Catalytic Asymmetric Allylation of Ketones and a Tandem Asymmetric Allylation/Diastereoselective Epoxidation of Cyclic Enones

Jeung Gon Kim, Karen M. Waltz, Iliana F. Garcia, David Kwiatkowski, and Patrick J. Walsh*

Contribution from the P. Roy and Diana T. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received April 19, 2004; E-mail: pwalsh@sas.upenn.edu

Abstract: A simple procedure is reported for the catalytic asymmetric allylation of ketones, utilizing titanium tetraisopropoxide, BINOL, 2-propanol additive, and tetraallylstannane as allylating agent. A variety of ketone substrates, including acetophenone derivatives and α,β-unsaturated cyclic enones, reacted to form tertiary homoallylic alcohols in good yields (67−99%) and with high levels of enantioselectivity (generally >80%). A novel one-pot enantioselective allylation/diastereoselective epoxidation has also been introduced. Thus, upon completion of the allyl addition to conjugated cyclic enones, 1 equiv of *tert*-butyl hydroperoxide is added and the directed epoxidation of the allylic double bond ensues to afford the epoxy alcohol with high diastereoselectivity.
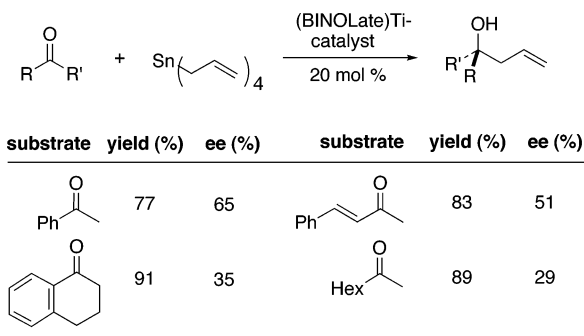
Introduction

Catalytic asymmetric additions of carbon-based nucleophiles to carbonyl groups constitute an important class of C−C bond-forming reactions that are of great value in synthetic organic chemistry.[1−5] Many catalysts will efficiently promote such additions to aldehydes; however, in almost all cases, those same catalysts fail to exhibit similar levels of reactivity and enantioselectivity with ketones.[1−5] As a result, the catalytic enantioselective synthesis of tertiary alcohols has remained a long-standing goal in asymmetric catalysis.[6] The synthetic potential of these challenging reactions has attracted considerable interest. Recent successes include efficient and highly enantioselective catalysts for the asymmetric addition of alkyl,[7−9] aryl,[10−13] and alkynyl[3,14,15] groups to ketones and alkyl[16,17] and alkynyl[18]

groups to α-keto esters.[19] We have been actively involved in the development of catalysts for this class of reactions.[7−9,11,20]

A related carbonyl addition reaction that has also attracted significant attention is the asymmetric allylation of aldehydes[21−37] and ketones.[4,5,37−40] The products of these reactions, secondary and tertiary homoallylic alcohols, are useful intermediates that have been used in organic synthesis.[41−48] Several closely related

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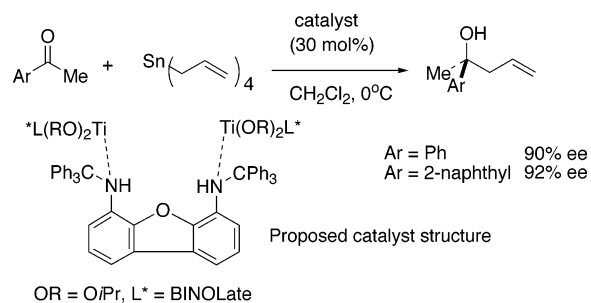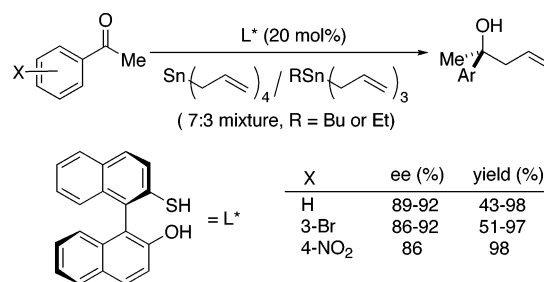(42) Marshall, J. A.; Liao, J. L. *J. Org. Chem.* **1998**, *63*, 5962−5970.

