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Tandem Reactions for Streamlining Synthesis: Enantio- and Diastereoselective One-Pot Generation of Functionalized Epoxy Alcohols

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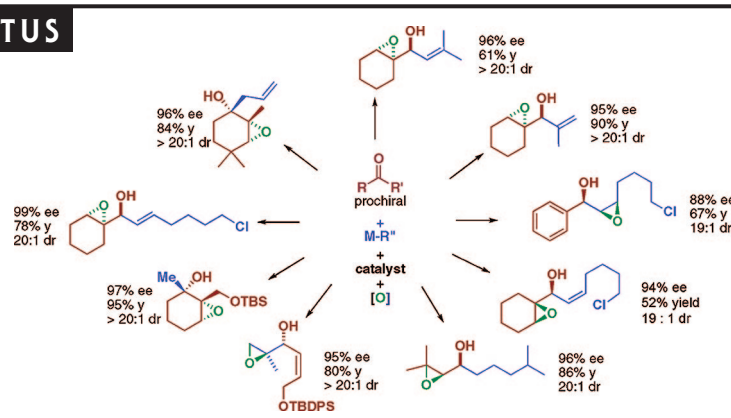
CONSPECTUS



In 1980, Sharpless and Katsuki introduced the asymmetric epoxidation of prochiral allylic alcohols (the Sharpless–Katsuki asymmetric epoxidation), which enabled the rapid synthesis of highly enantioenriched epoxy alcohols. This reaction was a milestone in the development of asymmetric catalysis because it was the first highly enantioselective oxidation reaction. Furthermore, it provided access to enantioenriched allylic alcohols that are now standard starting materials in natural product synthesis.

In 1981, Sharpless and co-workers made another seminal contribution by describing the kinetic resolution (KR) of racemic allylic alcohols. This work demonstrated that small-molecule catalysts could compete with enzymatic catalysts in KRs. For these pioneering works, Sharpless was awarded the 2001 Nobel Prize with Knowles and Noyori.

Despite these achievements, the Sharpless KR is not an efficient method to prepare epoxy alcohols with high enantiomeric excess (ee). First, the racemic allylic alcohol must be prepared and purified. KR of the racemic allylic alcohol must be stopped at low conversion, because the ee of the product epoxy alcohol *decreases* as the KR progresses. Thus, better methods to prepare epoxy alcohols containing stereogenic carbinol carbons are needed.

This Account summarizes our efforts to develop one-pot methods for the synthesis of various epoxy alcohols and allylic epoxy alcohols with high enantio-, diastereo-, and chemoselectivity. Our laboratory developed titanium-based catalysts for use in the synthesis of epoxy alcohols with tertiary carbinols. The catalysts are involved in the first step, which is an asymmetric alkyl or allyl addition to enones. The resulting intermediates are then subjected to a titanium-directed diastereoselective epoxidation to provide tertiary epoxy alcohols. Similarly, the synthesis of acyclic epoxy alcohols begins with asymmetric additions to enals and subsequent epoxidation. The methods described here enable the synthesis of skeletally diverse epoxy alcohols.

1. Introduction

Great progress has been made in the development and application of methods for the synthesis of complex natural products. Given sufficient time, resources, and personnel, the synthesis of even the most complex targets is either achievable or feasible. Thus, synthetic organic chemistry is often considered a mature field. Many syntheses, however, require numerous synthetic steps and purifications, ultimately producing minute quantities of the final product. Although

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organic synthesis may be mature, there is a great deal of room for improvement! One approach to streamline organic synthesis is to perform reactions in tandem, circumventing the traditional isolation and purification of each intermediate.

This Account details our development of novel tandem reactions for the synthesis of epoxy alcohols with excellent control over enantio-, diastereo-, and chemoselectivity. Enantioenriched epoxy alcohols are among the most widely utilized precursors in asymmetric synthesis.[1,2] Efficient and highly stereoselective methods to prepare these valuable building blocks will facilitate both target- and diversity-oriented synthesis.

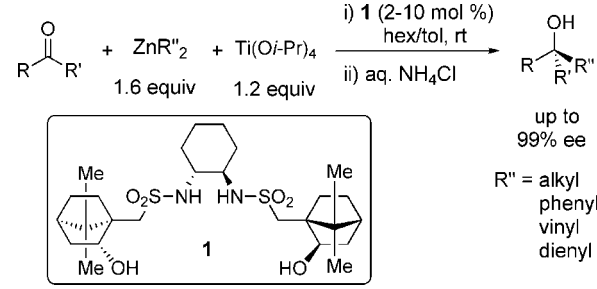
The first step in these tandem sequences involves an asymmetric organozinc or allylstannane addition to an unsaturated ketone or aldehyde. The resulting allylic alkoxide intermediate is then subjected to a diastereoselective epoxidation to establish up to two additional stereogenic centers.

2. Tandem Enantioselective Additions to Enones and Diastereoselective Epoxidations

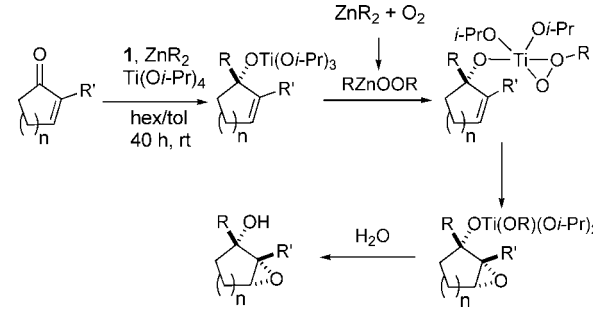
Our initial epoxy alcohol synthesis begins with the asymmetric alkylation of enones. Although many efficient and highly enantioselective catalysts have been reported for the alkylation of aldehydes,[3] the same catalysts usually exhibit little or no reactivity with ketones. This reactivity difference stems partly from the lower affinity of Lewis acids for ketones relative to their aldehyde counterparts. Likewise, asymmetric reactions with ketones are more challenging than those with aldehydes because discrimination of the enantiotopic faces of the ketone carbonyl is more difficult. With both lone pairs *syn* to non-hydrogen substituents, the lone pairs often have similar steric environments, unlike those in aldehydes. Thus, it is not surprising that a long-standing challenge in asymmetric catalysis had been the synthesis of tertiary alcohols with high enantioselectivity.

