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# Asymmetric Epoxidation of 1,1-Disubstituted Terminal Olefins by Chiral Dioxirane via a Planar-like Transition State

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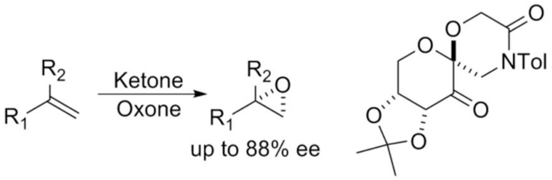
## Abstract



Various 1,1-disubstituted terminal olefins have been investigated for asymmetric epoxidation using chiral ketone catalysts. Up to 88% ee has been achieved with a lactam ketone, and a planar transition state is likely to be a major reaction pathway.

## Keywords

asymmetric epoxidation; chiral dioxirane; 1,1-disubstituted terminal olefins

## Introduction

Chiral dioxiranes have recently been shown to be effective for asymmetric epoxidation of olefins, and a number of laboratories have extensively investigated chiral ketones of various structures.[1] In our own studies, we found that fructose-derived ketone **1** is a very effective catalyst for the epoxidation of *trans*- and trisubstituted olefins,[2] and oxazolidinone-bearing ketones **2** can give high ee's for olefins such as conjugated aromatic *cis*-olefins,[3a,c,d,e,g] conjugated *cis*-dienes[3k] and enynes,[3a,c,l] styrenes,[3b,c,d,f] certain trisubstituted,[3h,j] and tetrasubstituted olefins[3i,j] which had not been effective with ketone **1** (Figure 1). Studies have shown that the enantioselectivity afforded by ketone **2** results from an apparent attractive interaction between the $R_\pi$ group of the olefin and the spiro oxazolidinone of the ketone catalyst.[3]

Among six classes of olefins (Figure 2), 1,1-disubstituted terminal olefins (**VI**) have generally been challenging for asymmetric epoxidation.[4–8] Epoxidation of α-methylstyrene and α-isopropylstyrene with ketone **2a** gave (*S*)-α-methylstyrene oxide in 30% ee and α-isopropylstyrene oxide in 58% ee.[3c] Several possible spiro and planar transition states for epoxidation with ketone **2** are shown in Figure 3.[2b,3c] Spiro transition states (**A-D**) are generally favored stereoelectronically as a result of the stabilizing interaction of an oxygen lone pair with the π* orbital of the alkene.[1,9,10] However, planar transition states **E** and **G** appear to be sterically more favored as compared to spiro transition states. Planar transition states **F** and

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**H** are disfavored both electronically and sterically, thus are unlikely to be significant contributors. Between the two planar transition states **E** and **G**, **E** is likely to be favored over **G** due to the associative interaction between the phenyl group of the olefin and the oxazolidinone of the ketone catalyst. We hypothesized that planar **E** might be the major transition state for the epoxidation of α-methylstyrene based on the *S* configuration of the resulting epoxide obtained with ketone **2a**. A higher ee obtained by with α-isopropylstyrene could be due to disfavoring competing spiro **D** by a larger isopropyl group.[3c] Based on these observations, we decided to search for ketone catalysts that can further favor planar **E**-like transition state to enhance the enantionselectivity for the epoxidation of 1,1-disubstituted terminal olefins. We have found that lactam ketones **3** provide very promising results (Figure 1). Herein we wish to report our studies on this subject.

## Results and Discussion

The synthesis of lactam ketone **3** is outlined in Schemes 1 and 2. Diol **4**, prepared from D-glucose as previously reported,[11] was treated with $BrCH_2COBr$ to form compound **5**, which was then converted to ketone **3a** after cyclization and oxidation. Upon introduction of a Boc or Ac group, ketone **3a** was converted to ketones **3b** and **3c** (Scheme 1). Ketones **3d-h** were prepared from D-glucose in four steps by Amadori rearrangement,[12] ketalization,[3d] formation of the six-membered lactam, and subsequent oxidation (Scheme 2). The X-ray structure of ketone **3d** is shown in Figure 4. An overlay of ketones **2b** and **3d** is shown in Figure 5. In contrast to ketone **2b**,[3d] the *N*-phenyl group and the lactam carbonyl group in **3d** are not coplanar.

Initial studies on the epoxidation of α-isopropylstyrene with ketone **3d** showed that 1,4-dioxane was among the best solvents, giving 94% conversion and 84% ee (Table 1, entry 4). The enantioselectivity was also affected by the *N*-substituents of ketone catalysts with ketones **3a**, **3d**, **3e**, **3f**, and **3h** giving the highest enantioselectivity (82-84% ee) (Table 1, entries 7, 4, 10, 11, and 13). Ketone **3d**, readily synthesized from inexpensive starting materials, was subsequently investigated for the epoxidation of 1,1-disubstituted terminal olefins. As shown in Table 2, a variety of aryl-substituted 1,1-disubstituted olefins can be effectively epoxidized in good enantioselectivities (62-88% ee). Generally speaking, substrates with bulky alkyl groups at α positions of olefins produce epoxides with higher enantioselectivity than those with small groups. The substituents on the phenyl groups of olefins also have some effects on the enantioselectivities (74-88% ee) (Table 2, entries 7–14). Allylic, homoallylic, and bishomoallylic alcohols are also effective substrates (Table 2, entries 16–21). Up to 88% ee was obtained for 1,1-dialkyl-2-aryl allylic alcohols (Table 2, entries 19–21). A reasonable enantioselectivity (60% ee) was also obtained for a non-aromatic allylic alcohol (Table 2, entry 22).

Ketone **3d** gave a similar level of enantioselectivity to ketone **2** for epoxidation of *cis*-olefins (Table 3, entries 1 and 2), indicating that there still exists an electronic attraction between the amide moiety and the phenyl group of the olefin in spiro transition state **I** (Figure 6). When 1-phenylcyclohexene was epoxidized with ketone **3d**, the (*S*,*S*)-epoxide derived from planar **L** (Figure 7) was obtained with 80% ee while the epoxidation with ketones **2a** and **2b** gave 43% ee of the (*S*,*S*)-epoxide[3c] and 25% ee of the (*R*,*R*)-epoxide,[3d] respectively, suggesting that the six-membered lactam moiety provides a more favorable environment for the attraction between the lactam moiety of the ketone and the phenyl group of the olefin in the planar transition state as compared to ketones **2a** and **2b**. In the case of 1-phenyl-3,4-dihydronaphthalene, the epoxide resulting from the planar transition state was obtained in as high as 90% ee (Table 3, entry 4), further illustrating the aforementioned attraction in the planar transition state.

