

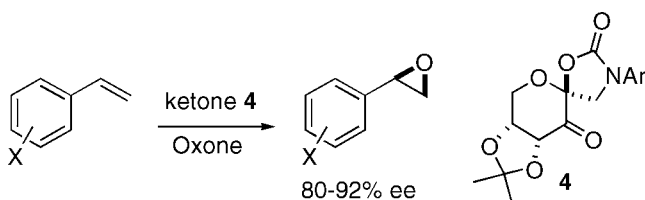
Effective Asymmetric Epoxidation of Styrenes by Chiral Dioxirane

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High enantioselectivity (80–92% enantiomeric excess (ee)) has been obtained for the epoxidation of various styrenes using an easily prepared ketone (**4**) catalyst.

Chiral styrene oxides are extremely useful and can be prepared by a number of methods, such as asymmetric reduction of α -halo acetophenones,¹ asymmetric dihydroxylation of styrenes,² and kinetic resolution of racemic epoxides.³ The asymmetric epoxidation of styrenes has also received a considerable amount of interest.^{4–6} Various chiral catalysts and

reagents have been investigated for the epoxidation of styrenes including chiral porphyrin complexes,⁴ chiral salen complexes,⁵ chiral oxaziridines, and oxaziridinium salts.⁶ Although significant progress has been made in this area, the development of a potentially useful epoxidation method for styrenes has been elusive.

Although chiral dioxiranes are effective for asymmetric epoxidation of *trans*-, trisubstituted, and certain *cis*-alkenes,⁷ styrenes have been challenging substrates.⁸ During our earlier studies, we found that fructose-derived ketone **1** (Scheme 1), a very effective catalyst for *trans*- and trisubstituted alkenes, gave only 24% enantiomeric excess (ee) for styrene.⁹ Encouragingly high ee's (74–85%) were subsequently obtained with ketone **2**.¹⁰ Our recent studies on the conformational and electronic effects of ketone catalysts on epoxidation have shown that ketone **3**, a carbocyclic analogue of **2**, gives high ee for styrenes (89–93% ee).¹¹ Although ketone **3** is mechanistically informative, its lengthy synthesis precludes its practical use. Very recently, we have shown that *N*-aryl-substituted oxazolidinone ketone **4a** (Ar = *p*-MePh) (Scheme 1), which is readily prepared from glucose and *p*-toluidine (Scheme 2), provides a potentially practical catalyst for epoxidation.¹² Herein, we wish to report our studies on the epoxidation of styrenes with this class of ketones.

Our studies showed that the *N*-substituents of the ketones have significant effects on the enantioselectivity of styrene epoxidation, with the ee varying from 55 to 87% using 15 mol % ketone catalyst in DME (Scheme 3, Table 1). Generally speaking, aniline substitution with hydrocarbons consistently shows higher ee than substitution with ethers or halogens. A combination of high enantioselectivity and low cost of aniline starting materials (*p*-toluidine and 4-ethylaniline) makes **4a** and **4b** good catalyst choices among all of these ketones. The ee obtained with ketone **4b** for styrene encouraged us to extend the epoxidation to other styrenes. As shown in Table 2, up to 92% ee was obtained with the observed enantioselectivity being dependent on the phenyl group substituents of the olefins.