2.1. The First Highly Enantioselective Catalyst for Ketone Alkylations. In 2002, we disclosed the first highly enantioselective catalyst for the asymmetric addition of alkyl groups to ketones. Our catalyst employs the bis(sulfonamide) diol ligand (**1**, Scheme 1).[4,5] Both enantiomers of **1** are easily synthesized from commercially available materials and have recently become commercially available from Aldrich. The Lewis acid catalyst formed on reaction of titanium tetraisopropoxide and the bis(sulfonamide) diol ligand promotes the addition of alkyl-,[4,6−8] phenyl-,[9,10] vinyl-,[11,12] and dienylzinc reagents[12] to ketones with enantioselectivities typically

SCHEME 1. Asymmetric Addition of Alkyl, Phenyl, Vinyl, and Dienyl Groups to Ketones with Our Catalyst Formed from Ligand **1**



SCHEME 2. Proposed Mechanism for the One-Pot Asymmetric Addition/Diastereoselective Epoxidation Reaction with Dioxygen

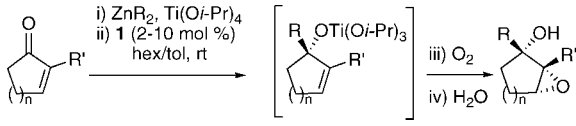


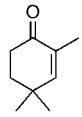
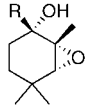
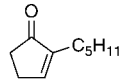
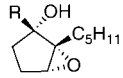
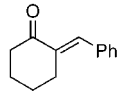
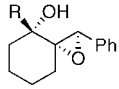
>90%.[13] A crucial element of the ligand is the diamine backbone. Substitution of *trans*-1,2-diaminocyclohexane in **1** with *trans*-1,2-diaminocyclopentane resulted in a significant reduction in activity and enantioselectivity, probably due to the increased conformational freedom of the cyclopentane ring.[14]

2.2. One-Pot Asymmetric Addition/Diastereoselective Epoxidation under Standard Conditions. Using the bis(sulfonamide) diol ligand **1** (10 mol %), we reported the asymmetric alkylation of cyclic α,β-unsaturated enones following the general protocol in Scheme 1.[6] We also discovered that if the initially formed alkoxide intermediate was exposed to dioxygen, epoxidation of the allylic double bond took place to afford *syn*-epoxy alcohols (Scheme 2). It is noteworthy that the titanium complex has a dual role in this tandem sequence, first promoting the asymmetric addition then directing the diastereoselective epoxidation. These tandem reactions enable the establishment of three contiguous stereogenic centers with high enantio- and diastereoselectivity.[6]

A proposed mechanism for this reaction is illustrated in Scheme 2. It is well documented that dialkylzinc reagents readily react with dioxygen to generate zinc peroxides.[15,16] We propose that the epoxidation is initiated by insertion of dioxygen into the Zn−C bond to generate a peroxy zinc species. Transmetalation of the zinc-bound peroxide to the titanium allylic alkoxide is followed by oxygen atom transfer to the double bond. Aqueous work up affords the epoxy alcohol products. In support of this proposal, we have also found

TABLE 1. One-Pot Synthesis of Epoxy Alcohols via Dioxygen-Initiated Epoxidation



entry	substrates	products[a]	ZnR_2	% ee (% y)
1			R = Me	99 (82)
2			R = Et	99 (80)
3			R = Me	98 (50)
4			R = Et	97 (60)
5			R = Me	99 (67)
6			R = Et	99 (60)
7			R = Et	96 (34)

[a] Only one diastereomer observed in each case.

that *tert*-butyl hydroperoxide (TBHP) can be substituted for dioxygen in the directed epoxidation step with similar yields.[17] Presumably, the TBHP protonates an alkyl of the dialkylzinc to generate an alkyl zinc peroxide (RZnOO-*t*-Bu), which then follows the same reaction pathway. An advantage of TBHP over dioxygen in the epoxidation is that the rate of addition of the TBHP (5.5 M in decane) can be easily regulated. In our initial report, the addition/epoxidation was conducted using hexanes and toluene as solvent, which is referred to as our "standard conditions".[6]

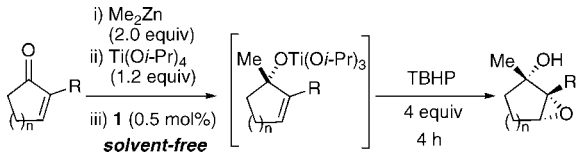
The scope of the tandem enantioselective addition/diastereoselective epoxidation under our standard solvent conditions is illustrated in Table 1. 2-Substituted enones are excellent substrates for the enantioselective addition (entries 1−6), while conjugated enones devoid of alkyl substituents α to the carbonyl group, such as 2-cyclohexenone, give poor enantioselectivities. Aryl-substituted enones also underwent alkylation with high enantioselectivity, but with diminished yields (entry 7). Epoxidations in the presence of $ZnEt_2$ and dioxygen (1 atm) resulted in complete conversion to the *syn*-epoxy alcohols in less than 4 h. In the presence of $ZnMe_2$, however, epoxidations were very slow. This issue was initially circumvented by adding 2 equiv of $ZnEt_2$ before exposure to dioxygen. It is noteworthy that the epoxidation is conducted on the allylic alkoxide under *aprotic* conditions, making it very different from Ti(O*i*-Pr)$_4$/TBHP epoxidation of allylic alcohols.[18,19]

2.3. One-Pot Asymmetric Addition/Diastereoselective Epoxidation under Solvent-Free Conditions. In a bid to transform our bis(sulfonamide) diol-based catalyst into a more efficient and environmentally friendly system, we envisioned conducting the tandem reaction under highly concentrated or solvent-free conditions. In a recent review on highly concentrated and solvent-free catalytic asymmetric reactions,[20] we defined highly concentrated reactions as those that use <5 equiv of solvent relative to substrate and solvent-free reactions as those with less than a 5-fold excess of one of the reagents relative to substrate. We hypothesized that reducing the amount of solvent in the ketone alkylation would increase catalyst and reagent concentrations and could raise the catalyst turnover frequency, ultimately allowing a reduction in catalyst loading. Solvent-free enantioselective reactions are rare, because two of the most important variables for reaction optimization, solvent polarity and reagent concentrations, are forfeited.[20] Furthermore, under solvent-free conditions the reaction medium can change dramatically as reagents and substrates are converted to products.

