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A C_2 Symmetric Chiral Ketone for Catalytic Asymmetric Epoxidation of Unfunctionalized Olefins

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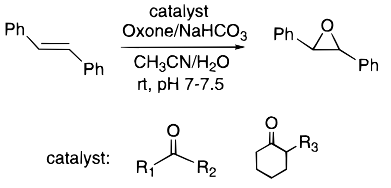
Dioxiranes[1] are important oxidants for organic reactions such as epoxidation,[2] heteroatom oxidation,[3] and oxygenation of C−H bonds.[4] In particular, epoxidation mediated by dioxiranes is stereospecific and highly efficient toward both electron-rich and electron-deficient olefins.[5] Moreover, dioxirane epoxidation can be a catalytic process as dioxiranes can be generated *in situ* from ketones and Oxone.[6] Chiral ketones are thus expected to be ideal catalysts for asymmetric epoxidation. However, limited progress has been made in this direction, as the reported chiral ketones exhibit poor catalytic activities and low asymmetric induction.[7,8] Here we report the first C_2 symmetric chiral ketone as a promising catalyst for asymmetric epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins.[9−11]

We recently discovered that, in a homogeneous CH_3CN−H_2O solvent system, epoxidation with Oxone can be catalyzed efficiently by trifluoroacetone.[6d] This simple protocol allows us to directly compare the catalytic activities of various ketones in epoxidation of *trans*-stilbene. The results for acyclic ketones **1a**−**g** and cyclic ketones **2a**−**c** are summarized in Table 1. Here two general trends are observed. (1) Ketones with electron-withdrawing groups, such as F, Cl, and OAc, at α positions show higher activities (entries 2−6 vs entry 1; entry 9 vs entry 8). (2) Steric hindrance at α positions decreases the activity (entry 7 vs entry 2; entry 10 vs entry 8). Therefore, both steric and electronic factors need to be considered in designing efficient ketone catalysts.

Table 1. Activities of Various Ketones in Catalyzing *in Situ* Epoxidation of *trans*-Stilbene[a]



1 **2**

entry	catalyst R$_1$	R$_2$	R$_3$		reaction time (min)[b]
1	CH_3	CH_3		(**1a**)	300
2	CH_3	CF_3		(**1b**)	<4
3	CH_3	CH_2F		(**1c**)	20
4	CH_3	CH_2Cl		(**1d**)	18
5	CH_3	CH_2OAc		(**1e**)	30
6	CH_2OAc	CH_2OAc		(**1f**)	30
7	Ph	CF_3		(**1g**)	70
8			H	(**2a**)	210
9			Cl	(**2b**)	15
10			CH_3	(**2c**)	>720

[a] Reaction conditions: room temperature, 0.1 mmol of *trans*-stilbene, 1.0 mmol of catalyst, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2·EDTA (4 × 10^{-4} M). [b] Time when epoxidation was completed as shown by TLC.

We also note that dioxiranes have two faces for oxygen transfer. It is expected that ketone catalysts with C_2 symmetry and rigid conformations have the potential for asymmetric epoxidation. Therefore, cyclic analogs of 1,3-diacetoxyacetone **1f** were designed and synthesized.[12] Among them, ketone **3** showed unprecedented catalytic activity (Table 2).[13] In a 1:1 ketone:substrate ratio at room temperature, *in situ* epoxidation of *trans*-stilbene catalyzed by ketone **3** proceeded faster than that by trifluoroacetone (**1b**) or acyclic ketone **1f**. Ketone **3** was stable under the reaction conditions and can be recovered in high yield without loss of catalytic activity.[14] To further demonstrate the catalytic efficiency of ketone **3**, epoxidation of *trans*-stilbene was carried out using 1 mol % of ketone **3** at

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† On leave from the Shanghai Institute of Organic Chemistry.

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[13] Ketone **3** was synthesized in one step from diphenic acid and 1,3-dihydroxyacetone in 45% yield using 2-chloro-1-methylpyridinium iodide as the coupling reagent (Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49).

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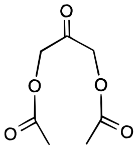
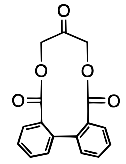
Table 2. Activity of Ketone **3** in Catalyzing *in Situ* Epoxidation of *trans*-Stilbene[a]

catalyst	reaction time (min)	epoxide yield (%)	ketone recovery (%)
1b	30	96	
1f	50	90	85
3	7	99	93[b]

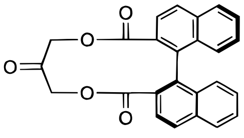
[a] Reaction conditions: room temperature, 0.1 mmol of *trans*-stilbene, 0.1 mmol of catalyst, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 1.5 mL of CH_3CN, 1.0 mL of aqueous Na_2•EDTA (4×10^{-4} M). [b] Flash column purification with Et_3N (ref 14).

room temperature. The epoxidation was completed in 12 h, and the *trans*-stilbene epoxide was isolated in 98% yield.


1f


3

Since ketones with chiral centers at α positions are prone to racemization, we chose to put the C_2 symmetric chiral element away from the catalytic center (i.e., the keto group). A C_2 symmetric, 11-membered-ring ketone **4** was designed when the diphenic unit of ketone **3** was replaced by a chiral binaphthalene unit.[15] X-ray analysis[16] revealed that ketone **4** indeed has a rigid and C_2 symmetric structure (Figure 1): the keto group lies on the C_2 axis of the molecule; the two ester groups, anti-parallel to each other, retain the favorable *s-trans* geometry and are nearly perpendicular to the macrocyclic ring plane; and the dihedral angle of the two naphthalene rings is ca. 70°.


