# JOC Article

One-Pot Asymmetric Synthesis of Acyclic Chiral Epoxy Alcohols via Tandem Vinylation−Epoxidation with Dioxygen

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yield = 68-92%
ee = 77-98%
d.r. = up to 4.5 :1
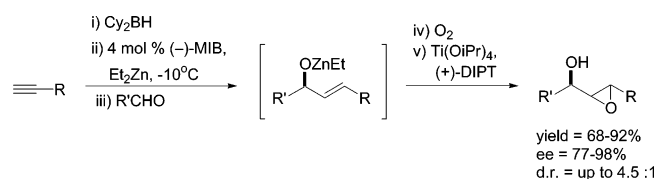
We have developed a one-pot procedure for the asymmetric synthesis of a synthetically challenging class of acylic secondary epoxy alcohols with three contiguous stereocenters from simple achiral starting materials. The epoxy alcohols are synthesized via a tandem catalytic asymmetric vinylation of an aldehyde coupled with a diastereoselective epoxidation reaction. A vinylzinc reagent generated in situ undergoes enantioselective addition to an aldehyde in the presence of a zinc catalyst to provide an allylic zinc alkoxide. This species is then epoxidized by addition of dioxygen and a titanium tartrate catalyst to give epoxy alcohols with excellent enantioselectivities, in most cases, and with diastereoselectivities up to 4.5:1 in favor of the *threo*-diastereomer. The system described herein represents a significant advance in terms of synthetic efficiency and selectivity.

Introduction

Chiral epoxy alcohols are versatile synthetic building blocks that have found extensive utility in natural product synthesis, particularly due to their potential for undergoing regioselective ring-opening reactions.[1,2] Much effort has been directed, therefore, toward the development of methods for the regio- and stereoselective construction of this class of compounds.[3,4] Chiral epoxy alcohols are typically synthesized by selective epoxidation of the corresponding allylic alcohols, a process which can take place under reagent control, in the case of achiral allylic alcohols,[4] or under substrate control, in the case of chiral allylic alcohols.[5]

The Sharpless asymmetric epoxidation reaction, using catalytic titanium tetraisopropoxide, tartrate ester ligands, and *tert*-butyl hydroperoxide (TBHP) in the presence of 4 Å molecular sieves is the premier method for the construction of epoxy alcohols from achiral substrates (Scheme 1).[6−10] This methodology exhibits high enantioselectivity for a range of structurally diverse achiral

SCHEME 1. Sharpless Asymmetric Epoxidation
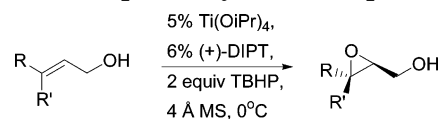
allylic alcohols and has been successfully employed in many natural product syntheses, as well as in the preparation of numerous small molecules and chiral building blocks.[4]

In contrast to the synthesis of epoxy alcohols from achiral allylic alcohols, the direct synthesis of epoxy alcohols containing a stereogenic center at the carbanol carbon from achiral reagents requires that three contiguous stereocenters be established with high enantio- and diastereoselectivity. This transformation, therefore, is typically performed in a multistep procedure involving synthesis of a secondary allylic alcohol with high enantioselectivity, or racemic synthesis and resolution of

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the allylic alcohol, followed by a directed epoxidation reaction. The epoxidation of chiral secondary allylic alcohols is generally carried out using an organic peracid, such as *m*CPBA, or with a transition-metal catalyst in combination with a stoichiometric oxidant.[5]

The diastereoselectivity of the directed epoxidation step ranges from poor to excellent, depending on the nature of the allylic alcohol. Good to excellent diastereoselectivities have been achieved with cyclic allylic alcohols and with acyclic allylic alcohols having substitution on the olefin such that significant $A^{1,3}$ or $A^{1,2}$ strain exists in one of the diastereomeric transition states (Table 1). Thus, $A^{1,3}$ strain encountered in the transition state leading to the minor diastereomer can result in high diastereoselectivity for allylic alcohols that are *Z*-substituted with respect to the carbanol moiety (entries 1 and 2, Table 1). Likewise, substrates with substitution geminal to the carbanol group can exhibit $A^{1,2}$ strain in one of the diastereomeric transition states and be epoxidized with high diastereoselectivity (entry 3, Table 1). On the other hand, allylic alcohols containing disubstituted (*E*)-olefins are among the most difficult substrates for directed epoxidation. In the absence of significant $A^{1,3}$ and/or $A^{1,2}$ strain in the diastereomeric transition states, diastereoselectivities for these substrates are typically less than 2:1 with both peracid- and transition-metal-catalyzed epoxidation reactions (entry 4, Table 1).[11-16]

