20]
8			98 (86)[f]	[20 : 1]	94 (80)[d]	[20 : 1]	98 (85)[f]	[20 : 1]
9					99 (78)[e]	[20 : 1]	99 (89)[e]	[19 : 1]
10					85 (89)[e]	[1 : 10]	85 (65)[e]	[1 : 10]
11					96 (60)[e]	[1 : 18]	96 (72)[e]	[1 : 18]
Scheme 2, Route B: Vinylzinc additions to aldehydes								
12			96 (82)[f]	[16 : 1]	94 (89)[d]	[16 : 1]	96 (90)[f]	[20 : 1]
13			90 (75)[f]	[1 : 19]	97 (90)[d]	[1 : 20]	90 (80)[f]	[1 : 20]

[a] Stereochemistry indicated corresponds to that of the major diastereomer. [b] Determined by chiral HPLC or GC analysis. [c] Determined by ^1H NMR analysis. [d] Ligand L*$_1$ was used. [e] Ligand L*$_2$ was used. [f] Ligand L$_3$* was used.

Scheme 2. Two Routes in Our One-Pot Asymmetric Approach to the Synthesis of Epoxy Alcohols.



Scheme 3. Two Routes in Our One-Pot Asymmetrc Approach to the Synthesis of Allylic Epoxy Alcohols.



Since our previous investigations, we have sought to expand the versatility of our one-pot approach for the synthesis of epoxy alcohols with three contiguous stereocenters from prochiral starting materials. We now demonstrate that this method is applicable to the synthesis of densely functionalized allylic epoxy alcohols with high enantio-, diastereo-, and chemoselectivity (Scheme 3). Additionally, we outline a procedure whereby TBHP can be substituted for dioxygen in the diastereoselective epoxidation step. This new protocol for the tandem addition/diastereoselective epoxidation allows greater control in the oxidation step and is more amenable to scale-up.

Results and Discussion

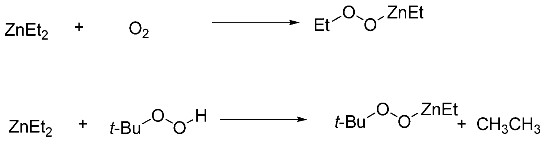
In the present study, we describe highly enantio- and diastereoselective methods to synthesize acyclic epoxy alcohols and allylic epoxy alcohols with three contiguous stereocenters from prochiral starting materials in good to excellent yields (Table 2). This one-pot two-step protocol begins with a highly enantioselective C−C bond-forming reaction to install the initial chiral center of the allylic alkoxide (Schemes 2 and 3). In the second step, the resulting allylic alkoxide is then diastereoselectively epoxidized in situ in the presence of a zinc peroxide species and a titanium tetra-alkoxide.

Our approach employs several different methods for the first step in our one-pot procedure, the synthesis of the allylic alkoxide intermediate (Scheme 2, Routes A and B). The first of these is alkyl addition to enals promoted by one of three different ligand systems: two different bis(sulfonamide) ligands (Scheme 2, Route A, L^*_1, and L^*_2) and Nugent's (−)-MIB (L^*_3).[22] To demonstrate the ability of different catalyst systems to facilitate the initial C−C bond-forming reaction, various alkyl zincs were added to aldehydes asymmetrically in the presence of either MIB (Table 2, column 1) or one of 2 bis(sulfonamide) ligands (Table 2, column 2).[23−26] Both catalyst systems have previously been shown to exibit good enantioselectivities and yields for diethylzinc additions to aldehydes.[23,27] The reaction times decreased from over 24 h for the amino alcohol ligand, MIB, to under 2 h with the bis(sulfonamide) ligands, L^*_1 and L^*_2. Both of the catalyst systems promoted the reaction with enantioselectivities >90%. (Table 2, entries 1−8).

It is known that the rate of dimethylzinc addition to enals with MIB and related amino alcohol ligands is slow; therefore, we were unable to achieve satisfactory yields of the methyl addition products, even after 2 days at room temperature.[28] The bis(sulfonamide) ligand L^*_2 and $Ti(O^{t}Bu)_4$ were employed in this reaction, because the resulting catalyst is known to promote dimethylzinc additions to aldehydes with high levels of enantioselectivity (Table 2, entries 9−11).[24,29] In our reaction system, 4 mol % of ligand L^*_2 and 1.2 equiv of $Ti(O^{t}Bu)_4$ were utilized to successfully promote the addition of dimethylzinc to enals.