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The known absolute configurations of selected epoxides (Table 2, entries 1, 2, 15, 16, 19, and 21) are consistent with the notion that the epoxidation proceed mainly via planar transition state **P** (Figure 8). A bulky R substituent on the olefin disfavors spiro **O**, thus resulting in higher ee's as observed. Further improvement of the enantioselectivity will require further disfavoring spiro **N** and/or planar **Q** transition states.

In summary, a variety of 1,1-disubstituted terminal olefins can be enantioselectively epoxidized using lactam ketone **3d** as catalyst and Oxone as oxidant, giving up to 88% ee. Studies indicate that the epoxidation of 1,1-disubstituted terminal olefins with ketone **3** proceeds mainly via a planar transition state. Ketone **3** provides a promising lead for further improvement of the enantioselectivity for this challenging class of olefins.

## Experimental

### Representive Ketone Synthesis

To a solution of amino alcohol **7d** (prepared from D-glucose in two steps)[3d] (3.09 g, 10.0 mmol) and $Et_3N$ (1.11 g, 1.54 mL, 11.0 mmol) in dry THF (50 mL), a solution of 2-bromoacetyl bromide (2.22 g, 0.95 mL, 11.0 mmol) in dry THF (10 mL) was added dropwise at rt over 2 h. After the resulting mixture was stirred at rt for 3 h, NaH (95 %, 0.6 g, 23.7 mmol) was added into the reaction mixture carefully. Upon stirring at rt for 0.5 h, the reaction mixture was quenched with MeOH (0.25 mL) and filtered. The filtrate was concentrated and purified by flash chromatography (silica gel, hexane /EtOAc = 1/6) to give lactam **8d** as a white solid (1.42 g, 41% yield): mp 198–199 °C; $[\alpha]_D^{25} = -144.6$ ($c$ 1.0, $CHCl_3$); IR (film) 3410, 1661 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.21-7.14 (m, 4H), 4.40-4.36 (m, 1H), 4.30-4.21 (m, 4H), 4.12 (d, $J$ = 13.2 Hz, 1H), 3.96 (dd, $J$ = 13.2, 2.8 Hz, 1H), 3.62-3.59 (m, 1H), 3.53-3.48 (m, 1H), 3.10-2.88 (m, 1H), 2.33 (s, 3H), 1.51 (s, 3H), 1.37 (s, 3H); $1^3C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.6, 138.4, 137.4, 130.1, 125.8, 109.7, 96.2, 76.5, 73.4, 71.7, 62.7, 60.5, 54.2, 28.2, 26.2, 21.2; HRMS Calcd for $C_{18}H_{24}O_6N$ (M+H): 350.1604; Found: 350.1607.

AcOH (0.15 mL) was added to a slurry of lactam **8d** (4.8 g, 13.76 mmol), PDC (10.3 g, 27.5 mmol), and 3Å MS (6.5 g) in $CH_2Cl_2$ (300 mL). Upon stirring at rt for 3 d (no SM left as judged by TLC), the reaction mixture was filtered through a pad of silica gel, and the filter cake was washed with EtOAc. The filtrate was concentrated and purified by flash chromatography (silica gel, hexane/EtOAc = 3/1) to give ketone **3d** as a white solid (4.5 g, 95% yield): mp 184–185 °C; $[\alpha]_D^{25} = -86.5$ ($c$ 1.0, $CHCl_3$); IR (film) 1753, 1674 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.24-7.18 (m, 4H), 4.86 (d, $J$ = 5.7 Hz, 1H), 4.66-4.64 (m, 1H), 4.49-4.23 (m, 5H), 3.64 (d, $J$ = 13.8 Hz, 1H), 2.36 (s, 3H), 1.47 (s, 3H), 1.43 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 197.7, 165.2, 138.2, 137.7, 130.2, 125.8, 111.0, 96.1, 78.4, 75.7, 63.2, 59.9, 51.9, 27.3. 26.2, 21.3; HRMS Calcd for $C_{18}H_{22}NO_6$ (M+H): 348.1447; Found: 348.1447; Anal. Calcd. For $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09. Found: C, 62.02; H, 6.01.

### Representative Epoxidation Procedure (Table 2, Entry 19)

To a solution of the olefin (0.324 g, 0.20 mmol), tetrabutylammonium hydrogen sulfate (0.0038 g, 0.010 mmol), and ketone **3d** (0.0208 g, 0.06 mmol) in dioxane (3 mL) was added buffer (0.1 M $K_2CO_3$-AcOH in $4 \times 10^{-4}$ M aqueous EDTA, pH = 9.3; 2 mL) with stirring. After the mixture was cooled to −10 °C (bath temperature), a solution of Oxone (0.20 M in $4 \times 10^{-4}$ M aqueous EDTA, 1.6 mL) (0.197 g, 0.32 mmol) and a solution of $K_2CO_3$ (0.84 M in $4 \times 10^{-4}$ M aqueous EDTA, 1.6 mL) (0.185 g, 1.344 mmol) were added separately and simultaneously via a syringe pump over a period of 2 h. The reaction mixture was quenched with hexane, extracted with EtOAc, dried over $Na_2SO_4$, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% $Et_3N$ in organic solvent; hexane/$Et_2O$ = 5/1 as eluent) to give the epoxide as white solid (0.027 g, 76% yield, 87% ee).

