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Studies of Substituent Effect on Asymmetric Epoxidation of Chromenes by Chiral Dioxirane

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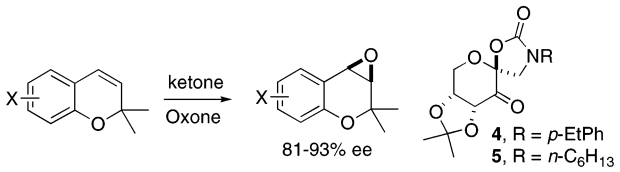


A series of 6- and 8-substituted chromenes has been investigated for asymmetric epoxidation using chiral ketone catalysts. Up to 93% ee was achieved. Higher ee's are obtained when substrates are substituted at the 6-position. The enhanced enantioselectivity is likely due to the beneficial interaction between the 6-substituent of the substrate and the *N*-aryl or alkyl group of the ketone catalyst.

Chiral dioxiranes have recently been shown to be effective asymmetric epoxidation reagents, and a variety of chiral ketones have been extensively investigated in various laboratories.[1] In our earlier studies, fructose-derived ketone **1** (Figure 1) has been shown to be a very effective catalyst for the epoxidation of *trans*- and trisubstituted olefins.[2] Subsequently, we have found that an oxazolidinone-bearing ketone **2** provided encouragingly high ee's in the epoxidation of *cis*-olefins and styrenes.[3] Our recent studies have also shown that readily available *N*-aryl-substituted ketone **3** is an effective catalyst for asymmetric epoxidation of a variety of *cis*-β-methylstyrenes.[4] Interestingly, it was observed that substituents on the phenyl group of *cis*-β-methylstyrenes have a significant positive effect on the enantioselectivity of the epoxidation. Our earlier studies suggested that the asymmetric induction during the epoxidation with ketone **3** is likely due to an attraction between the phenyl group of the olefin and the oxazolidinone moiety of the catalyst in the transition state, causing spiro **A** to be more favorable than spiro **B** (Figure 2).[3,4] It appears that substituents on the phenyl group of the olefin further enhance the interaction between the phenyl group of the olefin and the phenyl group of the ketone catalyst, thus further favoring spiro transition state **A** and increasing the enantioselectivty (Figure 2). However, in the case of 3-substituted *cis*-β-methylstyrenes, there are two possible reacting approaches for the favored spiro transition state (**A-1** and **A-2**) (Figure 3). We decided to probe the difference between transition states **A-1** and **A-2** using cyclic olefins, so that the reacting approach can be defined. Thus, a series of 6- and 8-substituted 2,2-dimethylchromenes were examined for the epoxidation.[5,6] Herein we report our studies on this subject.

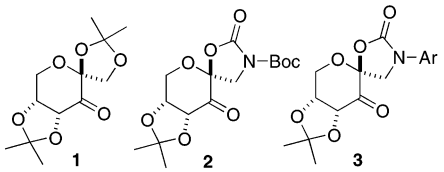


FIGURE 1. Ketone catalysts for asymmetric epoxidation.

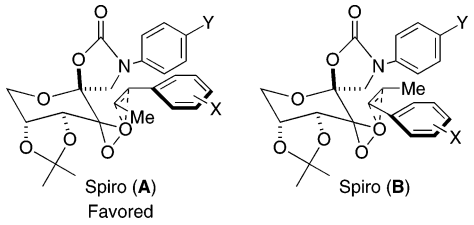


FIGURE 2. Transition states for the epoxidation of *cis*-β-methylstyrenes.

