Enantioselective Synthesis of Ephenamine Employing Sharpless Asymmetric Dihydroxylation

Thesis submitted in partial fulfillment of the requirements

For the award of the degree of

Masters of Science

In

Chemistry

Submitted By:

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Roll No.: 301202010

Under the guidance of

Dr. Satyendra Kumar Pandey

to the

School of Chemistry and Biochemistry

Thapar University

Patiala-147004 (Punjab)

INDIA

July 2014

Certificate

This is to certify that the project entitled **"Enantioselective Synthesis of Ephenamine Employing Sharpless Asymmetric Dihydroxylation"** being submitted by **Ms. Ramandeep Kaur** in the partial fulfillment of requirement for the award of the degree of Masters of Science in the School of Chemistry and Biochemistry, Thapar University, Patiala, is a bonified work carried under the supervision of Dr. Satyendra Kumar Pandey and no part of this project has been submitted for award of any other degree by me.

18-07-2014

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Candidate's Declaration

I hereby declare that the work being presented in the dissertation entitled "**Enantioselective Synthesis of Ephenamine Employing Sharpless Asymmetric Dihydroxylation**"in partial fulfillment of the requirements for the award of the degree of Masters in Chemistry, School of Chemistry and Biochemistry, Thapar University, Patiala, is my own work during the period of January to July 2014, under the supervision of **Dr. Satyendra Kumar Pandey.** My thesis has not previously formed the basis for award of any degree, or other similar title or recognition.

Ramandeep Kaur

Ramandeep Kaur

Patiala

Date: 18.7.2014

This is to certify that the above statement made by the candidate is correct and true to the best of our knowledge.

18.07.2014

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I am obliged to Miss Suraksha for her cordial support. I am grateful to all laboratory staff for their cooperation during the period of my assignment, which helped me in compelting this task through various stages. In my daily work I have been blessed with a friendly and cheerful group of rearch scholars Mr. Yuvraj Garg, Mr. Lalit Mehta and Mr. Akul Sen Gupta.

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Ramandeep Kaur

LIST OF CONTENT

ABSTRACT

A pratical and highly enantioselective synthesis of Ephenamine **1** has been achieved by applying Sharpless asymmetric dihydroxylation and cyclic sulfite methodology as the key step. The merits of this synthetic approach is high enantioselective with high yielding steps. This synthetic strategy has significant potential for further extension to other seteroisomers via double inversion at the α-carbon. Pencillin salt of Ephenamine is recommended as an anti-allergenic and used as feed additive to stimulate growth in poultry and livestock and also used to resolve penicillin and glycine derivatives.

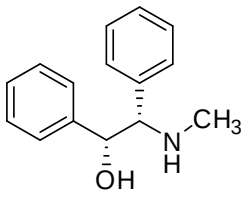
Keywords: Sharpless Asymmetric Dihydroxylation, cyclic sulfite opening, Boc protection, LAH reduction.

Enantioselective synthesis of Ephenamine employing Sharpless Asymmetric Dihydroxylation

1.Introduction

Antibiotics, also known as antibacterials, are types of medications that slow down the growth of bacteria. With advances in medicinal chemistry, most modern antibacterials are semisynthetic modifications of various natural compounds. These include, for example, the β-lactam antibiotics, which include the penicillins**.** Ephenamine ((*R,S*)-2-methylamino-1,2-diphenylethanol) when combines with pencillin G, it works as an antibiotic.

The term "Ephenamine" was used in the Federal Registrar (June 7, 1951) to describe *(R,S)*-1 and *(S,R)*-2-methylamino-1,2-diphenylethanol **2** in a salt form of penicillin G, an antibiotic/feed additive used to stimulate growth in poultry and livestock. Ephenamine-glutamine salts have also been prepared to provide effective amounts of glutamine for human consumption. Ephenamine has also been used to resolve penicillin and glycine derivatives. We use the term "pseudoephenamine" to describe, *(1S,2S)*-2-methylamino-1,2-diphenylethanol **3** and *(1R,2R)*-2-methylamino-1,2-diphenylethanol **4**, the the diastereomer of ephenamine. Pseudoephenamine has been used as a chiral auxiliary in alkylation reaction.



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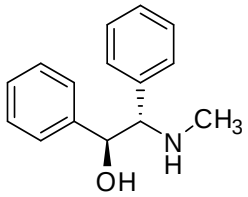

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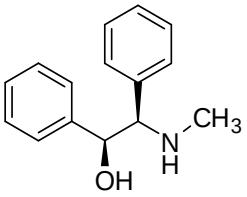

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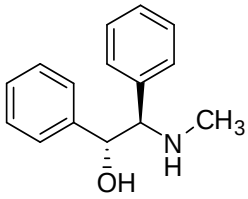


4

Figure 1: Structures of related 1,2-diphenyl-2-aminoalcohols.

1.1 Sharpless Asymmetric Dihydroxylation (AD)

Catalytic asymmetric reactions afford an especially practical entry into the chiral world due to their economical use of asymmetric inducing agents[1]. Especially useful is the carbon-heteroatom bond forming reaction, since the resulting functionality can be readily manipulated to generate many important classes of compounds. Therefore, it is not amazing that the oxidative addition of heteroatoms to olefins has been a profitable area.