TABLE 1. Diastereomeric Ratios for the Directed Epoxidation of Chiral Secondary Allylic Alcohols with Various Oxidizing Agents[12]

entry	substrate	Ti(O*i*Pr)₄ *t*BuOOH	VO(acac)₂ *t*BuOOH	*m*CPBA
		Diastereomeric Ratios (*threo* : *erythro*)		
1		10 : 1	2.4 : 1	19 : 1
2		19 : 1	6.1 : 1	19 : 1
3		1 : 3.5	1 : 19	1 : 1.2
4		1.9 : 1	1 : 2.4	1.8 : 1

Proposed transition states illustrating the formation of the *threo*- and *erythro*-epoxy alcohols with peracids and vanadium or titanium catalysts are depicted in Scheme 2. The peracid is proposed to associate with the allylic alcohol via hydrogen bonding with a dihedral angle of approximately 120°, while in the case of vanadium- and titanium-based peroxide catalysts, the binding of the allylic alkoxide to the metal is proposed to favor a dihedral angle of 40−50° and 70−90°, respectively.[11] This dihedral angle 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 state. Therefore, the preferred diastereomer of the product epoxy alcohol and the extent to which it dominates may differ for a given allylic alcohol substrate, depending upon the epoxidizing agent used. For any given epoxidizing agent, the favored diastereomer is dictated by the substitution pattern of the allylic alcohol, which determines whether $A^{1,2}$ or $A^{1,3}$ strain is the dominant steric interaction in the transition state. As illustrated in Scheme 2, there is no strong steric bias disfavoring formation of either the *threo*- or *erythro*-epoxy alcohol in the case of *E*-disubstituted olefins (where R^2 and R^3 = H), and we are unaware of general substrate-directed methods for the synthesis of chiral epoxy alcohols derived from these substrates with high diastereoselectivity. Epoxidation with VO(acac)₂/TBHP slightly favors the *erythro*-product, and Ti(O*i*Pr)₄/TBHP and *m*CPBA slightly favor the *threo*-product (entry 4, Table 1).

Sharpless kinetic resolution[17-19] of racemic secondary allylic alcohols with a titanium tartrate catalyst can, in principle, be used to afford the corresponding chiral epoxy alcohol products with good selectivity, regardless of the substitution pattern on the olefin. As with all kinetic resolutions, however, this approach is limited to a maximum yield of 50%. The enantioselectivity of the kinetic resolution is controlled by the difference in the relative rates of reaction of the two enantiomers of the allylic alcohol and by the extent of conversion. If the difference in rate is large enough, and the reaction is quenched at low conversion, the ee of the epoxy alcohol can be very high. Diastereoselectivity in the Sharpless system strongly favors the *erythro*-product, leading to *erythro*:*threo* ratios as high as 49:1.[18,19] As such, it is the only existing method that achieves high diastereoselectivities in the synthesis of *trans*-disubstituted *erythro*-epoxy alcohols. To our knowledge, no method exists for achieving high *threo* selectivity for this class of compounds.

In practice, the Sharpless kinetic resolution is more often used as a method to isolate resolved allylic alcohols.[4] Resolved 2- and 3-*Z*-substituted allylic alcohol substrates can then undergo directed epoxidation with an appropriate oxidizing agent. If the product of such a resolution is an *E*-disubstituted allylic alcohol, however, obtaining high diastereoselectivity in a second substrate-directed epoxidation step remains a challenge for the reasons outlined above. Under reagent control, using the Sharpless system, enantioenriched allylic alcohol substrates of this type can be epoxidized in good yield and with high *erythro* selectivity, but one is still left with the task of first synthesizing and/or resolving the enantioenriched allylic alcohol substrates.[18,20,21]

We have sought to address the limitations of existing methods for the enantio- and diastereoselective synthesis of acyclic epoxy alcohols with three contiguous stereo-

