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for the Preparation
of Organic Compounds

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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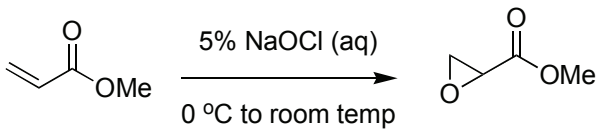
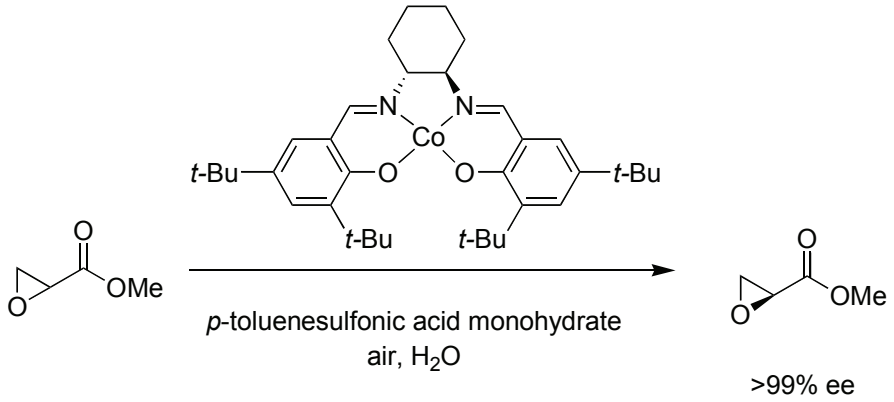
PREPARATION OF (*S*)-METHYL GLYCIDATE VIA HYDROLYTIC KINETIC RESOLUTION
(Oxiranecarboxylic acid, methyl ester, (2*S*)-)

A.



B.



Submitted by Christian P. Stevenson, Lars P. C. Nielsen and Eric N. Jacobsen.[1]
Checked by Jason D. McKinley, Timothy D. White, Michel A. Couturier, and John Ragan.

1. Procedure

A. (±)-Methyl glycidate (Note 1). A 3-L, round-bottomed flask equipped with a magnetic stir bar and an internal thermometer is charged with aqueous sodium hypochlorite solution (6.0 wt%, 940 mL, 0.755 mol, Note 2) and cooled to 0 °C in an ice bath. Methyl acrylate (58.5 g, 0.680 mol, 1 equiv) is added in one portion, and the flask is capped loosely under air (Note 3). The biphasic mixture is stirred vigorously at 0 °C (Note 4). After 30 min, the ice bath is removed, and the solution is stirred for an additional 1.5 h (Note 5). During this time, the internal temperature gradually rises to 30−37 °C, and the biphasic, yellow mixture becomes turbid and colorless. The reaction mixture is then cooled to 20−25 °C in an ice bath, transferred to a separatory funnel, and extracted with dichloromethane (4 x 150 mL). The organic extracts are dried over sodium

sulfate, filtered, and concentrated to a volume of approximately 50 mL by rotary evaporation (Note 6). The solution is transferred to a 100-mL recovery flask and purified by fractional vacuum distillation (bp 84−87 °C/70 mmHg, Notes 7-9) to afford racemic methyl glycidate (30.3−31.6 g, 44−46%) as a colorless liquid (Note 10).

B. (S)-Methyl glycidate. A 200-mL, round-bottomed flask equipped with a magnetic stir bar is charged with (*R*,*R*)-(–)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (0.916 g, 1.52 mmol, 0.50 mol%), *p*-toluenesulfonic acid monohydrate (0.304 g, 1.60 mmol, 0.53 mol%, Note 11), and dichloromethane (20 mL). The solution rapidly turns from bright red to dark green/brown and is stirred open to air for 30 min (Note 12). After removing the stir bar, the solution is concentrated by rotary evaporation, then the residue is dried under vacuum (<1 mmHg) for 30 min (Note 13). The stir bar is returned to the flask, racemic methyl glycidate (31.0 g, 0.304 mol, 1 equiv) is added, and the flask is loosely capped with a greased glass stopper (Note 14). After dissolving most of the catalyst residue by swirling the solution for 1-2 min, distilled water (3.85 mL, 0.214 mol, 0.70 eq) is added, the reaction vessel is immersed in a room temperature water bath and stirred vigorously for 24 hours. The stopper and water bath are removed, and the reaction flask is fitted with a reflux condenser. The mixture is heated at 85-90 °C (oil bath temperature) for two h. Upon cooling to room temperature and stirring for 30 min, the precipitated red (salen)Co(II) complex is recovered by vacuum filtration, and washed with distilled water (3 x 15 mL, Notes 15 and 16). The filtrate is extracted with dichloromethane (3 x 60 mL). The combined organic extracts are dried over sodium sulfate, filtered, and concentrated to a volume of less than 20 mL by rotary evaporation (Note 6). This brown solution is transferred to a 50-mL recovery flask, and short path vacuum distillation (bp 54−57 °C/33 mmHg, Notes 7-9) affords (*S*)-methyl glycidate (11.1-11.4 g, 36-37%) as a colorless liquid in >99% enantiomeric excess (Notes 10 and 17).