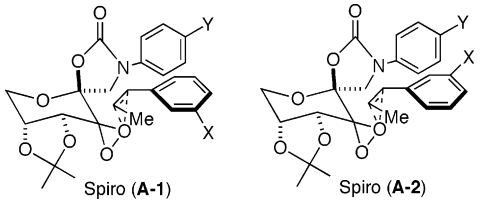
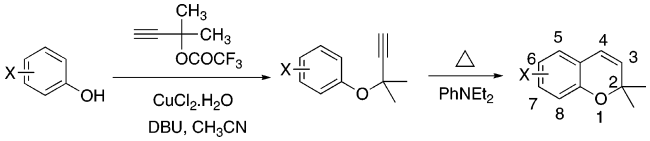


FIGURE 3. Two reacting approaches for the epoxidation of 3-substituted *cis*-β-methylstyrenes.

SCHEME 1. Synthesis of 2,2-Dimethylchromenes



Substituted chromenes were prepared on the basis of a reported procedure (Scheme 1).[7] The epoxidation was initially investigated using ketone **4**[8] as a catalyst (Figure 4). Subjecting

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(5) For leading reviews on highly enantioselective epoxidation of chromenes by chiral salen catalysts, see: (a) Jacobsen, E. N. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 159. (b) Katsuki, T. *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; p 287.

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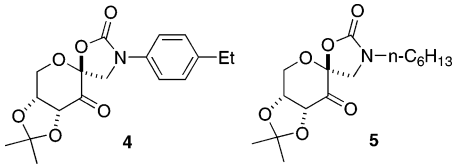
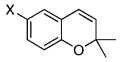
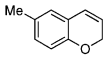


FIGURE 4. Ketone catalysts used for the asymmetric epoxidation of chromenes.

TABLE 1. Asymmetric Epoxidation of Chromenes Catalyzed by Ketones 4 and 5

		ketone **4**[a]		ketone **5**[b,j]	
entry	substrate	conv. (yield) (%)[e]	ee (%)	conv. (%)[e]	ee (%)
1[c]		100 (86)	84[f,i]	100	84[f]
					
2[c]	X = OMe	100 (65)	90[f]	100	88[f]
3[c]	X = Me	100 (75)	92[f]	100	92[f]
4[c]	X = Et	80 (59)	90[f]		
5[c]	X = *n*-Pr	75 (70)	91[f]		
6[c]	X = *i*-Pr	79 (69)	90[f]		
7[d]	X = F	100 (77)	89[g]	94	89[g]
8[d]	X = Cl	100 (81)	93[f]	58	93[f]
9[d]	X = Br	81 (66)	91[f]	76	93[f]
10[d]	X = CN	83 (75)	93[f,i]	71	89[f]
11[c]		100 (38)	90[f]		
					
12[d]	X = OMe	100 (63)	82[h]	100	82[h]
13[d]	X = Me	80 (63)	81[h]	100	85[h]
14[d]	X = F	100 (82)	84[h]	81	84[h]
15[d]	X = Cl	85 (71)	83[h]	76	86[h]
16[d]	X = Br	83 (70)	82[h]	76	85[h]
17[d]	X = CN	95 (88)	88[g]	87	89[g]

[a] All reactions were carried out with olefin (0.40 mmol), ketone **4** (0.08 mmol), Oxone (1.07 mmol), K_2CO_3 (4.23 mmol), Bu_4NHSO_4 (0.003 mmol) in DME/DMM (3:1 v/v) (6.0 mL), and buffer (0.1 M K_2CO_3−AcOH, pH 9.3) (4.0 mL) at 0 °C (bath temperature). [b] All reactions were carried out with olefin (0.20 mmol), ketone **5** (0.04 mmol), Oxone (0.53 mmol), K_2CO_3 (2.12 mmol), Bu_4NHSO_4 (0.0015 mmol) in DME/DMM (3:1 v/v) (3.0 mL), and buffer (0.1 M K_2CO_3−AcOH, pH 9.3) (2.0 mL) at 0 °C (bath temperature). [c] Reaction time 6 h. [d] Reaction time 12 h. [e] The conversion was determined by NMR. The yield is the isolated yield. The epoxides were purified by flash chromatography (buffered with 1% NEt_3) and gave satisfactory spectroscopic characterization. For entry 11, a diol resulting from the opening of the epoxide was also isolated in 42% yield. [f] Enantioselectivity was determined by chiral HPLC (Chiralcel OD). [g] Enantioselectivity was determined by chiral GC (Chiraldex B-DM). [h] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [i] The epoxides have (3*R*,4*R*) configurations as determined by comparing the measured optical rotations with reported ones (ref 9). [j] The epoxides were isolated in 52−83% yields.