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SCHEME 2.   Transition States for the Directed Epoxidation of Chiral Allylic Alcohols via a Peracid or a Transition-Metal Peroxide
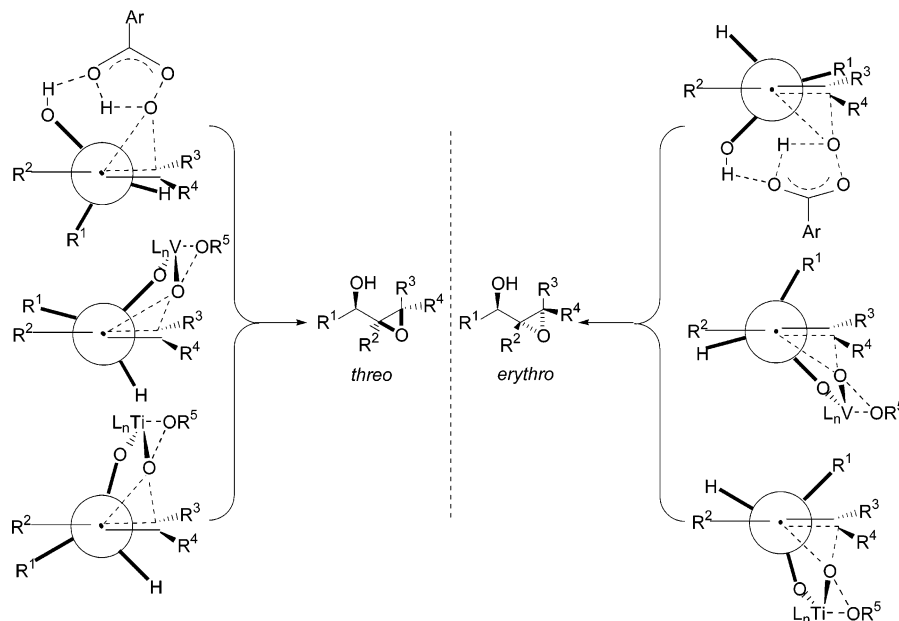
centers by developing a one-pot tandem vinylation–epoxidation approach to these compounds from simple achiral starting materials.[22] In a separate study on the addition of diethylzinc to cyclic enones in the presence of a titanium catalyst, we discovered that exposure of the newly formed allylic alkoxide to dioxygen led to smooth epoxidation, providing the corresponding epoxy alcohols with high enantioselectivity. As would be expected for cyclic allylic alkoxides, the reaction proceeded with high diastereoselectivity. We proposed that diethylzinc or an ethylzinc alkoxide and dioxygen react to give an intermediate zinc peroxide, EtZn(OOEt) or ROZn(OOEt).[23–32] In this way, the dialkylzinc reagent acts in the dual roles of nucleophile and oxidant precursor. Transfer of the peroxy group to the titanium allylic alkoxide intermediate provides the activated complex. Intramolecular atom transfer to the allylic alkoxide and hydrolysis of the reaction mixture afford the epoxy alcohols.[33] Our research group has also generated acyclic chiral allylic zinc alkoxides with substitution on the olefin α to the carbanol

carbon or *cis* to the carbanol via amino alcohol-promoted asymmetric alkylzinc addition to α,β-unsaturated aldehydes or addition of divinylzinc reagents **A** and **B** (Scheme 3) to simple aldehydes. We have shown that these zinc alkoxide intermediates will undergo directed epoxidation upon exposure to dioxygen and a catalytic amount of Ti(OiPr)$_4$.[34] As a result of their substitution patterns, these substrates exhibit A^{1,2} or A^{1,3} strain in one of their two diastereomeric epoxidation transition states. Therefore, the epoxidation step proceeds with moderate to high levels of diastereoselectivity.

SCHEME 3.   One-Pot Synthesis of 2- and 3-Z-Substituted Epoxy Alcohols
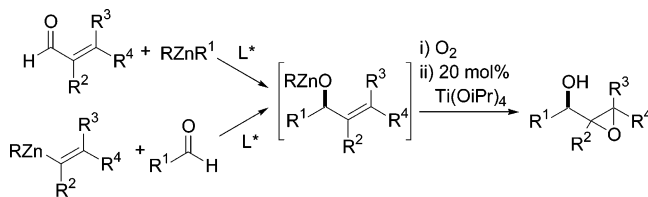
A: R^2 = Me; R^3, R^4 = H
B: R^2 = H; R^3, R^4 = Me

In the present study, we have addressed the enantio- and diastereoselective synthesis of *trans*-disubstituted epoxy alcohols, a class of compounds that cannot be synthesized via traditional directed epoxidation methods. Our method begins with in situ generation of a vinylzinc species via hydroboration of a terminal alkyne, followed by transmetalation to zinc.[35] Asymmetric addition of the vinylzinc intermediate to an aldehyde in the presence of Nugent's morpholino isoborneol ligand[36–38] (MIB; Scheme 4) affords the chiral allylic alkoxide intermediate. Replac-

