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Electronic Probing of Ketone Catalysts for Asymmetric Epoxidation. Search for More Robust Catalysts

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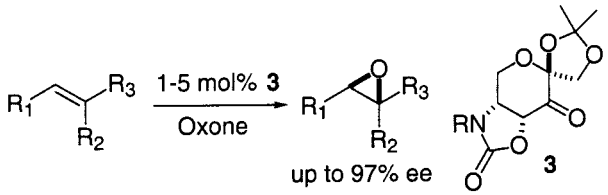
ABSTRACT



Ketones with a fused oxazolidinone were synthesized and investigated to determine the electronic effect of the substituents at α-positions of ketone catalysts on the Baeyer–Villiger oxidation and catalytic properties for asymmetric epoxidation. These new ketones give high yields and ee's with only 1–5 mol % catalyst. The current studies further show that the electronic effect is very important for the ketone-catalyzed epoxidation.

Asymmetric epoxidation using chiral dioxiranes generated in situ from chiral ketones has received intensive interest in recent years.[1−4] During the course of our studies, the fructose-derived ketone (**1**) has provided high enantioselectivities for a wide range of *trans*- and trisubstituted olefins (Scheme 1).[4] One drawback of this ketone is that it decomposes under the oxidative reaction conditions, thus requiring relatively high catalyst loading (typically 20−30%). It has been postulated that the Baeyer−Villiger reaction is the likely decomposition pathway, although corresponding lactones (**1a** or **1b**) have not been isolated or detected from the reaction mixture, presumably as a result of the facile hydrolysis of the lactones under the aqueous reaction conditions.

Since the migratory trend of Baeyer−Villiger oxidations could be influenced by electronic factors,[5,6] it was envisioned that the Baeyer−Villiger oxidation of ketone **1** could possibly be reduced by increasing the electron deficiency of the α-carbons via decreasing the electron density of the oxygen attached, thus providing more stable ketone catalysts. As part of our efforts to further understand the factors affecting the ketone stability, some close analogues

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(2) For examples of in situ generation of dioxiranes, see: (a) Edwards, J. O.; Pater, R. H.; Curci, R.; Di Furia, F. *Photochem. Photobiol*. **1979**, *30*, 63. (b) Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J. O.; Pater, R. H. *J. Org. Chem*. **1980**, *45*, 4758. (c) Gallopo, A. R.; Edwards, J. O. *J. Org. Chem*. **1981**, *46*, 1684. (d) Cicala, G.; Curci, R.; Fiorentino, M.; Laricchiuta, O. *J. Org. Chem*. **1982**, *47*, 2670. (e) Corey, P. F.; Ward, F. E. *J. Org. Chem*. **1986**, *51*, 1925. (f) Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber*. **1991**, *124*, 227. (g) Kurihara, M.; Ito, S.; Tsutsumi, N.; Miyata, N. *Tetrahedron Lett*. **1994**, *35*, 1577. (h) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem*. **1995**, *60*, 1391. (i) Yang, D.; Wong, M. K.; Yip, Y.-C. *J. Org. Chem*. **1995**, *60*, 3887. (j) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288. (k) Denmark, S. E.; Wu, Z. *J. Org. Chem*. **1997**, *62*, 8964. (l) Boehlow, T. R.; Buxton, P. C.; Grocock, E. L.; Marples, B. A.; Waddington, V. L. *Tetrahedron Lett*. **1998**, *39*, 1839. (m) Denmark, S. E.; Wu, Z. *J. Org. Chem*. **1998**, *63*, 2810. (n) Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 6425. (o) Yang, D.; Yip, Y.-C.; Jiao, G.-S.; Wong, M.-K. *J. Org. Chem*. **1998**, *63*, 8952. (p) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* **1998**, *63*, 9888.

