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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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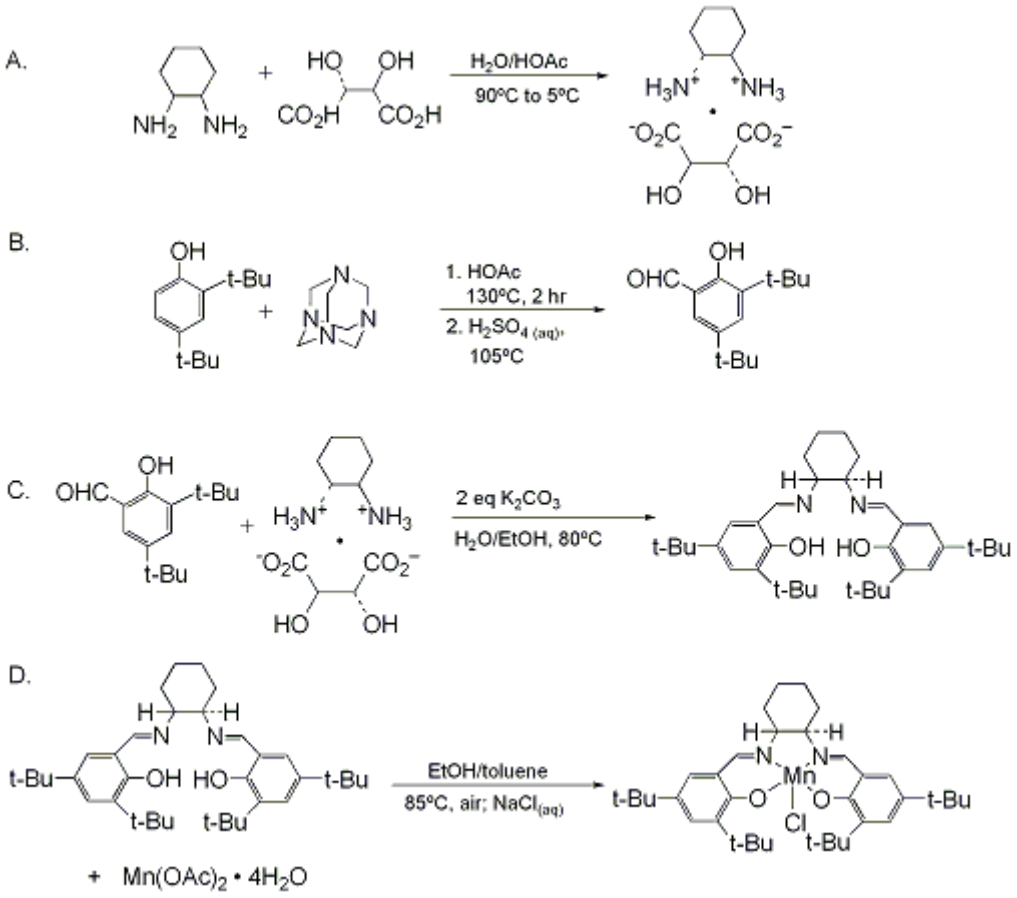
(R,R)-N,N'-BIS(3,5-DI-tert-BUTYLSALICYLIDENE)-1,2-CYCLOHEXANEDIAMINO MANGANESE(III) CHLORIDE, A HIGHLY ENANTIOSELECTIVE EPOXIDATION CATALYST

[Manganese, chloro[[2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]-bis[4,6-bis (1,1-dimethylethyl)phenalato]](2-)-N,N',O,O']-, [SP-5-13-(1R-trans-]-]



