A New Type of Ketone Catalyst for Asymmetric Epoxidation

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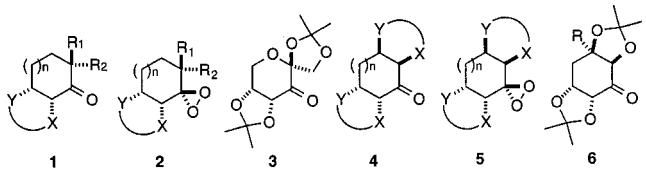
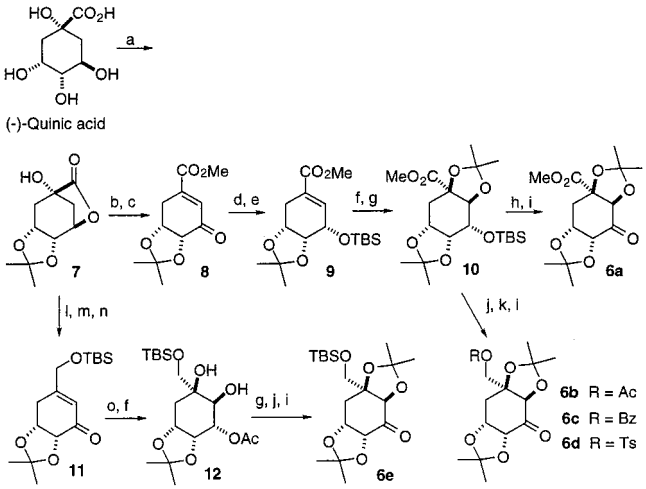
Dioxiranes generated *in situ* from Oxone and chiral ketones have been shown to be remarkably promising oxidation reagents for asymmetric epoxidation of olefins.[1−4] Our efforts have been focusing on ketones that have stereogenic centers in the vicinity of the reacting carbonyl groups and fused ring(s) or a quaternary carbon α to the carbonyl groups (ketones **1** and **4** in Chart 1). The closeness of the stereogenic centers to the carbonyl group (reacting center) was intended to optimize the stereochemical communication between olefin substrates and the catalyst during the epoxidation. The introduction of the fused ring(s) and quaternary carbon was intended to maintain the chiral elements in the ketones by minimizing the potential epimerization due to the acidity of the protons α to the carbonyl group. Among the ketones closely related to **1**, we recently found that a fructose-derived ketone **3** displayed high enantioselectivity for the epoxidation of a wide range of *trans*- and trisubstituted olefins.[4] In addition to ketone **1**, we have also been actively studying ketone **4**, which uses another fused ring to replace the quaternary center existing in **1**.[5] As an initial part of our study, ketones **6a**−**e**, as close analogues of **4**, were prepared and tested for asymmetric epoxidation. Herein, we wish to report our preliminary results on the epoxidation catalyzed by these ketones.

Ketones **6a**−**e** were prepared from (−)-quinic acid in a straightforward manner based on the existing procedures.[6] The detailed synthesis is outlined in Scheme 1.[7]

Chart 1



Scheme 1[a]



[a] Reaction Conditions: (a) 2,2-dimethoxypropane, benzene, TsOH (cat.), reflux (15 h), 83.8%; (b) MeONa, MeOH, rt, 5 h, 82%; (c) PCC, 3A MS, pyridine, CH_2Cl_2, rt, 24 h, 60%; (d) $NaBH_4$, MeOH, 1 h, 98%; (e) TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 3 h, 96%; (f) OsO_4, NMO, tBuOH, pyridine, H_2O, reflux, 4 h, 90−95%; (g) 2-methoxypropene, CSA (cat.), CH_2Cl_2, rt, 96−99%; (h) TBAF, rt, 0.5 h, 70%; (i) DMSO, oxalyl chloride, CH_2Cl_2, −78 °C, 90−100%; (j) DIBAL-H (1 M in hexane), THF, −20 to 0 °C, 92−94%; (k) (1) for **6b** Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, then TBAF, rt, 86% two steps, (2) for **6c** BzCl, Et_3N, DMAP, CH_2Cl_2, rt, then TBAF, rt, 99% two steps, (3) for **6d** TsCl, Et_3N, DMAP, CH_2Cl_2, rt, then TBAF, rt, 82% two steps; (l) $NaBH_4$, EtOH, aq NaCl, rt, 30 h, 100%; (m) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C; (n) PCC, 3A MS, CH_2Cl_2, then $POCl_3$, pyridine, 54% two steps; (o) $NaBH_4$, MeOH, rt, then Ac_2O, pyridine, DMAP, CH_2Cl_2, rt, 96%.