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## Supplementary Material

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## Acknowledgements

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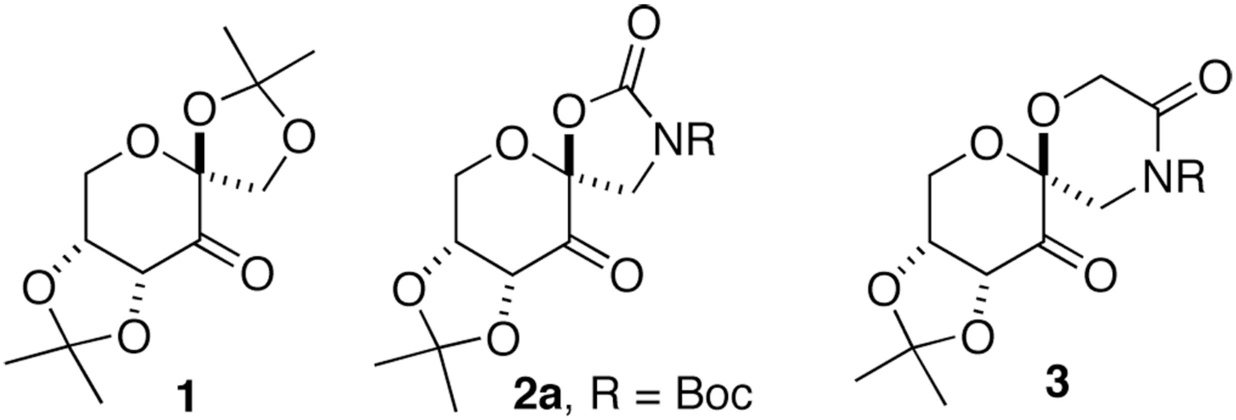

**1**

**2a**, R = Boc
**2b,** R = *p*-MePh
**2c**, R = *p*-EtPh

**3**

**Figure 1.**

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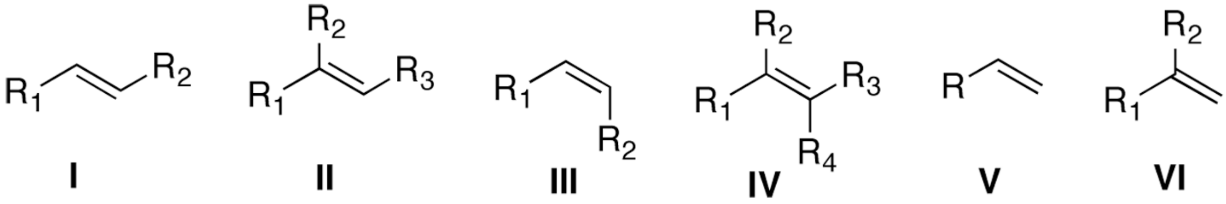

**Figure 2.**

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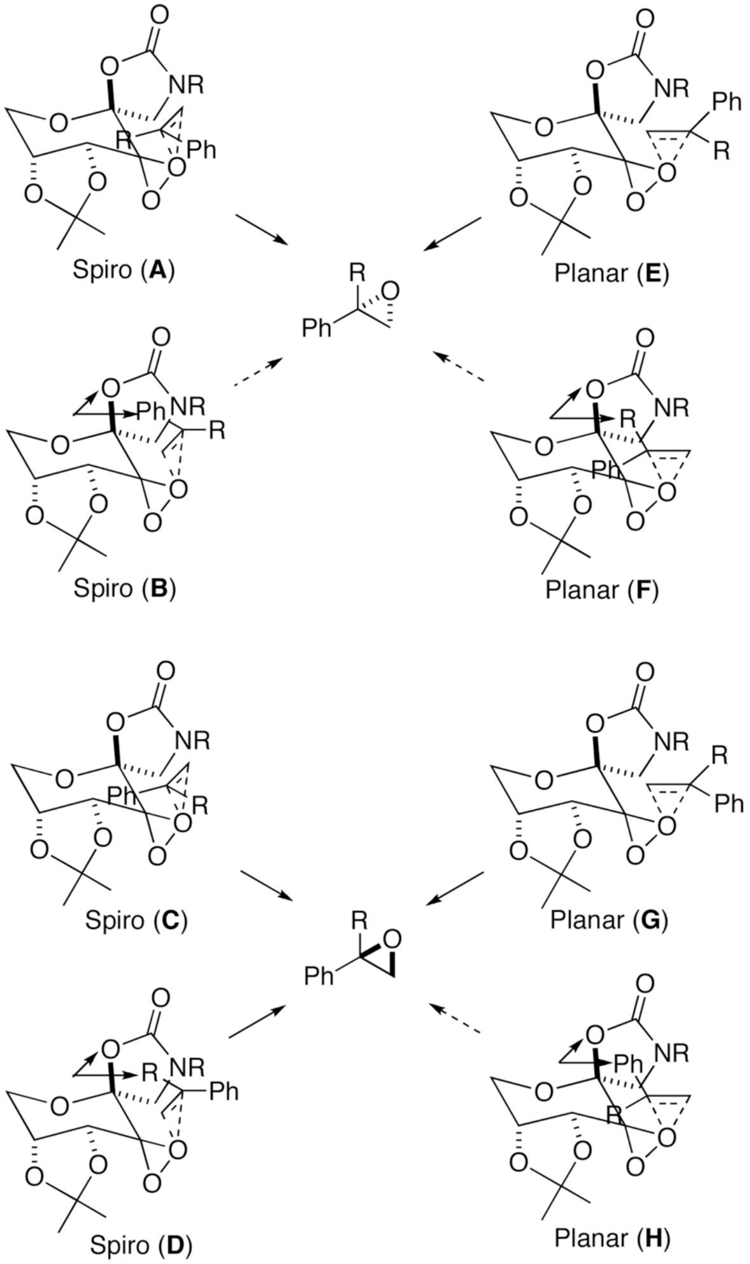

**Figure 3.**

The proposed spiro and planar transition states for the epoxidation of 1,1- disubstituted terminal olefins

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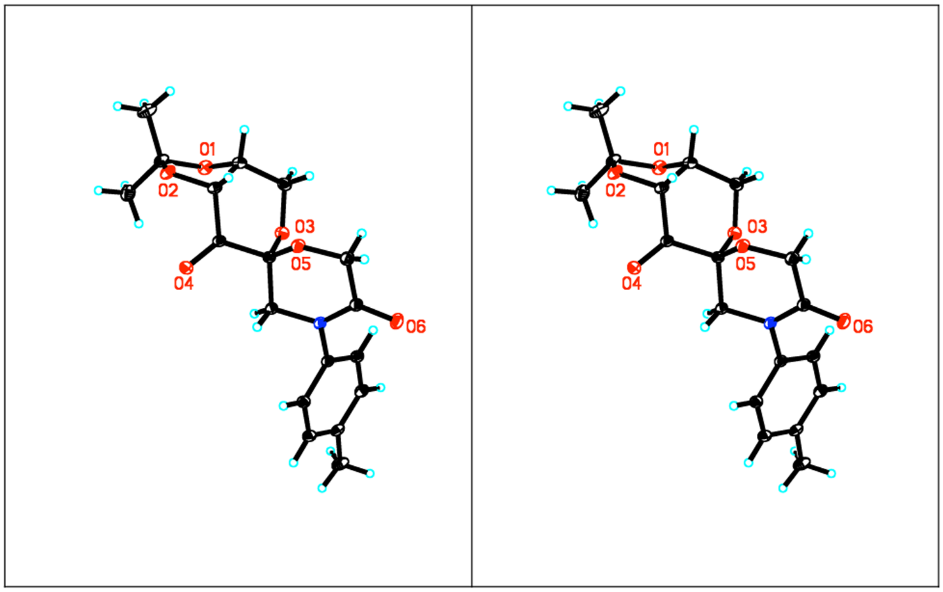

