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Asymmetric epoxidation of *cis*-alkenes with arabinose-derived ketones: enantioselective synthesis of the side chain of Taxol®

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Abstract—The ee values of asymmetric epoxidation of *cis*-ethyl cinnamate **15** with arabinose-derived ketones as catalyst and Oxone® as the terminal oxidant were found to increase inversely with the size of the catalyst acetal blocking group. Ketone catalyst **2**, with the least bulky methoxy acetal group, displayed the best enantioselectivity and afforded ethyl (2*R*,3*R*)-3-phenylglycidate **16** in 68% ee. Epoxide **16** was readily converted into a protected side chain of Taxol® in five steps with an overall yield of 89%. The enantioselectivity of the epoxidation of other *cis*-alkenes was moderate to poor.

1. Introduction

Catalytic asymmetric epoxidation of alkenes is a versatile synthetic method used to induce chirality into organic molecules and the resultant epoxide moiety can be transformed into a variety of target molecules.[1] Great success has been achieved in the epoxidation of allylic alcohols,[2] *trans*- and trisubstituted alkenes.[3–11] For asymmetric epoxidation of unfunctionalized *cis*-alkenes, Mn-salen catalyst is very effective and practical.[12] In recent years, chiral ketones[13] and iminium salts,[14] also have become promising reagents for asymmetric epoxidation of unfunctionalized *cis*-alkenes.

Our long-term interest in the application of carbohydrates in asymmetric synthesis has employed arabinose-derived alcohols as chiral auxiliaries in asymmetric Diels–Alder[15] and Hosomi–Sakurai reactions.[16] Our efforts towards enantioselective epoxidation of alkenes have furnished chiral ketone catalysts derived from D-glucose[17] as well as 2-uloses and 3-uloses derived from L-arabinose.[18] We then have concentrated our research on arabinose because it is commercially available in large quantities for both enantiomers. Recently, we reported a series of arabinose-derived 4-uloses,[19] containing a tunable steric blocker, which displayed increasing enantioselectivity with the size of the acetal alkoxy group in catalytic asymmetric epoxidation of *trans*-disubstituted and trisubstituted alkenes. However, most organocatalytic epoxidization of *cis*-alkenes proceeded with moderate enantioselectivity.[13,14] In this paper, we report our study of the asymmetric epoxidation of *cis*-alkenes with arabinose-derived ketones, using Oxone® as an oxidant and the conversion of ethyl (2*R*,3*R*)-3-phenylglycidate into a protected side chain of Taxol®.

2. Results and discussion

Dimethyl acetal **1**[19,20] was readily accessible from L-arabinose in two steps involving Fischer glycosidation[21] and *trans*-diol protection[22] with 2,2,3,3-tetramethoxybutane in 76% overall yield. Oxidation of the free alcohol in **1** with pyridinium dichromate (PDC) gave ketone **2** in 90% yield. Ketones **8**–**12** were readily accessible from dimethyl acetal **1** via transacetalization[23] and oxidation in good overall yields (Scheme 1).[19]

We also prepared a ketone catalyst **14**, which had a dioxane in place of the diacetal unit. Reduction of acetal **1** using Et_3SiH and $BF_3 \cdot Et_2O$[24] in acetonitrile gave 1,4-dioxane **13** in 88% yield. Oxidation of the free alcohol in **13** with PDC afforded ketone **14** in 92% yield (Scheme 2). In the ^1H NMR spectrum, the coupling constant between the two new protons in ketone **14** was 9.0 Hz, which showed that they were diaxially disposed.

On the basis of our previous studies,[17–19] the enantioselectivity towards *trans*-disubstituted and trisubstituted alkenes is sensitive to the size of the acetal steric blocker. For example, ketone **10** with a more bulky neopentyl acetal group displayed better chiral induction than ketone **2**, as the ee of epoxidation of *trans*-stilbene was improved from 42% to 83%.[19a] Encouraged by these results, we went on to investigate the chiral induction capabilities of these ketones in the asymmetric epoxidation of *cis*-ethyl cinnamate, a starting material for the synthesis of Taxol® side chain.[25]

Keywords: Asymmetric synthesis; Dioxirane; Epoxidation.
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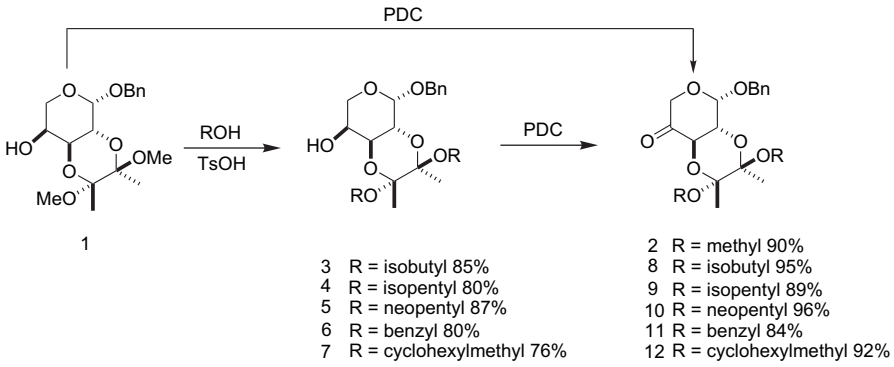
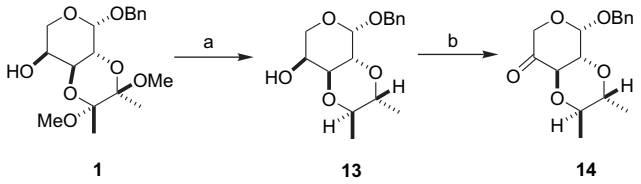


Scheme 1. Preparation of chiral ketone catalysts.



