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Mechanism and Conditions for Highly Enantioselective Epoxidation of α,β-Enones Using Charge-Accelerated Catalysis by a Rigid Quaternary Ammonium Salt

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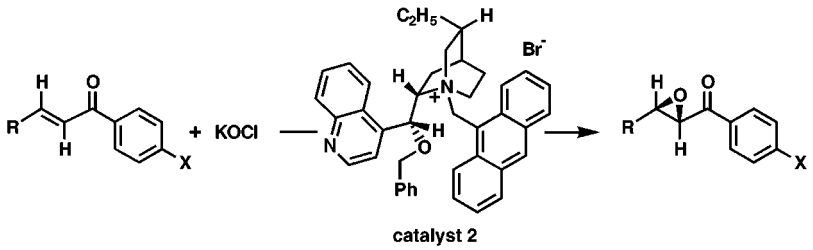
ABSTRACT



catalyst 2

Highly enantioselective (up to 130:1) epoxidation of a variety of α,β-enones to form α,β-epoxy ketones is described along with a rational analysis of the mechanistic basis for this strong absolute stereochemical control by the chiral catalyst 2.

We have recently reported the development of the chiral quaternary cinchonidinium cation **1** as a superior catalyst for enantioselective alkylation[1,2] and Michael,[3] aldol,[4] and nitroaldol[5] reactions. For example, with **1** as catalyst a wide variety of chiral α-amino acids can be synthesized with enantioselectivities as high as 400:1 by alkylation of the benzophenone Schiff base of *tert*-butyl glycinate.[1,6] The mechanistic reasons for the extraordinarily high enantioselectivities achieved with **1** have also been clarified. In brief, these reactions are channeled through a specific three-dimensional arrangement of a contact ion pair in which a nucleophilic site of the substrate is proximate to the quaternary cationic center in which there is optimum van der Waals attractive interaction between the two. This mechanistic insight is important to the design of new catalysts and the discovery of other catalytic enantioselective reactions that are subject to control by chiral quaternary ammonium ions. For some time we have been studying the nucleophilic epoxidation of α,β-enones to form α,β-epoxy ketones, a reaction pioneered by Prof. Hans Wynberg[7] (with ee's on the order of 25%) and subsequently investigated by several other groups.[8,9] In the most recent work[9] enantioselectivities averaging ca. 80% have been reported with benzalacetophe-

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(4) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.
(5) Corey, E. J.; Zhang, F.-Y. *Angew. Chem. Intl. Ed.* **1999**, *38*, 1931.
(6) For earlier work on the enantioselective alkylation of the benzophenone Schiff base of *tert*-butyl glycinate, see: (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507. (c) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991,** *56*, 5181.
(7) (a) Helder, R.; Hummelen, J. C.; Laane, R. W. P. M.; Wiering, J. S.; Wynberg, H. *Tetrahedron Lett.* **1976**, 1831. (b) Wynberg, H.; Greijdanus, B. *J. Chem. Soc., Chem. Commun.* **1978**, 427. (c) Hummelen, J. C.; Wynberg, H. *Tetrahedron Lett.* **1978**, 1089. (d) Wynberg, H.; Marsman, B. *J. Org. Chem.* **1980**, *45*, 158. (e) Pluim, H.; Wynberg, H. *J. Org. Chem.* **1980**, *45*, 2498.

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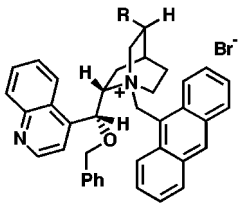
none type substrates using our *N*-9-anthracenylmethylcinchonidinium salt[1,10] and *N*-benzylcinchoninium salts.[11]

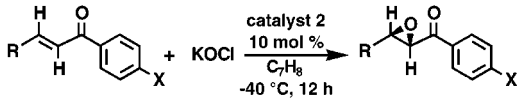


1 R = CH=CH$_2$
2 R = C$_2$H$_5$

In this Letter we describe the achievement of truly useful enantioselectivities for the nucleophilic epoxidation of various α,*β*-enones (ranging from 92 to 98.5% ee for various benzalacetophenones) and the use of this process for practical syntheses of chiral α,*β*-epoxy esters, α-hydroxy esters, *β*-hydroxy esters, and *β*-hydroxy ketones. These results clearly demonstrate the scope and versatility of the enantioselective epoxidation. Furthermore, because of the high degree of enantioselection in the epoxidation process, the analysis of the fundamental factors that are responsible for enantiocontrol by the rigid chiral cation **1** is greatly facilitated. Specifically, the data described herein lead to a simple stereomechanistic rationale in which the chiral cation assembles the oxidant (OCl^-) and the α,*β*-enone in a specific three-dimensional arrangement which channels the epoxidation through an energetically and entropically favored transition state assembly, as detailed below. This pathway involves structured contact ion pairs, related to those previously discussed,[1,2,5] which allow charge-accelerated face-selective conjugate addition of ion-paired hypochlorite to an α,*β*-enone substrate that is held in proximity by electrostatic and van der Waals forces.