Scheme 1. Catalytic Asymmetric Ketone Allylation by Tagliavini and Co-workers[38]

substrate	yield (%)	ee (%)	substrate	yield (%)	ee (%)
Ph (acetophenone)	77	65	Ph (enone)	83	51
(tetralone)	91	35	Hex	89	29

catalysts for the allylation of aldehydes have been developed. Initial successes in this area were reported in 1993 from the groups of Tagliavini[24,25,30] and Keck,[21−23] who employed (BINOLate)Ti-based catalysts. The search for catalysts for the allylation of ketones that exhibit high levels of enantioselectivity, however, remained challenging for almost a decade.

We report herein the development of a highly enantioselective ketone allylation catalyst and define the substrate scope of this system. We find that high enantioselectivities are obtained with acetophenone derivatives (84−96%). In comparison with the three other catalysts that promote allylation of aryl methyl ketones,[37,38,40,49,50] our catalyst gives higher enantioselectivities with these substrates. Outside of our work, no substrates other than acetophenone derivatives give enantioselectivities above 71%.[50] As outlined in the Results and Discussion section, our catalyst gives high enantioselectivities with a wide range of previously unexplored substrates, including cyclic enones, making it the most general and enantioselective catalyst developed to date for the allylation of ketones.

Important early contributions in ketone allylation chemistry were made by several groups that set the stage for the development of catalysts for this reaction. For example, Baba and co-workers[39] reported the stoichiometric allylation of ketones employing tetraallylstannane in methanol with 200 mol % BINOL. Homoallylic alcohols were generated in this system with up to 60% ee.

Building on these results and their previous investigations into the asymmetric allylation of aldehydes,[24,30] Tagliavini and co-workers reported the first catalytic asymmetric allylation of ketones in 1999 (Scheme 1).[38] As outlined below, these workers employed a (BINOLate)Ti-based catalyst with tetraallylstannane. They observed formation of the ketone allylation product with up to 65% ee at 20 mol % BINOL and titanium tetraisopropoxide (80% ee with 40 mol % BINOL and titanium tetraisopropoxide).

Scheme 2. Catalytic Asymmetric Ketone Allylation by Maruoka and Co-workers[37]

Ar = Ph   90% ee
Ar = 2-naphthyl   92% ee

OR = OiPr, L* = BINOLate

Scheme 3. Catalytic Asymmetric Ketone Allylation by Woodward and Co-workers[49]

X	ee (%)	yield (%)
H	89−92	43−98
3-Br	86−92	51−97
4-NO2	86	98

The first highly enantioselective catalyst for the asymmetric allylation reaction was introduced by Maruoka and co-workers (Scheme 2).[37] This catalyst has the distinction of promoting the asymmetric allylation of both aldehydes and acetophenones. The catalyst, based on titanium tetraisopropoxide (60 mol %), BINOL (60 mol %), and a diamine ligand (30 mol %), gave 90 and 92% enantioselectivity with acetophenone and 2-acetonaphthone, respectively (Scheme 2). The scope of this catalyst with ketone substrates remains undefined, because only these two structurally similar ketones have been reported. The authors speculate that the role of the bridging ligand is to position the titanium centers such that they can both activate the substrate simultaneously.

Later, Woodward and co-workers[49,50] demonstrated that monothiobinaphthol will catalyze the allylation of acetophenone derivatives with a mixture of tri- and tetraallylstannane (Scheme 3). Two procedures were introduced; one gave higher enantioselectivities and low yields while the other gave lower enantioselectivities but high yields. Enantioselectivities of up to 92% were obtained with acetophenones (51% yield).

In addition to the substrate scope of our catalyst, we report here a one-pot asymmetric allylation/diastereoselective epoxidation reaction that results in the synthesis of functionalized 2,3-epoxy alcohols containing three contiguous stereogenic centers. Enantioenriched epoxy alcohols are among the most synthetically useful building blocks.[51−55] A portion of this work has been previously communicated.[20]

Experimental Section

General Methods. All reactions using titanium(IV) isopropoxide were carried out in a Vacuum Atmospheres drybox or under nitrogen