Despite these potential complications, we tested the addition of dialkylzinc reagents to ketones under solvent-free conditions.[8] We were surprised to find that in the vast majority of asymmetric additions, the product alcohol ee was ±3% of the value obtained under standard conditions with toluene and hexanes. Furthermore, under solvent-free conditions, the catalyst loading could be reduced by up to 20-fold (to 0.5 mol %). With some substrates, however, the enantioselectivity dropped significantly under solvent-free conditions. We found that addition of 2 equiv of toluene (with respect to ketone substrate) and 1 mol % of ligand **1** restored the enantioselectivity in most cases. The optimal protocol for our asymmetric alkylation of ketones employs solvent-free or highly concentrated conditions.[8]

In the tandem reaction the asymmetric addition was conducted under solvent-free conditions followed by injection of 5.5 M TBHP in decane at −10 °C. The reaction mixture was warmed to room temperature and stirred for 4 h to generate epoxy alcohols in high isolated yields (87−95%, Table 2). These yields are significantly higher than those obtained under our standard solvent conditions (Table 1).[6] To investigate the scalability of the epoxy alcohol synthesis, we used 5.0 g of 2-pentyl-2-cyclopenten-1-one, 2 equiv of dimethylzinc, 1.2 equiv of titanium tetraisopropoxide, and 0.5 mol % of ligand **1** in the addition plus 4 equiv of TBHP for the epoxidation. The resultant epoxy alcohol was isolated in 90% yield

TABLE 2. One-Pot Asymmetric Addition/Epoxidation of Cyclic Enones under Solvent-Free Conditions with TBHP



entry	time (h): addition	time (h): epoxidation	% ee (% y)[a]
1	45	4	97 (87)
2	44	4	97 (95)
3	44	4	95 (95)

[a] Only one diastereomer observed in each case.

(5.45 g, 97% ee) with 90% recovery of the ligand. Other substrates were successfully employed on a gram scale but are not shown here.[8] The solvent-free conditions for the tandem reactions are both practical and scalable.[8]

3. Tandem Asymmetric Allylation/ Diastereoselective Epoxidation of Cyclic Enones

Asymmetric allylation of aldehydes and ketones[21] generates synthetically valuable homoallylic alcohols. Asymmetric catalysts for the allylation of aldehydes were introduced in the early 1990s by the groups of Tagliavini[22] and Keck.[23] Development of analogous catalysts for ketone allylation, however, proved more challenging. We were attracted to this chemistry by Tagliavini's enantioselective (BINOLate)Ti-based catalyst, which exhibited moderate enantioselectivities in ketone allylations.[24] Our attraction stemmed from our long-standing interest in the structures and mechanisms of titanium-based asymmetric catalysts.[25−29] During our mechanistic investigations of this system, we discovered a new (BINOLate)Ti-based catalyst that formed in the presence of 20 equiv of isopropanol relative to the substrate. This observation eventually led to the first enantioselective catalyst for the asymmetric allylation of ketones with broad substrate scope (Scheme 3).[30,31] Ironically, mechanistic studies on this system have been complicated by an induction period. The role of the isopropanol, the catalyst structure, and the reaction mechanism remain elusive. Despite the high enantioselectivities of our catalyst, a significant drawback is that it requires high catalyst loadings (20−30 mol %). As outlined below, we have made progress in reducing the titanium loading.

SCHEME 3. Our Catalytic System for the Asymmetric Allylation of Cyclic Enones

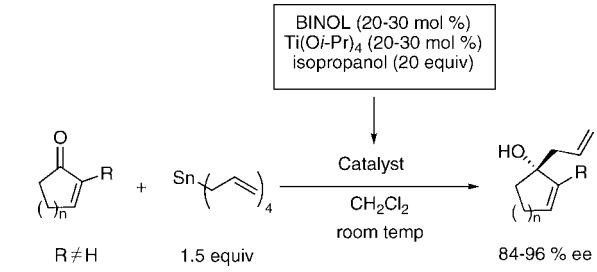
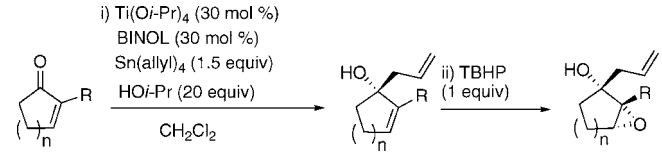


TABLE 3. Tandem Asymmetric Allylation under Standard Conditions followed by a Chemo- and Diastereoselective Epoxidation.



entry	substrates	products[a]	% ee (% y)
1			96 (84)
2	Ph	Ph	95 (89)
3	n-Pent	*n*-Pent	94 (72)
4	OTBS	OTBS	88 (88)

[a] Only one diastereomer observed in each case.

3.1. Tandem Allylation/Epoxidation Reaction under Standard Conditions. After introduction of our asymmetric allylation catalyst,[30] we turned our attention to the development of a tandem asymmetric allylation of cyclic α,β-unsaturated enones followed by a chemo- and diastereoselective directed epoxidation of the allylic alcohol (Table 3).[31] As with the alkylation of cyclic enones, the α-substituent is crucial in the enantioselective allylation of enones because it allows the catalyst to readily differentiate between the two lone pairs on the carbonyl oxygen. Unlike the ketone alkylation chemistry, the tandem asymmetric allylation/epoxidation reaction

involves alkoxide exchange via the alcohol and not the alkoxide (see Scheme 2).