The results of our studies on the nucleophilic epoxidation of 15 substrates are summarized in Table 1 for standardized conditions as follows: 10 mol % of the dihydrocinchonidinium salt **2** as catalyst in toluene at −40 °C with 8 M aqueous potassium hypochlorite[12] as the stoichiometric oxidant. The presence of a phenyl substituent on the carbonyl carbon is important for enantioselectivity.[13] Further, the 4-fluorophenyl substituent is definitely better than phenyl

Table 1. Enantioselective Epoxidation of (*E*)-Aroylethylenes with a Chiral Quaternary Ammonium Catalyst

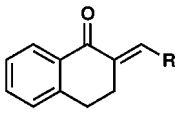


	R	X	ee%,[a,b]	(yield)	$[\alpha]_D^{23}$/CH_2Cl_2
1	C_6H_5	H	93	(96)	+ 229
2	C_6H_5	F	98	(93)	+ 213
3	C_6H_5	Br	93	(92)	+ 171
4	4-NO_2-C_6H_4	H	94	(90)	+ 236
5	4-NO_2-C_6H_4	F	95	(97)	+ 266
6	*n*-C_5H_{11}	F	91	(90)	+ 6.7
7	*cyclo*-C_6H_{11}	H	94	(85)	- 1.5
8	*cyclo*-C_6H_{11}	F	95	(87)	+ 4.7
9	4-CH_3-C_6H_4	H	94	(70)	+ 242
10	4-Cl-C_6H_4	H	92	(94)	+250
11	4-Cl-C_6H_4	F	98.5	(94)	+227
12	4-CH_3O-C_6H_4	H	95	(70)	+221
13	C_6H_5	C_6H_5O	93	(89)	+158
14	C_6H_5	2,4-$Br_2C_6H_3O$	98	(90)	+113
15	β-naphthyl	H	93	(87)	- 84

[a] Enantiomeric excess was determined by HPLC analysis with the columns and conditions indicated in the experimental at the end of this note. [b] For absolute configurations see: Marsman, B.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2312.

(ee's 95−98.5%). A 2,4-dibromophenoxyphenyl group attached to carbonyl also leads to an excellent ee (98%). The *β*-substituent on the *E*-α,*β*-double bond of the phenyl or 4-substituted phenyl ketone may be varied from aryl to *n*-alkyl or cycloalkyl without a major effect on enantioselection.

Of key mechanistic significance is the finding that when the aromatic ring attached to the carbonyl group of the α,*β*-enone is constrained to be coplanar with the carbonyl *σ* plane, enantioselection drops precipitously. Thus the α,*β*-enones **3** and **4** are epoxidized under the standard conditions of Table



3 R = CH$_3$
4 R = C$_6$H$_5$

1 to give products of only 76 and 61% ee, respectively. These results argue that the highly enantioselective epoxidations summarized in Table 1 probably proceed via transition states in which the phenyl substituent and the carbonyl *σ* plane are nonplanar, i.e., out of *π*-conjugation. An important feature of this geometrical orthogonality is that it allows placement of the α,*β*-enone structures listed in Table 1 in a binding mode with quaternary ammonium **2** similar to that which explains a number of other highly enantioselective reactions

(8) (a) Mazaleyrat, J. P. *Tetrahedron Lett.* **1983**, *24*, 1243. (b) Shi, M.; Kazuta, K.; Satoh, Y.; Masaki, Y. *Chem. Pharm. Bull.* **1994**, *42*, 2625. (c) Shi, M.; Masaki, Y. *J. Chem. Res.* **1994**, 250. (d) Baba, N.; Oda, J.; Kawaguchi, M. *Agric. Biol. Chem.* **1986**, *50*, 3113.