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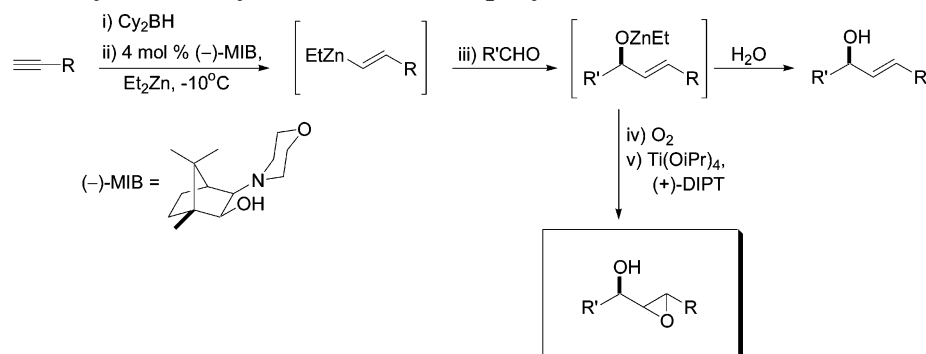(31) Yamamoto, K.; Yamamoto, N. *Chem. Lett.* **1989**, *1989*, 1149–1152.
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SCHEME 4. One-Pot Asymmetric Synthesis of Chiral Epoxy Alcohols

mixture to dioxygen led cleanly to the epoxy alcohol product with a diastereomeric ratio (dr) of approximately 2:1. Comparison of the ee's of the epoxy alcohol products and the allylic alcohols formed on quenching the alkoxide intermediates with dilute acid led us to conclude that the enantioselectivity set in the vinyl addition step was not eroded during the epoxidation.

ing the nitrogen atmosphere with dioxygen followed by addition of a titanium tartrate catalyst promotes clean and efficient epoxidation of the allylic alkoxide (Scheme 4). In this fashion, epoxy alcohols can be isolated directly in good to excellent yields without the need to prepare and isolate the enantioenriched allylic alcohol precursors. Enantioselectivities are excellent, in most cases, and diastereoselectivities are moderate, typically ranging from 3:1 to 4:1 in favor of the *threo*-diastereomer. In addition, we are able to use molecular oxygen as the oxidant in these epoxidations, thereby avoiding the need to dry or handle TBHP or other peroxides.

Results and Discussion

In previous work on the synthesis of α- and β-amino acid derivatives,[39,40] we have demonstrated the highly enantioselective addition of various vinylzinc species to aromatic and aliphatic aldehydes catalyzed by Nugent's MIB ligand.[35] In an effort to improve synthetic efficiency and diastereoselectivity in the formation of epoxy alcohols derived from secondary *E*-disubstituted allylic alcohols, we aimed to combine this asymmetric vinylation protocol with a selective epoxidation using diethylzinc and dioxygen to generate the stoichiometric oxidant.

In our initial experiments, the asymmetric vinyl addition reaction was performed by hydroborating a terminal alkyne with Cy_2BH, transmetalating it with Et_2Zn at −10 °C, and adding it to an aldehyde in the presence of (−)-MIB at 0 °C. Upon completion of the vinylation reaction, as determined by thin-layer chromatography, dioxygen was introduced by capping the reaction flask with a balloon containing dioxygen at 0 °C. No epoxidation product was detected, even after warming to room temperature and stirring for 2 days, indicating that zinc did not promote the epoxidation reaction under these conditions.

Screening of Transition-Metal Catalysts. A series of transition-metal complexes were then examined to determine their ability to promote the epoxidation and their diastereoselectivity. We found that addition of 1 equiv of $Ti(OiPr)_4$ directly after exposing the reaction

After observing the formation of the chiral epoxy alcohol product in the presence of stoichiometric $Ti(OiPr)_4$, we investigated the possibility of a catalytic reaction. It was found that no significant change in diastereoselectivity occurred at catalyst loadings down to 20 mol % $Ti(OiPr)_4$ (Table 2). At 10 mol % $Ti(OiPr)_4$, a slight decrease in dr was observed, along with lower yields of the epoxy alcohol products. Changing the size of the alkoxide ligands on titanium by using $Ti(OtBu)_4$ led also to a slight decrease in diastereoselectivity (entry 5, Table 2). When catalytic $VO(acac)_2$ was added to the vinyl addition reaction mixture, the vanadium species rapidly changed from green to dark purple, and no epoxidation product was observed (entry 6, Table 2). Presumably, the $VO(acac)_2$ was reduced by the organozinc reagent under these reaction conditions.