For the tandem reaction, the ketone allylation was conducted in the usual fashion and 1 equiv of anhydrous TBHP (5.5 M) was subsequently added to the reaction mixture. The epoxidation proceeded readily at room temperature to afford the *syn*-epoxy alcohols in good yields (72−89%, Table 3). No erosion of ee was observed during the epoxidation, and only a single diastereomer was detected by NMR spectroscopy.[31]

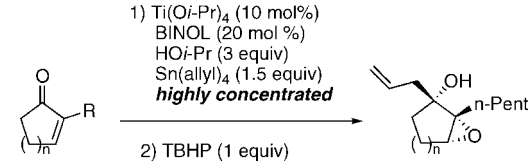
3.2. Asymmetric Allylation Reaction under Highly Concentrated Conditions. Our allylation catalyst, formed from a 1:1 ratio of titanium tetraisopropoxide to BINOL and excess isopropanol, required 20−30 mol % loading to achieve maximum enantioselectivity. In an effort to reduce the amount of solvent employed and lower the catalyst loading, the tandem allylation/epoxidation was conducted in the absence of dichloromethane solvent. The enantioselectivity, however, fell sharply under the highly concentrated condition with this catalyst system.[32]

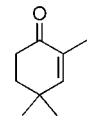
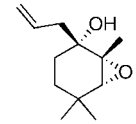
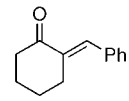
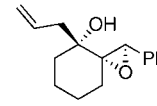
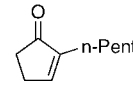
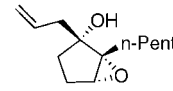
It is known that the ratio of titanium to BINOL can impact the enantioselectivity in the asymmetric allylation of aldehydes.[33] In order to adapt our allylation catalyst to highly concentrated conditions, we reoptimized the catalyst with a 1:2 ratio of titanium tetraisopropoxide to BINOL and only 3 equiv of isopropanol with respect to the ketone substrate (no other solvent). In this process, a new catalyst was developed for highly concentrated conditions. With this catalyst, the titanium tetraisopropoxide loading could be lowered from 30 mol % under standard solvent conditions to 10 mol % with the highly concentrated conditions. Furthermore, dichloromethane was eliminated from the reaction.

3.3. Tandem Allylation/Epoxidation under Concentrated Conditions. Adaptation of the asymmetric allylation under concentrated conditions to the tandem allylation/epoxidation was straightforward. The allylation was followed by addition of 1 equiv of anhydrous TBHP (5.5 M) resulting in smooth epoxidation to afford the *syn*-epoxy alcohols as single diastereomers in 84−87% yield and with enantioselectivities around 90% (Table 4).[32]

Starting from achiral precursors, both our asymmetric alkylation/diastereoselective epoxidation and our asymmetric allylation/diastereoselective epoxidation result in the generation of three contiguous stereocenters with excellent enantio-, diastereo-, and chemoselectivity. Furthermore, our tandem reactions result in a significant increase in molecular complexity. It is noteworthy that both tandem reactions could be adapted to solvent-free and highly concentrated reaction conditions, suggesting that other catalysts may also perform successfully

TABLE 4. Tandem Asymmetric Allylation under Concentrated Conditions Followed by a Chemo- and Diastereoselective Epoxidation



entry	substrates	products[a]	% ee (% y)
1			91 (84)
2			91 (87)
3			90 (85)

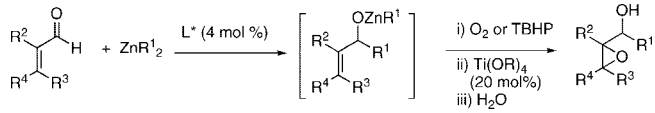
[a] Only one diastereomer observed in each case.

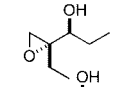
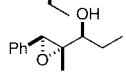
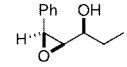
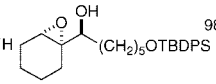
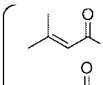
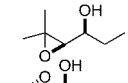
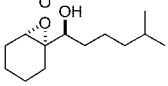
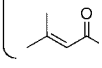
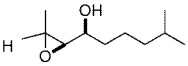
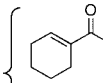
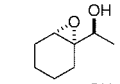
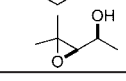
at high concentrations.[20] The outstanding diastereoselectivities observed are a result of the titanium-directed epoxidation reaction. Because of the constrained nature of these cyclic allylic alkoxides and allylic alcohols, epoxidation can only occur *syn* to the alkoxy or hydroxy groups. In the next section, we focus on acyclic substrates in which diastereoselective epoxidations are more challenging.

4. Tandem Asymmetric Additions to Aldehydes with Diastereoselective Epoxidations

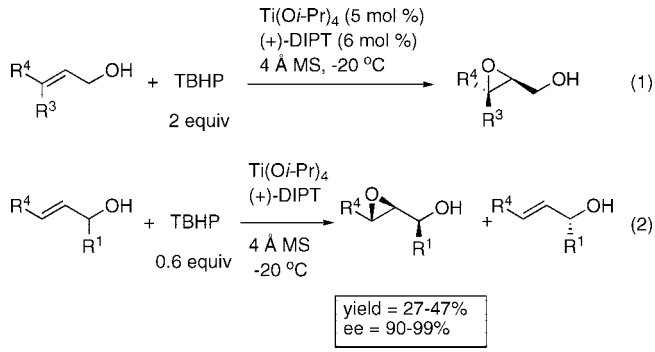
4.1. Synthesis of Acyclic Epoxy Alcohols. Acyclic epoxy alcohols are among the most versatile and useful intermediates in organic synthesis due to their straightforward synthesis and potential for undergoing regioselective ring-opening reactions.[1] Enantioenriched epoxy alcohols are typically synthesized by the Sharpless−Katsuki asymmetric epoxidation of prochiral allylic alcohols (eq 1).[18,34] If the desired epoxy alcohol contains an additional stereogenic center at the carbinol carbon, the Sharpless kinetic resolution of racemic allylic alcohols can be employed (eq 2).[35] Despite the enormous impact of the latter method, it suffers from significant limitations, including a maximum yield of 50%. Furthermore, if the desired product is the epoxy alcohol, the kinetic resolution must be quenched at low conversion to ensure product of high ee. Alternatively, the resolved allylic alcohol can be isolated from the KR and subjected to a diastereoselective epoxi-

TABLE 5. Synthesis of Epoxy Alcohols from Enals



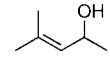
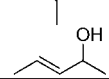
entry	L*, $Ti(OR)_4$ and oxidant	substrate	product	% ee (% y)	[dr]
1	(–)-MIB, O_2, $Ti(O\textit{i}\text{-}Pr)_4$			93 (60)	[17 : 1]
2				96 (65)	[18 : 1]
3				91 (96)	[1 : 10]
4				98 (86)	[20 : 1]
5	O_2, $Ti(O\textit{i}\text{-}Pr)_4$			95 (93)	[1 : 20]
6				97 (85)	[20 : 1]
7				96 (86)	[1 : 20]
8	TBHP, $Ti(O\textit{t}\text{-}Bu)_4$			99 (89)	[19 : 1]
9				96 (72)	[1 : 18]

dation. In order to address these drawbacks, we investigated three related one-pot procedures to synthesize highly enantio- and diastereoenriched epoxy alcohols with up to three contiguous stereocenters.