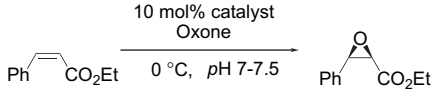
Scheme 2. Reagents and conditions: (a) $BF_3 \cdot Et_2O$ (3 equiv), Et_3SiH (6 equiv), CH_3CN, −20 °C→0 °C, 8 h, 88%; (b) PDC (1.5 equiv), 4 Å MS, CH_2Cl_2, rt, 12 h, 92%.

Chemical synthesis of Taxol® side chain has drawn much attention during the past decade.[26–28] Asymmetric epoxidation catalyzed by the readily available and low costing (salen)-Mn(III) complex on *cis*-ethyl cinnamate **15** was reported by Jacobsen.[12d] Since only *trans*-ethyl cinnamate is commercially available, the desired *cis*-ethyl cinnamate **15** was synthesized (Scheme 3).[12d] Partial reduction of ethyl phenyl propiolate with Lindlar catalyst under H_2 gave the desired *cis*-ethyl cinnamate **15** in high yield (Scheme 3).[29]

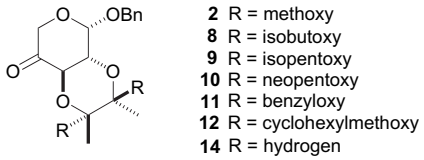
Scheme 3. H_2, Lindlar catalyst, *n*-hexane, 96%.

The epoxidation reactions were carried out at 0 °C with 0.1 mmol of alkene and 10 mol % of catalyst in different solvents at almost neutral conditions (pH 7–7.5). Table 1 shows that acetonitrile (entry 1) was more suitable than *tert*-butanol and 1,4-dioxane as a solvent (entries 2 and 3). In all cases, the epoxides were isolated in high chemical yields (79–95% yield), indicating that all the ketones are efficient catalysts in terms of turnover. Ketones **2** and **14**, with the least bulky blocking groups, displayed the best chiral induction (67–68% ee) (entries 1 and 9). Ketones with bulkier acetal groups did not display better chiral induction with *cis*-alkene **15** as the ee decreased from 68% to 63% in the best case (entries 1 and 7). When the R group changes to the very bulky isopentoxy and neopentoxy groups (entries 5 and 6), the ee drops to 44% and 36%, respectively. It is noteworthy that ketone **10**, with the most bulky neopentoxy group, gave the poorest results (36% ee) whereas this ketone afforded the best enantioselectivities with *trans*-disubstituted and trisubstituted alkenes.[19a] Anyway, ethyl (2*R*,3*R*)-3-phenylglycidate

Table 1. Asymmetric epoxidation of *cis*-ethyl cinnamate using ketones **2**, **8**–**12** and **14** as catalysts at 0 °C



Catalysts:



Entry[a]	Catalysts	Solvent	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**2**	CH_3CN	93	68	(+)-(2*R*,3*R*)[25]
2	**2**	^tBuOH	85	37	(+)-(2*R*,3*R*)[25]
3	**2**	1,4-dioxane	95	61	(+)-(2*R*,3*R*)[25]
4	**8**	CH_3CN	83	56	(+)-(2*R*,3*R*)[25]
5	**9**	CH_3CN	79	44	(+)-(2*R*,3*R*)[25]
6	**10**	CH_3CN	84	36	(+)-(2*R*,3*R*)[25]
7	**11**	CH_3CN	93	63	(+)-(2*R*,3*R*)[25]
8	**12**	CH_3CN	87	49	(+)-(2*R*,3*R*)[25]
9	**14**	CH_3CN	93	67	(+)-(2*R*,3*R*)[25]

[a] All epoxidations were carried out with substrate (0.1 mmol), ketone (0.01 mmol), Oxone® (1 mmol) and $NaHCO_3$ (3.1 mmol) in CH_3CN/4×10^{-4} M aqueous EDTA (5:1, v/v) for 24 h.
[b] Isolated yield.
[c] Enantioselectivity was determined by ^1H NMR analysis of the epoxide products directly with shift reagent Eu(hfc)$_3$.
[d] The absolute configuration of the enantiomer in excess was determined by comparing the sign of the optical rotation with the reported one.

16 was obtained in 68% ee using ketone **2** as the catalyst, which is better than existing chiral ketone catalysts (Shi's 44% ee[13d] and Seki's 26% ee[30]). The Jacobson (salen)-Mn(III) catalyst (95–97% ee) is still the best choice for this epoxidation.[12d]

In our previous studies, we have presented a facile and stereocontrolled synthetic avenue for the construction of the functionalized CD ring of Taxol®.[31] With ethyl (2*R*,3*R*)-3-phenylglycidate **16** readily accessible, we now describe a synthesis of a protected form of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine **17** (Fig. 1), Taxol® side chain.

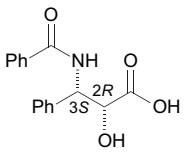


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Figure 1. *N*-benzoyl-(2*R*,3*S*)-phenylisoserine.