Screening of Tartrates and Other Chiral and Achiral Diol Ligands. Given the success of tartrate-based complexes at promoting both enantio- and diastereoselectivity in the Sharpless epoxidation system with allylic alcohol substrates, we decided to explore the use of such ligands with $Ti(OiPr)_4$ and our allylic zinc

TABLE 2. Diastereoselectivities for One-Pot Synthesis of Epoxy Alcohols with Different Catalysts and Catalyst Loadings

entry	epoxidation catalyst	dr (*threo:erythro*)
1	10 mol % $Ti(OiPr)_4$	1.7 : 1
2	20 mol % $Ti(OiPr)_4$	2.0 : 1
3	30 mol % $Ti(OiPr)_4$	1.8 : 1
4	100 mol % $Ti(OiPr)_4$	1.9 : 1
5	100 mol % $Ti(OtBu)_4$	1.4 : 1
6	20 mol % $VO(acac)_2$	NR

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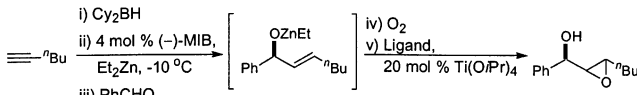
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**TABLE 3. Effects of Different Ligands on Diastereoselectivity in the One-Pot Epoxy Alcohol Synthesis**

entry	ligand	dr (*threo:erythro*)
1	20 mol % (+)-DMT	1.6 : 1
2	20 mol % (+)-DET	1.3 : 1
3	20 mol % (+)-DIPT	3.7 : 1
4	40 mol % (+)-DIPT	3.1 : 1
5	20 mol % (−)-DIPT	2.5 : 1
6	20 mol % *meso*-DIPT	1.5 : 1
7	20 mol % (*R*)-BINOL	NR
8	20 mol % (*S*)-BINOL	NR

alkoxide system. To begin, we stirred a 1:1 mixture of Ti(OiPr)$_4$ and (+)-diisopropyl tartrate (DIPT) in dichloromethane for 45 min at room temperature and then removed the solvent and the liberated 2-propanol under reduced pressure. When the resulting titanium tartrate catalyst (20 mol % with respect to the allylic alkoxide intermediate) was redissolved in dichloromethane and added to the reaction flask containing the allylic zinc alkoxide at −10 °C under an oxygen atmosphere, epoxidation occurred cleanly, and diastereoselectivity increased to almost 4:1 (entry 3, Table 3). This can be compared to diastereoselectivities of about 2:1 with Ti(OiPr)$_4$ in the absence of ligand. Chiral tartrate ligands (+)-dimethyl tartrate (DMT) and (+)-diethyl tartrate (DET), bearing smaller alkyl groups, gave lower selectivities, as did the opposite enantiomer of the isopropyl derivative, (−)-DIPT (entries 1, 2, and 5, Table 3). Adding *meso*-DIPT as an achiral ligand led to lower diastereoselectivity than in the case of (+)- or (−)-DIPT (entry 6, Table 3), and use of (*R*)- or (*S*)-BINOL as a chiral ligand on titanium resulted in only trace amounts of the epoxidation product (entries 7 and 8, Table 3). When Ti(OiPr)$_4$ and (+)-DIPT were added directly to the reaction flask containing the allylic zinc alkoxide intermediate without premixing the catalyst or without removal of the liberated 2-propanol, lower diastereoselectivities were observed. Increasing the premixing time of the Ti(OiPr)$_4$ and (+)-DIPT, addition of 4 Å molecular sieves in the premixing process, or increasing the ratio of tartrate ligand to Ti(OiPr)$_4$ did not improve the ratio of epoxide diastereomers formed.

Substrate Scope. Ultimately, our best results for the one-pot synthesis of chiral *trans*-disubstituted epoxy alcohols were achieved using 20 mol % Ti(OiPr)$_4$ and 20 mol % (+)-DIPT. These operationally simple reactions were run using 1.1 equiv of vinylborane, generated from the in situ hydroboration of a terminal alkyne with Cy$_2$BH, 3.1 equiv of Et$_2$Zn, 4 mol % (−)-MIB, and 1.0 equiv of aldehyde to form the chiral allylic zinc alkoxide. Upon capping of the reaction flask with a balloon of