**Figure 4.**
The X-ray structure of ketone **3d** (stereoview)

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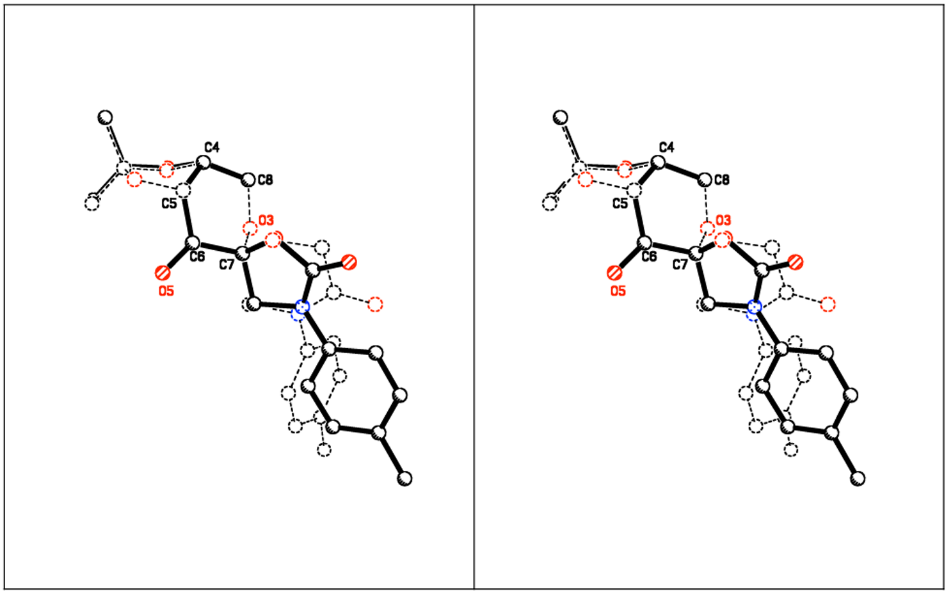

**Figure 5.**
Crystal structure overlay of ketones **2b** and **3d** (stereoview)

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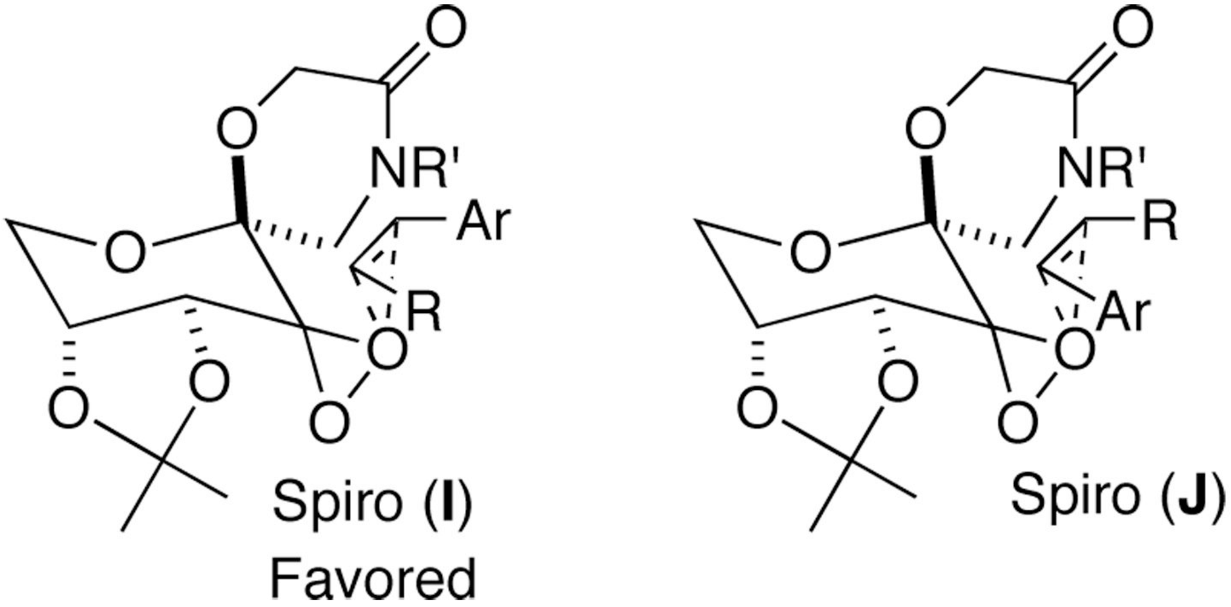