Asymmetric epoxidation catalyzed by catalyst **2** gave epoxide **16** in 93% yield with 68% ee (Scheme 4). The optical rotation of epoxide **16** was positive in sign, which is in agreement with the literature data of the enantiomerically enriched product.[25] Mild acid catalyzed epoxide opening at the benzylic position with NaN_3 and NH_4Cl gave azide **18**, which was then benzoylated under standard conditions to give benzoate **19** in 94% yield. The azide was readily reduced under hydrogenolysis conditions to give an amine. Owing to the stability of an amide being greater than that of an ester, the benzoyl group migrated to the amine group in the presence of *p*-TsOH[27b] to give benzamide **20** in very good yield. To prevent the epimerization of the hydroxyl group during further manipulation, protection became necessary, which was accomplished by acetalization using 2-methoxypropene in PPTS to give acetal **21** in 98% yield. The ee of **21** was determined to be 68% using ^1H NMR spectral analysis with chiral shift reagent, Eu(hfc)$_3$. Under basic conditions (LiOH, MeOH, H_2O), the ester **21** was saponified to give acid **22** in 93% yield as a crystalline solid.

At this point, the ee of acid **22** was at best 68%. Huge efforts to increase the ee of **22** were made using recrystallization, the excess amount of the desired (2*R*,3*S*)-enantiomer still remained in the mother liquor. An X-ray crystallographic analysis of a crystal confirmed the structure of acid **22** (Fig. 2).

The specific rotations of the crystals and the concentrated mother liquor were measured. As shown in Scheme 5, the crystals gave almost no specific rotation, which hinted at a racemic mixture. On the other hand, the specific rotation of the mother liquor was +70 and the literature value[27a] for the enantiomerically enriched acid was +99.1. Enantiomeric excess measurement using chiral shift reagent was performed to determine the relative amount of the enantiomers in the mixture. The results showed that the ee of the mother liquor was 82% while that of the crystal counterpart was only 5%.[32]

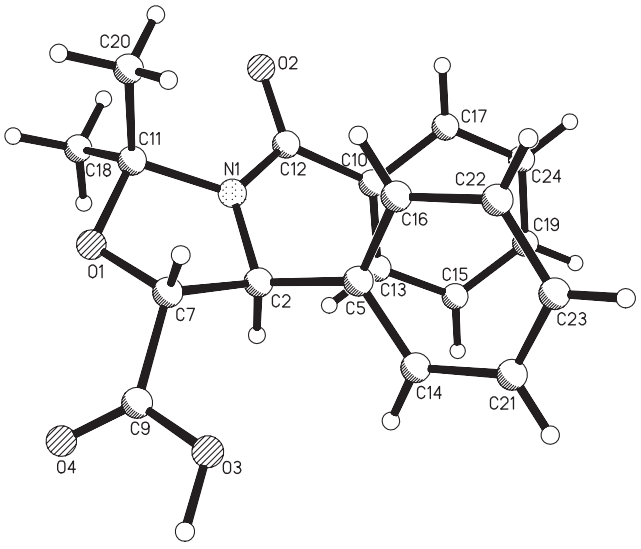
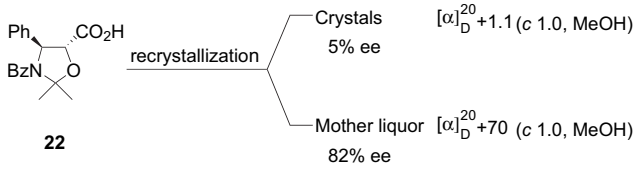


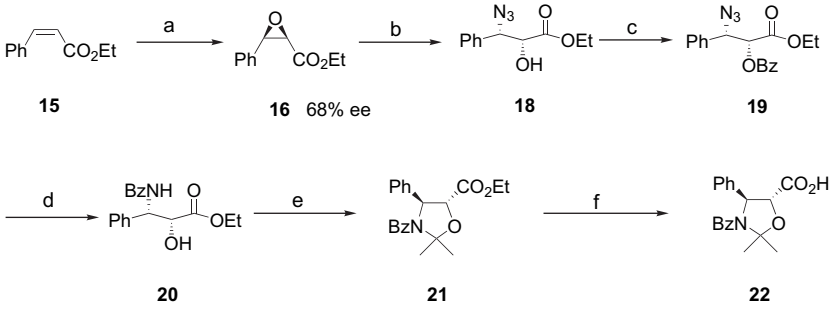
Figure 2. X-ray structure of acid **22** (ORTEP view) (CCDC no. 185892).



Scheme 5. Specific rotations of solid **22** and liquid **22**.

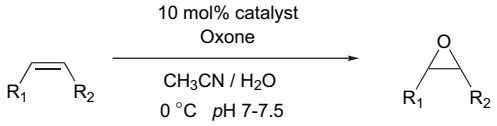
The asymmetric epoxidation of other *cis*-alkenes was studied using ketones **2**, **10**, **11** and **14** as catalysts and the results are shown in Table 2. In all cases, the epoxides were isolated in high chemical yields (80–96% yield), indicating that all the ketones are conversion-efficient. Ketones **14** and **2**, with the least bulky group, again consistently displayed the best chiral induction (12–33% ee) (entries 1, 2, 5, 6, 9, 10, 13 and 14) among the ketones except for entry 9. Ketones **10** and **11** with the more bulky acetal group consistently displayed poor results.

On the basis of the established spirol transition states[6i,10h] for chiral dioxirane epoxidation and of our previous studies on *trans*- disubstituted and trisubstituted alkenes,[18,19] we found

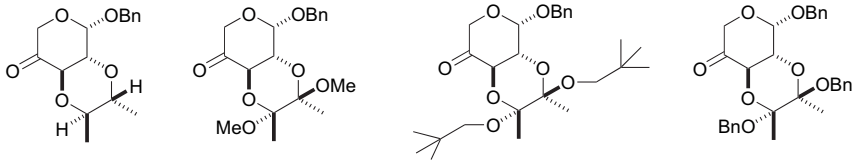


Scheme 4. Reagents and conditions: (a) catalyst **2** (0.1 equiv), Oxone® (9 equiv), $NaHCO_3$ (29 equiv), CH_3CN–EDTA (1:1, v/v), 93%; (b) NaN_3 (2 equiv), NH_4Cl, EtOH, reflux, 92%; (c) Et_3N (4 equiv), DMAP, BzCl (1.5 equiv), 94%; (d) H_2, 10% Pd/C, *p*-TsOH, 98%; (e) 2-methoxypropene (10 equiv), PPTS, toluene, reflux, 98%; (f) LiOH (2 equiv), MeOH, H_2O, 93%.