4.1.1. Asymmetric Alkylation of Enals with Diastereoselective Epoxidations. We performed highly enantioselective alkyl additions to α,β-unsaturated aldehydes with 4 mol % of various catalysts (Table 5). The asymmetric catalysts are formed from Nugent's (2*S*)-(−)-3-*exo*-(morpholino)isoborneol [(−)-MIB][36,37] (entries 1−4) or the bis(sulfonamide) ligands (entries 5−9). Upon completion of the addition, the resulting allylic alkoxide was exposed to 1 atm of dioxygen at 0 °C for 30 min and cooled to −20 °C.[38] When (−)-MIB was used, which generates a zinc-based catalyst, titanium tetraisopropoxide (20 mol %) was added to initiate the diastereoselective epoxidation. With the bis(sulfonamide) ligands, which are titanium-based catalysts, the titanium tetraalkoxide used in the asymmetric addition also promotes the epoxidation. As illustrated in Table 5, both the (−)-MIB and bis(sulfonamide)-based catalysts gave excellent enantioselectivities with a range of aldehyde substitution patterns. In the case of dimethylzinc additions (entries 8 and 9), the bis(sulfonamide)/$Ti(O\textit{t}\text{-}Bu)_4$ catalyst system[39] is the best choice, because it is significantly faster than the MIB-based catalyst in methyl addition reactions.

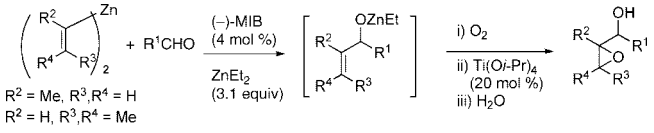
TABLE 6. Diastereoselective Epoxidations of Different Classes of Allylic Alcohols with $Ti(O\textit{i}\text{-}Pr)_4$/TBHP, $VO(acac)_2$/TBHP, and *m*CPBA

			Diastereomeric Ratios (*erythro: threo*)		
entry	strain	substrate	$Ti(O\textit{i}\text{-}Pr)_4$ *t*-BuOOH	$VO(acac)_2$ *t*-BuOOH	*m*CPBA
1	$A^{1,3}$		1 : 10	1 : 2.4	**1 : 19**
2	$A^{1,3}$		**1 : 19**	1 : 6.1	**1 : 19**
3	$A^{1,2}$		3.5 : 1	**19 : 1**	1.2 : 1
4	none		1 : 1.9	2.4 : 1	1 : 1.8

As outlined in Table 5, the diastereomeric ratios [dr] observed in the epoxidation step are excellent. This is surprising, because the allylic alkoxides generated in Table 5 exhibit either $A^{1,2}$ or $A^{1,3}$ strain in one of the diastereomeric epoxidation transition states. To facilitate discussion of diastereoselectivity in the epoxidations throughout section 4, reactions will be presented such that interaction between R^1 and R^2 ($R^2 \neq H$, $R^3 = H$) gives rise to $A^{1,2}$ strain, whereas interaction between R^1 and R^3 ($R^3 \neq H$, $R^2 = H$) results in $A^{1,3}$ strain. Due to the disposition of R^4, it has a small impact on the dr. The three most common diastereoselective epoxidation systems are $Ti(O\textit{i}\text{-}Pr)_4$/TBHP, $VO(acac)_2$/TBHP (acac = acetylacetonate), and *m*-chloroperbenzoic acid (*m*CPBA). The diastereoselectivities of these reagents with a series of allylic alcohols are listed in Table 6.[19] None of these reagents give good diastereoselectivity with substrate classes leading to both $A^{1,2}$ and $A^{1,3}$ strain (Table 6). Our alkoxide-based epoxidation is unique because of its high diastereoselectivity with substrates resulting in *either $A^{1,2}$ or $A^{1,3}$ strain* (Table 5). It is possible that the observed diastereoselectivities in Table 5 stem from a C=C−C−O dihedral angle of 90°.

4.1.2. Asymmetric Vinylation/Diastereoselective Epoxidations. The second route to epoxy alcohols entails the addition of divinylzinc reagents to aliphatic and aromatic alde-

TABLE 7. One-Pot Synthesis of Epoxy Alcohols Using Isolated and Purified Divinylzinc Reagents



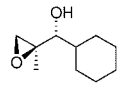
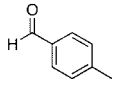
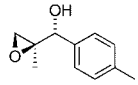
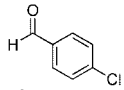
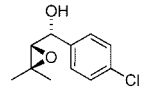
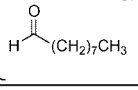
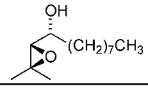
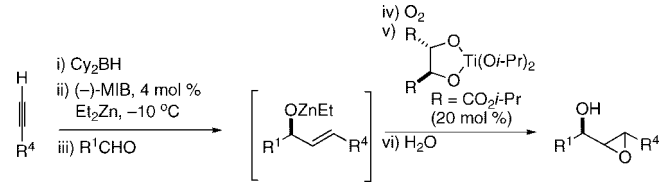
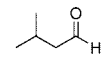
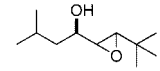
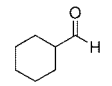
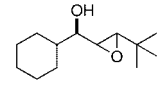
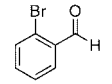
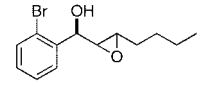
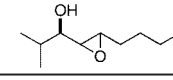
entry	vinylzinc reagent	substrate	product	% ee (% y)	[dr]
1	ZnEt			92 (87)	[17 : 1]
2	ZnEt			96 (82)	[16 : 1]
3	ZnEt			96 (84)	[1 : 18]
4	ZnEt			85 (78)	[1 : 17]