2. Notes

1. This procedure is a modification of that described by Nemes and coworkers,[2] first developed in these laboratories by K. B. Hansen.[3]

2. The checkers used 6 wt% NaOCl (Aldrich). The submitters used Clorox® brand household bleach solution (5.25 wt% NaOCl), which required 1.07 L to achieve 0.755 mol.

3. For both procedures, reagents were purchased from Aldrich Chemical Company, Inc. (the submitters purchased (salen)Co(II) pre-catalyst from Strem Chemicals, Inc.). All reagents were used as received without further purification.

4. Rapid stirring must be maintained to ensure sufficient mixing of the biphasic reaction.

5. Longer reaction times lead to diminished yields due to saponification of methyl glycidate under the basic reaction conditions (pH = 11−12).

6. Care should be taken to minimize losses of the volatile methyl glycidate. The submitters concentrated the solution at 20 °C/40 mmHg and lost <2% of the material.

7. Upon reaching 115 mmHg, the pressure of the distillation apparatus is lowered slowly. Vigorous stirring is maintained to keep the solution from foaming over into the receiving flask. Upon reaching the desired distillation pressure, the apparatus is maintained at room temperature with vigorous stirring for one hour to ensure removal of all residual solvent.

8. The receiving flask is maintained at 0 °C once the product starts to distill. At the end of the distillation, when the distillation head temperature starts to fall, the head is warmed gently with a heat gun to maximize product recovery.

9. The submitters reported a boiling point of 59−61 °C/20 mmHg. The checkers found that distillation at slightly higher pressures provided a more distinct boiling point separation between residual solvent/starting material and the product epoxide.

10. The product was found to be >98% pure by gas chromatography on a 30 m HP5 capillary column from Agilent Technologies, Inc. (65 °C isothermal, t_R = 1.31 min). The product has been characterized as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.92 (dd, *J* = 6.0, 4.0, 1 H), 2.95 (dd, *J* = 6.0, 2.5, 1 H), 3.43 (dd, *J* = 4.0, 2.5, 1 H), 3.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 46.5, 47.1, 52.3, 169.9; IR (neat) cm^{-1}: 1740, 1441, 1394, 1298, 1209, 1027, 883; HRMS (*m/z*) (CI NH_3) calc. for $C_4H_{10}NO_3$ $(M+NH_4)^+$ 120.0661, found 120.0661; *d* = 1.16 g/mL. Distilled racemic methyl glycidate stored for two years at 0 °C under air showed no decomposition by ^{1}H NMR and GC analysis. However, this racemate developed an undetectable contaminant that significantly retarded the rate of the resolution (14 h, 25% ee vs 93% ee with freshly prepared epoxide). Even redistilled, the old epoxide was never as reactive as freshly prepared

material. Enantioenriched product isolated from procedure B did not develop this contaminant upon storage.

11. Similar results can also be obtained by replacing *p*-toluenesulfonic acid with electron-deficient benzoic acids, although these catalysts require somewhat higher loadings (for example, 0.7 mol% (salen)Co(II) with 3,5-bis(trifluoromethyl)benzoic acid, 0.8 mol% (salen)Co(II) with 3,5-dinitrobenzoic acid, or 0.9 mol% (salen)Co(II) with 4-nitrobenzoic acid). Such electronic tuning of the catalyst may be beneficial for certain epoxides (see Discussion).

12. Oxidation to the catalytically active Co(III) complex is dependent on maintaining sufficient oxygenation of the solution. Use of a smaller flask or slow stirring can lead to incomplete oxidation and substantially slower kinetic resolution reactions.