Table 2. Asymmetric epoxidation of *cis*-alkenes using ketones **2**, **10**, **11** and **14** as catalysts at 0 °C

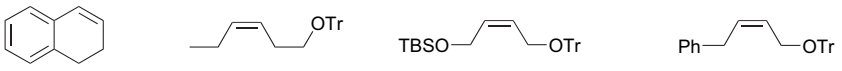


Catalysts:



14 **2** **10** **11**

Substrates:



a **b** **c** **d**

Entry[a]	Catalysts	Substrates	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**14**	a	93	33	(−)-(1*S*,2*R*)[33]
2	**2**	a	93	32	(−)-(1*S*,2*R*)[33]
3	**10**	a	81	11	(−)-(1*S*,2*R*)[33]
4	**11**	a	85	11	(−)-(1*S*,2*R*)[33]
5	**14**	b	84	17	(+)[e]
6	**2**	b	88	14	(+)[e]
7	**10**	b	80	9	(+)[e]
8	**11**	b	86	3	(+)[e]
9	**14**	c	92	12	(+)[e]
10	**2**	c	92	21	(+)[e]
11	**10**	c	83	5	(+)[e]
12	**11**	c	81	6	(+)[e]
13	**14**	d	96	24	(+)[e]
14	**2**	d	93	18	(+)[e]
15	**10**	d	80	8	(+)[e]
16	**11**	d	88	8	(+)[e]

[a] All epoxidations were carried out with substrate (0.1 mmol), ketone (0.01 mmol), Oxone® (1 mmol) and $NaHCO_3$ (3.1 mmol) in $CH_3CN/4\times10^{-4}$ M aqueous EDTA (5:1, v/v) for 24 h.
[b] Isolated yield.
[c] Enantioselectivity was determined by ^1H NMR analysis of the epoxide products directly with shift reagent $Eu(hfc)_3$.
[d] The absolute configuration of the enantiomer in excess was determined by comparing the sign of the optical rotation with the reported one.
[e] The major absolute configurations were not determined.

that the enantioselectivity was sensitive and increased with the size of the acetal steric blocker.[19] However, in the present case with *cis*-alkenes, the ee increases inversely with the size of the blocking groups. These evidences showed that the transition state for epoxide formation of *cis*-alkenes may be different with that of *trans*-alkenes. In order to rationalize all the possible transition states and the corresponding stereochemistry of the epoxides, more *cis*-alkene substrates need to be investigated. This research is underway.

In conclusion, the ee of the asymmetric epoxidation of *cis*-alkenes decreased with the size of the acetal blocking groups using arabinose-derived ketones. Ketone catalyst **2** with the least bulky acetal group displayed the best enantioselectivity and afforded ethyl (2*R*,3*R*)-3-phenylglycidate **16** in 69% ee. Epoxide **16** was converted into acid **22**, the protected side chain of Taxol®, in five steps with an overall yield of 89%.

3. Experimental

3.1. General

For general experimental section and procedure for ee determination, see Ref. 15a.

3.1.1. General epoxidation procedure at 0 °C. To a stirred solution of 1,2-dihydronaphthalene (0.1 mmol), ketone (10 mol %) and *n*-Bu_4NHSO_4 (0.5 mg) in CH_3CN (10 mL) was added an aqueous buffer (5 mL, 4×10^{-4} M aqueous EDTA). The resulting solution was cooled to 0 °C (bath temperature). A solution of Oxone® (307 mg, 0.5 mmol) in aqueous EDTA (5 mL, 4×10^{-4} M) and a solution of $NaHCO_3$ (252 mg, 3.0 mmol) in H_2O (5 mL) were added dropwise concomitantly via two dropping funnels. The pH of the mixture was maintained at about 7–7.5 over a period of 24 h. The reaction mixture was then poured into water

(10 mL), extracted with Et_2O (3×), dried with anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by flash column chromatography to give the epoxide.

3.1.2. Alcohol 13. To a solution of dimethyl acetal **1** (160 mg, 0.45 mmol) in dry CH_3CN (8 mL) at −20 °C was added slowly $BF_3\cdot Et_2O$ (0.17 mL, 1.35 mmol). The mixture was stirred for 1 h and Et_3SiH (0.43 mL, 2.71 mmol) was added at −20 °C. The temperature of the resulting mixture was raised to 0 °C and stirred for another 8 h. The cooled reaction mixture was then treated with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to give alcohol **13** as a pale yellow syrup (117 mg, 88%): R_f 0.30 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +140.03 (*c* 1.64, $CHCl_3$); IR (thin film) 3473 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.17 (5H, m), 4.91 (1H, d, *J*=1.8 Hz), 4.70 (1H, d, *J*=12.6 Hz), 4.56 (1H, d, *J*=12.3 Hz), 3.89 (1H, d, *J*=1.5 Hz), 3.80 (2H, m), 3.75 (1H, d, *J*=1.5 Hz), 3.66 (1H, dd, *J*=12.6, 1.8 Hz), 3.48 (1H, dq, *J*=8.7, 6.2 Hz), 3.32 (1H, dq, *J*=9.0, 6.3 Hz), 2.08 (1H, br s), 1.09 (3H, d, *J*=6.3 Hz), 1.06 (3H, d, *J*=6.0 Hz); ^{13}C NMR (acetone) δ 139.5, 129.3, 128.7, 128.5, 98.4, 78.4, 78.3, 74.4, 74.0, 69.9, 68.9, 64.8, 18.0, 17.9; MS (EI) *m/z* (relative intensity) 294 ([M]$^+$, 100), 295 (15); HRMS (EI) calcd for $C_{16}H_{22}O_5$ [M]$^+$ 294.1462, found 294.1461; Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 64.94; H, 7.69.