2,2-dimethylchromene to the epoxidation conditions with 20 mol % of ketone **4** at 0 °C gave (3*R*,4*R*)-(+)-2,2-dimethylchromene oxide with 100% conversion and 84% ee (Table 1, entry 1).[9] Introducing an electron-donating or electron-withdrawing substituent at the 6-position increases the ee by 5−9%, with electron-withdrawing groups giving generally higher ee's (Table 1, entries 2−10). Furthermore, 6-methylchromene was studied

(8) Goeddel, D.; Shu, L.; Yuan, Y.; Wong, O. A.; Wang, B.; Shi, Y. *J. Org. Chem.* **2006**, *71*, 1715.

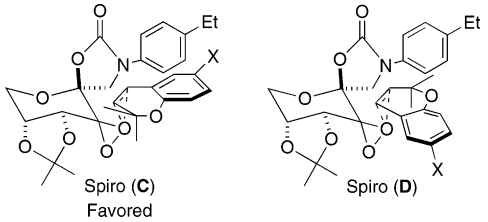


FIGURE 5. Two competing spiro transition states for the epoxidations of 6-substituted 2,2-dimethylchromenes.

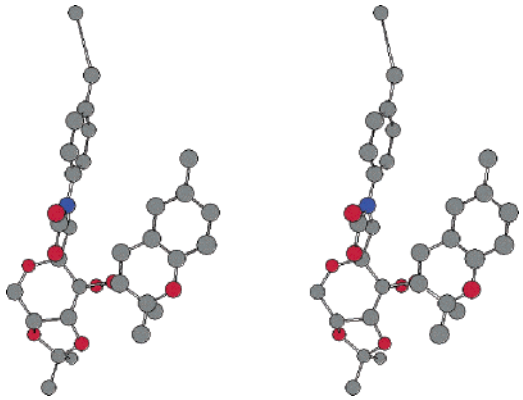


FIGURE 6. Chem3D molecular modeling of TS spiro **C** for the epoxidation of 6-methyl-2,2-dimethyl chromene with ketone **4** (stereoview).

to investigate the effect of the *gem*-dimethyl groups on enantioselectivity (Table 1, entry 11). The epoxidation of this substrate gave 90% ee, only slightly lower than 2,2-dimethyl-6-methylchromene (Table 1, entry 3), suggesting the *gem*-dimethyl groups do not have a significant effect on enantioselectivity. On the other hand, when the substituent is at the 8-position, the ee's increase with electron-withdrawing groups, such as cyano, but decrease with electron-donating groups, such as methoxy and methyl (Table 1, entries 12−17).

The effect of substituents at the 8-position on the enantioselectivity is likely to be electronic in nature. In the case of 6-substituted chromenes, besides the electronic effect, the proximity of substitutents on chromenes to the phenyl group of the catalyst in spiro transition state **C** might cause additional beneficial nonbonding interactions between the substituent at the 6-position of the substrate and the phenyl group of the catalyst, further favoring spiro transition state **C** (Figure 5) (examples of Chem3D molecular modeling of transition states spiro **C** and **D** for the epoxidation of 6-methyl-2,2-dimethyl-chromene with ketone **4** are shown in Figures 6 and 7). On the other hand, such interaction is not feasible for 8-substituted substrates (Figure 8) (examples of Chem3D molecular modeling of transition states spiro **E** and **F** for the epoxidation of 8-methyl-2,2-dimethylchromene with ketone **4** are shown in Figures 9 and 10). To further probe this interaction, the epoxidation of some chromenes was also carried out with *N*-hexyl-substituted ketone **5** (Figure 4). As shown in Table 1, a similar trend was

(9) The absolute configuration was determined by comparing the measured optical rotations with reported ones; see: (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (b) Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055. (c) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541. (d) Scheurer, A.; Mosset, P.; Spiegel, M.; Saalfrank, R. W. *Tetrahedron* **1999**, *55*, 1063. (e) Reference 6.