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using standard Schlenk techniques. All NMR spectra were obtained on either a Brüker 500 or 300 MHz Fourier transform spectrometer at the University of Pennsylvania NMR facility. ^{1}H NMR spectra were referenced to tetramethylsilane in CDCl$_3$ or residual protiated solvent in C$_6$D$_6$; ^{13}C{^{1}H} NMR spectra were referenced to residual solvent. The infrared spectra were obtained using a Perkin-Elmer 1600 series spectrometer. Thin-layer chromatography was performed on Whatman precoated silica gel 60 F-254 plates and visualized by ultraviolet light or by staining with ceric ammonium molybdate stain or phosphomolybdic acid hydrate stain. Silica gel (230−400 mesh, Silicycle) was used for air-flashed chromatography. All reagents were purchased from Aldrich, Acros, or Gelest chemical companies. Titanium(IV) isopropoxide, tetraallylstannane, 2-propanol, and all liquid ketone substrates were distilled prior to use and stored under an inert atmosphere. All glassware was flame- or oven-dried (150 °C). Full characterization of some of the products listed in Table 1 has been previously reported.[20] Only representative procedures and characterization of the products are described here. Full details can be found in the Supporting Information.

Procedures for the Enantioselective Allylation of Ketones. Preparation of 1-Allyl-2-pentyl-cyclopent-2-enol (General Procedure A). (*R*)-BINOL (42.9 mg, 0.15 mmol) was weighed into a Schlenk flask and purged with nitrogen. Dichloromethane (1 mL) and titanium(IV) isopropoxide (44.3 μL, 0.15 mmol) were then added, giving a red homogeneous solution. 2-Propanol (766 μL, 10 mmol) and tetraallylstannane (180 μL, 0.75 mmol) were added successively. The substrate, 2-pentyl-2-cyclopenten-1-one (82.6 μL, 0.5 mmol), was added and the reaction was stirred at room temperature until the solution turned pale yellow. After completion (48 h, TLC), the reaction was quenched with saturated aqueous NH$_4$Cl and extracted with dichloromethane (3 × 20 mL). The organic layer was dried over MgSO$_4$, and the solvent was removed under reduced pressure. Hexanes were added, and the solution was filtered through Celite and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexanes:EtOAc, 95:5) to give the product (89.0 mg, 92% yield, 94% ee) as an oil: [α]$^{20}_D$ = −7.62 (*c* = 0.315, MeOH); ^{1}H NMR (C$_6$D$_6$, 500 MHz) 0.90 (t, *J* = 6.9 Hz, 3H), 1.30 (m, 4H), 1.4−2.2 (m, 9H), 2.24 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.42 (dd, *J* = 13.6, 7.6 Hz, 1H), 4.9−5.1 (m, 2H), 5.35 (t, *J* = 1.8 Hz, 1H), 5.79 (m, 1H) ppm; ^{13}C{^{1}H} NMR (C$_6$D$_6$, 125 MHz) 14.3, 23.1, 26.3, 28.2, 29.2, 32.4, 38.3, 43.8, 85.5, 117.6, 125.5, 134.9, 148.6 ppm; IR (neat) 3362, 3075, 2927, 2856, 1640, 1458, 1378, 1164 cm^{-1}; HRMS calcd for C$_{13}$H$_{22}$O (M − H$_2$O)$^+$ 176.1565, found 176.1560.