**Figure 6.**
The proposed competing spiro transition states for the epoxidation of *cis*-olefins with ketone **3**

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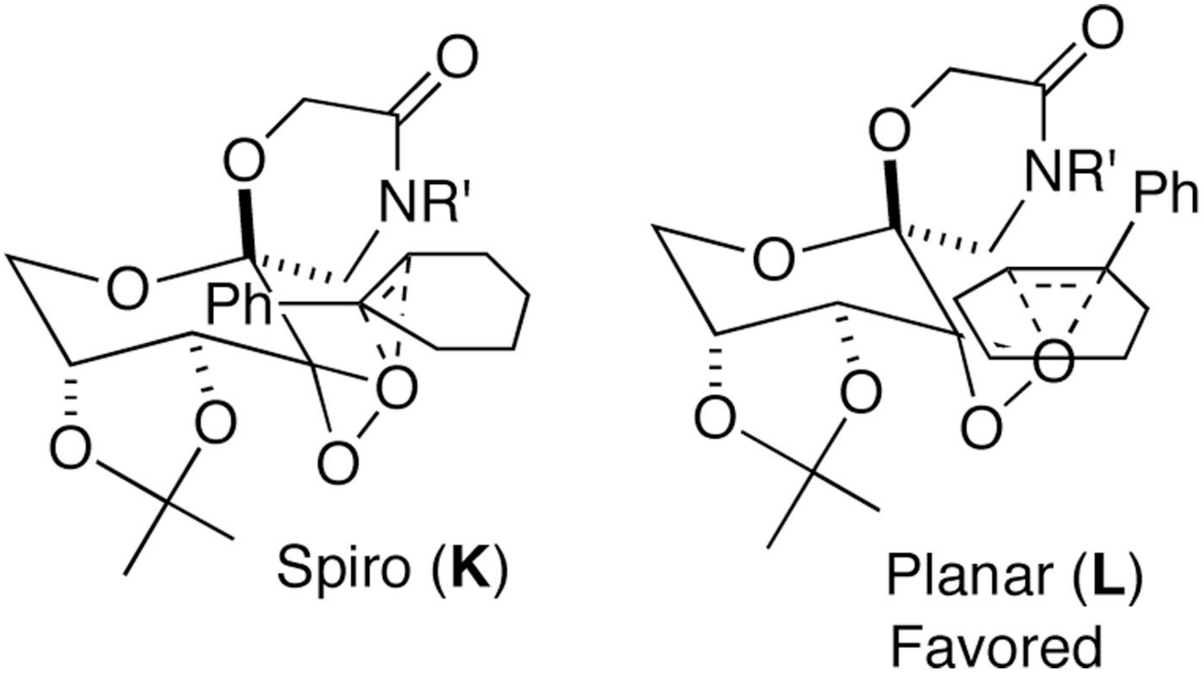

**Figure 7.**
The proposed competing spiro and planar transition states for the epoxidation of 1-phenylcyclohexene with ketone **3**

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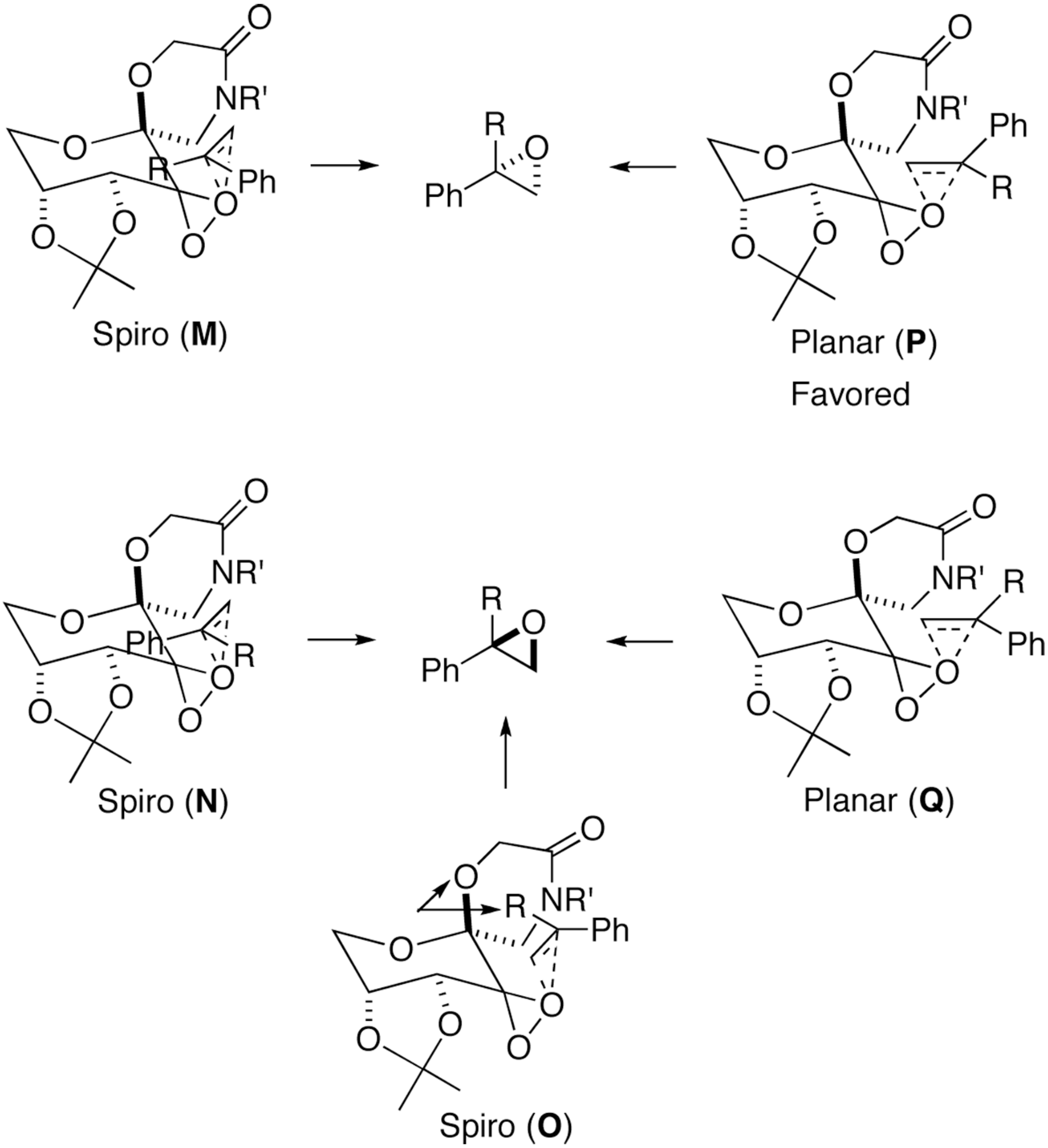

**Figure 8.**

The proposed competing transition states for the epoxidation of 1,1-disubstituted terminal olefins with ketone **3**

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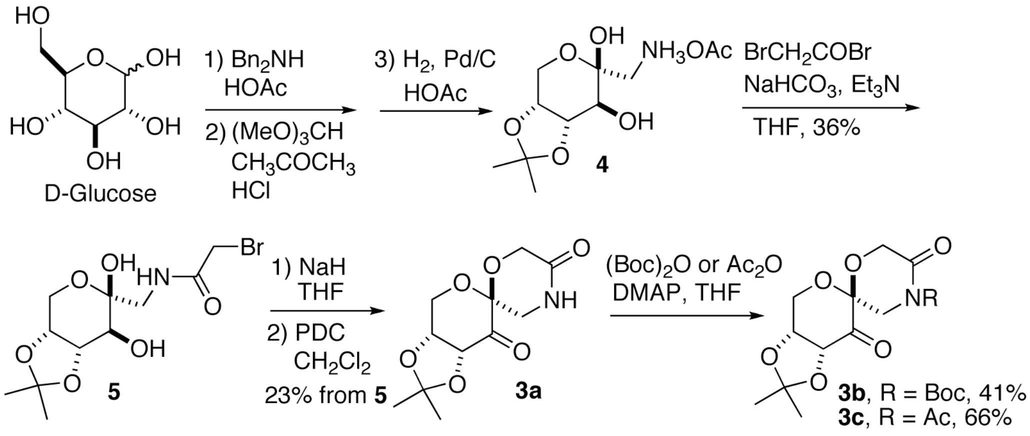