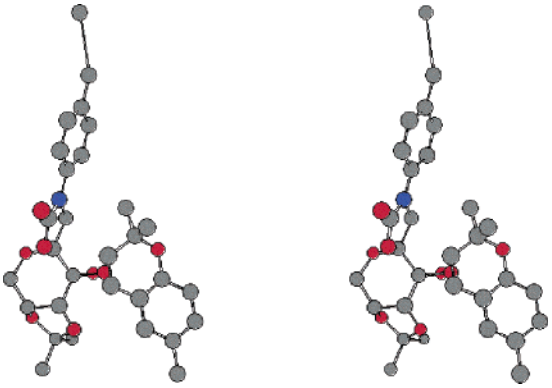


FIGURE 7. Chem3D molecular modeling of TS spiro **D** for the epoxidation of 6-methyl-2,2-dimethyl chromene with ketone **4** (stereoview).

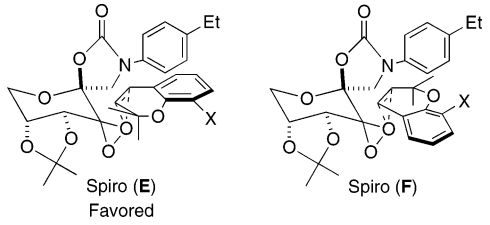


FIGURE 8. Two competing spiro transition states for the epoxidations of 6-substituted 2,2-dimethylchromenes.

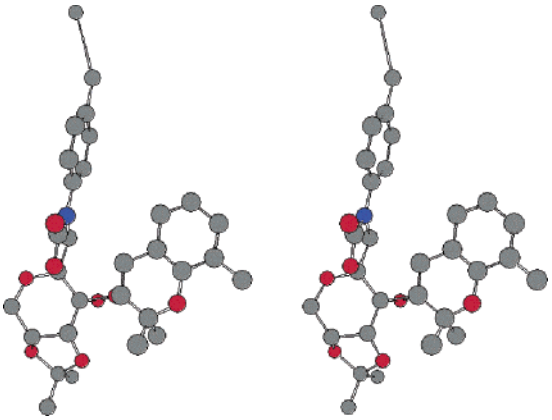


FIGURE 9. Chem3D molecular modeling of TS spiro **E** for the epoxidation of 8-methyl-2,2-dimethylchromene with ketone **4** (stereoview).

observed (the ee's of 6-substituted chromenes are higher than that of 8-substituted chromenes), suggesting that a nonaromatic group on the nitrogen could also provide the beneficial interaction between the 6-substituent of the substrate and the *N*-substituent of the ketone catalyst. The fact that both electron-donating and electron-withdrawing groups enhance the enantioselectivity of the epoxidation with ketones **4** and **5** suggests that nonbonding interactions, such as van der Waals forces and/or hydrophobic interactions, are important components of the interaction between the substituent on the phenyl group of the olefin and the *N*-substituent of the ketone catalyst.