Preparation of 1-Allyl-2-methyl-cyclopent-2-enol (General Procedure B). (*R*)-BINOL (25.7 mg, 0.09 mmol) was weighed into a Schlenk flask and purged with nitrogen. Dichloromethane (0.6 mL) and titanium(IV) isopropoxide (26.6 μL, 0.09 mmol) were added, giving a red homogeneous solution. 2-Propanol (459 μL, 6 mmol) and tetraallylstanne (108 μL, 0.45 mmol) were added successively. This mixture was maintained at room temperature under a static nitrogen atmosphere with stirring for 24 h. The substrate, 2-methyl-2-cyclopenten-1-one (29.5 μL, 0.3 mmol), was added, and the reaction was stirred at room temperature until the solution turned pale yellow (48 h). The reaction was worked up as outlined in general procedure A. The residue was purified by column chromatography on silica gel (pentane:Et$_2$O, 95:5) to give the product (31.2 mg, 75% yield, 87% ee) as an oil: [α]$^{20}_D$ = −9.10 (*c* = 1.165, CHCl$_3$); ^{1}H NMR (C$_6$D$_6$, 500 MHz) 1.11 (s, 1H),1.61 (dd, *J* = 3.8, 2.0 Hz, 3H), 1.67 (m, 1H), 1.9−2.15 (m, 3H), 2.18 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.36 (dd, *J* = 13.6, 7.5 Hz, 1H), 4.9−5.1 (m, 2H), 5.28 (m, 1H), 5.76 (m, 1H) ppm; ^{13}C{^{1}H} NMR (C$_6$D$_6$, 125 MHz): 11.7, 29.0, 38.0, 43.5, 85.0, 117.6, 127.2, 134.8, 143.91 ppm; IR (neat): 3364, 3076, 2925, 2854, 1640, 1438, 1376, 1164 cm^{-1}; HRMS calcd for C$_9$H$_{14}$O(M − H$_2$O)$^+$: 120.0939; found: 120.0937.
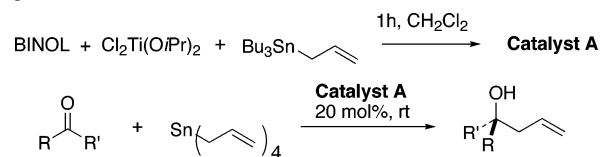
One-Pot Synthesis of Epoxy Alcohols. Preparation of 2-Allyl-1-pentyl-6-oxa-bicyclo[3.1.0]hexan-2-ol. (*R*)-BINOL (34.4 mg, 0.12

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mmol) was weighed into a Schlenk flask and purged with nitrogen. Dichloromethane (0.8 mL) and titanium(IV) isopropoxide (35.4 μL, 0.12 mmol) were added, giving a red homogeneous solution. 2-Propanol (612 μL, 8 mmol) and tetraallylstannane (144.4 μL, 0.6 mmol) were added successively. The substrate, 2-pentyl-2-cyclopenten-1-one (66 μL, 0.4 mmol), was added and the reaction was stirred at room temperature until it turned pale yellow (48 h). After the allylation reaction was complete (TLC), TBHP (80 μL, 5−6 M solution in decane, >0.4 mmol) was added. After 18 h, the reaction was quenched with saturated aqueous NH$_4$Cl and extracted with dichloromethane (3 × 20 mL). The remainder of the workup is identical to that in General Procedure A. The residue was purified by column chromatography on silica gel (hexanes:EtOAc, 95:5) to give the product (59.8 mg, 72% yield, 94% ee) as an oil. [α]$^{20}_D$ = 11.57 (*c* = 0.47, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) 0.90 (t, *J* = 6.8 Hz, 3H), 1.20−1.75 (m, 9H), 1.81−1.90 (m, 2H), 1.95−2.06 (m, 2H), 2.24 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.45 (ddd, *J* = 13.9, 7.0, 1.0 Hz, 1H), 3.38 (s, 1H), 5.10−5.22 (m, 2H), 5.84 (m, 1H) ppm; ^{13}C{^{1}H} NMR (CDCl$_3$, 75 MHz) 14.4, 22.9, 24.3, 25.9 (2C), 32.6, 33.5, 41.2, 62.1, 70.0, 81.3, 119.0, 133.4 ppm; IR (neat) 3472, 2930, 2859, 1641, 1462, 1379, 1174, 1113, 1055, 1000, 912, 887 cm^{-1}; HRMS calcd for C$_{13}$H$_{22}$O$_2$(MH)$^+$ 211.1718, found 211.1709.

Results and Discussion

Catalyst Development. At the time we initiated our investigations into the catalytic asymmetric allylation of ketones, the only reported example of this reaction was from Tagliavini and was based on titanium(IV) and BINOL.[38] Our interest in studying this reaction was to gain sufficient insight into the nature of the catalyst to expedite development of catalysts that exhibited increased levels of enantioselectivity. As shown in Scheme 4, the Tagliavini protocol involved precatalyst generation by reaction of Cl$_2$Ti(O*i*Pr)$_2$ and BINOL with allyltributylstannane. After mixing for 1 h, tetraallylstannane and the ketone substrate were added. Homoallylic alcohols were isolated in good yields and moderate enantioselectivities.
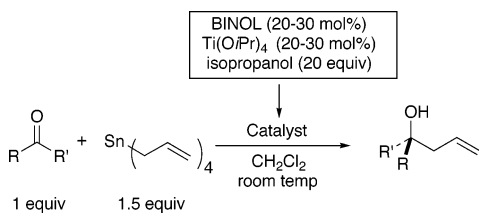
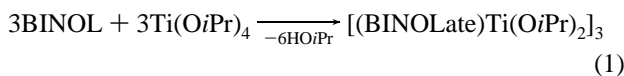**Scheme 4.** Catalyst Preparation and Ketone Allylation Using the Tagliavini Protocol[38]