13. If desired, this catalyst may be further purified by suspension in pentane, filtration, and drying under vacuum. This provides the (salen)Co(III)OTs•H_2O catalyst as a free-flowing, green powder. This catalyst remains fully active for at least four months when stored under air on the benchtop. Reactions with this catalyst are initiated by simply adding the (salen)Co(III) species to a stirring mixture of epoxide and water at room temperature.[4d]

14. A glass stopper is preferable to a septum, which can absorb solvent and epoxide.

15. Heating the mixture to reflux induces catalyst reduction and allows removal of most of the Co-containing species by filtration. The aqueous extraction serves to remove most of the diol product. This workup procedure was developed to eliminate catalyst- and diol-induced foaming during distillation of the epoxide. This is not a significant problem in the hydrolytic kinetic resolution of many other epoxides, in which case direct distillation of the epoxide from the reaction mixture remains the most convenient isolation method.[4]

16. After drying under vacuum for 1 h, the recovered (salen)Co(II) complex (0.758-0.789 g, 83-86% recovery) can be recycled without any further purification. The reuse of this catalyst has been demonstrated by resolving an additional 31.0 g of methyl glycidate by using recovered (salen)Co(II) (plus a small amount of fresh complex to reach the desired 0.5 mol% catalyst loading).

17. The enantiomeric purity was determined by chiral gas chromatography on a 20 m Chiraldex γ-TA capillary column from Advanced Separation Technologies, Inc. Using an 80°C isothermal method, the (*R*)- and (*S*)- enantiomers had retention times of 4.1 and 7.3 min, respectively. The optical rotations of (*S*)-methyl glycidate were found to be $[\alpha]_D^{27}$ –17.3 (neat) and $[\alpha]_D^{26}$ –10.3 (methanol, c 5.34).

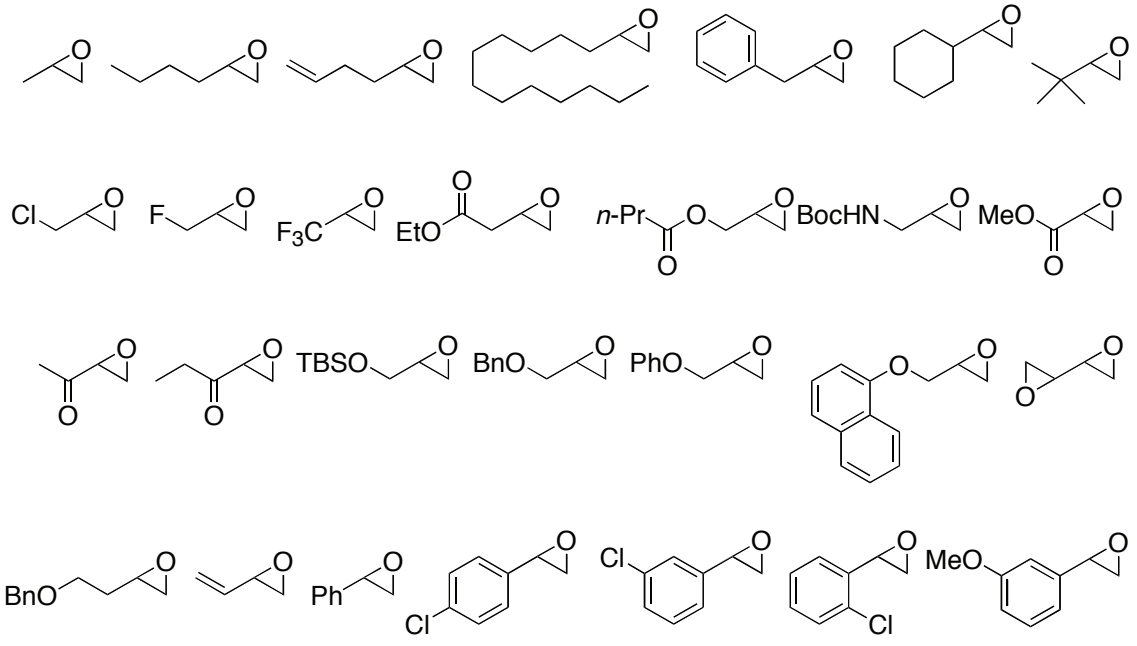
Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by chiral (salen)Co complexes affords highly enantioenriched unreacted epoxides and 1,2-diol products.[4] The HKR displays extraordinary scope, as a wide assortment of sterically and electronically varied epoxides can be resolved to ≥99% ee (Figure 1). The general availability of racemic