Another route to generation of allylic alkoxide intermediates is via synthesis and isolation of a divinylzinc species and subsequent addition to a simple aldehyde (Scheme 2, Route B). The trisubstituted, tetrasubstituted, or α-methyl vinylzinc species are all generated by exposing the corresponding vinyl bromide to lithium metal and zinc bromide. After sonication of the reaction mixture in diethyl ether at 0 °C under an argon atmosphere, the substituted divinylzinc is isolated and purified by sublimation. Vinyl additions to aldehydes in the presence of MIB or the titanium bis(sulfonamide) catalyst L^*_1 typically lead to allylic alcohols with ee's >90% (Table 2, entries 12 and 13).

Scheme 4. Proposed Formation of Zinc Peroxide Species.



The second step of our one-pot approach consists of a diastereoselective epoxidation of the allylic zinc alkoxide intermediate in the presence of a zinc peroxide species and a titanium tetraalkoxide. The first route to generation of the zinc peroxide species is by insertion of dioxygen into a zinc-alkyl bond (Scheme 4).[30−39] We have previously demonstrated that this zinc peroxide, in the presence of $Ti(O^{i}Pr)_4$ or $Ti(O^{t}Bu)_4$, will epoxidize the allylic alkoxide intermediate.[20,21,40] Intramolecular oxygen atom transfer from the peroxide to the allylic alkoxide and hydrolysis of the reaction mixture, affords the epoxy alcohol product.[40] Due to the practical difficulties associated with controlling the rate of delivery of dioxygen to reaction mixtures containing dialkylzinc reagents, an alternative route to the formation of a zinc peroxide was explored. TBHP is a commercially available stoichiometric oxidant that is commonly used in the transition-metal catalyzed epoxidations of allylic alcohols.[1] In our system, TBHP would protonate an ethyl group on the organozinc reagent to yield ethane and an alkyl zinc *tert*-butyl peroxide species (Scheme 4).

When MIB was used as the ligand, in the asymmetric addition/diastereoselective epoxidation, a catalytic amount of titanium tetraisopropoxide was added (20 mol %) after the generation of the zinc peroxide species at −20 °C. In the case of the titanium bis(sulfonamide)-based catalysts, the reaction mixture was simply cooled to −20 °C and exposed to the oxidant, TBHP or dioxygen.

The results of the asymmetric addition/diastereoselective epoxidation are shown in Table 2. Entries 1−11 have been synthesized via dialkylzinc additions to enals. The remaining entries were generated from vinylzinc addition to simple aldehydes. For the most part, the diastereoselectivities and yields are similar, regardless of whether the epoxidation step is carried out in the presence of dioxygen or TBHP. (Compare columns 1 and 2 of Table 2 with column 3.) The yields tended to be slightly higher in the reactions with TBHP, as the crude epoxy alcohols generated were cleaner. The stereochemistry of the product in entry 4 was confirmed by X-ray crystallography.[41]

Our system is unique in that it demonstrates high levels of diastereoselectivity in the epoxidation step for substrates that exhibit either $A^{1,2}$ or $A^{1,3}$ strain in one of their diastereomeric transition states. Other known substrate-directed epoxidation methods tend to show high diastereoselectivity for one type of substrate, but not the other, as illustrated in Table 1.[15] We suspect that our titanium allylic alkoxide/zinc peroxide species has a different set of diastereomeric transition states from the

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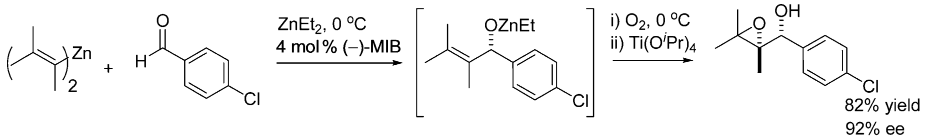
Scheme 5. Determination of the Predominant Steric Interaction in the Epoxidation Transition State for Our One-Pot Approach.