3.1.3. Ketone 14. To a solution of alcohol **13** (170 mg, 0.57 mmol) in dry CH_2Cl_2 (10 mL) were added slowly PDC (261 mg, 0.69 mmol) and powdered 4 Å molecular sieves (260 mg). The mixture was stirred at room temperature for 12 h. The mixture was suction filtered through a pad of silica gel and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford ketone **14** as a colourless syrup (154 mg, 92%): R_f 0.22 (hexane–EtOAc, 1:1); $[\alpha]_D^{20}$ +136.43 (*c* 5.98, $CHCl_3$); IR (thin film) 1742 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37–7.26 (5H, m), 5.08 (1H, d, *J*= 3.3 Hz), 4.79 (1H, d, *J*=12.3 Hz), 4.70 (1H, d, *J*=12.3 Hz), 4.59 (1H, d, *J*=10.2 Hz), 4.15 (1H, d, *J*=14.7 Hz), 3.86 (1H, d, *J*=14.7 Hz), 3.74 (1H, dd, *J*=10.4, 3.3 Hz), 3.45 (1H, dq, *J*=9.0, 6.3 Hz), 3.34 (1H, dq, *J*=8.7, 6.3 Hz), 1.17 (3H, d, *J*=6.3 Hz), 1.14 (3H, d, *J*=6.0 Hz); ^{13}C NMR ($CDCl_3$) δ 199.3, 136.5, 128.1, 127.6, 127.3, 96.0, 77.3, 77.2, 76.9, 76.4, 69.7, 66.3, 16.7, 16.4; MS (EI) *m/z* (relative intensity) 292 ([M]$^+$, 100), 290 (35); HRMS (EI) calcd for $C_{16}H_{20}O_5$ [M]$^+$ 292.1305, found 292.1303.

3.1.4. Epoxide 16. To a stirred solution of *cis*-ethyl cinnamate (32 mg, 0.18 mmol), ketone **2** (7 mg, 10 mol %) and *n*-Bu_4NHSO_4 (0.5 mg) in CH_3CN (10 mL) was added an aqueous buffer (5 mL, 4×10^{-4} M aqueous EDTA). The resulting solution was cooled to 0 °C (bath temperature). A solution of Oxone® (550 mg, 0.9 mmol) in aqueous EDTA (5 mL, 4×10^{-4} M) and a solution of $NaHCO_3$ (453 mg, 5.2 mmol) in H_2O (5 mL) were added dropwise concomitantly via two dropping funnels. The pH of the mixture was maintained at about 7–7.5 over a period of 24 h. The reaction mixture was then poured into water (10 mL), extracted with Et_2O (3×), dried with anhydrous magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue that was purified by flash column chromatography to give the epoxide **16** as a colourless syrup (32 mg, 93%): R_f 0.40 (hexane–Et_2O, 5:1); The ee of the epoxide was determined to be 68% by ^1H NMR analysis with chiral shift reagent, Eu(hfc)$_3$. Data for epoxide **16**: $[\alpha]_D^{20}$ +33.9 (*c* 0.32, $CHCl_3$); IR (thin film) 1740, 1697, 1649, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (2H, m), 7.33 (3H, m), 4.27 (1H, d, *J*=4.5 Hz), 3.99 (2H, m), 3.82 (1H, d, *J*=4.5 Hz), 1.01 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 166.6, 132.8, 128.4, 127.9, 126.6, 61.2, 57.4, 55.7, 13.8; MS (CI) *m/z* (relative intensity) 193 ([M+H]$^+$, 100), 165 (20), 119 (40), 91 (42); HRMS (CI) calcd for $C_{11}H_{13}O_3$ [M+H]$^+$ 193.0895, found 193.0861.

3.1.5. Azide 18. Sodium azide (14 mg, 0.208 mmol) and NH_4Cl (2.5 mg, 14 mmol) were added to a stirred solution of epoxide **16** (20 mg, 0.104 mmol) in 80% aqueous EtOH (3 mL) at room temperature. The reaction mixture was refluxed for 24 h and quenched with saturated $NaHCO_3$. The aqueous phase was extracted with Et_2O (3×) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford azide **18** as a colourless oil (22 mg, 92%): R_f 0.25 (hexane–Et_2O, 2:1); IR (thin film) 3462, 2359, 2107, 1736, 1266, 1112 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (5H, m), 4.85 (1H, d, *J*=3.0 Hz), 4.37 (1H, dd, *J*=6.9, 3.0 Hz), 4.29 (2H, q, *J*=7.2 Hz), 3.13 (1H, d, *J*=6.6 Hz), 1.30 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 128.8, 128.7, 128.6, 127.8, 73.9, 67.1, 62.4, 14.1; MS (CI) *m/z* (relative intensity) 236 ([M+H]$^+$, 5), 208 (100), 193 ([M−N$_3$]$^+$, 76); HRMS (CI) calcd for $C_{11}H_{14}N_3O_3$ [M+H]$^+$ 236.1030, found 236.1031.