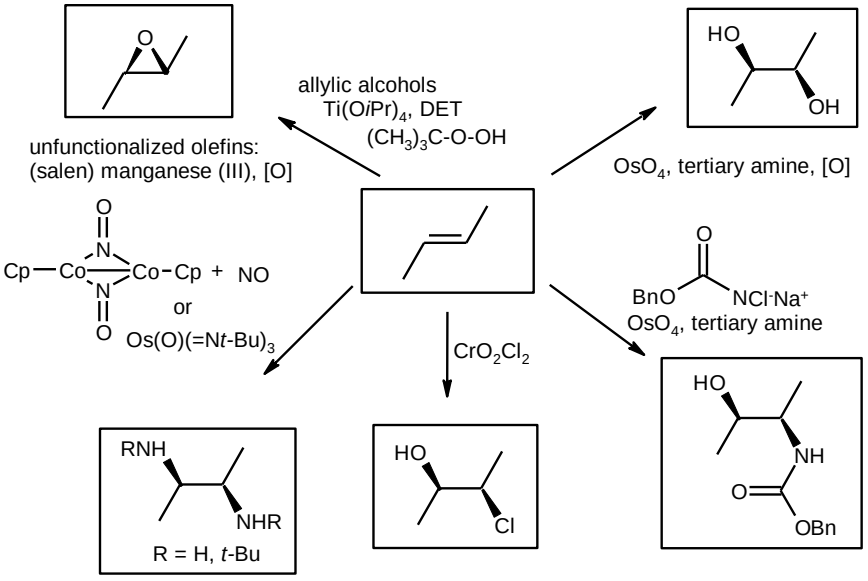


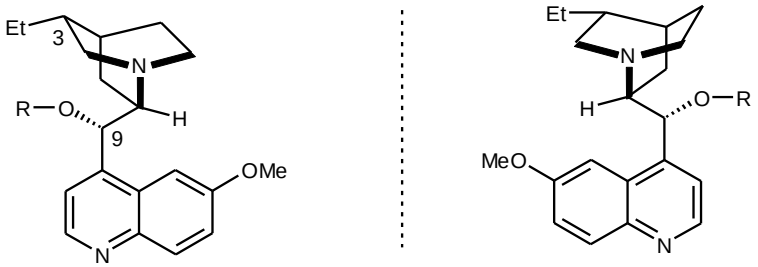
Figure 2. Suprafacial 1,2-difunctionalization of olefins mediated by transition metal.

A number of transition metal-mediated methods for the oxidative cyclization,[2-6] epoxidation,[7-8] halohydrin formation,[9-13] dihydroxylation,[14] and aminohydroxylation[15] have emerged. A common feature of most of these processes is the phenomenon of ligand acceleration[16-18] whereas a metal catalyzed process turns over faster in the presence of a coordinating ligand. This causes the reaction to be pass through the ligated pathway with the additional consequence that the ligand may leave its print on the selectivity determining step. Thus, ligand can influence the chemo-, regio-, and stereoselectivity of the reaction.

Initial efforts by Sharpless and Hentges to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4[19] quinuclidine derivatives were used instead of pyridines for further investigations due to their inherently higher affinity for OsO_4. Moderate to good enantiomeric excess using acetate esters of

cinchona alkaloids as chiral ligands was obtained. By using cinchona alkaloid catalyzed AD, recycling of the Os and the ligand is achievable.

Cinchona Alkaloid Ligands for AD under Catalytic Conditions

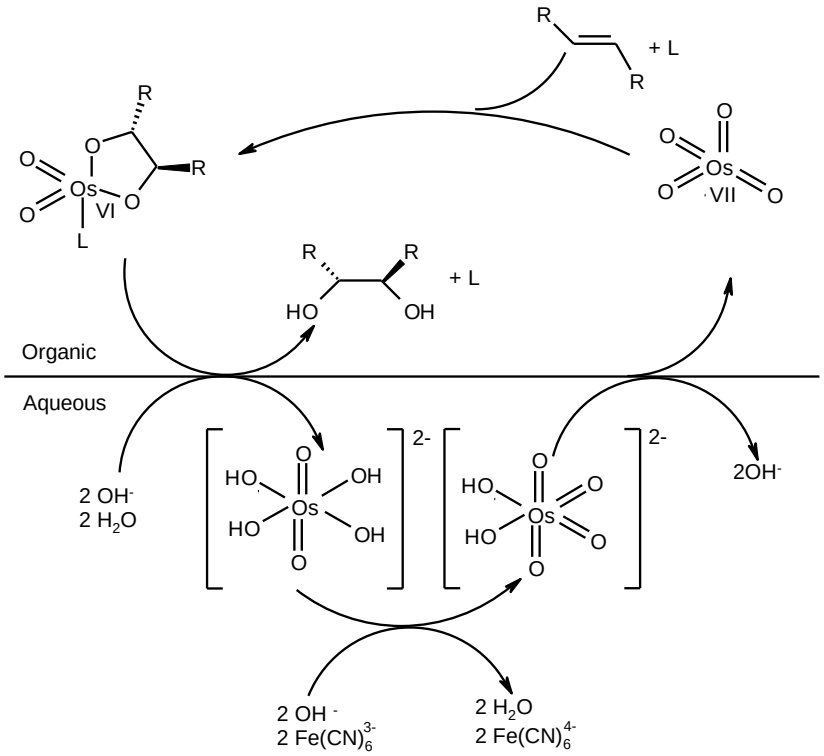


Dihydroquinidine (R = H)
DHQD

Dihydroquinine (R = H)
DHQ

Figure 3. Ligands for AD reaction.

Initially, the asymmetric dihydroxylation using the derivatives of cinchona alkaloids was performed under stoichiometric conditions, but in 1987 Marko and Sharpless[20] found that the process became catalytic when NMO was employed as the co-oxidant. However, the enantiomeric excess of the diol products obtained under these catalytic conditions was initially lower than that produced by the stoichiometric reaction. The origin of this discrepancy was found to be the presence of a second catalytic cycle which exhibited only low or no enantioselectivity. Wai[21] discovered a partial remedy in slow addition of the olefin. Kwong[22] found that the participation of second catalytic cycle can be virtually eliminated by performing the reaction under two-phase conditions with $K_3Fe(CN)_6$ as the stoichiometric re-oxidant. Under these conditions there is no oxidant other than OsO_4 in the organic layer.