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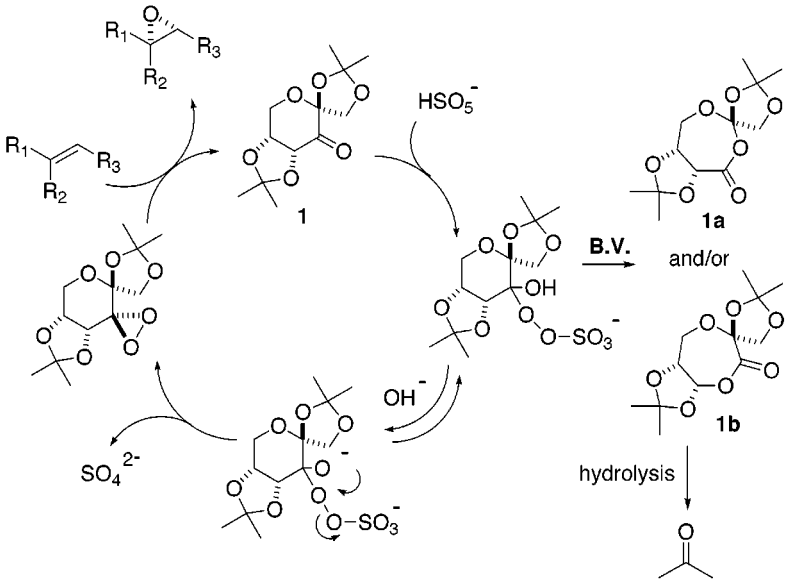
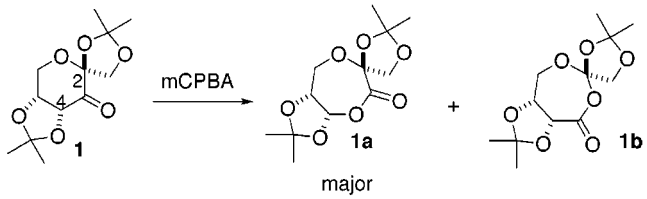
Scheme 1



of ketone **1** were prepared to investigate the electronic effects on catalyst stability. Herein we wish to report such studies.

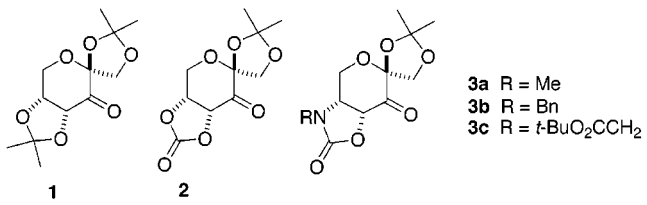
When the Baeyer−Villiger reaction of ketone **1** was carried out using *m*CPBA under anhydrous conditions, lactone **1a** was detected as the major product by the ^{1}H NMR of the crude reaction mixture (Scheme 2), indicating that

Scheme 2



C_4 in ketone **1** is more prone to migrate than C_2 in the Baeyer−Villiger reaction. Increasing the electron deficiency of C_4, therefore, became our initial focus. To maintain the high enantioselectivity of the epoxidation, our studies focused on ketones with minimal skeletal change from **1**. Our initial target was ketone **2**, where the fused ketal in **1** was replaced with an electron-withdrawing cyclic carbonate (Scheme 3). C_4 should be less likely to migrate in the Baeyer−Villiger oxidation, resulting in a more robust ketone.

Scheme 3

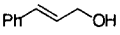
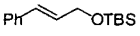