**Scheme 1.**

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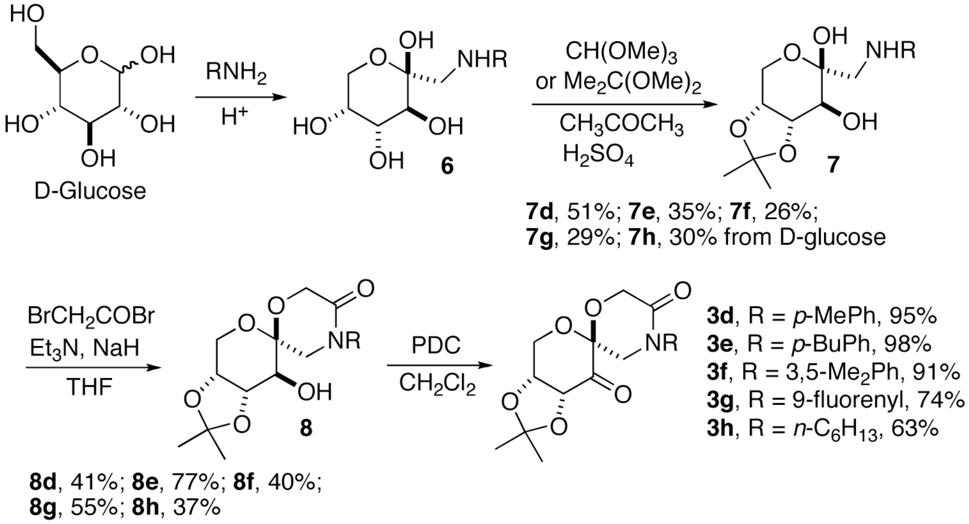

**Scheme 2.**

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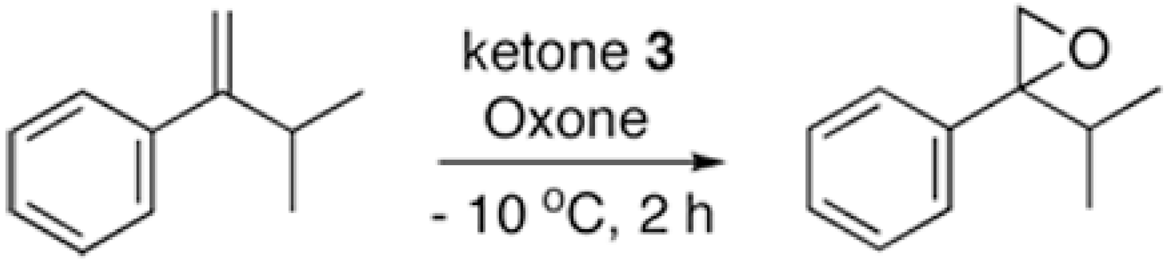
## Table 1

Asymmetric Epoxidation of α-Isopropylstyrene with Ketones **3**[a]



| entry | ketone | solvent | conv. (%)[b] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **3d** | $CH_3CN$/DMM (1/2) | 97 | 71 |
| 2 |  | DME | 94 | 81 |
| 3 |  | DME/*n*-BuOH | 99 | 76 |
| 4 |  | 1,4-dioxane | 94 | 84 |
| 5 |  | 1,4-dioxane/DME (2/1) | 99 | 80 |
| 6 |  | 1,4-dioxane/*n*-BuOH (1/1) | 100 | 78 |
| 7 | **3a** |  | 91 | 82 |
| 8 | **3b** |  | 69 | 71 |
| 9 | **3c** |  | 10 | nd |
| 10 | **3e** |  | 100 | 83 |
| 11 | **3f** |  | 98 | 83 |
| 12 | **3g** |  | 80 | 52 |
| 13 | **3h** |  | 99 | 84 |

[a] All epoxidations were carried out with the olefin (0.2 mmol), ketone **3** (0.06 mmol), Oxone (0.32 mmol), and $K_2CO_3$ (1.344 mmol) in organic solvent (3 mL) and buffer (0.1 M $K_2CO_3$/AcOH, pH 9.3; 2 mL) at −10 °C for 2 h.

[b] The conversion and ee were determined by chiral GC (B-DM column).

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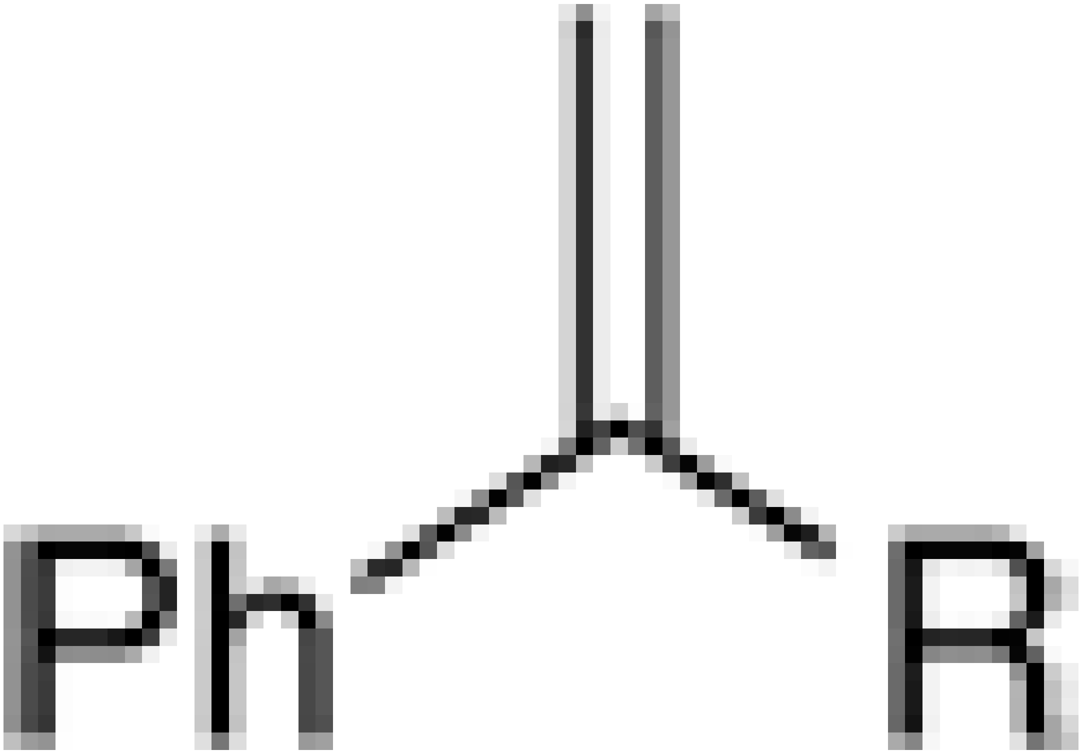
**Table 2**