Figures 4. Catalytic cycle of the AD reaction with $K_3Fe(CN)_6$ as the co-oxidant.

Since the actual osmylation takes place in this layer, the resulting osmium (VI) monoglycolate ester undergoes hydrolysis, releasing the diol and the ligand to the organic layer and Os (VI) to the aqueous layer before its regeneration can occur, and consequently entry of the osmium glycolate into the second cycle is prevented.

Sharpless *et al*.[23] found that the hydrolysis of the osmium (VI) glycolate product might be accelerated considerably by using $MeSO_2NH_2$. The reaction time can be as much as 50 times shorter in the presence of this additive. This allows high catalytic turnover even with sterically encumbered substrates, and tetra substituted olefins are now within the scope of the reaction. Due to this "sulfonamide effect", most AD reactions can be carried out at 0°C rather than at room temperature, which may have beneficial effect on the selectivity.[13] For terminal olefins, $MeSO_2NH_2$ is not recommended. Surprisingly, terminal olefins actually react slower in the presence of $MeSO_2NH_2$ However this weak inhibitory effect is noticeable only if very small amount of OsO_4 (0.2 mol%) is employed.

Empirical rules for predicting the face selectivity

Despite the mechanistic investigations, the face selectivity of the dihydroxylation can reliably be predicted using an empirical 'mnemonic device'.[24] The plane of the olefin is divided into the four quadrants according to a simple set of rules. The SE quadrant is sterically inaccessible and, with few exceptions, no substituent other than hydrogen can be placed here. The NW quadrant, lying diagonally across from the SE quadrant, is slightly more open and the NE quadrant appears to be quite spacious. The SW quadrant is special in that its preferences are ligand dependent. Even though this SW quadrant normally accepts the largest group, especially in the case of PYR ligands, it is especially attractive for aromatic groups in the case of PHAL ligands.[15] An olefin which is placed into this olefin according to the above constraints receives the two OH groups from above, i.e. from the β-face, in the case of DHQD derived ligands and from the bottom, i.e. from the α-face, in the case of DHQ derivatives.

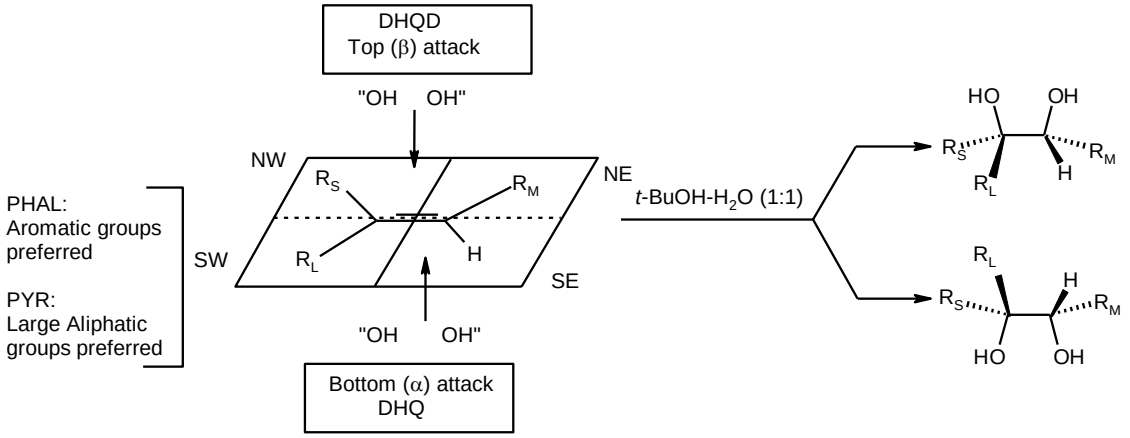
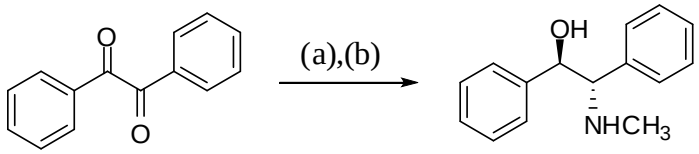


Figure 4. The mnemonic device for predicting the face selectivity.

2.Review of literature

Wheatley,W.B. *et al.* (1953)[26]

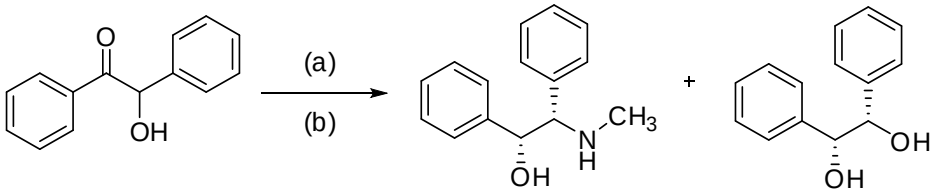
Wheatley,W.B. and co-workers was reported first to synthesize recemic Ephenamine **1** and its derivative. Recemic mixture of Ephenamine, *(R,S)*-2-methylamino-1,2-diphenyl ethanol, **2** has been synthesized from condensation of benzil **5** and methylamine followed by catalytic hydrogen in the presence of platinum or activated aluminum or Raney nickel.



5 **(±)-1**

Scheme 1: (a) CH_3NH_2, (b) H_2, Pt or Raney Ni or activated Ni.

Wheatly and co-workers synthesized recemic Ephenmaine **2** and **3** from the condensation of benzoin **6** and methylamine followed by the catalytic hydrogenation with Raney nickel, albeit with a lower yield(55%) and meso-hydrobenzoin as a by-product.