(3) For leading references on asymmetric epoxidation mediated in situ by chiral ketones, see: (a) Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun*. **1984**, 155. (b) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. *Tetrahedron Lett*. **1995**, *36*, 5831. (c) Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem*. **1995**, *60*, 1391. (d) Brown, D. S.; Marples, B. A.; Smith, P.; Walton, L. *Tetrahedron* **1995**, *51*, 3587. (e) Yang, D.; Yip, Y.-C.; Tang, M. W.; Wong, M. K.; Zheng, J. H.; Cheung, K. K. *J. Am. Chem. Soc*. **1996**, *118*, 491. (f) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. *J. Am. Chem. Soc*. **1996**, *118*, 11311. (g) Song, C. E.; Kim, Y. H.; Lee, K. C.; Lee, S. G.; Jin, B. W. *Tetrahedron: Asymm*etry **1997**, *8*, 2921. (h) Adam, W.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1997**, *8*, 3995. (i) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem*. **1997**, *62*, 8288. (j) Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1997**, *62*, 8622. (k) Armstrong, A.; Hayter, B. R. *Chem. Commun*. **1998**, 621. (l) Yang, D.; Wong, M.-K.; Yip, Y.-C.; Wang, X.-C.; Tang, M.-W.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc*. **1998**, *120*, 5943. (m) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc*. **1998**, *120*, 7659. (n) Adam, W.; Saha-Moller, C. R.; Zhao, C.-G. *Tetrahedron: Asymmetry* **1999**, *10*, 2749. (o) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem*. **1999**, *64*, 6443. (p) Carnell, A. J.; Johnstone, R. A. W.; Parsy, C. C.; Sanderson, W. R. *Tetrahedron Lett*. **1999**, *40*, 8029. (q) Armstrong, A.; Hayter, B. R. *Tetrahedron* **1999**, *55*, 11119. (r) Armstrong, A.; Hayter, B. R.; Moss, W. O.; Reeves, J. R.; Wailes, J. S. *Tetrahedron: Asymmetry* **2000**, *11*, 2057. (s) Solladie-Cavallo, A.; Bouerat, L. *Org. Lett*. **2000**, *2*, 3531.

(4) For examples of asymmetric epoxidation mediated in situ by fructose-derived ketones, see: (a) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc*. **1996**, *118*, 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Shi, Y. *J. Org. Chem*. **1997**, *62*, 2328. (c) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc*. **1997**, *119*, 11224. (d) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 2948. (e) Wang, Z.-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 3099. (f) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 4425. (g) Zhu, Y.; Tu, Y.; Yu, H.; Shi, Y. *Tetrahedron Lett*. **1998**, *39*, 7819. (h) Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 8475. (i) Wang, Z.-X.; Cao, G.-A.; Shi, Y. *J. Org. Chem*. **1999**, *64*, 7646. (j) Warren, J. D.; Shi, Y. *J. Org. Chem*. **1999**, *64*, 7675. (k) Frohn, M.; Zhou, X.; Zhang, J.-R.; Tang, Y.; Shi, Y. *J. Am. Chem. Soc*. **1999**, *121*, 7718. (l) Shu, L.; Shi. Y. *Tetrahedron Lett*. **1999**, *40*, 8721.

(5) For a recent review of the Baeyer−Villiger oxidation, see: Krow, G. R. *Org. React*. **1993**, *43*, 251.

Table 1. Asymmetric Epoxidation of Olefins by Ketones **3**[a]

entry	substrate	ketone (mol%)	t (h)	yield[b] (%)	ee (%)	config.[f]
1		**3a**(5)	5	91[c]	85[d]	(R,R)[4c]
2		**3b**(5)	5	81[c]	83[d]	(R,R)
3		**3c**(5)	5	100[c]	88[d]	(R,R)
4		**3c**(5)	7	67	96[e]	(R,R)[4c]
5		**3c**(5)	5	89	87[e]	(R,R)[4e]
6		**3c**(5)	5	73	94[e]	(R,R)[4c]
7		**3c**(5)	7	80	93[e]	(R,R)[4c]
8		**3c**(5)	5	93	90[e]	(R,R)[4g]
9		**3c**(2)	5	93	97[d]	(R,R)[4c]
		3c(1)	7	74	92[d]	(R,R)
10		**3c**(5)	7	80	93[e]	(R,R)[4c]