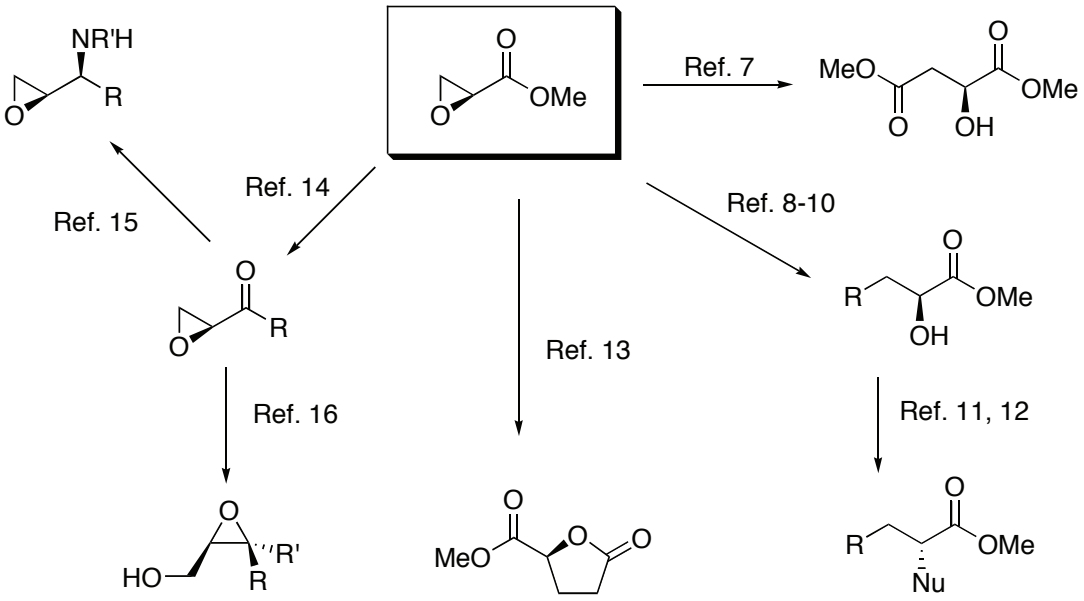
Figure 1: Epoxides Resolved to >99% ee via the HKR[4c]



epoxides, the use of water as the resolving agent, and the low loadings of a recyclable, commercially available catalyst make this methodology particularly practical. Accordingly, the utility of the HKR has already been widely demonstrated in organic synthesis.[5] Recent mechanistic studies[4d] have revealed that the more electrophilic (salen)Co(III)OTs catalyst is significantly more reactive than the (salen)Co(III)OAc catalyst originally reported.[4a-c] The increased Lewis acidity of the (salen)Co(III)OTs catalyst has, however, been shown to be detrimental to the HKR's of styrene oxide and propargyl epoxides, presumably due to participation of less selective S_N1 pathways.

While the broad utility of epoxides as synthetic intermediates has been well documented,[6] methyl glycidate is a particularly versatile chiral building block. A range of reactions has been developed that selectively transform either the epoxide or ester functionality (Scheme 1). The epoxide can be converted to an α-hydroxyester by carbonylation[7] or by organocuprate,[8] phenol,[9] or indole[10] addition. The resulting hydroxyl group can then be displaced under Mitsunobu conditions[11] or as the sulfonate.[12] The epoxide can also be opened with 1-morpholino-2-trimethylsilyl acetylene yielding a γ-lactone.[13] Alternatively, methyl glycidate can be converted to a variety of epoxyketones by addition of Grignard or organolithium reagents.[14] The resulting epoxyketones undergo diastereoselective reductive amination,[15] or can be converted to tri-substituted epoxyalcohols by using a Grignard addition/Payne rearrangement protocol.[16]