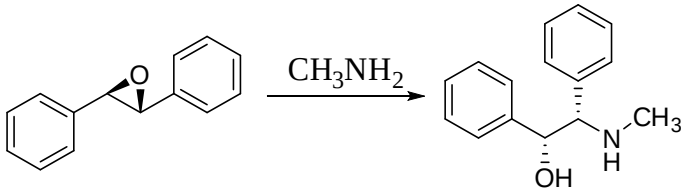


6 **(±)-1** **(±)-7**

Scheme 2: (a) CH_3NH_2, (b) H_2, Pt or Raney Ni

Anderson,W.K. *et al.* (1986)[27]

Anderson,W.K. and co-workers also synthesized Ephenamine **1** by the opening of trans-stilbene oxide **8** with methylamine.

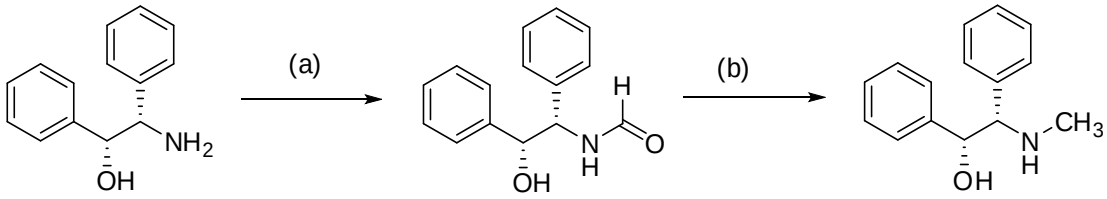


8 **(±)-1**

Scheme 3:

Effenberger, F *et al.* (1997)[28-29]

Effenberger, F and co-workers prepared the optically pure ephenamine **1** by following the Tishler synthesis of erythro-1,2-diphenyl-2-aminoethanol **9** followed by *N*-formylation with acetic formic anhydride resulting N-(2-hydroxy-1,2-diphenyl)formamide **10** then by reduction with lithium aluminum hydride.



9 **10** **1**

Scheme 4: (a) Acetic formic anhydride, Et_2O at -40^0 C (b) $LiAlH_4$, THF.

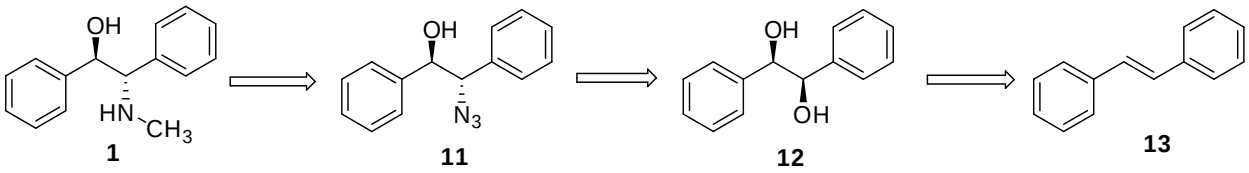
3. Present work

3.1. Objective:

Various methods for the synthesis of Ephenamine have been well-documented in the literature. Most of the approaches gave recemic Ephenamine and those approaches which gave optically pure Ephenamine were using chiral pool starting material. As part of our research program aimed at developing enantioselective synthesis of Ephenamine, we became interested in developing an efficient synthetic route using achiral starting material. Herein, we wish to report a new synthetic approach for Ephenamine using Sharpless asymmetric dihydroxylation and regioselective nucleophilic opening of cyclic sulfite as the key steps.

3.2. Retro Synthetic Approach:

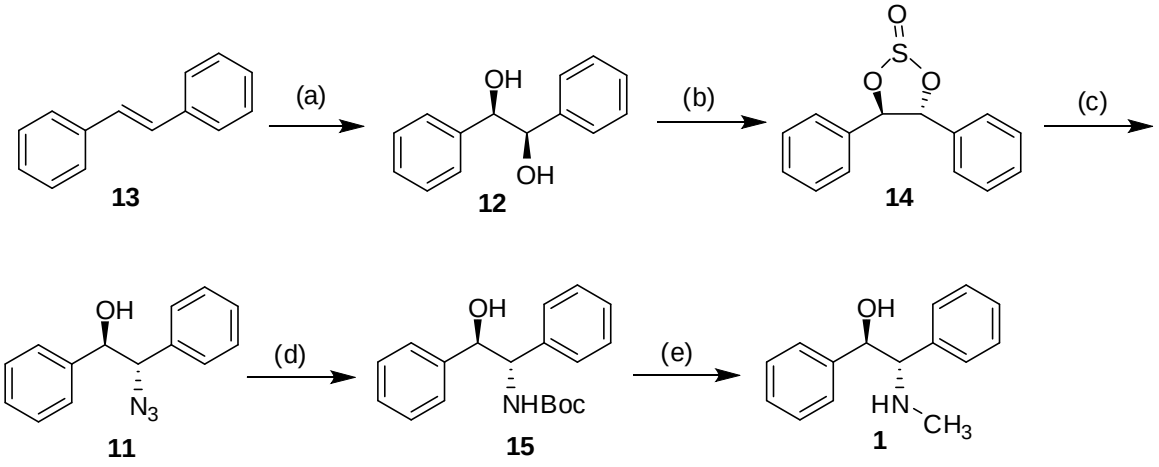
The retrosynthesis of *(1R,2S)*-2-(methylamino)-1,2-diphenylethanol **1** is outlined in the Scheme **5**. Ephenamine **1** could be obtained from the reduction of Boc protected amine with LAH which in turn could be prepared by catalytic reduction of azide **11**. Azide **11** could be prepared by opening of cyclic sulfite prepared from diol **12** using Sharpless asymmetric dihydroxylation.



Scheme 5: Retrosynthesis of Ephenamine.