High yields were obtained in almost all the steps. These ketones exist partially in hydrate forms, suggesting that the carbonyl groups are quite electrophilic. The epoxidation of *trans*-β-methylstyrene as substrate using ketone **6b** was initially carried out to determine the solvent effect on the reaction. Among the solvents tested (Table 1), dimethoxyethane (DME) was found to be the solvent of choice for both reactivity and selectivity.

Ketones **6a**−**e** differ from one another in the substituents at the β position to the carbonyl group. To test whether these substituents have any effect on the epoxidation, three types of olefins, i.e., *trans*- and *cis*-olefins and terminal olefins, were employed as substrates. The results presented in Table 2 show that the substituents have some effects on both the conversion of the substrate and the enantiomeric excess of the epoxides, and the response of the three olefins to the substituent change is somewhat different. The effect could result from the conformational and electronic changes of the catalysts imposed by the substituents. This observation opens up the possibilities that substituents on ketone catalysts could be used as handles to fine-tune the catalyst reactivity and selectivity.

To further reveal the catalytic features of these ketones, **6b** was chosen as a representative to explore the epoxidation of a variety of olefins. The results are shown in Table 3. Compared to ketone **3**, **6b** is less enantiose-

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(7) New compounds have been fully characterized spectroscopically. Elemental compositions have been established by combustion analysis and/or high-resolution mass spectrometry.

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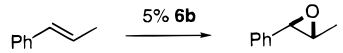
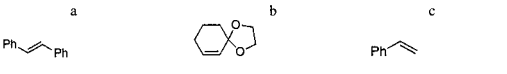
Table 1. Solvent Effect on Asymmetric Epoxidation of β-Methylstyrene with Ketone 6b[a]



cntry	solvent	T (° C)	t (h)	convn (%)	ee (%)
1	CH_3CN	0	4	58.4	63
2	DME[b]	0	4	100	70
3	DME	−10	4	95	73
4	DMM[b]	0	4	43	66
5	dioxane	0	4	99.4	67
6	DMM/CH_3CN (2/1)	0	4	91	67
7	DMF	0	3	99	64

[a] All reactions were carried out with *trans*-β-methylstyrene (0.4 mmol), ketone **6b** (0.02 mmol), Oxone (0.55 mmol), and K_2CO_3 (2.31 mmol) in organic solvent (6 mL) and buffer (0.05 M $Na_2B_4O_7 \cdot 10H_2O$ in 4×10^{-4} M aqueous EDTA) (4 mL). The conversion was determined by GC (HP-17 column), and the enantioselectivity was determined by Chiral GC (Chiraldex γ-TA column). [b] DME = dimethoxyethane, DMM = dimethoxymethane.

Table 2. Epoxidation of Representative Olefins with Ketones 6a−e



Catalyst	Cat (mol%)	Yield[d] (%)	ee[e] (%)	Cat (mol%)	Conv.[f] (%)	ee[g] (%)	Cat (mol%)	Conv.[f] (%)	ee[g] (%)
6a	10	66	95	10	56	66	10	90	67
6b	10	95	90	10	82	68	5	96	65
6c	10	91	90	10	67	71	5	99	65
6d	10	74	90	10	62	71	5	70	67
6e	10	77	90	10	70	73	10	100	66