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1. Procedure

A. (R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate (Note 1). A 1-L beaker assembled with a mechanical overhead stirrer and a thermometer is charged with 250 mL of distilled or deionized water. L-(+)-Tartaric acid (75 g, 0.5 mol) is added with stirring in one portion (Note 2). The solution is stirred as 114 g (120 mL, 1 mol) of racemic trans-1,2-diaminocyclohexane is added carefully in one portion (Note 3). A slurry is formed initially but complete dissolution is observed once addition is complete. Glacial acetic acid (50 mL) is then added in one portion (Note 4). Product begins to precipitate during the addition, and continues to precipitate while the reaction mixture is allowed to cool from 90°C to 5° C, with stirring, over 3 to 4 hr. The temperature is maintained at 5°C for an additional hour and the product is isolated by filtration. The filter cake is washed with 50 mL of cold (5°C) water followed by 4 × 50-mL portions of ambient temperature methanol (Note 5). The enantiomeric excess of the derivatized diamine is determined by sampling the top and bottom of the filter cake using the procedure below (Note 6). The product is dried at 40-45°C under reduced pressure to give 105-110 g (80-83%) of the (R,R)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt as a white powder. (R,R)-1,2-

Diaminocyclohexane obtained from this salt exhibits >98.0% enantiomeric excess (Note 7).

Derivatization and enantiomeric excess determination of 1,2-diaminocyclohexane: A 13 × 100-mm test tube is charged with 25 mg of the diammonium tartrate salt , 1.5 mL of methylene chloride (CH_2Cl_2), and 0.5 mL of 4 N aqueous sodium hydroxide . The two phases are mixed thoroughly for 30 sec using a vortex mixer, then m-toluoyl chloride (50 µL) is added and the two phases are mixed for an additional 30 sec. The phases are allowed to separate and a 250-µL sample of the lower organic layer is removed. The sample is diluted to 10 mL with isopropyl alcohol and the resultant solution (10 µL) is analyzed by HPLC. The enantiomers are separated using a Pirkle covalent L-Leucine-DNB column and eluting with hexane/isopropyl alcohol (90:10; v/v) at a flow rate of 1.0 mL/min and at ambient temperature. The enantiomers are detected by measuring the absorbance of the eluent at 254 nm (Note 8).

B. 3,5-Di-tert-butylsalicylaldehyde (Note 9). A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and thermometer is charged with 125 g (0.60 mol) of 2,4-di-tert-butylphenol , 170 g (1.20 mol, 2 eq) of hexamethylenetetramine , and 300 mL of glacial acetic acid (Note 10). Complete dissolution results within minutes after stirring is initiated. The reaction mixture is heated to 130°C over a period of 60 min or less, and the temperature is diligently maintained within a range of 125-135°C for 2 hr as stirring is continued (Note 11). The reaction mixture is then cooled to 75-80°C and aqueous sulfuric acid [300 mL of 33% (w/w)] is added with stirring while the temperature is maintained below 100°C (Note 12). After the resulting mixture is heated to reflux (105-110°C) for 30-60 min, the reaction mixture is cooled to 75-80°C and transferred to a 1-L separatory funnel wrapped with electrical heating tape (Note 13). The phases are allowed to separate while the temperature is maintained at 75-80°C; the lower aqueous phase (650 to 750 mL; pH 4-5) is drawn off (Note 14). The organic layer is transferred to an Erlenmeyer flask and cooled to 50°C, at which point methanol (100 mL) is added with stirring. The mixture is cooled to room temperature, then to ≤5°C with an ice bath and maintained at that temperature for 1 hr with continued stirring. The product is collected by vacuum filtration and the solid is washed with 30 mL of cold (≤5°C) methanol . Air is pulled through the filter cake for not less than 30 min to remove most of the solvent (Note 15). The crude product is suspended in methanol (approximately 1:1; w/v) and the mixture is heated to 50-55°C for 30 min with stirring (Note 16). The solution is cooled to ≤5°C over a 1-hr period and this temperature is maintained for another hour. The product is collected by vacuum filtration and washed with 20 mL of cold methanol . The product is allowed to air dry and is isolated as a free-flowing yellow solid, mp ≥52°C (Note 17) and (Note 18).