4. Results and discussion

A synthesis has been designed herein for *(1R,2S)*-2-(methylamino)-1,2-diphenylethanol **1** which was prepared from the commercially available stilbene as shown in the Scheme 6. The stilbene **13** on treatment with osmium tetraoxide and potassium ferricyanide as co-oxidant, in the presence of $(DHQ)_2PHAL$ under Sharpless asymmetric conditions, gave diol **12** in 97% yield with 98% ee $[\alpha]_D$ = , Lit.,$[\alpha]_D^{25}$ = +90.0^o (c 1.2, EtOH) . The physical and spectroscopic data were in full agreement with the literature. With enantiomerically pure *(1R,2R)*-1,2-diphenylethane-1,2-diol **12** in hand ,we then subjected it to thionyl chloride to afford 1**4** which on subsequent treatment with NaN_3 afforded *(1R,2S)*-2-azido-1,2-diphenylethanol **11**. The azide **11** on treatment with palladium-carbon under hydrogen atmosphere in presence of Boc anhydride afforded Boc protected derivative which on LAH reduction afforded *(1R,2S*)-2-(methylamino)-1,2-diphenylethanol **1** as desired product.



Scheme 6: Synthesis of ephenamine (a) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$, *t*-BuOH, H_2O, OsO_4,$CH_3SO_2NH_2$, Na_2SO_3; (b) ET_3N, $SOCl_2$, DCM; (c) NaN_3, DMF; (d) Pd/c, $(Boc)_2$, EtOAc; (e) LAH, THF.

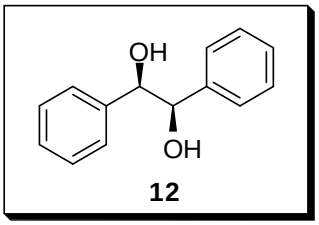
The ^{1}H NMR spectrum of 1,2-diphenylethane-1,2-diol **12** showed hydroxyl proton at 2.83 (br, 2H), benzylic proton at 4.72 (s, 2H), aromatic proton at 7.12-7.26 (m, 10H) ppm. The ^{13}C NMR spectrum of 1,2-diphenylethane-1,2-diol **12** showed benzylic carbon at 79.0, ortho carbons at 126.8, para carbons at 127.8, meta carbons at 128.0 and carbon directly attached to benzylic carbon at 139.7 ppm. The ^{1}H NMR spectrum of cyclic sulfite **14** showed benzylic protons at 5.21 (d, *J*=10 Hz, 1H) and at 5.69 (d, *J*=9.64 Hz, 1H), aromatic protons at 7.24-7.39 (m, 10H) ppm. The ^{13}C NMR spectrum of cyclic sulfite **14** showed benzylic carbon at 85.9 and 91.1, ortho carbons at 127.1 and 127.5, para carbons at 128.8 and 128.9, meta carbons at 129.3 and 129.6, carbons attached to benzylic carbon at 132.0 and 133.1 ppm. The ^{1}H NMR spectrum of 2-azido-1,2-diphenylethanol **11** showed hydroxyl proton at 2.13 (br, 1H), benzylic proton attached to azide at 4.69 (d, *J*=6.88 Hz, 1H), benzylic proton attached to hydroxyl group at 4.83 (d, *J*=6.88 Hz, 1H), aromatic proton at 7.25-7.37 (m, 10H) ppm. The ^{1}H NMR spectrum of tert-butyl (1S,2R)-2-hydroxy-1,2-diphenylcarbamate **15** showed proton of t-butoxy group at 1.59 (s, 9H), proton of hydroxyl group at 2.7 (br, 1H), benzylic proton attached to hydroxyl group at 5.1 (d, 1H), benzylic proton attached to Boc protected amine at 5.3 (d, 1H) and aromatic protons at 7.23-7.26 (m, 10H) ppm. The ^{1}H NMR spectrum of (1R,2S)-2-(methylamino)-1,2-diphenylethanol **1** showed proton of amino group at 1.2 (br, 1H), proton of methyl group attached to amine at 2.49 (s, 3H), benzylic proton attached to methyl amine at 4.47 (d, *J*=8 Hz, 1H), benzylic proton attached to hydroxyl group 5.3 (d, *J*=8 Hz, 1H), proton of hydroxyl group at 4.64 (d, 1H), aromatic protons at 7.0-7.4 (m, 10H) ppm.

5. Conclusion:

In conclusion, a pratical and highly enantioselective synthesis of Ephenamine **1** has been achieved by applying Sharpless asymmetric dihydroxylationand cyclic sulfite methodology as the key step. The merits of this synthetic approach is high enantioselective with high yielding steps. This synthetic strategy has significant potential for further extension to other seteroisomers via double inversion at the α-carbon. Currently work is in progress in this direction.

6. Experimental section

6.1*(1R,2R)*-1,2-diphenylethane-1,2-diol (12)



12

To a mixture of $K_3Fe(CN)_6$ (10.95 g, 33.28 mmol), K_2CO_3 (4.60 g, 33.28 mmol) and $(DHQ)_2PHAL$ (0.08 g, 1 mol%), in *t*-BuOH/H_2O (1:1,60 mL) cooled at 0^oC was added OsO_4 (0.56 mL, 0.1 M solution in toluene, 0.5 mol%) followed by methanesulfonamide (1.05 g, 11.09 mmol). After being stirred for 2 min at 0^oC, the olefin (2.0 g, 11.09 mmol) was added in one portion. The reaction mixture was stirred at 0^oC for 24 h and then quenched with solid sodium sulfite (4.00 g). The stirring was continued for an additional 45 min, and then the solution was extracted with EtOAc (3 x 10 mL) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc as eluent gave the diol as a white solid.