(*R*)-**4**

Preliminary results of asymmetric epoxidation catalyzed by chiral ketone **4** are summarized in Table 3. Similar to ketone **3**, chiral ketone **4** was highly efficient in catalyzing epoxidation reactions.[17] More importantly, chiral ketone **4** gave moderate to good enantioselectivity for epoxidation of *trans*-olefins and trisubstituted olefins (entries 1−5) but not for *cis*-olefins or terminal olefins (entries 6−8). It is significant that, even with 10 mol % of ketone **4**, 87% ee was obtained for epoxidation of *trans*-stilbene derivative **6**. This is the highest ee reported for epoxidation of unfunctionalized *trans*-olefins using chiral ketones as catalysts.

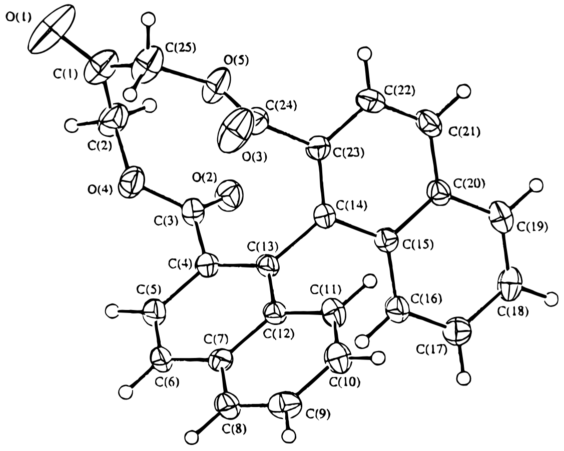
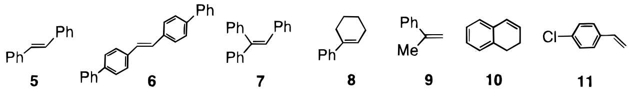


Figure 1. X-ray structure of racemic ketone **4** (ORTEP view; only one molecule is shown).

Table 3. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Ketone **4**[a]



entry	catalyst	substrate	time (min)	epoxide yield (%)[b]	epoxide config	ee (%)[c]
1	(*R*)-**4**	**5**	20	99	(−)-(*S*,*S*)[d]	47
2[e]	(*R*)-**4**	**6**	480	82	(−)-(*S*,*S*)[d]	87
3[e]	(*S*)-**4**	**6**	480	80	(+)-(*R*,*R*)[d]	87
4	(*R*)-**4**	**7**	60	98	(+)-(*S*)[f]	50
5[g]	(*R*)-**4**	**8**	90	83	(−)-(*S*,*S*)[f]	33
6[h]	(*R*)-**4**	**9**	210	70	nd[i]	18
7[j]	(*R*)-**4**	**10**	80	85	nd[i]	<5
8[j]	(*R*)-**4**	**11**	60	83	(−)-(*S*)[k]	18

[a] Unless otherwise indicated, all the epoxidation reactions were carried out at room temperature with 0.1 mmol of substrate and 0.1 mmol of ketone **4**, 0.5 mmol of Oxone, 1.55 mmol of $NaHCO_3$, 2 mL of CH_3CN, and 1.7 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [b] Isolated yield after flash column chromatography. [c] Determined by ^1H NMR using chiral shift reagent Eu(hfc)$_3$ (Aldrich Cat. No. 16,474-7). [d] Determined by circular dichroism spectroscopy (see supporting information). [e] 0.01 mmol of ketone **4**, 2.5 mL of CH_3CN, and 2 mL of aqueous Na_2•EDTA solution (4×10^{-4} M). [f] Reference 11a. [g] 0.2 mmol of the substrate. [h] 0.5 mmol of the substrate. [i] Not determined. [j] 0.2 mmol of the substrate, 0.01 mmol of ketone **4**. [k] Reference 18.

Despite recent advances, catalytic asymmetric epoxidation of unfunctionalized *trans*-olefins and trisubstituted olefins still represents a great challenge.[10,11] In this paper, we have shown the potential of the chiral dioxirane approach to this problem. Further work should be directed at understanding the mechanism of the chiral induction as well as developing better ketone catalysts.

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Supporting Information Available: Experimental details for *in situ* epoxidation reactions and preparation and characterization of ketones **3** and **4**, assignment of absolute configurations and characterization data of epoxides from Table 3, and X-ray structural analysis of ketone **4** containing tables of atomic coordinates, thermal parameters, and bond lengths and angles (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(14) It was noted that ketone **3** is not very stable toward silica gel; therefore, NEt_3 is needed to buffer the silica gel during column chromatography (see supporting information).

(15) Chiral ketone **4** was synthesized in one step from chiral 1,1′-binaphthyl-2,2′-dicarboxylic acid and 1,3-dihydroxyacetone in 20−30% yield using 2-chloro-1-methylpyridinium iodide as the coupling reagent (see ref 13).

(16) There are two independent molecules present in one asymmetric unit. Crystal data: ketone **4**, $C_{25}H_{16}O_5$, triclinic, $P\bar{1}$ (No. 2) with $a = 11.066(5)$ Å, $b = 18.688(6)$ Å, $c = 10.931(4)$ Å, $\alpha = 101.53(4)°$, $\beta = 118.99(3)°$, $\gamma = 87.93(3)°$, $V = 1932(1)$ Å^3, $Z = 4$, with 541 parameters refined on 2367 reflections having $I > 3.0\sigma(I)$, $R = 0.042$ and $R_w = 0.042$ (the details of the X-ray analysis are provided as supporting information).

(17) Chiral ketone **4** was recovered in over 90% yield by flash column chromatography (see supporting information) and was reused without loss of chiral induction.

(18) (a) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791. (b) Reference 10b.