In our initial experiments, we repeated the precatalyst synthesis introduced by Tagliavini[38] to investigate the structure of the resulting titanium complex. The procedure above was conducted in CDCl$_3$, and the resulting (BINOLate)Ti species was examined by NMR spectroscopy. Like Tagliavini[38] and co-workers, we observed production of tributyltin chloride. We were surprised to find, however, that the main (BINOLate)Ti-containing product was (BINOLate)Ti(O*i*Pr)$_2$, which is dimeric in solution and trimeric in the solid state.[56,57] We were able to identify this compound, because we had previously prepared it for use in a mechanistic study,[58] and we reported a high-quality crystal structure of this complex.[57] It can be prepared on a multigram scale by mixing titanium tetraisopropoxide and

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Scheme 5. Our Procedure for the Catalytic Asymmetric Allylation of Ketones

BINOL, followed by removal of the solvent and liberated 2-propanol (eq 1).[57] Using isolated [(BINOLate)Ti(O*i*Pr)$_2$]$_3$ in

$$3\text{BINOL} + 3\text{Ti}(\text{O}i\text{Pr})_4 \xrightarrow[-6\text{HO}i\text{Pr}]{} [(\text{BINOLate})\text{Ti}(\text{O}i\text{Pr})_2]_3$$

(1)

place of catalyst A (Scheme 4), we found that the enantiose-lectivities in the allylation reaction were very similar to those reported by Tagliavini, suggesting that the same catalyst was involved in both allylation protocols.

A key discovery was made when the catalyst was prepared directly from a 1:1 mixture of titanium tetraisopropoxide and BINOL (20 or 30 mol %) without removal of the liberated 2-propanol. Utilizing this catalyst preparation, the enantiose-lectivity in the asymmetric allylation with our test substrate, 3-methylacetophenone, rose from 51% to 73%. These results suggested to us that the liberated 2-propanol had a beneficial impact on the enantioselectivity of the catalyst. We then performed a series of experiments preparing the catalyst from titanium tetraisopropoxide, BINOL, and increasing amounts of 2-propanol. As the concentration of 2-propanol was raised, the enantioselectivity of the catalyst climbed, peaking at 96% where the ratio of 2-propanol:substrate was 20:1 (Scheme 5). A further increase in the amount of 2-propanol to 100 equiv resulted in a slight decrease in the ee of the tertiary homoallylic alcohol. Interestingly, the asymmetric allylation reaction can be per-formed in neat 2-propanol, giving an enantioselectivity of 92%. This surprising result indicates that the affinity of the BINOL for the titanium is sufficiently high that it can compete effectively with a large excess of 2-propanol.

Mechanistic studies on group(IV) alkoxide-based catalysts are notoriously difficult, because of the tendency of these elements to oligomerize.[59,60] The same attributes that render them efficient catalysts, such as their rapid exchange of alkoxide ligands, cause them to be difficult to study. Not surprisingly then, little solid mechanistic information has been reported for (BINOLate)Ti-based catalysts, despite their successful applica-tion to asymmetric catalysis.[61] Further complicating the issue is the tendency of these complexes to form bridging-oxo complexes that likely play a significant role in some group(IV)-based asymmetric catalysts.[62-68] Unfortunately, mechanistic

Table 1. Asymmetric Allylation of Ketones (Scheme 5)[a]

entry	substrate	product	yield (%)[b]	ee (%)[c]
1	3-Me		82	96
2	4-OMe		99	89
3	3-CF$_3$		93	92
4	2-Me		77[d]	84
5			96	95
6[e]			99	87
7			88	90
8			99	90
9[e]			95	83
10			96	80
11			99	76
12			67	84

[a] Reactions run with 30 mol % catalyst except for entry 1, where 20 mol % was used. [b] Isolated yields. [c] Ee's determined by GC or HPLC (see Supporting Information for conditions). [d] 7% recovered substrate after 4.5 d. [e] Reactions run at 0 °C.

studies on our asymmetric allylation procedure have been complicated by an induction period.[69] As a result, the role of the 2-propanol remains elusive at this time.