Yield: 2.32 g, 97%

Mol. Formula: $C_{14}H_{14}O$

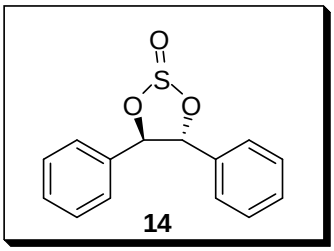
^{1}H NMR (400Hz, $CDCl_3$): δ 2.83 (br, 2H), 4.72 (s, 2H), 7.12-7.26 (m, 10H).

^{13}C NMR (100MHz, $CDCl_3$): δ 79.0, 126.8, 127.8, 128.0, 139.7.

$[\alpha]_D$: ,

Lit.,$[\alpha]_D^{25}$: $+90.0^o$ (c 1.2, EtOH).

6.2 Cyclic sulfite (14)



14

To a stirred solution of diol **12** (1.50 g, 7 mmol) in dry CH_2Cl_2 (25 mL) cooled at 0^oC were added Et_3N (1.94 mL, 1.41 g, 14 mmol) and a solution of $SOCl_2$ (0.91 g, 0.55 mL, 7.7 mmol) added over a period of 10 min. Stirring was continued for 20 min at 0^oC and then the

solution was quenched by adding water and extracted with CH_2Cl_2. The organic layer was separated and the filtrate was concentrated to give cyclic sulfite as a solid.

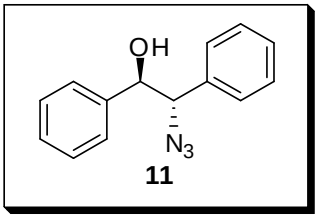
Yield: 1.47 g, 81%

Mol. Formula: $C_{14}H_{12}O_3S$

^{1}H NMR (400Hz, $CDCl_3$): δ 5.21 (d, J=10 Hz, 1H), 5.69 (d, J=9.64 Hz, 1H), 7.24-7.39 (m, 10H).

^{13}C NMR (100MHz, $CDCl_3$): δ 85.9, 91.1, 127.1, 127.5, 128.8, 128.9, 129.3, 129.6, 132.0, 133.0 ppm.

6.3 *(1R, 2S)*-2-azido-1,2-diphenylethanol (11)



11

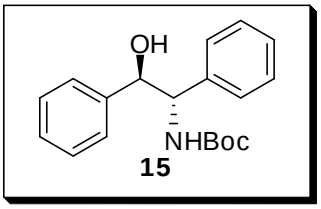
To a solution of cyclic sulfite **14** (1.7 g, 6.505 mmol) in dry DMF (10 mL) was added NaN_3 (1.26 g, 19.51 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 20 h under argon. The solvent was removed under reduced pressure and to the residue, was added 20% aq. H_2SO_4:Et_2O (1:1, 10 mL) and stirred at room temperature for 12 h. Excess $NaHCO_3$ was added to it and the reaction mixture was stirred for 20 min and then extracted with ether (3 x 20 mL). The organic layer was separated. Removal of solvent afforded the crude product as a dark yellow oil which was purified on a silica gel column using petroleum ether:EtOAc as eluent to give azido alcohol.

Yield: 1g, 80%

Mol. Formula: $C_{14}H_{13}N_3O$

^{1}H NMR (400Hz, $CDCl_3$): δ 2.13 (br, 1H), 4.69 (d, J=6.88, 1H), 4.83 (d, J=6.88, 1H), 7.25-7.37 (m, 10 H).

6.4 tert-butyl *(1S,2R)*-2-hydroxy-1,2-diphenylcarbamate (15)



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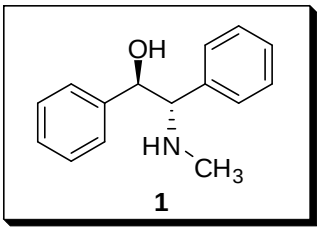
To a solution of azide **4c** (0.4 g, 1.67 mmol) in ethyl acetate was added 10% Pd/C (25 mg) and Boc_2O (0.95 mL 4.34 mmol). The resulting solution was stirred under hydrogen atmosphere for 12 h at room temperature until disappearance of the azido alcohol as monitored by TLC. The reaction mixture was filtered through a celite pad to remove the catalyst and the filtrate was concentrated in vacuo. Silica gel column chromatography of the crude product using EtOAc/pet ether (3:7) as eluent gave (0.24 g) as a white solid.

Yield: 0.4 g, 76%

Mol. Formula: $C_{19}H_{23}NO_3$

^{1}H NMR (400Hz, $CDCl_3$): δ 1.59 (s, 9H), 2.7 (br, 1H), 5.1 (d, 1H), 5.3 (d, 1H), 7.23-7.26 (m, 10 H).

6.5 *(1R,2S)*-2-(methylamino)-1,2-diphenylethanol (1)



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To a solution of **15** (0.5 g, 1.59 mmol) in dry THF (20 mL), LAH (0.30 g, 7.97 mmol) was added. The resulting solution was refluxed under hydrogen atmosphere for 12 h. Then solution was quenched with 10% NaOH and extracted with etheyl acetate. The organic layer was separated. Removal of solvent afforded the crude product as white solid which was purified by silica gel chromatography using methanol:DCM (0.1:10).

Yield : 0.265 g, 60%

Mol. Formula : $C_{15}H_{17}NO$

^{1}H NMR (400Hz, DMSO-d_6): δ 1.2(br,1H), 2.49 (s, 3H), 4.47 (d, *J*=8 Hz, 1H), 4.64 (br,1H), 5.3 (d, *J*=8Hz, 1H), 7.0-7.4 (m,10H).