SCHEME 5. Optimized Conditions for Tandem Asymmetric Vinylation−Epoxidation
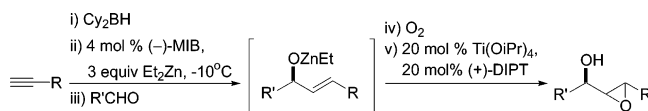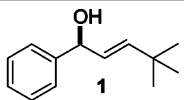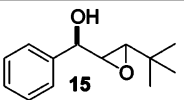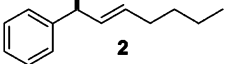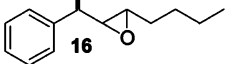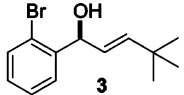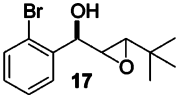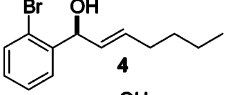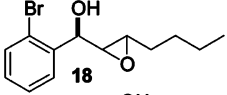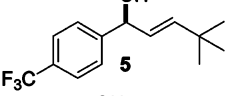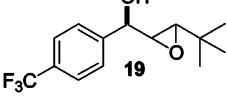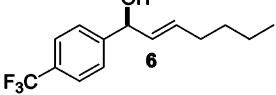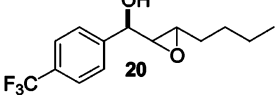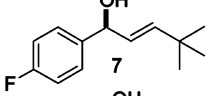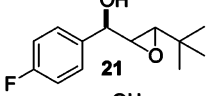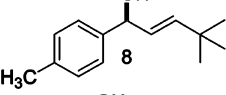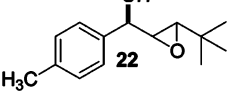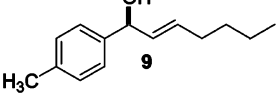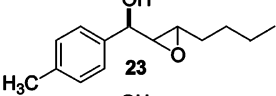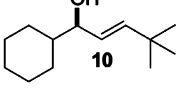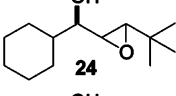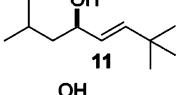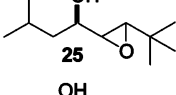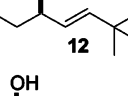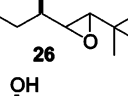

dioxygen and addition of a premixed titanium tartrate complex, the epoxy alcohols were formed in high enantiopurity and with diastereoselectivities ranging from 2.9:1 to 4.5:1 (Scheme 5 and Table 4).

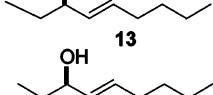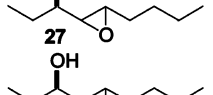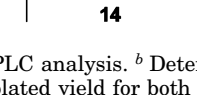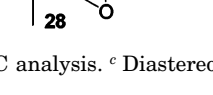X-ray crystal structures of the minor diastereomer of epoxy alcohols **19** and **21** in Table 4 (see structures in the Supporting Information) indicate that the major diastereomer formed in these reactions is the *threo*-diastereomer, and comparison of the ^{1}H NMR spectra for all other substrates tested showed the predominance of the *threo*-diastereomer to be general.

This one-pot method avoids the need to synthesize and isolate chiral allylic alcohol substrates of high enantiopurity and achieves improved *threo* diastereoselectivities for this class of chiral epoxy alcohols, as compared to substrate-directed epoxidation reactions with Ti(OiPr)$_4$/TBHP, VO(acac)$_2$/TBHP, and *m*CPBA. In addition, it precludes the handling of TBHP or other peroxides by employing molecular oxygen to generate a peroxide species in situ. For comparison with the results obtained in our one-pot system, allylic alcohol **2** (Table 4) was isolated with 94% ee by working up the allylic alkoxide intermediate with satd aq NH$_4$Cl solution, and it was then subjected to substrate-directed epoxidation conditions. Reaction with 1.5 mol % VO(acac)$_2$ and 1.5 equiv of TBHP resulted in a 1.8:1 *erythro:threo* ratio of diastereomers. Epoxidations with 1.6 equiv of *m*CPBA and with 5 mol % Ti(OiPr)$_4$/2.0 equiv of TBHP both led to a predominance of the *threo*-diastereomer in ratios of 1.4:1 and 1.6:1, respectively. In no case was the diastereomeric ratio in the epoxy alcohol product **16** (Table 4) higher than the 3.5:1 *threo:erythro* ratio achieved in our one-pot reaction. Although diastereoselectivities are not nearly as high as those obtained with the Sharpless kinetic resolution, our system represents complimentary chemistry. We have eliminated the need to synthesize and isolate the allylic alcohol substrates; yields are not limited to a maximum of 50%, and our system provides access to the opposite diastereomer of the epoxy alcohol products.

A range of simple achiral starting aldehydes and terminal alkynes can be used successfully in our system. Electron-rich or -poor aromatic aldehydes with *ortho* or *para* substitution, as well as aliphatic aldehydes with α or β substitution, give products of high ee. In addition, the substituent at the propargyl position of the alkyne can be sterically demanding, as in the case of *tert*-butylacetylene, or not, as in the case of 1-hexyne. Straight chain aliphatic aldehydes give allylic alcohol products with ee's around 80%, and we had hoped to observe enhancement of the ee via kinetic resolution during the in situ epoxidation. Unfortunately, the difference in the rates of reaction for the two enantiomers of the allylic alkoxide intermediate turned out to be too small for such a kinetic resolution to take place.