TABLE 8. One-Pot Synthesis of Epoxy Alcohols Using in Situ Generated Vinylzinc Reagents



entry	vinylzinc R^4	substrate	product	% ee (% y)	[dr][a]
1	*t*-Bu			85 (89)	[4.3 : 1]
2	*t*-Bu			96 (74)	[3.8 : 1]
3	*n*-Bu			94 (77)	[3.8 : 1]
4	*n*-Bu			92 (77)	[3.1 : 1]

hydes (Table 7). The divinylzinc reagents were prepared and then purified by sublimation.[40,41] To minimize the equivalents of divinylzinc employed, 3.1 equiv of diethylzinc was added to generate the mixed ethyl–vinyl zinc species, which transfers the vinyl group orders of magnitude faster than the ethyl group. Following the asymmetric addition with the (–)-MIB-based catalyst, epoxidation was carried out as above. High enantioselectivities were obtained with most aldehydes with the exception of unbranched aldehydes, which gave enantioselectivities around 80% (Table 7, entry 4). Diastereoselectivities in the epoxidation were also quite high with allylic alkoxides leading to $A^{1,2}$ (entries 1 and 2) or $A^{1,3}$ (entries 3 and 4) strain.

4.1.3. Tandem Vinylation–Epoxidation with in Situ Formed Vinylzinc Reagents. Although the above route provides epoxy alcohols with high enantio- and diastereoselectivity, the need to prepare and isolate the divinylzinc reagents is inconvenient. An in situ method to prepare vinylzinc reagents was developed by Srebnik[42] and Oppolzer[43] involving hydroboration of a terminal alkyne, transmetalation of the resulting vinylborane to zinc, and asymmetric addition. Using Oppolzer's method, we performed the hydroboration and asymmetric addition in the presence of the (–)-MIB-based catalyst (4 mol %) and exposed the resulting allylic alkoxide reaction mixture to dioxygen and titanium isopropoxide (Table 8). Unfortunately, the epoxidation proceeded with low diastereoselection (~2:1) due to the absence of $A^{1,2}$ or $A^{1,3}$ strain in the epoxidation transition states (see Table 6, entry 4). To our knowledge, all allylic alcohol epoxidation reagents exhibit low diastereoselectivity in the absence of either $A^{1,2}$ or $A^{1,3}$ strain, with the exception of the Sharpless–Katsuki asymmetric epoxidation catalyst.[34] At the outset of these experiments, we were unaware of the formidable challenge to development of a highly diastereoselective epoxidation system for this class of substrates. After many unsuccessful experiments, however, we decided to emulate the Sharpless–Katsuki catalyst. Thus, a preformed titanium diisopropoxy tartrate complex, which was generated by combining titanium tetraisopropoxide with (+)-diisopropyltryptamine (DIPT) and removal of the liberated isopropanol under reduced pressure, was added after exposure of the reaction mixture to dioxygen. While this modification resulted in increased diastereoselectivity, the dr was still low ranging from 2.9:1 to 4.5:1 in the matched case favoring the *threo*-diastereomer (Table 8). The same epoxy alcohol diastereomer was obtained in the mismatched case with (–)-DIPT.[44] Although our catalyst system is more *threo* selective than the reagents listed in Table 6, there is considerable room for improvement. It is noteworthy that the predominant diastereomer is opposite of the epoxy alcohol expected from the Sharpless KR, highlighting the significant differences between the Sharpless–Katsuki catalyst and our diastereoselective titanium/zinc-based epoxidation catalyst.

4.2. Synthesis of Allylic Epoxy Alcohols. With an eye on increasing the versatility and molecular complexity of our epoxy alcohol products, we developed a one-pot method for the synthesis of densely functionalized allylic epoxy alcohols (Scheme 4). This chemistry adds another layer of complexity to the reactions described above in that the epoxidation must be both chemoselective and diastereoselective.[17] The first step

SCHEME 4. Synthesis of Allylic Epoxy Alcohols Involving Chemo- and Diastereoselective Epoxidations

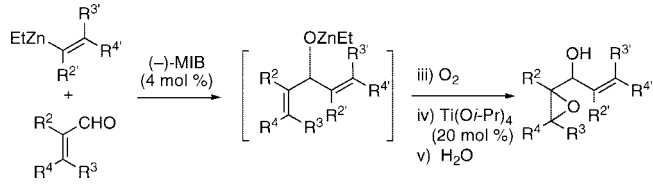
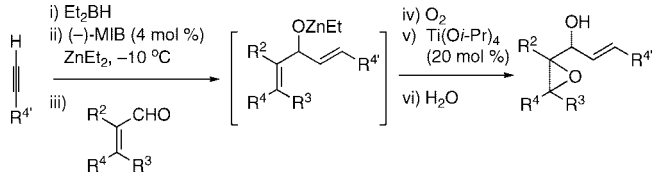
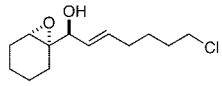
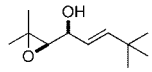
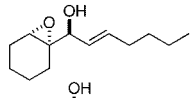
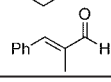
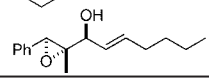


TABLE 9. Allylic Epoxy Alcohol Synthesis Using in Situ Generated Vinylzinc Reagents



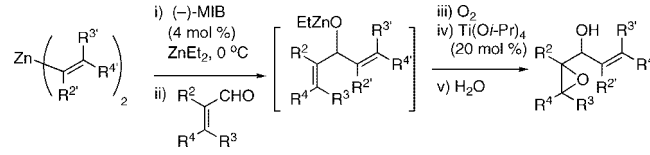
entry	$R^{4'}$	substrate	product	% ee (% y)	[dr]
1	C_4H_8Cl			99 (78)	[20 : 1]
2	*t*-Bu			98 (76)	[1 : 20]
3	*n*-Bu			99 (78)	[20 : 1]
4	*n*-Bu			90 (80)	[20 : 1]

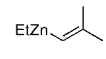
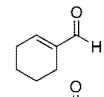
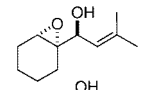
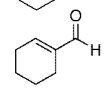
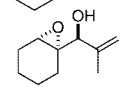
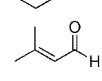
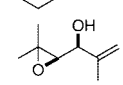
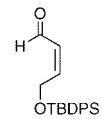
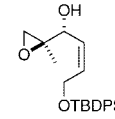
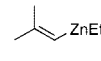
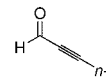
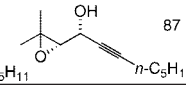
is to generate unsymmetric bis(allylic alkoxide) intermediates by vinylation of α,β-unsaturated aldehydes. The key to success in the chemoselective epoxidation is the electrophilic nature of the peroxy titanium species, which reacts faster with more electron-rich double bonds.