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(10) For the original publication on the use of the *N*-9-anthracenylmethyl group as a rigidifying element with cinchonidinium derivatives, see: Corey, E. J.; Noe, M. C.; Ting, A. Y. *Tetrahedron Lett.* **1996**, *37*, 1735.

(11) Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563.

(12) Potassium hypochlorite solution (8.0 M) was prepared by treatment of 50% aqueous potassium hydroxide with chlorine and filtration of the precipitate of KCl. The resulting cold light straw-colored solution must be used promptly or stored at −20 °C since it is unstable above 0 °C. Potassium hypochlorite is superior to sodium hypochlorite because it leads to more rapid and more enantioselective epoxidation under phase transfer conditions with **2**.

(13) The epoxidation of a variety of α,*β*-enones with alkyl or other nonphenyl groups attached to carbonyl under the standard conditions defined herein leads to only modest enantioselection.

catalyzed by **1** or **2**.[1−5] The specific three-dimensional arrangement of cation **2**, benzal-4-fluoroacetophenone, and hypochlorite ion which is consistent with previous results and also with all the data reported herein for nucleophilic epoxidation of α,β-enones by hypochlorite is shown in Figure 1. In this figure, two different views of the complex are

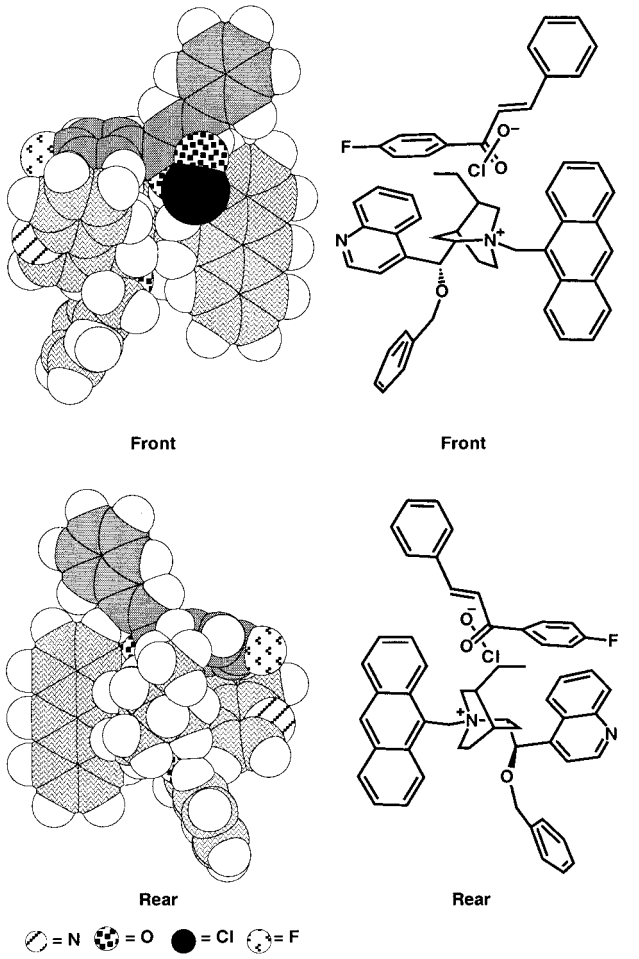


Figure 1.

displayed which are related by a 180° rotation about the vertical axis. The hypochlorite ion is contact ion-paired with the sole accessible face of the charged nitrogen with the Cl of ClO^- and N^+ as nearest neighbors. The α,β-enone in the complex is situated so that the 4-fluorophenyl group is wedged between the ethyl and quinoline substituents on the quinuclidine ring and simultaneously the carbonyl oxygen is placed as close to N^+ as permitted by van der Waals forces. In this arrangement the nucleophilic oxygen of ClO^- is proximate to the β-carbon of the α,β-enone, i.e., correctly positional for nucleophilic epoxidation by conjugate addition. In fact, as the nucleophilic attack occurs, the negative charge which is developed at the carbonyl oxygen in the transition state is electrostatically stabilized by the proximate N^+ of catalyst **2**. Thus, cationic charge acceleration of the nucleophilic attack also favors reaction via the assembly shown in Figure 1, along the lines previously discussed for enantioselective nitroaldol reactions catalyzed by **1**.[5] Another feature of this geometry is that it allows a smooth transition of the resulting conjugate adduct to the α,β-epoxy ketone and Cl^- with the latter contact ion paired to cation **2**. Most importantly, the three-dimensional arrangement shown in Figure 1 corresponds unambiguously to the enantiomeric preference, i.e., absolute stereoselectivity, which has been observed experimentally.[14] We believe that these insights

(14) The beneficial effect of the 4-fluoro substituent in the examples of Table 1 relative to hydrogen (X = F or H) may be due to a stronger edge interaction of 4-fluorophenyl as compared with phenyl with the contacting quinoline ring, as shown in Figure 1.