TABLE 4. Enantio- and Diastereoselectivities for the One-Pot Asymmetric Synthesis of *trans*-Disubstituted Epoxy Alcohols

entry	allylic alcohol	% ee	epoxy alcohol	dr (threo:erythro)[c]	yield[d]
1	**1**	96[a]	**15**	4.3:1	77
2	**2**	94[a]	**16**	3.5:1	83
3	**3**	93[a]	**17**	4.1:1	78
4	**4**	94[a]	**18**	3.8:1	77
5	**5**	95[a]	**19**	3.6:1	85
6	**6**	95[a]	**20**	3.5:1	76
7	**7**	93[b]	**21**	2.9:1	92
8	**8**	95[a]	**22**	3.3:1	85
9	**9**	95[a]	**23**	3.3:1	83
10	**10**	96[b]	**24**	3.8:1	74
11	**11**	85[b]	**25**	4.3:1	89
12	**12**	79[b]	**26**	3.2:1	69
13	**13**	77[b]	**27**	4.5:1	68
14	**14**	92[b]	**28**	3.1:1	77

[a] Determined by chiral HPLC analysis. [b] Determined by chiral GC analysis. [c] Diastereomeric ratio of *threo* to *erythro* determined by ¹H NMR analysis. [d] Total isolated yield for both diastereomers.

Conclusions

We have introduced a new one-pot catalytic asymmetric approach to a synthetically challenging class of acyclic chiral secondary epoxy alcohols containing three contiguous stereocenters. The reactivity of dialkylzinc species has been exploited such that these reagents have served in the same reaction flask as nucleophiles and as oxidant precursors in conjunction with dioxygen. Our method involves in situ generation of a vinylzinc reagent that undergoes enantioselective addition to an aldehyde in the presence of a zinc catalyst to provide an allylic zinc alkoxide. This species is then epoxidized by addition of dioxygen and a titanium tartrate catalyst to give the *threo*-diastereomer with up to 4.5:1 diastereoselectivity. In addition to its synthetic efficiency, the catalytic system reported herein represents the most *threo* selective

system for the synthesis of secondary *trans*-disubstituted epoxy alcohols. Further study on the nature of the catalyst and the origin of selectivity in the system continues in our group.

Experimental Section

General procedures for the synthesis of allylic alcohols and epoxy alcohols are presented below. Synthesis and full characterization of all compounds are provided in the Supporting Information.

Caution! Caution should be used when handling organozinc reagents and exposing them to oxygen.

(*S*)-1-(2-Bromophenyl)hept-2-en-1-ol (4). General Procedure A. A 10 mL Schlenk flask was charged with Cy_2BH (98 mg, 0.55 mmol), prepared according to Oppolzer's procedure,[35] and 1.5 mL of hexanes. 1-Hexyne (64 μL, 0.55 mmol) was added dropwise, and the homogeneous reaction mixture was stirred for 30 min at room temperature. After the reaction flask was cooled to -10 °C, $(-)$-MIB (4.8 mg, 0.02 mmol) was added, followed by Et_2Zn (0.55 mL, 2.0 M) and then *o*-bromobenzaldehyde (58 μL, 0.50 mmol) dropwise. The reaction was stirred at -10 °C for 2 h and quenched with 2 mL of H_2O. The organic and aqueous layers were separated, and the aqueous layer was extracted with hexanes (3 × 5 mL). The combined organic layers were then washed with 5 mL of H_2O and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (5% ethyl acetate in hexanes) to afford the title compound in 77% yield (104 mg, 0.39 mmol) as a colorless oil: $[\alpha]^{20}_D = -31.3$ ($c = 3.2$, $CHCl_3$, 93% ee); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, 3H, $J = 7.1$ Hz), 1.25−1.37 (m, 4H), 2.03 (dt, 2H, $J = 7.0$, 6.7 Hz), 2.11 (br s, 1H), 5.51 (d, 1 H, $J = 6.1$ Hz), 5.58 (dd, 1H, $J = 15.2$, 6.4 Hz), 5.78 (dt, 1H, $J = 15.2$, 6.7 Hz), 7.10 (t, 1H $J = 7.6$ Hz), 7.31 (t, 1H, $J = 7.4$ Hz), 7.50 (d, 1H, $J = 7.9$ Hz), and 7.53 (d, 1H, $J = 7.7$ Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 13.9, 22.2, 31.3, 31.9, 73.5, 122.4, 127.70, 127.74, 128.8, 130.2, 132.7, 133.5, and 142.2 ppm; IR (neat) 3360, 3060, 2956, 2926, 2857, 1664, 1567, 1466, 1438, 1378, and 1193 cm^{-1}; HRMS-CI *m/z* 268.0471 [M$^+$; calcd for $C_{13}H_{17}BrO$, 268.0463].