3.1.6. Benzoate 19. Et_3N (1.7 mL, 11.9 mmol) and benzoyl chloride (0.56 mL, 4.8 mmol) were added to a stirring solution of azide **18** (700 mg, 2.98 mmol) and DMAP (5 mg) in dry CH_2Cl_2 (20 mL) under N_2. The reaction mixture was stirred for 30 min and quenched with saturated NH_4Cl. The mixture was extracted with Et_2O (3×) and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to give benzoate **19** as a colourless oil (950 mg, 94%): R_f 0.58 (hexane–Et_2O, 2:1); IR (thin film) 3328, 2106, 2107, 1729, 1250, 1110, 1020, 707 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (2H, m), 7.38 (8H, m), 5.45 (1H, d, *J*=5.1 Hz), 5.15 (1H, d, *J*=5.1 Hz), 4.15 (2H, dq, *J*=7.2, 0.9 Hz), 1.14 (3H, t, *J*=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 167.2, 165.5, 134.5, 133.6, 130.5, 129.9, 129.0, 128.7, 128.5, 127.8, 127.5, 126.4, 75.5, 65.5, 61.9, 13.8; MS (CI) *m/z* (relative intensity) 340 ([M+H]$^+$, 22), 298 ([M−N$_3$]$^+$, 100), 266 (100); HRMS (CI) calcd for $C_{18}H_{18}N_3O_4$ [M+H]$^+$ 340.1292, found 340.1294.

3.1.7. Benzamide 20. A suspension of 10% palladium on charcoal (100 mg, excess) in EtOAc (10 mL) was degassed and refilled with hydrogen gas three times and then stirred for 10 min. A solution of benzoate **19** (960 mg, 2.83 mmol) and *p*-TsOH (10 mg) in EtOAc (10 mL) was added. The

reaction mixture was stirred for 24 h under H_2, quenched with Et_3N, and filtered with filter paper. The solvents of the filtrate were removed under reduced pressure and the residue was purified by flash chromatography to afford benzamide **20** as a white solid (868 mg, 98%): mp 143–144 °C; R_f 0.38 (hexane–EtOAc, 2:1); IR (thin film) 3431, 3349, 1718, 1637, 1535, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.76 (2H, d, J=6.9 Hz), 7.45 (8H, m), 6.99 (1H, d, J=9.0 Hz), 5.76 (1H, dd, J=9.3, 2.1 Hz), 4.63 (1H, d, J=2.1 Hz), 4.28 (2H, m), 3.31 (1H, br s), 1.31 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 166.8, 138.7, 134.1, 131.7, 128.6, 128.5, 127.8, 127.6, 127.0, 126.9, 73.3, 62.6, 54.8, 14.1; MS (CI) m/z (relative intensity) 314 ($[M+H]^+$, 45), 297 ($[M-OH]^+$, 17), 208 (84), 193 (100); HRMS (CI) calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387, found 314.1383.

3.1.8. Acetal 21. 2-Methoxypropene (0.31 mL, 3.19 mmol) was added to a stirred solution of benzamide **20** (100 mg, 0.319 mmol) in dry toluene (7 mL) under N_2. Pyridinium p-toluenesulfonate (PPTS) (3 mg) was added to the mixture, which was refluxed for 20 h under N_2. The reaction mixture was quenched with aqueous $NaHCO_3$ and the aqueous phase was extracted with Et_2O (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to give acetal **21** as a colourless oil (110 mg, 98%): R_f 0.38 (hexane–EtOAc, 1:1); IR (thin film) 3368, 1736, 1645, 1528, 1275, 1112, 704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14 (9H, m), 6.93 (1H, br s), 5.24 (1H, d, J=5.7 Hz), 4.55 (1H, d, J=6.0 Hz), 4.25 (2H, m), 1.96 (3H, s), 1.87 (3H, s), 1.27 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 169.4, 169.1, 138.9, 137.6, 129.3, 128.4, 128.0, 127.7, 126.8, 126.1, 97.8, 81.2, 65.4, 61.9, 26.0, 25.6, 14.1; MS (EI) m/z (relative intensity) 353 ($[M]^+$, 17), 338 ($[M-CH_3]^+$, 99), 295 (100); HRMS (EI) calcd for $C_{21}H_{23}NO_4$ $[M]^+$ 353.1622, found 353.1632. The ee was determined to be 68% by ^1H NMR spectral analysis upon chiral shift reagent addition.

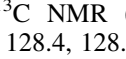
3.1.9. Acid 22. Lithium hydroxide (120 mL, 3.96 mmol) was added to a stirred solution of ester **21** (700 mg, 1.98 mmol) in 70% aqueous MeOH (9 mL) at room temperature. The reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo and H_2O (3 mL) was added to the residue. Saturated NH_4Cl (3 mL) was added to the mixture until the pH reached 4. The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford acid **22** as a white solid (600 mg, 93%). A single crystal suitable for X-ray crystallographic analysis was obtained in MeOH. The optical rotations of the crystals and the mother liquor obtained from recrystallization were different as indicated below.