(15) For a prior report of Baeyer−Villiger reactions of α,β-epoxy phenyl ketones to form α,β-epoxy acid phenyl esters, see: Baures, P. W.; Eggleston, D. S.; Flisak, J. R.; Gombatz, K.; Lantos, I.; Mendelson, W.; Remich, J. J. *Tetrahedron Lett.* **1990**, *45*, 6501.

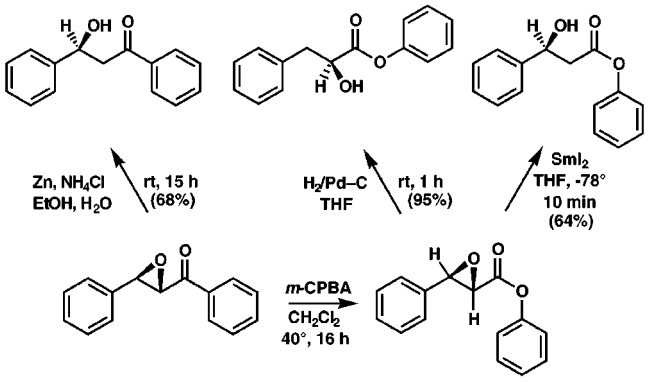
(16) Baeyer−Villiger products were prepared from a number of the α,β-epoxy benzalacetophenones shown in Table 1 (X = H) using *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 at reflux for 16 h in the indicated yields: R = C_6H_5 (81%); R = cyclo-C_6H_{11} (74%); R = 4-Cl-C_6H_4 (82%); R = 4-NO_2-C_6H_4 (84%); R = β-naphthyl (87%); R = 4-CH_3-C_6H_4 (73%).

(17) **Representative Procedure for Epoxidation: 4′-Fluorochalcone.** A mixture of 4′-fluorochalcone (226 mg, 1.0 mmol), chiral quaternary ammonium salt **2** (66 mg, 0.1 mmol), and toluene (10 mL) was cooled to −40 °C and treated with an aqueous solution of potassium hypochlorite (0.63 mL, 5.0 mmol, 8.0 M). After stirring at −40 °C for 12 h, the solvent was removed under reduced pressure and the solid quaternary ammonium salt was precipitated by addition of hexanes−ether (4:1) to give after filtration 53 mg of the chiral catalyst for reuse (80% recovery). The filtrate was washed with water and brine, concentrated, and chromatographed (silica gel, 6:1 hexanes−ethyl acetate) to afford 225 mg of (2*S*,3*R*)-*trans*-2,3-epoxy-3-phenyl-1-(4-fluorophenyl)propan-1-one (93% yield, 98% ee): mp 86−87 °C; $[\alpha]^{23}_D = +213.4$ ($c = 2.0$, CH_2Cl_2); IR (film) 1681.7, 1598.3, 1237.5, 1229.4, 1158.3, 885.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.08−8.04 (m, 2H), 7.41−7.36 (m, 5H), 7.18−7.14 (m, 2H), 4.24 (d, $J = 1.8$ Hz, 1H), 4.07 (d, $J = 1.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 191.6, 166.3 (d, $J = 255.0$ Hz), 135.4, 131.9 (d, $J = 3.1$ Hz), 131.2 (d, $J = 9.1$ Hz), 129.2, 128.9, 125.8, 116.2 (d, $J = 21.5$ Hz), 61.1, 59.3 ppm; HRMS (EI^+) calcd for $[C_{15}H_{11}FO_2]^+$ 242.0743, found 242.0741. Enantioselectivity was determined by HPLC analysis using a Chiralcel OB-H column and 5% isopropyl alcohol in hexanes as eluent on 0.5 mL/min at 23 °C, 254 nm, $t_R = 44.9$ min (major), $t_R = 59.9$ min (minor).