C. (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine. A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and an addition funnel is charged with 29.7 g of (R,R)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt (0.112 mol), 31.2 g of potassium carbonate (0.225 mol, 2 eq), and 150 mL of water. The mixture is stirred until dissolution is achieved, and 600 mL of ethanol is added. The cloudy mixture is heated to reflux with a heating mantle and a solution of 53.7 g (0.229 mol, 2.0 eq) of 3,5-di-tert-butylsalicylaldehyde in 250 mL of ethanol is then added in a slow stream over 30 min (Note 19). The addition funnel is rinsed with 50 mL of ethanol and the mixture is stirred at reflux for 2 hr before heating is discontinued. Water, 150 mL, is added and the stirred mixture is cooled to ≤5°C over 2 hr and maintained at that temperature for another hour. The yellow solid is collected by vacuum filtration and washed with 100 mL of ethanol . After the solid is air dried, it is dissolved in 500 mL of methylene chloride . The organic solution is washed with 2 × 300 mL of water, followed by 300 mL of saturated aqueous sodium chloride . The organic layer is dried over sodium sulfate , and filtered to remove the drying agent. The solvent is removed by rotary evaporation to yield the product as a yellow solid, mp 200-203°C (Note 20) and (Note 21).

D. *(R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride* . A 2-L, three-necked, round-bottomed flask equipped with a mechanical overhead stirrer, reflux condenser, and a 500-mL addition funnel is charged with 67.2 g (0.27 mol; 3 eq) of manganese acetate tetrahydrate ($Mn(OAc)_2 \cdot 4H_2O$) and 500 mL of ethanol . Stirring is begun and the solution is heated to reflux (75-80°C) with a heating mantle. A solution of 50.0 g (0.09 mol, 1 eq) of (R,R)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine in 250 mL of toluene is added in a slow stream over 45

min and the funnel is rinsed with 50 mL of toluene (Note 22) and (Note 23). The reaction mixture is stirred at reflux for 2 hr, at which time the addition funnel is replaced by a gas dispersion tube connected to an air source (Note 24) and (Note 25). Air is bubbled through the refluxing reaction mixture for 1 hr, and the reaction is monitored for complete ligand consumption by thin layer chromatography (Note 26). When ligand consumption is complete, heating and air addition are discontinued and 100 mL of saturated aqueous sodium chloride is added. The reaction mixture is cooled to room temperature then transferred to a 2-L separatory funnel. The flask is rinsed into the funnel with 300 mL of toluene (Note 27) and the organic solution is washed with 3 × 600-mL portions of water followed by 500 mL of saturated aqueous sodium chloride . The organic layer is dried over anhydrous sodium sulfate, then filtered to remove the drying agent. Most of the toluene is removed by low pressure distillation followed by rotary evaporation of the residual solvent. The dark brown solid is dissolved in 300 mL of methylene chloride in a 1-L, round-bottomed flask. Heptane (300 mL) is added (Note 28), and the methylene chloride is removed by reduced pressure rotary evaporation. After complete removal of the methylene chloride, the brown slurry is stirred for 1 hr at ≤5°C in an ice bath. The brown solid is collected by vacuum filtration and allowed to air dry. Heating of the solid at 50-60°C under high vacuum removes any residual solvent to yield the desired product, mp 324-326°C (Note 29), (Note 30) and (Note 31).

