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Enantioselective Catalytic Ring Opening of Epoxides with Carboxylic Acids

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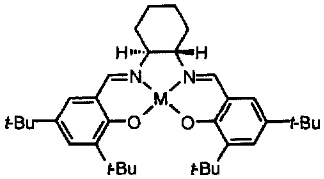
Abstract: The chiral Co(salen) complex **3** is an effective catalyst for the asymmetric ring-opening of meso epoxides with benzoic acid. Enantioselectivities of 55-93% were obtained with a range of substrates. © 1997, Elsevier Science Ltd. All rights reserved.

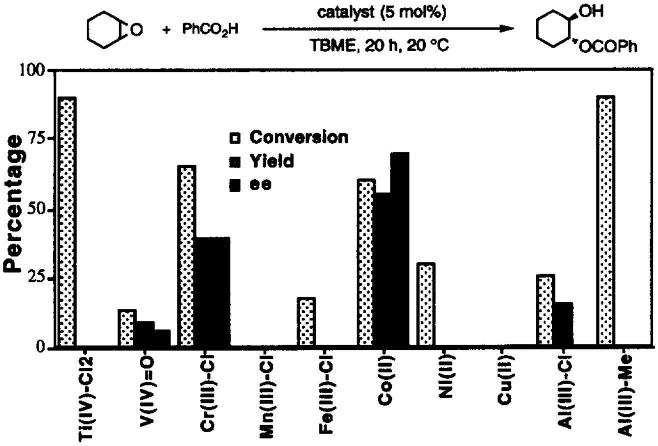
We recently reported the (salen)Cr-catalyzed asymmetric ring opening of meso epoxides[1] and kinetic resolution of terminal epoxides[2] using $TMSN_3$. The high enantioselectivity displayed in these reactions led us to evaluate the possible use of other nucleophiles in catalytic reactions with epoxides. Carboxylic acids are interesting candidates because of their low cost and ease of handling, and because their reaction with epoxides provides a direct and appealing route to 1,2-diol mono-esters.[3,4] Here we report the successful development of a system for the catalytic enantioselective ring-opening of meso epoxides with benzoic acid.

A screen of first-row transition metal complexes derived from the commercially-available salen ligand **1** revealed that several of them catalyzed epoxide decomposition, but only the Cr(III) complex **2**[1] and the Co(II) complex **3**[5] mediated clean transformation to the ring-opened product (Figure 1). Complex **2**, which is the preferred catalyst for asymmetric epoxide ring opening reactions with $TMSN_3$,[1] proved less enantioselective than **3** for reactions with benzoic acid (43% ee vs. 68% ee). The corresponding (salen)vanadium complex was the only other catalyst found to display any enantioselectivity (6% ee). Interestingly, the corresponding Mn(III) complex, a highly-effective catalyst for olefin epoxidation,[6] displayed no observable reactivity in the present system.



(S,S)-1: M = H, H
(S,S)-2: M = Cr(III)-Cl
(S,S)-3: M = Co(II)

Figure 1. Screen of metal complexes of (*S,S*)-1 as catalysts for enantioselective ring-opening of cyclohexene oxide with benzoic acid.

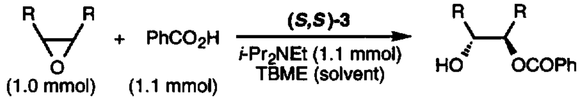


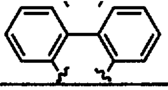
For reactions with complexes **2** and **3**, the rate, enantioselectivity, and yield of the ring opening reaction with benzoic acid were found to improve with addition of *i*-Pr_2NEt. With catalyst **3**, optimal results were obtained with one equivalent of base relative to benzoic acid. Several other amine bases (Et_3N, Et_2NPh, DABCO, 2,6-lutidine) also displayed beneficial effects as additives, but to a lesser extent than *i*-Pr_2NEt. Strongly coordinating bases such as pyridine, *i*-Pr_2NH, and DBU inhibited the ring opening reaction, presumably by forming an inactive complex with the catalyst. Inorganic bases (K_2CO_3, $NaHCO_3$, KF/Al_2O_3, Na_2HPO_4) and other additives (DMSO, 4-phenylpyridine-*N*-oxide, Ph_3PO) known to bind low valent transition metals also had a deleterious effect on the rate of the catalytic reaction. The mechanistic basis for the beneficial effects conferred by amine additives in this reaction remains unclear. Solution IR and conductance experiments provide evidence that benzoic acid is not deprotonated by *i*-Pr_2NEt in non-polar solvents such as TBME; however, the amine does confer high solubility to benzoic acid in TMBE, whereas the acid is only marginally soluble in TBME alone.

Benzoic acid and its derivatives were found to be the most useful nucleophiles in the ring opening reaction. Acetic acid was also delivered quantitatively to cyclohexene oxide in the presence of **3**, but with lower enantioselectivity (40% ee). The more hindered pivalic acid reacted with greater enantioselectivity (73% ee) but at a much slower rate (12% conversion in 7 h). Stronger acids such as TFA, TsOH, and trichlorobenzoic acid displayed a high level of background reactivity, leading to racemic ring-opened products or complex epoxide decomposition mixtures.