Asymmetric Epoxidation of 1,1-Disubstituted Terminal Olefins with Ketone **3d**[a]

| entry | substrate | yield (%)[b] |
|---|---|---|
| |  | |
| 1 | R = Me | 60 |
| 2 | R = Et | 71 |
| 3 | R = *n*-Pr | 90 |
| 4 | R = *i*-Bu | 54 |
| 5 | R = *c*-$C_6H_{11}$ | 62 |
| 6 | R = *t*-Bu | 43 |

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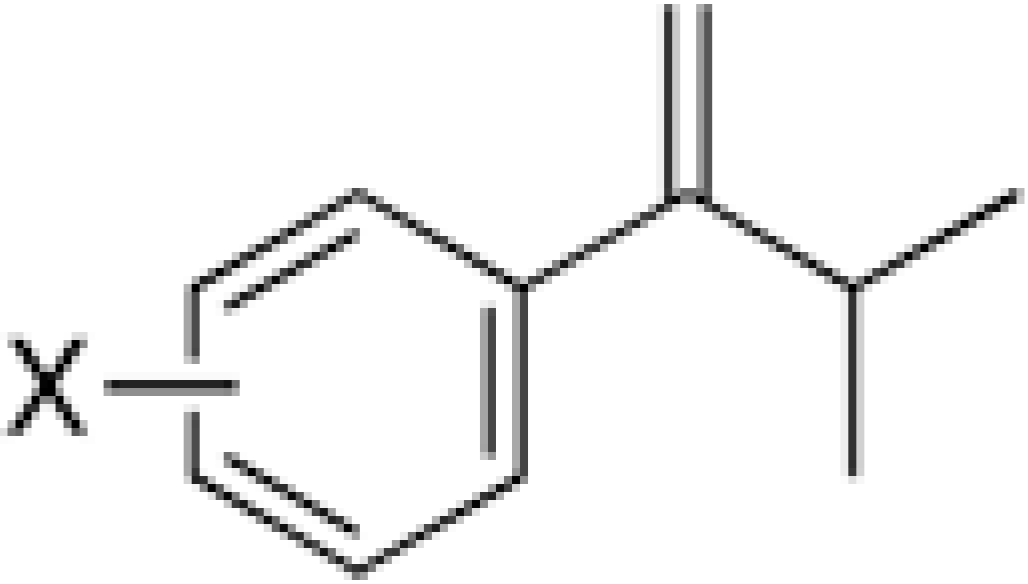
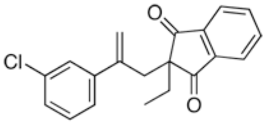
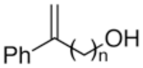
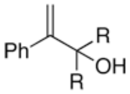
| **entry** | **substrate** | **yield (%)**[b] |
|---|---|---|
| |  | |
| 7 | X = H | 71 |
| 8 | X = *p*-*i*-Pr | 51 |
| 9 | X = *p*-MeO | 94 |
| 10 | X = *p*-F | 78 |
| 11 | X = *p*-Br | 68 |
| 12 | X = *m*-Me | 57 |
| 13 | X = *m*-F | 74 |
| 14 | X = *o*-F | 72 |
| 15 |  | 51 |
| |  | |
| 16 | n = 1 | 93 |
| 17 | n = 2 | 47 |
| 18 | n = 3 | 62 |
| |  | |
| 19 | R = Me | 76 |
| 20 | R = Et | 85 |
| 21 | R,R = $(CH_2)_4$ | 86 |

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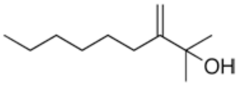
| entry | substrate | yield (%)[b] |
|---|---|---|
| 22 |  | 78 |

[a] All epoxidations were carried out with the olefin (0.2 mmol), ketone **3d** (0.06 mmol), Oxone (0.32 mmol), and $K_2CO_3$ (1.344 mmol) in 1,4-dioxane (3 mL), and buffer (0.1 M $K_2CO_3$/AcOH, pH 9.3; 2 mL) at −10 °C for 2 h (4 h for entries 6, 11, 13, and 14).

[b] Isolated yield except entry 7 which is crude yield.

[c] The ee was determined by chiral HPLC (Chiracel OD column).

[d] The ee was determined by chiral GC (B-DM column).

[e] The absolute configurations were determined by comparing the measured optical rotations and HPLC trace with reported ones.