[a] All reactions were carried out at 0 °C with substrate (1 equiv), ketone (0.01−0.05 equiv), Oxone (1.49−2.13 equiv), and K_2CO_3 (3.12−4.45 equiv) in (2:1:2, v/v) DMM/CH_3CN/buffer (0.2 M K_2CO_3/HOAc, pH 8.0). For 5 h reaction, 1.49 equiv of Oxone and 3.12 equiv of K_2CO_3 were used. For 7 h reaction, 2.13 equiv of Oxone and 4.45 equiv of K_2CO_3 were used. [b] The epoxides were purified by flash chromatography and gave satisfactory spectroscopic characterization. [c] The number is the conversion that is determined by GC. [d] Enantioselectivity was determined by chiral GC (Chiraldex G-TA column). [e] Enantioselectivity was determined by chiral HPLC (Chiralcel OD column). [f] The absolute configurations were determined by comparing the GC and HPLC chromatograms with the reported ones.

Attempts to synthesize ketone **2** were unsuccessful as a result of hydrolysis of the carbonate. Subsequently, ketone **3**, containing a hydrolytically more stable oxazolidinone, was investigated. Ketones **3a**−**c** were prepared from D-fructose as outlined in Scheme 4. These ketones exist largely in hydrate forms, indicating that the carbonyl groups are quite electrophilic.

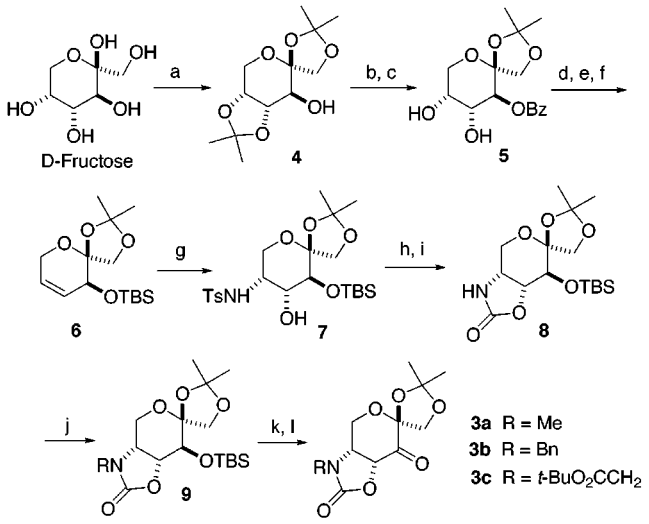
With ketones **3a**−**c** in hand, their catalytic properties for epoxidation were investigated using *trans*-*β*-methylstyrene as the test substrate. These ketones were indeed found to be active catalysts (Table 1, entries 1−3), with high conversions obtained when 5 mol % ketone was used.[7] The substituent on the nitrogen showed some effect on both conversion and enantioselectivity, with ketone **3c** giving the best results. Encouraged by this, additional olefins were then investigated for the epoxidation. As shown in Table 1 (entries 4−10), high yields and ee's were obtained in these cases using 5 mol % ketone **3c**. In one case (entry 9), the catalyst loading could be reduced as low as 1 mol %, still giving a good yield and high ee.

By adjusting the electron nature of the α carbons, the catalyst loading can be lowered from 20−30% for ketone **1** to 1−5 mol % for ketone **3c** while the yields and ee's are maintained. Upon the basis of the absolute configuration of the epoxide products, the epoxidation appears to occur via the spiro transition state similar to ketone **1**.[4c] The enantioselectivity obtained with ketone **3c** is very similar to that

(6) For leading references on the regioselective Baeyer−Villiger reaction of polyhydroxycyclohexanone derivatives, see: (a) Chida, N.; Yamada, E.; Ogawa, S. *J. Carbohydr. Chem.* **1988**, *7*, 555. (b) Chida, N.; Suzuki, M.; Suwama, M.; Ogawa, S. *J. Carbohydr. Chem.* **1989**, *8*, 319. (c) Chida, N.; Tanikawa, T.; Tobe, T.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1247. (d) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1994**, *35*, 7249.