Although the ring opening reaction with carboxylic acids can be effected using Co(II) complexes as precatalysts, it appears that the reactive species is in fact Co(III). Thus, reactions carried out with complex **3** under strictly anaerobic conditions take place at slower rates and with lower enantioselectivity than reactions carried out in air or under an oxygen atmosphere. The reactivities of several (salen)Co(III)(X) complexes (X = $PhCO_2^-$, OH^-, I^-, BF_4^-, OTf^-) were compared in the ring-opening reaction and found to be similar. It was found to be most convenient to carry out the reaction by generating the Co(III) complex *in situ*, by stirring complex **3** in the presence of carboxylic acid and reaction solvent under an oxygen atmosphere for 15-30 min. prior to addition of *i*-Pr_2NEt (the oxidation of the catalyst is inhibited by amine). Once this catalyst aging process has been accomplished, the epoxide ring-opening reactions proceed similarly under nitrogen, oxygen or air.

Table 1. Ring-opening of meso epoxides with benzoic acid catalyzed by **(*S,S*)-3**



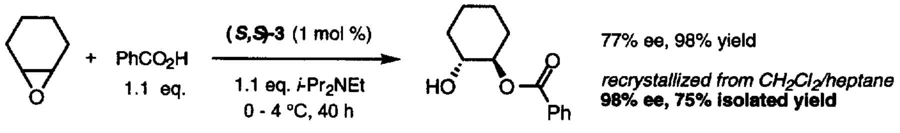
Entry	R	Catalyst loading (mol%)	Solvent volume (mL)	atm.	time (h)	temp.	Isolated yield (%)	ee[a] (%)
1	$-(CH_2)_4-$	2.5	0	N_2	40	0-4 °C	98	77
2	$-(CH_2)_3-$	5.0	0.2	O_2	72	RT	52	55
3	$-(CH_2)_5-$	5.0	0.2	O_2	132	RT	77	65
4	Me	2.5	0	N_2	40	0-4° C	97	73
5	Ph	5.0	0.5	O_2	144	RT	92	92
6		5.0	0.2	O_2	44	RT	95	71
7		5.0	1.0	N_2	40	RT	96	93

[a] All enantioselectivities were determined directly by HPLC analysis on a commercial Whelk-O column (Regis)

The optimized reaction conditions were applied to several meso epoxides (Table 1). Although enantioselectivities exceeding 90% were observed with only select substrates (entries 5 and 7), in general the crystallinity of the benzoate esters allows enhancement of their enantiomeric purity via recrystallization. For example, cyclohexanediol monobenzoate, generated in quantitative yield and 77% ee from the ring opening of cyclohexene oxide, was obtained in 98% ee and 75% overall yield after recrystallization from CH_2Cl_2/

heptane (Scheme 1). The ring opening was carried out successfully in the absence of solvent and on multi-gram scale, thus providing practical access to valuable C_2 symmetric diols in mono-protected form and in high enantiomeric purity from inexpensive starting materials.

Scheme 1



(*R*,*R*)-1,2-cyclohexanediol monobenzoate ester. A solution of (*S*,*S*)-**3** (0.62 g, 1.0 mmol) and benzoic acid (13.4 g, 110 mmol) in TBME (20 mL) was stirred under O_2 for 30 min. Volatile materials were removed *in vacuo*. The flask was recharged with nitrogen, *i*-Pr_2NEt (14.21 g, 19.16 mL, 110 mmol) was added, and the stirred mixture was cooled to 4°C. Cyclohexene oxide (9.82 g, 10.12 mL, 100 mmol) was added and the resulting dark brown solution was stirred at 4°C for 40 hr. The product mixture was diluted with ether (250 mL), washed with 1M aq. HCl (5 x 100 mL) and saturated aq. $NaHCO_3$ (2 x 100 mL), dried over $MgSO_4$, and filtered. The solution was concentrated *in vacuo* and the resulting solids were recrystallized 3 times from CH_2Cl_2/heptane to afford the product as colorless crystals, mp 105.5-107.5°C (17.4 g, 75% yield, 98% ee).

In conclusion, the (salen)Co-catalyzed epoxide ring opening with carboxylic acids provides convenient access to synthetically useful products and the first indication of generality in nucleophile-epoxide reactions catalyzed by chiral salen complexes. Extension of this methodology toward other classes of nucleophiles and electrophiles is under investigation.

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Notes and References

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3. There is very little precedent in the open literature for catalytic reactions between carboxylic acids and epoxides. For reactions mediated by alumina surfaces, see: Posner, G. H. *Angew. Chem. Intl. Ed. Engl.* **1978**, *17*, 487. For reactions of epoxyalcohols mediated by Ti(O*i*-Pr)$_4$, see: Carron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560.
4. Transacylation is often observed in 1,2-diols; however, this constitutes a degenerate pathway in monoesters derived from C_2 symmetric diols.
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