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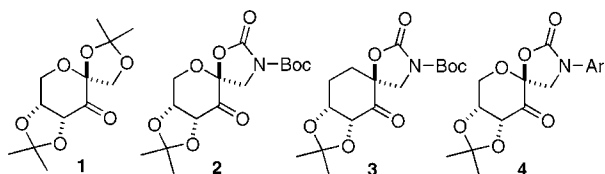
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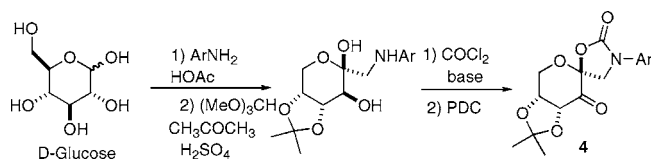
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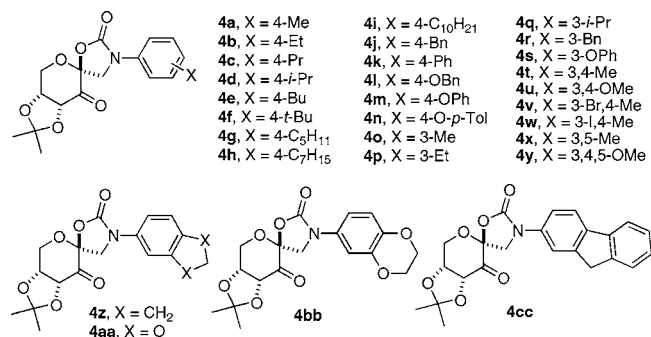
SCHEME 1



SCHEME 2



SCHEME 3

TABLE 1. Asymmetric Epoxidation of Styrene with Ketone **4**^a

entry	ketone	conv. (ee) (%) ^b	entry	ketone	conv. (ee) (%) ^b
1	4a	100 (84)	15	4o	100 (82)
2	4b	100 (86)	16	4p	97 (85)
3	4c	100 (84)	17	4q	100 (87)
4	4d	100 (84)	18	4r	100 (80)
5	4e	99 (84)	19	4s	100 (79)
6	4f	100 (86)	20	4t	100 (81)
7	4g	100 (82)	21	4u	77 (70)
8	4h	95 (85)	22	4v	49 (78)
9	4i	79 (83)	23	4w	52 (55)
10	4j	100 (78)	24	4x	98 (83)
11	4k	100 (86)	25	4y	98 (69)
12	4l	79 (75)	26	4z	87 (84)
13	4m	89 (85)	27	4aa	78 (78)
14	4n	100 (81)	28	4bb	89 (79)
			29	4cc	100 (86)

^a All reactions were carried out with olefin (0.10 mmol), ketone **4** (0.015 mmol), Oxone (0.212 M, 0.84 mL), K₂CO₃ (0.48 M, 0.84 mL), and Bu₄NHSO₄ (0.02 mmol) in DME (1.5 mL) and buffer (0.1 M K₂CO₃-AcOH, pH 8.0) (1.0 mL) at -10 °C (bath temperature) (NaCl ice bath) for 3.5 h. ^b The conversion and ee were determined by chiral GC (Chiraldex B-DM).

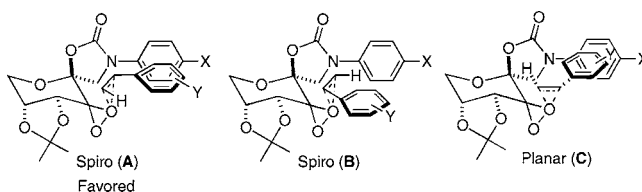
Our earlier studies suggest that the asymmetric induction for ketone class **4** is likely due to an attraction between the aryl group of the olefin and the oxazolidinone moiety of the ketone catalyst in the transition state.^{10–12} For styrenes, spiro **A** is likely to be the favored transition state with spiro **B** and planar **C** being competing transition states (Scheme 4). For ortho-substituted styrenes (Table 2, entry 2), observed enantioselectivity is lower than styrene itself, presumably because of unfavorable steric interactions between the substituents on the styrene and the oxazolidinone moiety of the catalyst for spiro transition state **A**. As a result, a net decrease in enantioselectivity is observed. For meta-substituted styrenes (Table 2, entries