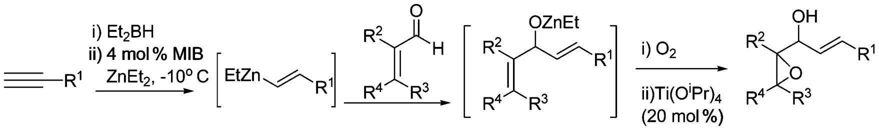


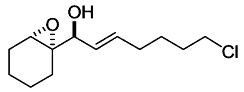
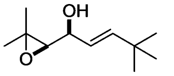
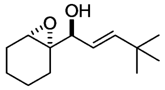
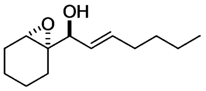
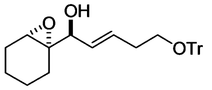
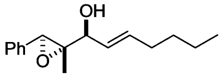
Diastereomeric Ratios (*erythro* : *threo*)[a]

One-Pot Method	Ti(O^{i}Pr)$_4$ TBHP	VO(acac)$_2$ TBHP	*m*CBPA
1 : 3	1 : 5[b]	2 : 1[b]	1 : 10[b]

[a] dr determined by ^{1}H NMR analysis.
[b] epoxidaton performed on isolated allylic alcohol.

Table 3. Results for Allylic Epoxy Alcohol Synthesis Using in Situ Generated Vinylzinc Reagents



entry	allylic epoxy alcohol	% ee(% y)	(*erythro : threo*)[c] [dr]
1		99[a](78)	[20 : 1]
2		98[a](76)	[1 : 20]
3		97[a](87)	[20 : 1]
4		99[a](78)	[20 : 1]
5		92[b](60)	[20 : 1]
6		90[b] (80)	[20 : 1]

[a] Determined by chiral GC anaylsis. [b] Determined by chiral HPLC anaylsis.
[c] Determined by ^{1}H NMR analysis.

more well-known Ti(O^{i}Pr)$_4$/TBHP system, and we are currently exploring this matter. To probe which type of allylic strain (A^{1,2} or A^{1,3}) has a greater impact on our system in the epoxidation transition state, a tetrasubstituted divinylzinc reagent was prepared and added to 4-chlorobenzaldehyde (Scheme 5). Epoxidation of the allylic alkoxide intermediate leads to A^{1,2} strain in one diastereomeric transition states, and A^{1,3} strain in the other.

The in situ asymmetric addition/diastereoselective epoxidation reaction yielded a 3:1 dr (Scheme 5). To assign the stereochemistry, we perfomed the diastereoselective epoxidation of the corresponding isolated allylic alcohol with Ti(O^{i}Pr)$_4$/TBHP, VO(acac)$_2$/TBHP, and the *m*CPBA systems. Epoxidation systems in which the dominant transition state steric interaction is A^{1,3} strain generate the *threo* diastereomer as the predominant product (Scheme 5). On the basis of the known diastereoselectivity patterns of these epoxidizing agents, the major diastereomer in the one-pot reaction shown in Scheme 5 was assigned as the *threo* diastereomer. We concluded, therefore, that the predominant steric interaction in the transition state for our one-pot Ti(O^{i}Pr)$_4$/O$_2$/ZnEt$_2$ epoxidation system is A^{1,3} strain.

Seeking to expand the utility of our chemistry, we developed a one-pot approach for the synthesis of allylic epoxy alcohols. The first step in our synthesis of these densely functionalized compounds is the generation of a bis(allylic alkoxide) intermediate. We have utilized two methods to generate these inter-