(18) **Baeyer−Villiger Oxidation of (2*S*,3*R*)-*trans*-2,3-Epoxy-1,3-diphenylpropan-1-one.** A solution of (2*S*,3*R*)-*trans*-2,3-epoxy-1,3-diphenylpropan-1-one (202 mg, 0.9 mmol, 93% ee) and *m*-chloroperoxybenzoic acid (650 mg, 2.7 mmol) in 5 mL of methylene chloride was heated at reflux for 16 h. The mixture was stirred with saturated aqueous sodium bisulfite at 23 °C for 2 h and then washed with a saturated sodium bicarbonate solution and brine. After evaporating, the residue was purified by flash chromatography (silica gel, 10:1 hexanes−ethyl acetate) to give 175 mg of (2*S*,3*R*)-phenyl-*trans*-2,3-epoxy-3-phenyl propionate (81% yield, 93% ee): mp 87−89 °C; $[\alpha]^{23}_D = +169.6$ ($c = 1.0$, THF); IR (film) 1754.1, 1457.9, 1263.6, 1204.5, 893.9 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.43−7.16 (m, 10H), 4.26 (d, $J = 1.6$ Hz, 1H), 3.74 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 166.7, 150.2, 134.6, 129.6, 129.2, 128.8, 126.3, 125.9, 121.2, 58.4, 56.7 ppm. Enantioselectivity was determined by HPLC analysis with a Chiralcel OD column, 3% isopropyl alcohol in hexanes, 1.0 mL/min, 254 nm, $t_R = 13.7$ min (minor), $t_R = 15.1$ min (major).

(19) **Preparation of (*S*)-Phenyl 2-Hydroxyl-3-phenylpropionate.** A mixture of (2*S*,3*R*)-phenyl-*trans*-2,3-epoxy-3-phenyl propionate (24 mg, 0.1 mmol), 5% Pd−C (10 mg), and THF (1 mL) was hydrogenated with 1 atm of hydrogen at ambient temperature for 1 h. After filtering and evaporating, 23 mg of the desired product was obtained (95% yield, 92% ee): mp 80−81 °C; $[\alpha]^{23}_D = -15.7$ ($c = 1.5$, CH_2Cl_2); IR (KBr) 3457.6, 3425.0, 2930.3, 1751.0, 1494.3, 1486.3, 1401.9, 1213.9, 1196.5, 1170.9, 1155.2, 1093.2 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.41−7.26 (m, 8H), 7.04−7.01 (m, 2H), 4.73 (dt, $J = 6.3$ and 4.7 Hz, 1H), 3.30 (dd, $J = 14.0$ and 4.7 Hz, 1H), 3.19 (dd, $J = 14.0$ and 6.3 Hz, 1H), 2.79 (d, $J = 6.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 172.8, 150.3, 136.0, 129.7, 129.6, 128.6, 127.2, 126.3, 121.2, 71.4, 40.6 ppm; HRMS (CI^+) calcd for $[C_{15}H_{14}O_3 + NH_4]^+$ 260.1287, found 260.1292. Enantioselectivity was determined by HPLC analysis with a Chiralcel OD column, 10% isopropyl alcohol in hexanes, 1.0 mL/min, 254 nm, $t_R = 13.4$ min (minor), $t_R = 15.0$ min (major).

Scheme 1



unify all the highly enantioselective catalytic reactions of **1** and **2** which are now known and, at the same time, provide a conceptual basis for the rational development of new enantioselective processes under chiral cation control.

Finally, it should be noted that the highly enantioselective epoxidations which are described herein afford access to a wide variety of highly useful organic intermediates of excellent enantiomeric purity, including α,β-epoxy esters[15,16] and acids, α-hydroxy ketones or acids, and β-hydroxy ketones or acids, as shown in Scheme 1.[17−20]

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(20) **Determination of Enantioselectivities for the Epoxidations Summarized in Table 1**. HPLC analysis of the epoxy ketones listed in Table 1 were carried out using commercially available chiral columns with isopropyl alcohol−hexanes as eluent at 23 °C and detection at 254 nm. For each product of Table 1, the corresponding enantiomers of a racemic reference sample of epoxy ketone were cleanly separated under the conditions used for analysis. The following chiral columns were used for the products in Table 1: for entries 1, 6, 7, and 13, Whelk 01 column (Regis Co.); for entries 2, 3, 11, and 14, OB-H column (Chiral Technologies Inc.); for entries 4, 9, 10, 12, and 15, OD column (Chiral Technologies Inc.); for entries 5 and 8, OJ column (Chiral Technologies Inc.).