2. Notes

1. This procedure is a modification of that described by Galsbøl, et al.[2]
2. For all procedures, the submitters employed reagents (Aldrich Chemical Company, Inc., or Spectrum Chemical Mgf. Corp.) and solvents as supplied from commercial suppliers without purification.
3. The addition of the diamine is exothermic and the reaction temperature rises to approximately 70°C by the end of addition. The temperature should not exceed 90°C.
4. The addition of acetic acid is also exothermic and the reaction temperature should rise to, but not exceed, 90°C.
5. The aqueous filtrates may be combined and saved for isolation of (S,S)-1,2-diaminocyclohexane as the bis-(+)-tartrate salt using an alternate procedure.[2] The methanol washes can be discarded.
6. The enantiomeric excess of the two samples should be >98.0% for the (R,R)-enantiomer and within 0.2% enantiomeric excess of each other. Otherwise, the product should be washed with more methanol to remove the undesired enantiomer. If this procedure fails to yield product of acceptable enantiomeric purity, the product can be further purified by recrystallization of the salt from water (1:10, w/v). This affords product in 60-70% overall yield and >99.5% ee.
7. The (S,S)-diamine can be obtained as the mono-(−)-tartrate salt by using the same procedure with D-(−)-tartaric acid .
8. The column employed by the submitters had 25 cm × 4.6-mm (ID) dimensions and was purchased from Regis International (Morton Grove, IL). The (S,S)-derivative elutes first (9 min) followed by the (R,R)-derivative (12 min).
9. This procedure is an adaptation of the Duff reaction.[3]
10. The order of addition does not seem to be important. If the sequence that is described is employed, a slight exotherm is observed upon addition of the acetic acid.
11. Extreme care should be taken to maintain the reaction mixture temperature within the stated limits. Heating too slowly results in increased formation of side products and decreased product yield, as does allowing the reaction temperature to increase above 135°C. A mild exotherm is exhibited once the reaction reaches about 110°C, and the upper temperature limit can be exceeded if the rate of heating is not carefully monitored.
12. Addition of the sulfuric acid solution is exothermic and can cause vigorous evolution of steam. The acid solution should be cooled to (or below) room temperature before addition.
13. The checkers used a 1-L resin kettle (Kontes #614010-1000) with a temperature controller and preheated at 80°C.
14. It is important that sufficient time be allowed for proper partitioning between the phases. The heating tape maintains the temperature in the desired range, preventing the precipitation of solids and allowing for better separation. The phases should be allowed to separate for at least 15 min. If a small amount of solids is observed, this should not interfere with the separation and the solids may be discarded with the aqueous phase.
15. The typical yield for the crude aldehyde is 71-85 g (50-60%).

16. Any solids remaining in the mixture after 30 min at 50-55°C should be removed by filtration. The amount of solid is typically less than 1 g.
17. The typical yield of the recrystallized product is 50.0-64.3 g (35-45%). The literature[4] melting point of the product is 58-60°C, but high purity samples (≥98% by GC) generally have melting points in the given range.
18. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (s, 9 H), 1.43 (s, 9 H), 7.35 (d, 1 H, J = 2.4), 7.59 (d, 1 H, J = 2.4), 9.87 (s, 1 H), 11.65 (s, 1 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.4, 31.4, 34.3, 35.1, 120.2, 127.8, 131.9, 137.8, 141.7, 159.2, 197.2 ; IR (KBr) cm^{-1}: 1653, 1612, 1373, 1322, 1265, 1170 .
19. Gentle heating may be required to dissolve all of the aldehyde. The reaction mixture immediately turns bright yellow upon addition of the aldehyde and precipitation of the ligand occurs as addition proceeds.
20. The typical yield of the ligand is 58.2-60.6 g (95-99%). If further purification is required, the product can be recrystallized in two crops from boiling acetone (1:20; w/v) with 86-93% recovery as a fluffy yellow solid.
21. The spectral properties of the product are as follows: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.27 (s, 18 H), 1.32-1.54 (m, 2 H), 1.4-2.0 (m, 6 H), 1.46 (s, 18 H), 3.31-3.70 (m, 2 H), 7.02 (d, 2 H, J = 2.2), 7.34 (d, 2 H, J = 2.2), 8.34 (s, 2 H), 13.76 (s, 2 H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.4, 29.5, 31.5, 33.3, 34.1, 35.0, 72.4, 117.9, 126.1, 126.8, 136.4, 139.9, 158.1, 165.9 ; IR (KBr) cm^{-1}: 2960, 2869, 1631, 1595, 1468, 1439, 1362, 1271, 1174, 829 .
22. The ligand is only moderately soluble in toluene and complete dissolution is often achieved with the aid of sonication and gentle warming.
23. The pinkish-brown solution turns to a dark brown heterogeneous mixture immediately upon addition of the ligand.
24. After 2 hr at reflux the dark solution should appear homogeneous.
25. The submitters employed a commercial aquarium pump, although any device used to supply low pressure air for flash chromatography should be suitable. The flow rate should be 10-30 mL/min.
26. TLC was performed on silica (Merck silica gel 60 F-254; 0.25-mm thickness) with EtOAc/hexanes (1:4). The complex remains at the baseline (R_f = 0), while the ligand has an R_f = 0.85. If ligand consumption is not complete, bubbling of air through the solution and heating are continued while the reaction is monitored every 20 min until completion. A small amount of 3,5-di-tert-butylsalicylaldehyde may be detected because of ligand decomposition.
27. The presence of an insoluble residue is common and this may be left in the reaction flask.
28. The catalyst may or may not precipitate upon addition of the heptane, but the end result is the same and isolation of the product is not affected.
29. The yield of this reaction is typically 54.9-57.2 g (95-99%).
30. Elemental analysis can be used to establish purity, although a melting point ≥320°C is generally a sufficient criterion of product purity. The complex does not exhibit a readily interpretable NMR spectrum because of the paramagnetic nature of the complex.
31. A procedure for the large-scale (>100 g) production of the complex as a DMF adduct has also been described.[5]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The product of this preparation is the most enantioselective catalyst developed to date for asymmetric epoxidation of a broad range of unfunctionalized olefins.[6 7 8 9 10 11] The procedure includes a highly efficient resolution of trans-1,2-diaminocyclohexane as well as a convenient analytical method for the determination of its enantiomeric purity. This method is general for the analysis of chiral 1,2-diamines. The Duff formylation described in Step B is a highly effective method for the preparation of 3,5-di-tert-butylsalicylaldehyde, and it circumvents the use of hazardous or sensitive materials, such as tin chloride ($SnCl_4$), which were employed in previously reported syntheses.[9] The Duff reaction is applicable to the preparation of other 3,5-substituted salicylaldehydes,[5] which in turn can be used to