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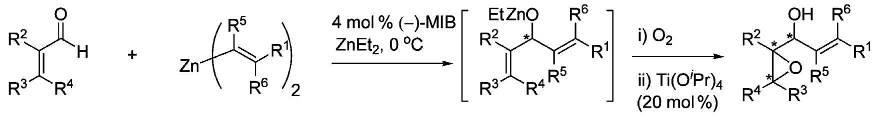
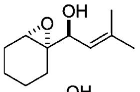
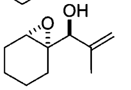
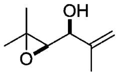
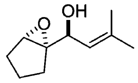
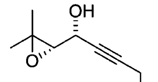
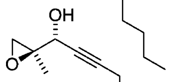
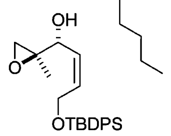
Table 4. Results of Allylic Epoxy Alcohol Synthesis Using Isolated, Purified Divinyl Zinc Reagents



entry	allylic epoxy alcohol	% ee (% y)	***(erythro : threo)***[c] [dr]
1		96[a] (61)	[20 : 1]
2		95[a] (90)	[20 : 1]
3		91[a] (91)	[1 : 20]
4		96[a] (76)	[20 : 1]
5		87[a] (92)	[1 : 5]
6		86[a] (90)	[4 : 1]
7		95[b] (80)	[20 : 1]

[a]Determined by chiral GC anaylsis. [b]Determined by chiral HPLC anaylsis.
[c]Determined by ^{1}H NMR analysis.

mediates, the first of which is the in situ generation of the vinylzinc species using the hydroboration/transmetalation protocol of Oppolzer.[21,42,43] When a trans-disubstituted vinylzinc reagent, generated in situ from a terminal alkyne, is added to an enal with substitution at the R^2 or R^3 position, it generates a bis(allylic alkoxide) intermediate with two differently substituted olefins (Scheme 3, Route C). We found that our epoxidation system is highly chemoselective, leading to epoxidation at the more electron-rich double bond. The allylic epoxy alcohols were produced, therefore, in high yield, and with high enantio- and diastereoselectivities (Table 3).

The second route involves addition of an isolated, purified divinylzinc reagent to an enal, as in Scheme 3, Route D. This leads to an intermediate with two differently substituted olefins, either of which can be diastereoselectively epoxidized, as they both have substituents on the olefin that lead to $A^{1,2}$ or $A^{1,3}$ strain in one of the diastereomeric transition states. In these reactions, it was found that cyclic olefins were chemoselectively epoxidized over di- or trisubstituted double bonds (Table 4, entries 1, 2, and 4). In Table 4, entry 7, the cis double bond was not epoxidized due to deactivation of the double bond by the electron withdrawing silyl ether. These synthetically challenging allylic epoxy alcohols were synthesized in high yields and with high enantio- and diastereoselectivities (Table 4, entries 1−4, 7). In the case of vinyl additions to ynals, the epoxy alcohol products were generated with slightly lower enantioselectivites (87% and 86%) and with a 5:1 or a 4:1 dr's. This is most likely due to the small size of the alkyne, which does not impart significant $A^{1,2}$ or $A^{1,3}$ strain in the disfavored transition state. Overall, this synthetic route to allylic epoxy alcohols is extremely efficient and selective.

Conclusions

We have developed a convenient one-pot method for the synthesis of epoxy alcohols and allylic epoxy alcohols. The versatility of this method has been demonstrated by a comparison of different catalyst systems (Table 2). All methods shown involve initial asymmetric C−C bond formation followed by in situ diastereoselective epoxidation. The oxidation can be achieved using either TBHP or dioxygen and an alkylzinc reagent to generate the active oxidant. Both protocols lead to the synthesis of epoxy alcohols in high yields and with high enantio- and diastereoselectivities. We believe that the use of our new protocol employing TBHP will facilitate implementation of this chemistry on large scale. Our method for the synthesis of epoxy alcohols offers several advantanges over existing methods. First, it circumvents the need to prepare and isolate the allylic or bis(allylic) alcohol intermediates, which can be susceptible to decomposition via highly delocalized carbocations. Second, different stoichiometric oxidants may be utilized. Third, the enantio- and diastereoselectivities are high for a wide range of substrates. Last, the initial C−C bond-

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(42) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170−173.
(43) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677−10683.

forming step can be catalyzed by literally hundreds of catalysts, although here we have employed only three.[27] We expect these epoxy alcohols to find widespread utility in asymmetric synthesis of natural and nonnatural products.

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Supporting Information Available: Experimental procedures, synthesis and full characterization of all compounds and conditions for the resolution of racemates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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