Allylation of Simple Ketones. The results of our catalytic asymmetric allylation of ketones are presented in Table 1. Only a marginal electronic influence with substituted acetophenones was observed, as 4-methoxy- and 3-(trifluoromethyl)acetophe-none underwent allylation with similar enantioselectivities (89 and 92%, entries 2 and 3). Increasing the size of the aryl group, as in 2-methyl acetophenone, resulted in a reduction in enan-tioselectivity (84%) and turnover frequency, with the allylation product formed in 77% yield after 4.5 d (entry 4).

The cyclic ketone, α-tetralone, is an excellent substrate for our catalyst, exhibiting an enantioselectivity of 95% with 96% yield (entry 5). Employing 1-indanone resulted in slightly lower enantioselectivity (87%, entry 6). Allylation of acyclic conju-gated enones gave exclusive 1,2-allylation products in high yield and enantioselectivity (entries 7−9). Interestingly, the saturated

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4-phenyl-2-butanone reacted to give the homoallylic alcohol in 80% ee (compare entries 8 and 10). The enantioselectivity of 80% with this dialkyl ketone is impressive, given that the catalyst must differentiate between the carbonyl oxygen lone pairs syn to a methyl vs syn to a methylene group.

The functionalized 3-chloropropiophenone exhibited moderate enantioselectivity (76%). Reaction of the heteroaromatic substrate acetylfuran under the conditions described in Scheme 5 furnished the homoallylic alcohol in 84% ee.

It should be noted that, when handling tertiary benzylic or allylic alcohols, caution must be exercised during workup and purification to avoid erosion of the enantiomeric excess through partial racemization.

Allylation of Cyclic Enones. Despite the level of interest in the catalytic asymmetric allylation of ketones, no examples of reactions with cyclic α,β-unsaturated ketones have been reported to our knowledge. This is, however, the most useful class of substrates for applications in organic synthesis. The products are densely functionalized, possessing both allylic and homoallylic double bonds that can be selectively elaborated.

Preliminary experiments in the enantioselective allylation of cyclic α,β-unsaturated enones in Scheme 5 revealed the importance of the 2-substituent for obtaining high enantioselectivity. Reaction of 2-cyclohexenone under the catalytic conditions resulted in generation of the product with only 11% enantioselectivity. In contrast, 2-substituted cyclic enones exhibited high levels of enantioselectivity (Table 2). The presence of the 2-substituent allows the catalyst to readily differentiate between the two lone pairs on the carbonyl oxygen. Five-, six-, and seven-membered enones with endocyclic double bonds proved to be very good substrates for the asymmetric allylation catalyst, giving 87−96% ee (Table 2, entries 2−6). 2-Bromo-2-cyclohexenone exhibited slightly lower enantioselectivity (84%), most likely due to the increased reactivity of this substrate as a result of the inductive effect of the halogen (entry 7). Presumably, the vinylic bromide of the product can participate in coupling reactions, allowing elaboration at this position.

The presence of a proximal hydroxyl group, as in 2-hydroxymethyl-cyclohexenone (entry 8), was detrimental to the enantioselectivity, probably due to chelation to the titanium catalyst. Protection of the alcohol with a TBS group resulted in an increase in the enantioselectivity to 85% and the yield to 88% (entry 9). Enones possessing exocyclic double bonds were excellent substrates, giving enantioselectivities of 91−96% (entries 10 and 11). The results listed in Tables 1 and 2 demonstrate the broad range of substrates that can be transformed into homoallylic alcohols with high levels of enantioselectivity.
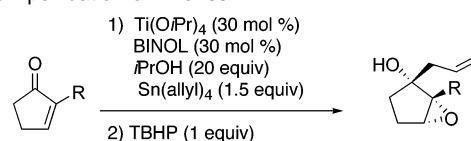
Tandem Allylation/Epoxidation Reaction. An important goal in asymmetric synthesis is the development of tandem reactions to rapidly increase molecular complexity with minimal isolation and purification.[70] The tertiary alcohols in Table 2 are suitable substrates for pursuit of this objective. With this aim in mind, we desired to transform the alcohol products through chemo- and diastereoselective directed epoxidation of the allylic double bond. Our approach involved exploitation of the titanium catalyst employed in the asymmetric allylation to conduct a diastereoselective epoxidation reaction. Thus, after the ketone