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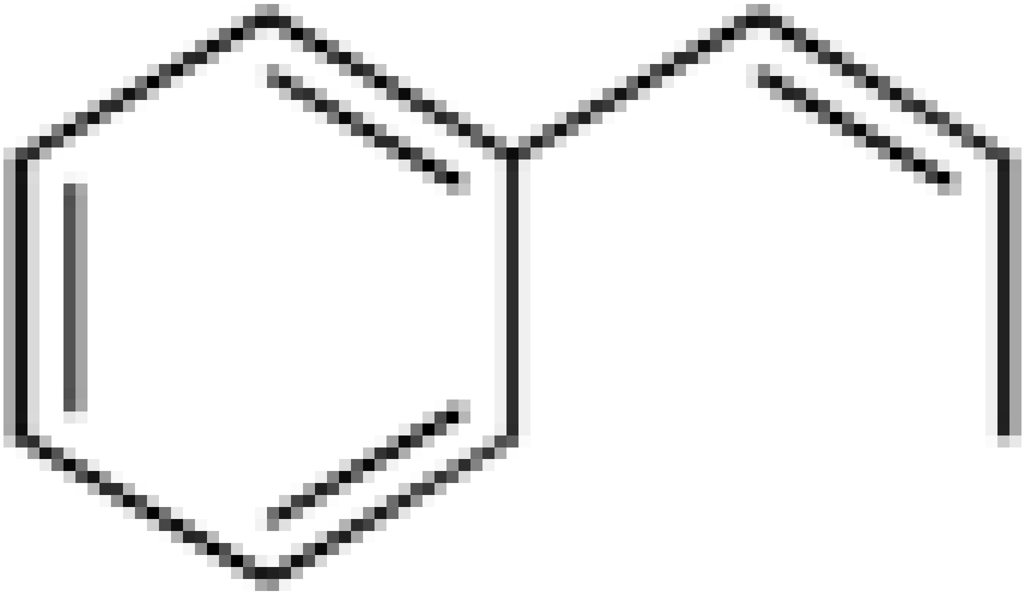
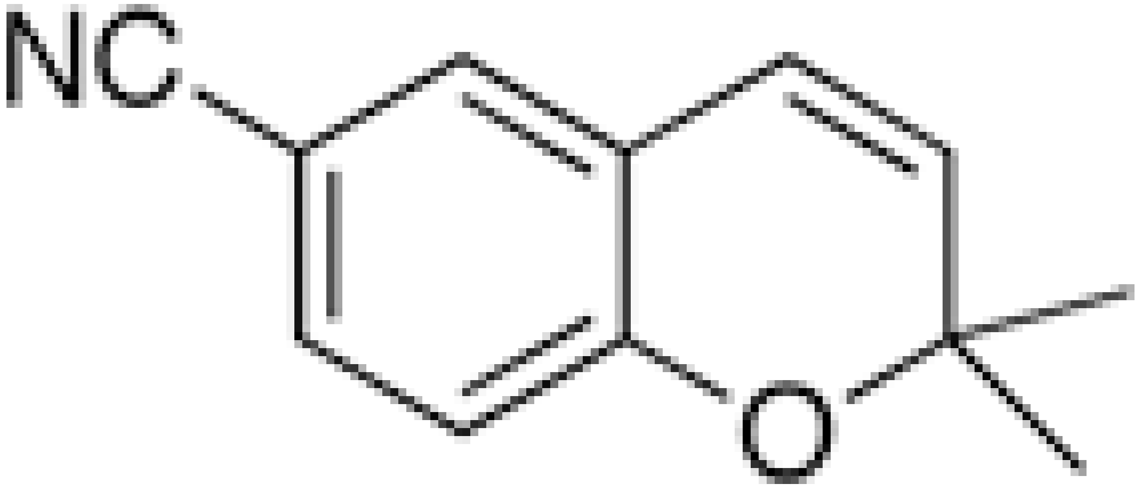
**Table 3**

Asymmetric Epoxidation of *cis*- and Trisubstituted Olefins by Ketone **3d**[a]

| entry | substrate | conv. |
|---|---|---|
| 1 |  | $100^{c}$(6 |
| 2 | <br> | $89^{d}$(8 |

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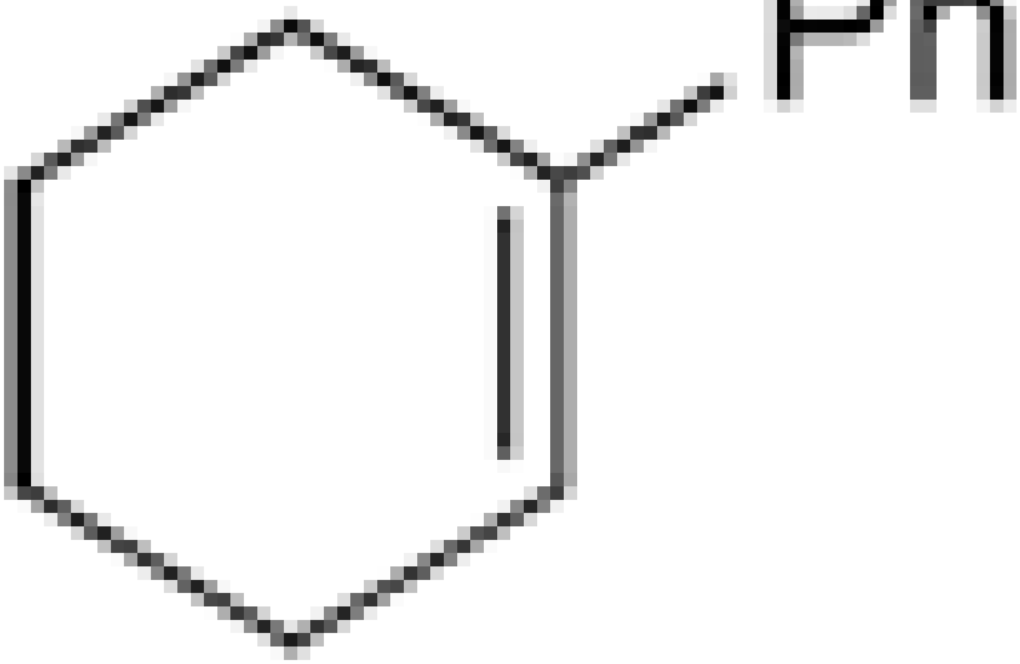
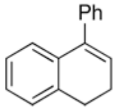
| entry | substrate | conv. |
|---|---|---|
| 3 |  | 99[c](89 |
| 4 |  | 88[d](56 |

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[a] All reactions were carried out with substrate (0.2 mmol), ketone **3d** (0.06 mmol for entry 1, 0.04 mmol for entries 2, 3, and 4), Oxone (0.32 mmol), and $K_2CO_3$ (1.344 mmol) in DME/DMM (3:1, v/v; 3.0 mL) and buffer (0.1 M $K_2CO_3$-AcOH in $4 \times 10^{-4}$ M aqueous EDTA, pH 9.3; 2 mL); For entries 1, 3, and 4, the reaction was carried out at −10 °C for 4 h; For entry 2, the reaction was carried out at 0 °C for 12 h.

[b] Isolated yield.

[c] The conversion was determined by GC (B-DM column).

[d] The conversion was determined by $^1$H NMR.

[e] The ee was determined by chiral GC (B-DM column).

[f] The ee was determined by chiral HPLC (Chiracel OD column).

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[g] The absolute configurations were determined by comparing the measured optical rotations and GC trace with reported ones.