4.2.1. Epoxy Allylic Alcohols from in Situ Generated Vinylzinc Reagents. The first route begins with in situ generation of (*E*)-disubstituted vinylzinc reagents using Oppolzer's procedure,[43] followed by asymmetric vinylation of an enal (Table 9). The enal must bear non-hydrogen substituents in the R^2 or R^3 position such that $A^{1,2}$ or $A^{1,3}$ strain will be present in one of the diastereomeric epoxidation transition states. The unsymmetrical bis(allylic alkoxide) then undergoes a highly chemoselective directed epoxidation of the more electron-rich double bond while minimizing $A^{1,2}$ or $A^{1,3}$ strain. As can be seen in the examples in Table 9, this method was surprisingly successful.[17]

4.2.2. Epoxy Allylic Alcohols from Isolated Divinylzinc Reagents. The second route involves addition of an isolated and purified divinylzinc reagent to an enal (Table 10). In these cases, both of the allylic groups possess substitution patterns that lead to $A^{1,2}$ or $A^{1,3}$ strain in the diastereomeric epoxidation transition states. In chemoselective epoxidations it was found that endocyclic trisubstituted allylic alkoxides were epoxidized more rapidly than acyclic trisubstituted allylic alkoxides and trisubstituted allylic alkoxides were epoxidized faster than disubstituted derivatives (Table 10, entries 1−3). Epoxidation of the *cis* double bond in entry 4 was not observed due to deactivation by the electron-withdrawing silyl ether. In the case of vinyl additions to ynals (Table 10, entry 5), the epoxy alcohol product was generated with slightly lower enantioselectivity (87%) and with a 5:1 dr. Although it should be possible to raise the enantioselectivity by optimization of the chiral ligand structure, the reduced diastereoselectivity is a result of the small size of the alkyne, which results in a decreased energy difference between the diastereomeric epoxidation transition states.[17]

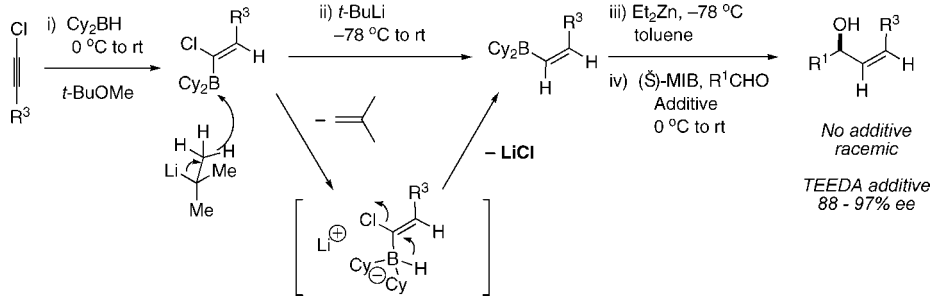
TABLE 10. Allylic Epoxy Alcohol Synthesis Using Purified Divinylzinc Reagents



entry	vinylzinc reagent	substrate	product	% ee (% y)	[dr]
1				96 (61)	[20 : 1]
2				95 (90)	[20 : 1]
3				91 (91)	[1 : 20]
4				95 (80)	[20 : 1]
5				87 (92)	[1 : 5]

4.3. Tandem Syntheses of Epoxy and Allylic Epoxy Alcohols from 1-Chloro-1-alkynes. Our tandem vinylation procedure of section 4.2.1 begins with hydroboration of terminal alkynes and proceeds via (*E*)-vinylzinc species, ultimately affording *trans*-disubstituted allylic epoxy alcohols. Complementary to this approach would be generation of the corresponding (*Z*)-vinylzinc reagents and their use in asymmetric addition to aldehydes. The difficulty is that nearly all hydrometalation reactions proceed via *cis* additions, while *trans* hydrometalation reactions are rare. Our approach to the generation of (*Z*)-vinylboranes in route to (*Z*)-vinylzinc reagents takes advantage of chemistry developed by Negishi,[45] Molan-

SCHEME 5. Proposed Reaction Pathway for the Generation of (*Z*)-Vinylboranes and Ultimately (*Z*)-Allylic Alcohols

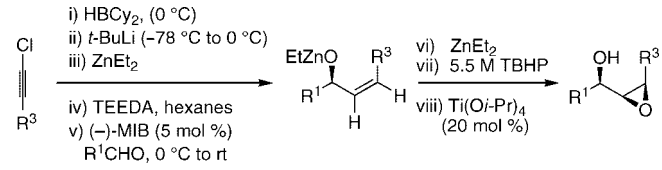


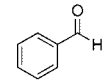
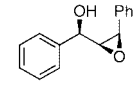
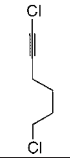
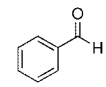
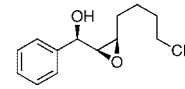
der,[46] and Brown.[47] It is known that hydroboration of 1-halo-1-alkynes proceeds with high regioselectivity to furnish 1-halo-1-alkenyl boranes (Scheme 5). The reaction of 1-halo-1-alkenyl boranes with hydride sources results in the exclusive generation of (*Z*)-vinylboranes. The resulting (*Z*)-vinylboranes are unreactive and have not been used outside of Suzuki cross-coupling reactions and oxidations. We envisioned transmetalation of the (*Z*)-vinylboranes to zinc followed by asymmetric addition under conditions used in the addition of (*E*)-vinylzinc reagents to aldehydes. We chose to use Molander's hydride source, *tert*-butyllithium, in the formation of the (Z)-vinylborane.[46] The reaction proceeded smoothly to afford (*Z*)-allylic alcohols in high yields and without contamination from (*E*)-allylic alcohols. However, the product was racemic.