TABLE 2. Asymmetric Epoxidation of Styrenes with Ketone **4**^a

entry	Substrates	yield ^d (conv. ^c) (%)	ee (%)	config. ^h
1 ^{im}	X = H	72 (100)	86 ^d	(-)-(R) ^{13a}
2 ^{im}	X = 2-F	89 (95)	80 ^d	(-) ^{13b}
3 ^{im}	X = 4-Cl	85 (100)	86 ^d	(-)-(R) ^{13a}
4 ^{im}	X = 4-Br	71 (99)	87 ^d	(-)-(R) ^{13c,d}
5 ^{kn}	X = 4-CN	86 (100)	90 ^d	(-)-(R) ^{13c,d}
6 ^{ln}	X = 4-NO ₂	73 (99)	90 ^d	(-)-(R) ^{13c,d}
7 ⁱⁿ	X = 4-CF ₃	73 (100)	92 ^d	(-) ⁴ⁱ
8 ^{kn}	X = 3-OBn	66 (79)	87 ^c	(-)
9 ^{im}	X = 3-Me	87 (100)	90 ^d	(-)
10 ^{kn}	X = 3-Cl	72 (100)	86 ^f	(-) ^{13a}
11 ^{kn}	X = 3-NO ₂	77 (100)	88 ^f	(-) ⁴ⁱ
12 ^{ko}	X = 3,4-(CHCH)-	91 (100)	87 ^g	(-)-(R) ^{13c}
13 ^{kn}	X = 3,4-Cl	75 (95)	90 ^d	(-) ^{13c}
14 ^{im}	X = 3,5-Me	86 (99)	90 ^d	(-)

^a All reactions were carried out with olefin (0.40 mmol), ketone **4b** (0.06–0.12 mmol), Oxone (1.07 mmol), K₂CO₃ (4.23 mmol), and Bu₄NHSO₄ (0.04 mmol) in DME (6.0 mL) and buffer (0.1 M K₂CO₃-AcOH, pH 9.3) (4.0 mL) at -10 to -15 °C (bath temperature). For entry 12, the reaction was carried out at -5 °C. For entry 13, the reaction was carried out in DME (5.0 mL)/dioxane (1.0 mL) at 0 °C. ^b Isolated yield. ^c The conversion was determined by GC, except for entries 8, 10, 11, and 12 which were determined by ¹H NMR. ^d The ee was determined by chiral GC (Chiraldex B-DM). ^e The ee was determined by chiral HPLC (Chiralcel AD). ^f The ee was determined by chiral HPLC (Chiralcel OD). ^g The ee was determined by chiral HPLC (Chiralcel OJ). ^h The absolute configurations were determined by comparing the measured optical rotations with the reported ones. ⁱ Reaction time of 6 h. ^j Reaction time of 8 h. ^k Reaction time of 12 h. ^l Reaction time of 16 h. ^m 0.06 mmol of ketone **4b** was used. ⁿ 0.12 mmol of ketone **4b** was used. ^o The reaction was carried out with 3.24 mmol of olefin and 0.98 mmol of ketone **4b**.

SCHEME 4



8–11), certain substituents on the phenyl group of the olefin appear to further favor spiro **A**, resulting in an increase in overall ee. For para-substituted styrenes (Table 2, entries 3–7), certain substituents do not significantly affect the competition of the transition states, thus giving an ee similar to styrene itself. However, electron-deficient olefins give higher ee's than their more electron-rich counterparts, presumably because of enhanced secondary orbital interactions further favoring spiro transition states.¹¹ Styrenes bearing multiple substituents give ee's that are consistent with the various electronic and structural patterns of the simpler monosubstituted styrenes.

In summary, the asymmetric epoxidation of various styrenes has been investigated with a variety of *N*-aryl-substituted oxazolidinone-containing ketones. High enantioselectivity has been achieved for both electron-rich and electron-poor styrenes. The availability of these ketone catalysts reveals the potential of this asymmetric epoxidation as a viable entry into this important class of molecules. Future studies will be devoted to

further understanding the interactions between olefin substituents and N-substituents of ketone catalysts and fully exploring the substrate scope of these effective chiral ketone catalysts.