[a] The reactions were carried out with *trans*-stilbene (0.2 mmol), ketone (0.02 mmol), Oxone (0.276 mmol), and K_2CO_3 (1.16 mmol) in DME/DMM (3 mL, 2/1, v/v) and buffer (prepared by mixing 100 mL of 0.1 M aqueous K_2CO_3 with 0.5 mL of AcOH) (2 mL) at −10 °C. The reactions were stopped after 6 h. [b] Everything is the same except that the reactions were carried out in DME (3 mL). [c] The reactions were carried out with styrene (0.4 mmol), ketone (0.02 or 0.04 mmol), Oxone (0.55 mmol), and K_2CO_3 (2.31 mmol) in DME (5 mL, 2/1, v/v) and buffer (the same as above) (3.2 mL) at −10 °C. The reactions were stopped after 6 h for ketone **6a** and 4 h for ketone **6b**−**e**. [d] Isolated yields. [e] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). [f] The conversion was determined by GC (HP-17 column). [g] Enantioselectivity was determined by chiral GC (Chiraldex γ-TA column).

lective for both *trans*- and trisubstituted olefins. However, a few noticeable features of this type of ketone are worth mentioning: (1) **6a**−**e** are more stable and reactive than **3**, and a smaller amount of catalyst is required to achieve good conversion. (2) Electron-deficient olefins can be epoxidized by **6b** (entries 2 and 3, Table 3), indicating that the dioxirane derived from this type of ketone is very electrophilic.[8] The high enantioselectivity obtained with the enone (entry 3, Table 3) suggests that the catalyst can effectively compete with the ketones present in the substrate and the epoxide product. (3) The enantiomeric excess for the epoxidation of the *cis*-olefins and terminal olefins is encouragingly high. The epoxidation of styrene gives up to 67% ee, which is close to the best reported.[9]

In summary, a ketone with a fused ring at each side of the carbonyl group has been shown to be an effective catalyst for asymmetric epoxidation. The results show that this type of ketone displays a distinct reaction pattern. The unique features associated with these

Table 3. Asymmetric Epoxidation of Representative Olefins by Ketone 6b[a]

Entry	Substrate	Cat. (mol%)	T (°C)	time (h)	Yield (%)[c]	ee (%)	Config.[g]
1[b]		10	-10	6	95	90[d]	(+)-(R,R)[10a]
2		10	0	8	34	86[e]	(+)-(2S,3R)[10b]
3		10	0	6	80	94[d]	(+)-(2S,3R)[8]
4		5	-15	4	92	75[e]	(+)-(R,R)[10c]
5		10	0	5	94	77[d]	(+)-(2S,3R)[4a]
6[b]		10	0	5	86	87[d]	(-)-(R)[10d]
7		5	-10	4	90	65[e]	(-)-(R)[10e]
8		5	-10	4	54	65[d]	(-)
9		5	-10	4	83	66[f]	(-)
10		5	-10	4	89	54[f]	(-)-(R)[10f]
11		5	-10	3	92	52[d]	(+)-(R)[10g]
12		10	-10	6	78	68[e]	(+)-(R,R)[10h]

[a] All reactions were carried out with substrate (1 equiv), ketone (0.05−0.1 equiv), Oxone (1.38 equiv), and K_2CO_3 (5.8 equiv) in (1.5:1, v/v) DME−buffer (prepared by mixing 100 mL of 0.1 M aqueous K_2CO_3 with 0.5 mL of AcOH) except for entries 1 and 6. [b] The reactions were carried out in (2:1:2, v/v) DME−DMM−buffer (the same as above). [c] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [d] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). [e] Enantioselectivity was determined by chiral GC (Chiraldex γ-TA column). [f] Enantioselectivity was determined by ^1H NMR shift analysis of the epoxide product directly with $Eu(hfc)_3$. [g] The absolute configurations were determined by comparing the measured optical rotations with the reported ones.

ketones provide a strong stimulus for further studies, particularly for the epoxidation of terminal olefins, which is still a challenging problem. Future efforts will be devoted to the elucidation of the structural requirements for a ketone to be an effective catalyst for asymmetric epoxidation. Efficient synthesis of ketone catalysts will also be pursued.

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Supporting Information Available: Characterizations of compounds **7**−**12** and **6a**−**e** along with the NMR spectral, GC, and HPLC data for the determination of the enantiomeric excess of the formed epoxides (11 pages).

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