In summary, asymmetric epoxidation of various chromenes using *N*-substituted oxazolidinone-containing ketones **4** and **5** has shown that 6-substituents on the phenyl group of the olefin have significant beneficial effects on the enantioselectivity. Up

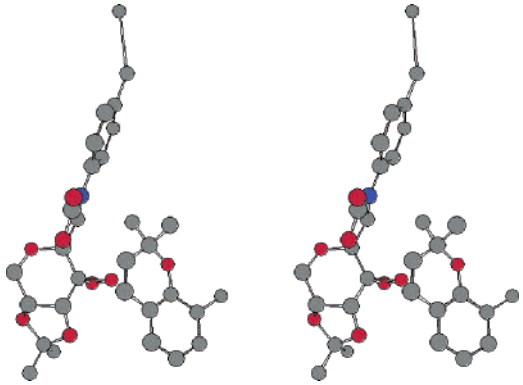


FIGURE 10. Chem3D molecular modeling of TS spiro **F** for the epoxidation of 8-methyl-2,2-dimethylchromene with ketone **4** (stereoview).

to 93% ee was obtained. Similar results obtained with both *N*-aryl- and alkyl-substituted ketone catalysts suggest that van der Waals forces and/or hydrophobic interactions play important roles in the beneficial interaction between the substitutent of the substrate and the *N*-substituent of the ketone catalyst. The information obtained could be useful for the prediction of stereochemical outcome for given substrates and the design of new ketone catalysts in the future.

Experimental Section

General Procedure for the Aysmmetric Epoxidation of 2,2-Dimethylchromenes. To a mixture of 2,2-dimethylchromene (0.4 mmol), Bu_4NHSO_4 (0.001 g, 0.003 mmol), and ketone **4** (0.028 g, 0.08 mmol) was added DME/DMM (v/v 3:1) (6.0 mL). After the mixture was stirred at rt for 20 min, buffer (0.1 M K_2CO_3−AcOH in 4×10^{-4} M aqueous EDTA, pH 9.3) (4.0 mL) was added. After being stirred at rt for 10 more min, the mixture was cooled by an ice bath (0 °C). Oxone (5.04 mL, 0.212 M in 4×10^{-4} M aqueous EDTA) and K_2CO_3 (5.04 mL, 0.84 M in 4×10^{-4}M aqueous EDTA) were added simultaneously and separately via a syringe pump over the period of time indicated. The reaction was quenched by the addition of diethyl ether and extracted with diethyl ether. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, concentrated, and purified by flash chromatography (silica gel was buffered with 1% NEt_3) to afford the corresponding epoxide.

2,2-Dimethylchromene (Table 1, Entry 1). The reaction mixture was purified by flash chromatography (silica gel was buffered with 1% NEt_3) to give the epoxide as a yellow solid (0.060 g, 86% yield, 84% ee): mp 27−29 °C; $[\alpha]^{20}_D = +28.0$ (*c* 0.82, THF) (84% ee); IR (film) 1491 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 7.2, 1.6 Hz, 1H), 7.25 (td, J = 7.6, 1.6 Hz, 1H), 6.94 (td, J = 7.2, 0.8 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 3.92 (d, J = 4.2 Hz, 1H), 3.51, (d, J = 4.2 Hz, 1H), 1.59 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 130.5, 129.8, 121.3, 120.1, 118.2, 73.2, 63.1, 51.2, 25.9, 22.8. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.20; H, 6.92.

6-Methoxy-2,2-dimethylchromene (Table 1, Entry 2). The reaction mixture was purified by flash chromatography (silica gel was buffered with 1% NEt_3) to give the epoxide as a white solid (0.053 g, 65% yield, 90% ee): mp 61−64 °C; $[\alpha]^{20}_D = +12.4$ (*c* 0.66, $CHCl_3$) (90% ee); IR (film) 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 (d, J = 3.2 Hz, 1H), 6.80 (dd, J = 8.8, 2.8 Hz, 1H), 6.75 (dd, J = 8.8 Hz, 1H), 3.87 (d, J = 4.2 Hz, 1H), 3.79 (s, 3H), 3.48 (d, J = 4.2 Hz, 1H), 1.57, (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 146.4, 120.8 118.9, 115.8, 114.9, 72.9,

63.0, 56.0, 51.3, 25.9, 22.5. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.02; H, 6.89.

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Supporting Information Available: Characterization of ketone **5** and epoxides along with data for the determination of the enantiomeric excess of the epoxides obtained with ketone **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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