(2-Bromophenyl)(3-butyloxiranyl)methanol (18). General Procedure B. A 10 mL Schlenk flask (A) was charged with Cy_2BH (98 mg, 0.55 mmol), prepared according to Oppolzer's procedure,[35] and 1.2 mL of hexanes. 1-Hexyne (64 μL, 0.55 mmol) was added dropwise, and the homogeneous reaction mixture was stirred for 30 min at room temperature. After the reaction flask was cooled to -10 °C, $(-)$-MIB (4.8 mg, 0.02 mmol) was added, followed by Et_2Zn (0.78 mL, 2.0 M) and then *o*-bromobenzaldehyde (58 μL, 0.50 mmol) dropwise. The reaction was stirred at -10 °C for 4 h until vinyl addition was complete by TLC. The reaction flask was then capped with a balloon of oxygen and allowed to stir at -10 °C

for 1 h. In a separate 10 mL Schlenk flask (B), 1 mL of dichloromethane, $Ti(OiPr)_4$ (100 μL, 1.0 M in hexanes), and $(+)$-DIPT (21 μL, 0.10 mmol) were combined. After its contents were stirred at room temperature for 45 min, flask B was evacuated for 1 h to strip off the solvent. The contents of flask B were then redissolved in 1 mL of dichloromethane and stripped again for 1 h. Finally, the contents of flask B were taken up in 1 mL of dichloromethane and transferred to reaction flask A. The reaction continued to stir at -10 °C under an O_2 atmosphere for 18 h. It was then quenched with 2 mL of 15% tartaric acid solution and allowed to stir for 45 min before the organic and aqueous layers were separated, and the aqueous layer was extracted with hexanes (3 × 5 mL). The combined organic layers were then washed with 5 mL of H_2O and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica (5% ethyl acetate in hexanes) to afford the title compound in 77% yield (110 mg, 0.39 mmol). Data for the *threo*-diastereomer: colorless oil; $[\alpha]^{20}_D = -40.5$ ($c = 0.39$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, 3H, $J = 7.1$ Hz), 1.27−1.44 (m, 4H), 1.53−1.61 (m, 2H), 2.51 (d, 1H, $J = 5.4$ Hz), 2.98 (dd, 1H, $J = 4.5$, 2.1 Hz), 3.24 (dt, 1H, $J = 5.6$, 2.0 Hz), 5.02 (t, 1H, $J = 4.9$ Hz), 7.18 (t, 1H, $J = 7.6$ Hz), 7.37 (t, 1H, $J = 7.5$ Hz), 7.56 (d, 1H, $J = 7.9$ Hz), and 7.61 (d, 1H, $J = 7.7$ Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 13.9, 22.4, 27.9, 31.1, 57.7, 61.1, 71.6, 122.1, 127.9, 128.0, 129.5, 132.8, and 139.8 ppm; IR (neat) 3424, 3063, 2962, 2930, 2861, 1562, 1468, 1434, 1383, and 1260 cm^{-1}; HRMS-CI *m/z* 285.0496 [MH$^+$; calcd for $C_{13}H_{18}BrO_2$, 285.0490]. Data for the *erythro*-diastereomer: colorless oil; $[\alpha]^{20}_D = -55.9$ ($c = 1.2$, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.82 (t, 3H, $J = 7.1$ Hz), 1.20−1.33 (m, 4H), 1.44 (m, 1H), 1.55 (m, 1H), 2.51 (s, 1H), 3.03 (dt, 1H, $J = 5.6$, 1.8 Hz), 3.20 (br t, 1H), 5.37 (br s, 1H), 7.17 (t, 1H, $J = 7.1$ Hz), 7.34 (t, 1H, $J = 7.5$ Hz), 7.50 (d, 1H, $J = 7.6$ Hz), and 7.54 (d, 1H, $J = 8.0$ Hz) ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ 13.8, 22.2, 27.9, 31.0, 54.8, 59.6, 69.1, 122.1, 127.7, 127.9, 129.4, 132.6, and 138.8 ppm; IR (neat) 3434, 3072, 2957, 2931, 2859, 1590, 1568, 1468, 1438, and 1378 cm^{-1}; HRMS-CI *m/z* 285.0496 [MH$^+$; calcd for $C_{13}H_{18}BrO_2$, 285.0490].

Supporting Information Available: Synthesis and full characterization of all compounds, X-ray crystal structures of **19** and **21**, and conditions for the resolution of racemates (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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