(7) **Representative Procedure for Asymmetric Epoxidation.** To a stirred solution of phenylcyclohexene (0.079 g, 0.50 mmol) in DMM/CH_3-CN (2:1 v/v) (7.5 mL) were added buffer (0.2 M K_2CO_3/AcOH, pH = 8.0) (5 mL), Bu_4NHSO_4 (7.5 mg, 0.020 mmol), and ketone **3c** (0.004 g, 0.01 mmol). The mixture was cooled to 0 °C via an ice bath. A solution of Oxone (0.458 g, 0.744 mmol) in aqueous Na_2EDTA (4×10^{-4} M, 3.5 mL) and a solution of K_2CO_3 (0.215 g, 1.558 mmol) in water (3.5 mL) were added dropwise simultaneously through two separate syringes via syringe pump over a period of 5 h. Upon quenching with hexane and water, the reaction mixture was extracted with hexane (3×30 mL), washed with brine, dried (Na_2SO_4), filtered, concentrated, and purified by flash chromatography [the silica gel was buffered with 1% Et_3N in hexane; hexanes/ether (1:0 to 10:1 v/v) was used as eluent] to afford phenylcyclohexne oxide as a colorless liquid (0.081 g, 93% yield, 97% ee) (Table 1, entry 9).

Scheme 4[a]



[a] Reaction conditions: (a) 2,2-dimethoxypropane, acetone, $HClO_4$, 0 °C, 53% (ref 4c). (b) PhCOCl, Et_3N, CH_2Cl_2, rt, 93%. (c) DDQ (0.1 equiv), CH_3CN/H_2O, rt, 24 h, 92%. (d) PPh_3, imidazole, I_2, Zn, 79%. (e) K_2CO_3, MeOH, rt, 12 h, 68%. (f) TBSCl, Et_3N, DMAP, CH_2Cl_2, rt, 24 h, 100%. (g) $K_2OsO_6H_4$, chloramine-T trihydrate, CH_3CN/H_2O, rt, overnight, 91%. (h) triphosgene, pyridine, CH_2Cl_2, 0 °C, 84%. (i) Li, NH_3(l), THF, −78 °C, overnight, 64%. (j) for **9a**, NaH, MeI, THF, rt, 2 h, 93%; for **9b**, NaH, BnBr, THF, rt, 2 h, 70%; for **9c**, NaH, *t*-BuO_2CCH_2Br, THF, rt, 96%. (k) TBAF, THF, rt, 91−96%. (l) PCC, 3 Å MS, CH_2Cl_2, rt, 3−12 h, 73−93%.

of ketone **1**, indicating that the configuration of the ketone was not greatly changed by changing the electronic nature of C_4.

In summary, the replacement of the fused ketal of ketone **1** with an oxazolidinone creates a more stable and reactive catalyst for asymmetric epoxidation. Presumably the enhanced stability of ketone **3** is due to the reduction of Baeyer−Villiger decomposition.[8,9] The ketones synthesized are highly active, giving good yields and enantioselectivities for a variety of olefin substrates. The catalyst loading can be reduced to 5 mol % and even 1 mol % in some cases. Generally speaking, developing catalysts using small loading is still one of the challenges for the chiral ketone-catalyzed asymmetric epoxidation. The information gained from this study is helpful for the further understanding of the ketone-catalyzed epoxidation and for the design of more efficient catalysts in the future.

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Supporting Information Available: The preparation and characterization of ketones **3a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The Baeyer−Villiger reactions of ketones **3a**−**c** with *m*CPBA were attempted. However, the results were not conclusive since the NMR spectra of the reaction mixture were not clean, partly as a result of the hydration of the ketones.

(9) The recovery of ketones **3a**−**c** was found to be difficult partly because of the low catalyst loading and high water solubility of the ketones (highly hydrated).