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Table 2. Asymmetric Allylation of α,β-Unsaturated Enones

entry	substrate	product	yield (%)[a]	ee (%)[b]
1			75	11
2	n-Pen	n-Pen	92	94
3			75	87
4			84	96
5			86	90
6			99	88
7	Br	Br	84	84
8	OH	OH	80	50
9	OTBS	OTBS	88	85
10	Ph	Ph	99	96
11	Ph	Ph	82	91

[a] Isolated yields. *[b]* Ee's determined by GC or HPLC (see Supporting Information for conditions).

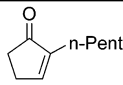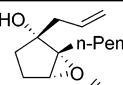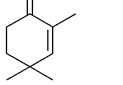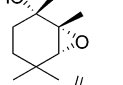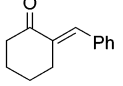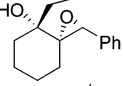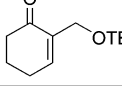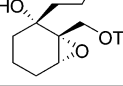***Scheme 6.*** Tandem Asymmetric Allylation/Diastereoselective Directed Epoxidation of Enones

allylation was conducted in the usual fashion, 1 equiv of anhydrous *tert*-butyl hydroperoxide (TBHP) was added to the reaction mixture. The epoxidation proceeded readily at room temperature to afford the syn epoxy alcohols (Scheme 6, Table 3). The representative substrates examined exhibited good yields for this tandem reaction (72−89%). No erosion in ee during the epoxidation was observed, and only a single diastereomer was detected in each case by NMR spectroscopy and GC analysis. In contrast, the epoxy alcohol in entry 1 of Table 3 was generated as a 10:1 ratio of the syn:anti diastereomers on epoxidation of the isolated allylic alcohol with *m*-CPBA.

The tandem asymmetric allylation/diastereoselective epoxidation reaction is operationally simple and circumvents the need to isolate and purify the intermediate allylic alcohols. Beginning from achiral precursors, this one-pot sequence effects the

Table 3. One-Pot Synthesis of Epoxy Alcohols

entry	substrate	product	yield (%)[a]	ee (%)[b]
1			72	94
2			84	96
3			89	95
4			88	88

[a] Isolated yields. [b] Ee's determined by GC or HPLC (see Supporting Information for conditions).

generation of three contiguous stereocenters with excellent enantio- and diastereoselectivity and with high yields. Such procedures are important to increase synthetic efficiency.

Summary. We have developed a (BINOLate)Ti-based catalyst for the asymmetric allylation of ketones. The catalyst exhibits good to excellent levels of enantioselectivity across a broad range of substrates. It is noteworthy that high enantioselectivities were obtained with a variety of cyclic enone substrates, providing access to tertiary alcohols possessing both allylic and homoallylic double bonds. This class of substrates was previously unexplored. The resultant enantioenriched products are, however, particularly useful intermediates in synthesis, because the double bonds can be differentially functionalized. This is exemplified by a novel tandem asym-

metric allylation/diastereoselective epoxidation reaction introduced here that chemoselectively oxidizes the allylic double bond. This epoxidation utilizes the titanium catalyst employed in the asymmetric allylation step to catalyze the epoxidation with TBHP, resulting in high diastereoselectivity and yield. It is well known that enantioenriched epoxy alcohols are among the most useful intermediates in synthetic organic chemistry, as demonstrated by their widespread application.[52,54,55] The tandem one-pot method introduced in this study provides easy access to functionalized chiral building blocks which would be otherwise difficult to prepare.

The titanium−BINOL-based catalyst describe herein is the most general and enantioselective catalyst for the asymmetric allylation of ketones to date. The catalyst is easily prepared in situ, and reactions are conveniently conducted under a nitrogen atmosphere at room temperature. This method also offers the option of further elaboration of the product through a diastereo- and chemoselective epoxidation of allylation products that possess allylic alcohols.[71]

Supporting Information Available: Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(71) After this manuscript was accepted, a related paper appeared: Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *125*, 8910−8911.