prepare chiral (salen)Mn, [N,N'-bis(salicylideneamino)ethane]Mn, epoxidation catalysts with sterically- and electronically-tuned reactivities.[12] As such, a wide range of (salen)metal complexes can be prepared by adaptation of the procedure described above, by variation of the diamine, the salicylaldehyde, or the metal center.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 29

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R,R)-N,N'-Bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamino manganese(III) chloride:
Manganese, chloro[[2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis[4,6-bis(1,1-dimethylethyl) phenolato]](2-)-N,N',O,O'-[SP-5-13-(1R-trans)] (12); (138124-32-0]

(R,R)-1,2-Diammoniumcyclohexane mono-(+)-tartrate:
1,2-Cyclohexanediamine, (1R-trans)-, [R-(R*,R*)-2,3-dihydroxybutanedioate (1:1) (9); (39961-95-0)

L-Tartaric acid:
Tartaric acid, L- (8);
Butanedioic acid, 2,3-dihydroxy-, [R-(R*,R*)]- (9); (87-69-4)

(±)-trans-1,2-Diaminocyclohexane:
1,2-Cyclohexanediamine, trans- (8,9); (1121-22-8)

m-Toluoyl chloride (8);
Benzoyl chloride, 3-methyl- (9); (1711-06-4)

3,5-Di-tert-butylsalicylaldehyde:
Benzaldehyde,3,5-bis(1,1-dimethylethyl)-2-hydroxy- (9); (37942-07-7)

2,4-Di-tert-butylphenol:
Phenol, 2,4-di-tert-butyl- (8);
Phenol, 2,4-bis(1,1-dimethylethyl)- (9); (96-76-4)

Hexamethylenetetramine (8);
1,3,5,7-Tetraazatricyclo[3.3.1.1^{3,7}]decane (9); (100-97-0)

Manganese acetate tetrahydrate:
Acetic acid, manganese (2+ salt), tetrahydrate (8,9); (6156-78-1)

(R,R)-N,N'-Bis-(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine:
Phenol, 2,2'-[1,2-cyclohexanediylbis(nitrilomethylidyne)]bis[4,6-bis(1,1-dimethylethyl)- [1R-(1a(E),2b(E)]]- (12); (135616-40-9]