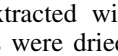
Data for crystals: mp 175–176 °C (lit.[27a] for enantiomerically enriched acid, mp 213 °C); $[\alpha]_D^{20}$ +1.1 (c 0.7, MeOH); R_f 0.32 ($CHCl_3$–MeOH, 4:1); IR (thin film) 3449, 2933, 1740, 1639, 1390, 1250, 1209 cm^{-1}; ^1H NMR (CD_3OD) δ 7.18 (8H, m), 6.95 (2H, br s), 5.26 (1H, d, J=5.7 Hz), 4.57 (1H, d, J=5.7 Hz), 1.92 (3H, s), 1.84 (3H, s); ^{13}C NMR ($CDCl_3$) δ 172.8, 169.5, 138.8, 137.2, 129.5, 128.5, 128.0, 127.7, 126.8, 126.1, 97.9, 81.1, 65.4, 26.1, 25.4; MS (EI) m/z (relative intensity) 325 ($[M]^+$, 15), 310 ($[M-CH_3]^+$, 87), 105 (100); HRMS (EI) calcd for $C_{19}H_{19}NO_4$ $[M]^+$ 325.1309, found 325.1304.

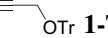
Data for the mother liquor: $[\alpha]_D^{20}$ +70.3 (c 0.6, MeOH) (lit.[27a] for enantiomerically enriched acid, $[\alpha]_D^{20}$ +99.1 (c 0.36, EtOH)). The acid **22** is not sensitive to chiral shift reagent $Eu(hfc)_3$ under various solvents and concentrations. To overcome this, the mother liquor from recrystallization was esterified to convert **22** back to ester **21**, which displayed better resolution of the separated signals in the ^1H NMR spectrum upon $Eu(hfc)_3$ addition. DBU (13 μL, 0.09 mmol) and ethyl bromide (7 μL, 0.09 mmol) were added to a stirred solution of the liquid acid **22** (15 mg, 0.046 mmol) in dry benzene (2 mL). The reaction mixture was stirred at reflux for 1 h and quenched with saturated NH_4Cl. The aqueous phase was extracted with Et_2O (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford ester **21** as a colourless oil (15 mg, 92%). The ee of ester **21** was measured to be 82% by the same method described above.

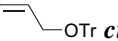
In the same manner, the ee of the ester prepared from crystalline acid **22** was determined to be 5%.

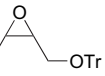
3.2. Preparation of alkene substrates

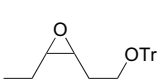
3.2.1.  ***cis*-Ethyl cinnamate.**[29] To a stirred mixture of ethyl phenyl propiolate (1 g, 5.74 mmol), n-hexane (25 mL) and 1-octene (6 mL) was added quinoline (1.03 g, 8 mmol). Palladium on calcium carbonate (Lindlar catalyst 290 mg, 1.7 mmol) was added and the resulting reaction mixture was stirred under H_2 with a hydrogen balloon at room temperature for 20 h. The resulting mixture was filtered through filter paper. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford *cis*-ethyl cinnamate as a colourless oil (960 mg, 96%): R_f 0.78 (hexane–Et_2O, 5:1); ^1H NMR ($CDCl_3$) δ 7.58 (2H, m), 7.35 (3H, m), 6.95 (1H, d, J=12.6 Hz), 5.95 (1H, d, J=12.6 Hz), 4.18 (2H, q, J=7.2 Hz), 1.25 (3H, t, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 142.9, 129.6, 128.9, 127.9, 119.9, 60.3, 14.1.

3.2.2.  ***cis*-1-Trityloxy-3-hexene.** Trityl chloride (2.46 g, 8.86 mmol) and DMAP (7 mg) were added to a stirring mixture of *cis*-3-hexen-1-ol (807 mg, 8.05 mmol) and pyridine (0.98 mL, 12.1 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred for 24 h. The reaction was with saturated aqueous NH_4Cl and extracted with Et_2O (3×30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford *cis*-1-trityloxy-3-hexene as a colourless oil (2.79 g, 92%): R_f 0.33 (hexane–Et_2O, 30:1); ^1H NMR ($CDCl_3$) δ 7.48–7.23 (15H, m), 5.48 (1H, m), 5.39 (1H, m), 3.11 (2H, t, J=6.9 Hz), 2.41 (1H, d, J=6.9 Hz), 2.34 (1H, d, J=6.9 Hz), 2.12 (1H, dq, J=7.5, 7.2 Hz), 0.99 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 144.7, 133.8, 129.0, 128.0, 127.2, 125.7, 86.8, 63.9, 28.5, 21.0, 14.7.

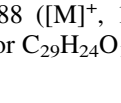
3.2.3.  **1-Trityloxy-4-phenyl-2-butyne.** ^{n}BuLi (1.6 M, 12.5 mL, 19.0 mmol) was added to a solution of the 1-trityloxy-2-propyne[34] (2.97 g, 9.96 mmol) in dry THF at 0 °C. The mixture was stirred at room temperature. After 1 h, BnBr was added to the reaction mixture. BnBr (2.37 mL, 19.0 mmol) was added to the mixture and the resulting solution was stirred for 24 h. The reaction was with saturated aqueous NH_4Cl and extracted with Et_2O (3×30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford 1-trityloxy-4-phenyl-2-butyne as a yellow oil (3.21 g, 79%): R_f 0.44 (hexane–Et_2O, 10:1); ^{1}H NMR ($CDCl_3$) δ 7.59–7.29 (20H, m), 3.91 (2H, t, J=2.1 Hz), 3.71 (2H, s); ^{13}C NMR ($CDCl_3$) δ 143.9, 136.9, 128.9, 128.8, 128.2, 128.1, 127.7, 127.4, 126.9, 87.7, 83.7, 79.2, 53.9, 25.6; MS (EI) *m/z* (relative intensity) 388 ([M]$^+$, 100), 243 (98), 211 (100); HRMS (EI) calcd for $C_{29}H_{24}O_1$ [M]$^+$ 388.1822, found 388.1816.