We hypothesized that racemic product was formed in a rapid LiCl-catalyzed background reaction. Our approach to suppressing this undesirable process was to identify a selective inhibitor to bind the Lewis acidic LiCl yet not inhibit the (−)-MIB-based zinc Lewis acid catalyst. In a related study concerning the catalytic enantioselective synthesis of diarylmethanols,[48] we found that *N*,*N*,*N*′,*N*′-tetraethylethylene diamine (TEEDA) would chelate selectively to LiCl but not significantly inhibit the (−)-MIB-based catalyst. Thus, beginning with readily available 1-chloroalkynes, hydroboration, addition of *t*-BuLi, and transmetalation to zinc affords (*Z*)-vinylzinc intermediates. Next (–)-MIB, the diamine inhibitor TEEDA, and finally the aldehyde were added. Workup with water furnished the (*Z*)-disubstituted allylic alcohols with high enantioselectivity (Scheme 5).[49]

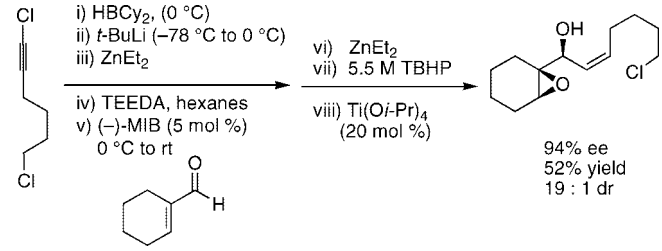
The generation and addition of (*Z*)-vinylzinc reagents to aldehydes was then applied to the synthesis of epoxy alcohols and (*Z*)-allylic epoxy alcohols. As illustrated in Table 11, preparation and addition of (*Z*)-vinylzinc reagents to aldehydes was performed as described above. The resulting allylic alkoxides were treated with diethylzinc, TBHP, and Ti(O*i*-Pr)$_4$ to perform the diastereoselective epoxidation. The epoxidation

TABLE 11. Tandem Syntheses of Epoxy and Allylic Epoxy Alcohols from Chloroalkynes



entry	vinylzinc reagent	substrate	product	% ee (% y)	[dr]
1				97 (59)	[19 : 1]
2				88 (67)	[19 : 1]

SCHEME 6. Tandem (*Z*)-Vinylation of an Enal Followed by Diastereo- and Chemoselective Epoxidation



proceeded with high diastereoselectivity because R^3 interacts with R^1 and causes A^{1,3} strain in the epoxidation transition states that leads to the minor diastereomer.

The asymmetric (*Z*)-vinylation reaction was also successfully employed in the synthesis of allylic epoxy alcohols as illustrated in Scheme 6.[49] In this fashion, the highly functionalized allylic epoxy alcohol could be prepared in good yield with high enantio-, diastereo-, and chemoselectivity.

The tandem reactions outlined in this section enable the efficient synthesis of an array of acyclic allylic alcohols in convenient one-pot procedures.

5. Outlook

The development of truly efficient, practical, and more environmentally friendly catalyst systems is an important goal in asymmetric catalysis and is central to green chemistry. Our approach to increase synthetic efficiency involves circumventing isolation and purification of the intermediates by conducting reactions in a tandem fashion. Furthermore, the same reagents have been used in both steps of the tandem process, as exemplified by titanium tetraisopropoxide, which promotes alkyl addition or allylation in the first step and epoxidation in the second step. We have employed dialkylzinc reagents in a similar fashion as an alkyl group donor that is converted to the oxidant in the epoxidation step. By reducing or eliminating solvents under our highly concentrated and solvent-free reaction conditions, circumventing intermediate purifications, and introducing processes where reagents have dual roles, we have increased the synthetic efficiency and environmental friendliness of our syntheses of enantio- and diastereoenriched epoxy alcohols.

In this Account, we outline a series of methods to prepare highly functionalized epoxy alcohols from simple ketone and aldehyde precursors. The reactions are initiated with Lewis acid catalyzed asymmetric carbonyl additions of organozinc or allylstannane reagents. In the case of ketone substrates, we have developed two novel catalysts for these processes. We have also introduced a new directed epoxidation process that involves reaction of dialkylzinc reagents with dioxygen or TBHP to generate the oxidant employed in the epoxidation. This new titanium/zinc-based epoxidation system is unique in that it is highly diastereoselective with substrates that possess either $A^{1,2}$ or $A^{1,3}$ strain in one of the diastereomeric epoxidation transition states. These developments have enabled the one-pot synthesis of a wide variety of acyclic enantio- and diastereoenriched epoxy alcohols and allylic epoxy alcohols that were previously not accessible or were difficult to prepare.

Given the rapid increase in molecular complexity with defined stereochemical outcome and the ease and efficiency of our one-pot procedures, we anticipate that these methods to synthesize stereodefined epoxy alcohols will be very useful in enantioselective target- and diversity-oriented synthesis.

We are grateful to the National Science Foundation (Grant CHE-0615210) and National Institutes of Health, National Institute of General Medical Sciences (Grant GM58101), for financial support of this work. P.J.W. is indebted to the talented students and postdoctoral researchers who made experimental and intellectual contributions to this chemistry.

BIOGRAPHICAL INFORMATION

Mahmud M. Hussain received his B.A in Chemistry from Bard College in 2005, where he was supported by a merit-based Distinguished Scientist Scholarship. He was an NSF-REU fellow with Professor John E. Baldwin at Syracuse University in 2004. In 2006, Hussain began his doctoral studies at the University of Pennsylvania under the direction of Patrick J. Walsh and is currently investigating applications of bimetallic reagents in organic synthesis. Hussain has received several awards such as the 2005 Ahmed Zewail Graduate Fellowship and 2003 ACS College Recognition Award.

Patrick J. Walsh received his B.A. from UC San Diego (1986) and Ph.D. in chemistry at UC Berkeley with Prof. Robert G. Bergman (Ph.D., 1991). He was an NSF postdoctoral fellow with Prof. K. B. Sharpless at the Scripps Research Institute. Moving across town from 1994−1999, he was an assistant professor at San Diego State University and also professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana, Mexico (1996−1999). In 1999, he moved to the University of Pennsylvania where he was promoted to associate professor in 2002, professor in 2005, and the Alan G. MacDiarmid Professor of Chemistry in 2008. Walsh has received several awards, most recent of which was the 2006 Philadelphia Section Award of the ACS. Walsh's interests are in asymmetric catalysis, development of new synthetic methods, reaction mechanisms, and inorganic synthesis. With Prof. Marisa Kozlowski, Walsh authored *Fundamentals of Asymmetric Catalysis*, which was published in August of 2008.

FOOTNOTES

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