Scheme 1: Synthetic Uses of Methyl Glycidate



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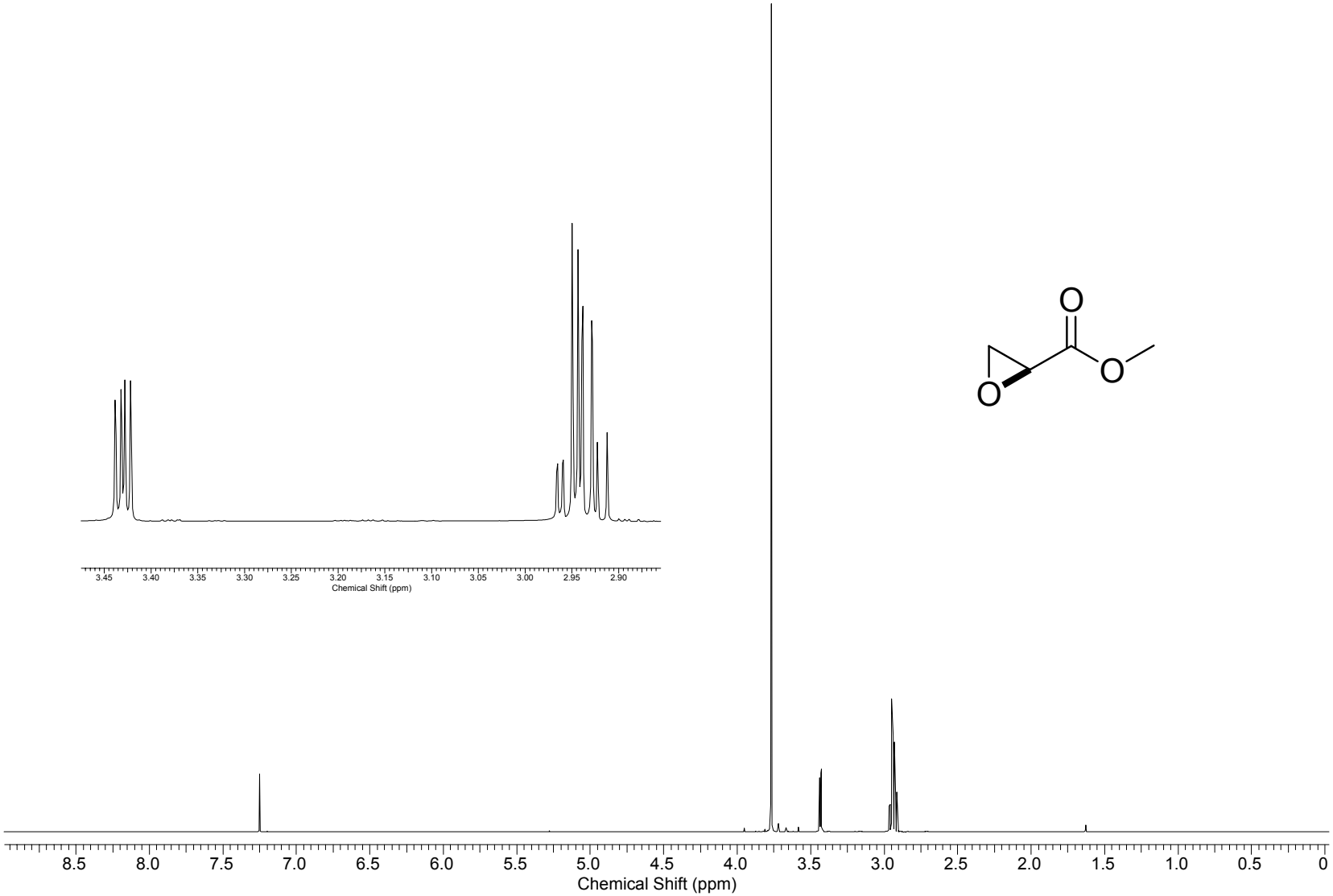
Appendix
Chemical Abstract Nomenclature;
(Registry Number)

(*S*)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester, (2*S*)-; (118712-39-3)

Methyl acrylate: 2-Propenoic acid, methyl ester; (96-33-3)

(±)-Methyl glycidate: Oxiranecarboxylic acid, methyl ester; (4538-50-5)

(*R*,*R*)-(–)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II): Cobalt, [[2,2'-[(1*R*,2*R*)-1,2-cyclohexanediylbis[(nitrilo-κ*N*)methylidyne]]bis[4,6-bis(1,1-dimethylethyl)phenolato-κ*O*]](2-)]-, (SP-4-2)-; (176763-62-5)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