Experimental

Representative Asymmetric Epoxidation Procedure (Table 2, Entry 3). To a solution of 4-chlorostyrene (0.055 g, 0.4 mmol) and ketone **4b** (0.021 g, 0.06 mmol) in DME (6.0 mL) were added buffer (0.1 M K₂CO₃-AcOH in 4 × 10⁻⁴ M aq EDTA, pH 9.3) (4.0 mL) and Bu₄NHSO₄ (0.010 g, 0.03 mmol) with stirring. After the mixture was cooled to about -10 to -15 °C (bath temperature) via a NaCl ice bath, a solution of Oxone (0.212 M in 4 × 10⁻⁴ M aq EDTA, 5.04 mL) and a solution of K₂CO₃ (0.84 M in 4 × 10⁻⁴ M aq EDTA, 5.04 mL) were added dropwise separately over 8 h via syringe pump. The reaction was quenched by addition of pentane and extracted with pentane. The combined organic layers were dried (Na₂SO₄), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered by 1% Et₃N in pentane; pentane/ether (1:0 to 10:1) was used as the eluent] to give 4-chlorostyrene oxide as a colorless oil (0.0526 g, 85%, 86% ee).

Representative Ketone Synthesis. To a mixture of D-glucose (50.0 g, 279.0 mmol) and 4-ethylaniline (40.3 g, 333.0 mmol) was added water (13.7 mL), followed by AcOH (0.34 g, 5.66 mmol). After the mixture was stirred at 95 °C (oil bath temperature) for 1 h (the mixture solidified), ether (200 mL) was added. Upon stirring at room temperature for 2 h and standing in the freezer overnight, the mixture was filtered. The filter cake was washed to white with additional ether and dried to give a white solid that was used without further purification (55.5 g, 70%).

To a suspension of the above product (10.1 g, 35.6 mmol) in acetone (420 mL) was added HC(OMe)₃ (8.9 mL, 81.3 mmol), followed by H₂SO₄ (3.1 mL, 55.8 mmol), at 0 °C. Upon stirring at 0 °C for 1 h, the reaction mixture was quenched with concentrated NH₄OH (8.9 mL) and quickly filtered through a pad of silica gel. The filter cake was washed with additional acetone. The acetone solution was dried (Na₂SO₄), filtered, and concentrated to give a yellow oil (9.32 g) that was used without further purification.

A mixture of the above oil and NaHCO₃ (12.2 g) was suspended in CH₂Cl₂ (142 mL). While stirring at 0 °C, 20% phosgene solution in toluene (21.3 mL, 40.5 mmol) was added via a syringe pump under argon over 2 h. After the mixture was stirred at 0 °C for an additional 4 h, triethylamine (17.3 mL) was then added. Upon stirring at room temperature overnight, the mixture was filtered through a pad of silica gel, concentrated, and purified on silica gel with hexane/AcOEt (2:1 to 1:2) to give the alcohol product as a light brown solid (6.78 g, 55% yield over two steps).

To a suspension of the alcohol (8.0 g, 22.9 mmol), PDC (12.9 g, 34.4 mmol), and 3A MS (14 g) in CH₂Cl₂ (23 mL) was added acetic acid (5 drops). Upon stirring at room temperature overnight, the reaction mixture was filtered through a pad of silica gel and washed with hexane/AcOEt (1:2). The filtrate was concentrated and dried on the high-vacuum line to give the ketone. Recrystallization (ether/hexanes) gave the product (**4b**) as a white solid (4.3 g, 54%): mp 135–136 °C; [α]_D²⁰ -40.6 (c, 0.32, CHCl₃); IR (film) 1774 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.87 (d, *J* = 5.1 Hz, 1H), 4.74 (d, *J* = 10.2 Hz, 1H), 4.66–4.59 (m, 2H), 4.26 (d, *J* = 13.5 Hz, 1H), 3.75 (d, *J* = 10.2 Hz, 1H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.48 (s, 3H), 1.43 (s, 3H), 1.22 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 195.1, 151.4, 141.3, 134.7, 128.7, 119.0, 111.2, 99.3, 77.7, 75.7, 61.2, 50.1, 28.5, 27.4, 26.3, 15.9; HRMS calcd for C₁₈H₂₂NO₆ (M⁺ + 1) 348.1447, found 348.1441.

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Supporting Information Available: The characterization of ketone catalysts, data for the determination of the enantiomeric excess of the epoxides, and NMR data for the ketone catalysts (54 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>

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