3.2.4.  ***cis*-1-Trityloxy-4-phenyl-2-butene.** To a stirred mixture of 1-trityloxy-4-phenyl-2-butyne (200 mg, 0.49 mmol), *n*-hexane (12 mL) and 1-octene (3 mL) was added quinoline (98 mg, 0.76 mmol). Palladium on calcium carbonate (Lindlar catalyst 30 mg, 0.25 mmol) was added and the resulting reaction mixture was stirred under H_2 with a hydrogen balloon at room temperature for 20 h. The resulting mixture was filtered through filter paper. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford *cis*-1-trityloxy-4-phenyl-2-butene as a pale yellow oil (181 mg, 90%): R_f 0.50 (hexane–Et_2O, 10:1); ^{1}H NMR ($CDCl_3$) δ 7.53–7.26 (20H, m), 5.86 (1H, m), 5.82 (1H, m), 3.80 (2H, d, J=6.3 Hz), 3.27 (2H, d, J=7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 144.5, 131.1, 129.0, 128.8, 128.7, 128.2, 127.9, 127.7, 127.3, 126.3, 87.2, 60.6, 34.3; MS (ESI) *m/z* (relative intensity) 413 ([M+Na]$^+$, 100), 414 (30); HRMS (ESI) calcd for $C_{29}H_{26}O_1$ [M+Na]$^+$ 413.1876, found 413.1882.

3.2.5.  **1-Trityloxy-4-phenyl-2,3-epoxybutane.** Colourless oil: R_f 0.25 (hexane–Et_2O, 10:1); ^{1}H NMR ($CDCl_3$) δ 7.53–7.26 (20H, m), 3.55 (1H, dd, J=10.2, 5.4 Hz), 3.33 (1H, dd, J=5.4, 4.2 Hz), 3.24 (2H, m), 2.78 (1H, dd, J=15.0, 6.0 Hz), 2.66 (1H, dd, J=15.0, 6.3 Hz); ^{13}C NMR ($CDCl_3$) δ 144.1, 137.8, 129.2, 129.0, 128.9, 128.2, 127.5, 126.9, 87.3, 62.4, 57.1, 55.7, 34.6; MS (CI) *m/z* (relative intensity) 389 (100), 390 (30), 407 ([MH]$^+$, 10); HRMS (CI) calcd for $C_{29}H_{26}O_2$ [MH]$^+$ 407.2006, found 407.1995.

3.2.6.  **1-Trityloxy-3,4-epoxyhexane.** Colourless oil: R_f 0.23 (hexane–Et_2O, 10:1); ^{1}H NMR ($CDCl_3$) δ 7.47–7.21 (15H, m), 3.28 (1H, t, J=6.3 Hz), 3.15 (1H, q, J=5.1 Hz), 2.93 (1H, q, J=5.1 Hz), 1.85 (2H, m), 1.54 (2H, dt, J=14.1, 6.9 Hz), 1.04 (3H, t, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 144.5, 129.0, 128.1, 127.3, 87.0, 61.5, 58.6, 55.4, 29.0, 21.5, 11.0; MS (CI) *m/z* (relative intensity) 358 ([M]$^+$, 30), 341 (100); HRMS (CI) calcd for $C_{25}H_{26}O_2$ [M]$^+$ 358.1927, found 358.1918.

3.2.7. **(*Z*)-1-Trityloxy-4-*tert*-butyldimethylsilyloxy-2-butene.** Trityl chloride (3.44 g, 15.7 mmol) and DMAP (8 mg) were added to a stirring mixture of (*Z*)-1-*tert*-butyldimethylsilyloxy-2-buten-4-ol[35] (2.50 mg, 12.3 mmol) and pyridine (1.0 mL, 15.7 mmol) in dry CH_2Cl_2 (40 mL). The reaction mixture was stirred for 24 h. The reaction was with saturated aqueous NH_4Cl and extracted with Et_2O (3×40 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography to afford (*Z*)-1-trityloxy-4-*tert*-butyldimethylsilyloxy-2-butene as a colourless oil (5.10 g, 93%): R_f 0.33 (hexane–Et_2O, 20:1); ^{1}H NMR ($CDCl_3$) δ 7.51–7.26 (15H, m), 5.75–5.65 (2H, m), 4.12 (2H, d, J=5.7 Hz), 3.71 (2H, d, J=5.4 Hz), 0.90 (9H, s), 0.04 (6H, s); ^{13}C NMR ($CDCl_3$) δ 144.4, 132.1, 129.0, 128.2, 127.5, 127.3, 87.2, 60.7, 60.1, 26.3, 18.6, −4.82.

3.2.8.  **1-Trityloxy-4-*tert*-butyldimethylsilyloxy-2,3-epoxybutane.** Colourless oil: R_f 0.34 (hexane–Et_2O, 10:1); ^{1}H NMR ($CDCl_3$) δ 7.53–7.26 (15H, m), 3.72 (1H, dd, J=12.0, 6.0 Hz), 3.55 (1H, dd, J=12.0, 4.2 Hz), 3.37–3.29 (2H, m), 3.21–3.16 (2H, m), 0.91 (9H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$) δ 144.1, 128.9, 128.2, 127.4, 87.2, 62.7, 62.1, 56.8, 55.4, 26.2, 18.6, −4.88, −5.05; MS (CI) *m/z* (relative intensity) 461 ([MH]$^+$, 10), 444 (45), 443 (100); HRMS (CI) calcd for $C_{29}H_{36}O_3Si_1$ [MH]$^+$ 461.2508, found 461.2503.

Acknowledgements

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