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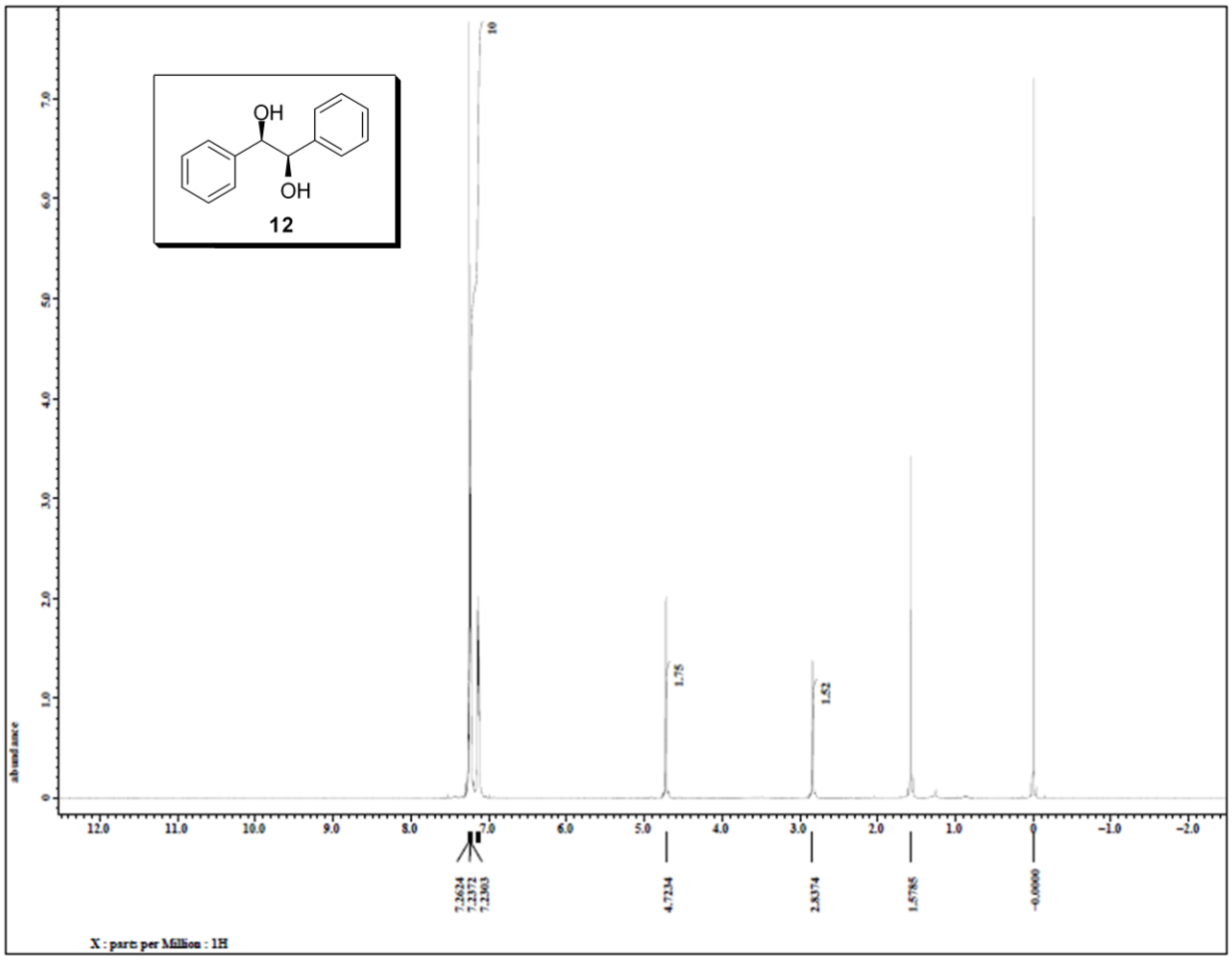
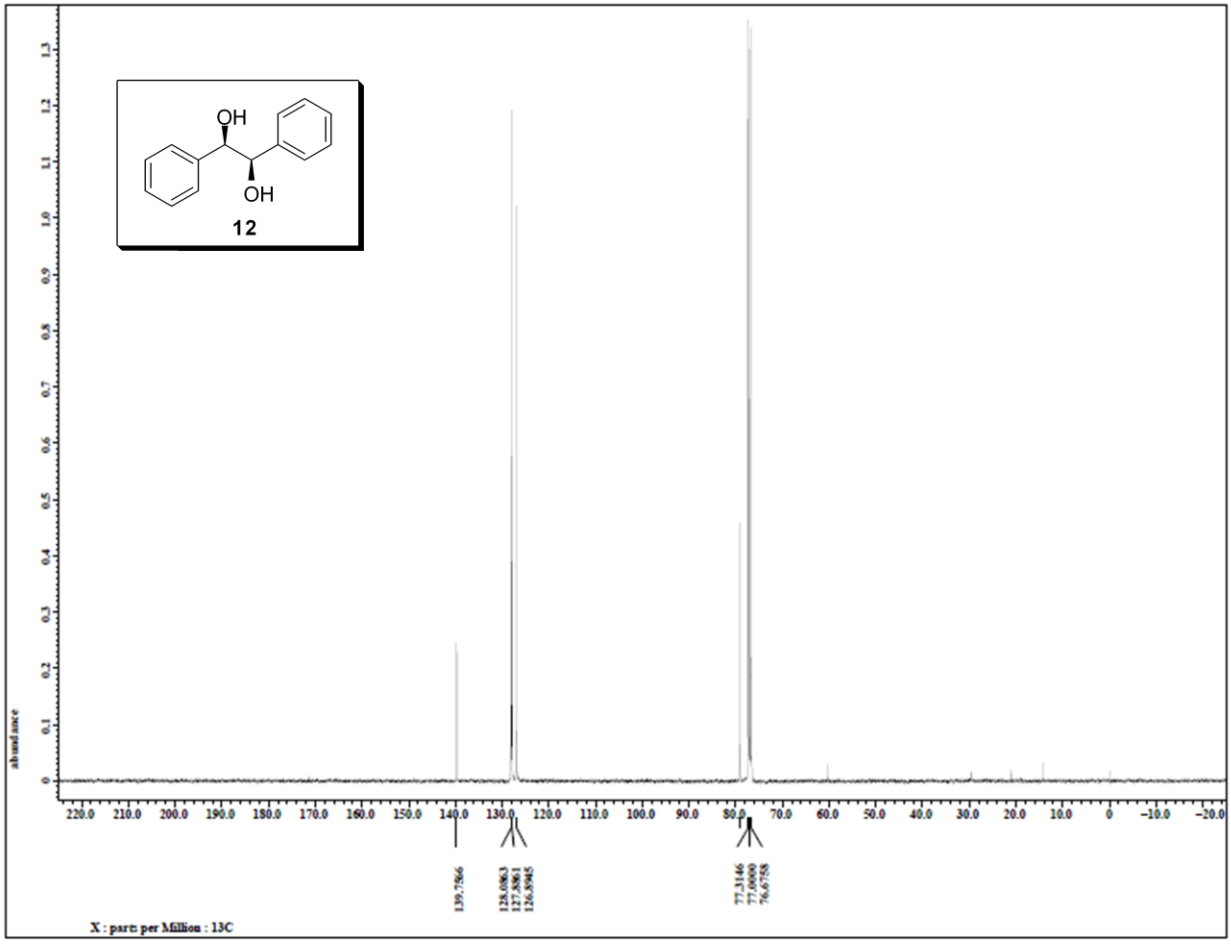
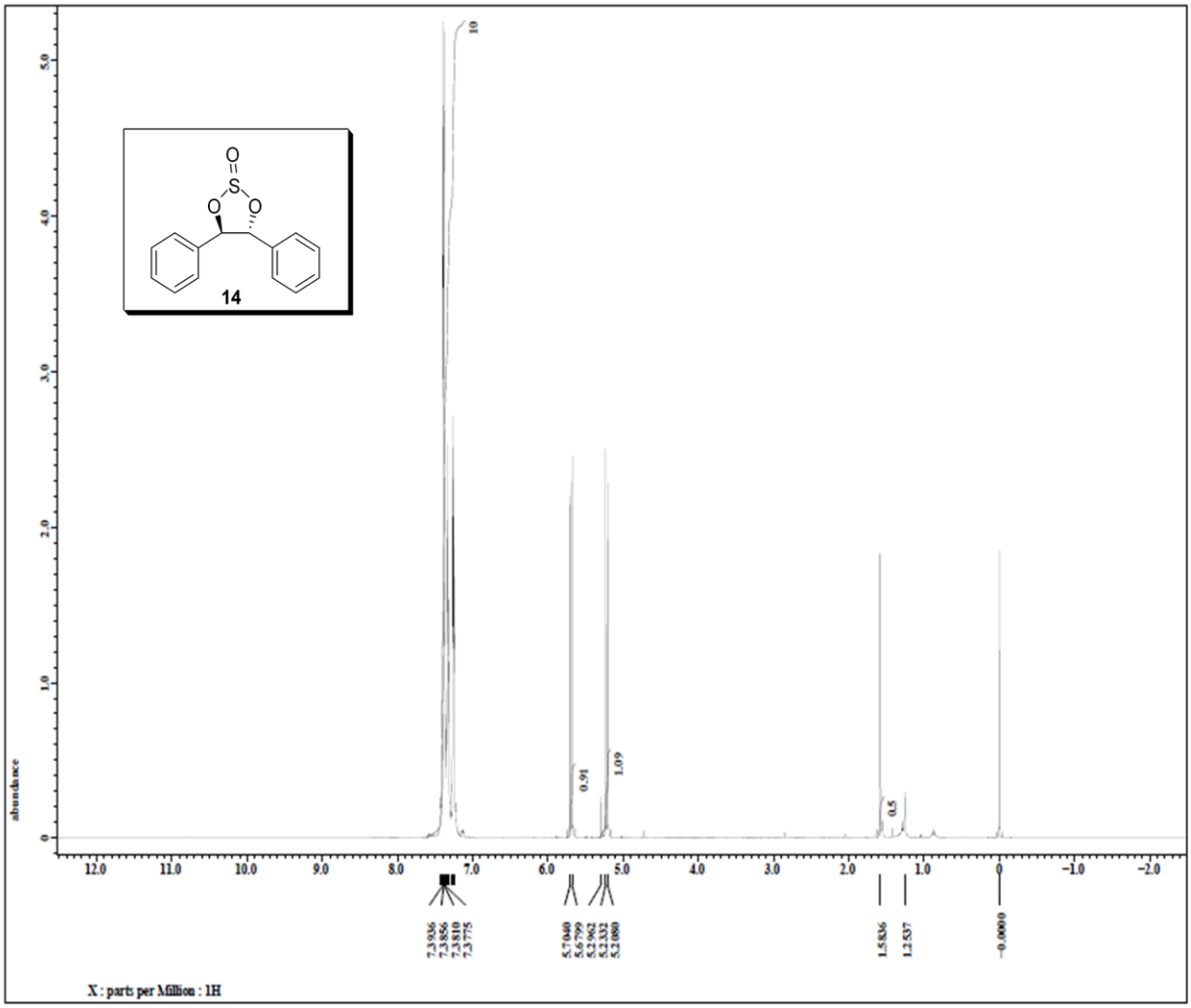
^{1}H-NMR of (*1R,2R*)-1,2-diphenylethane-1,2-diol



^{13}C-NMR of (*1R,2R*)-1,2-diphenylethane-1,2-diol



^{1}H-NMR of Cyclic sulfite



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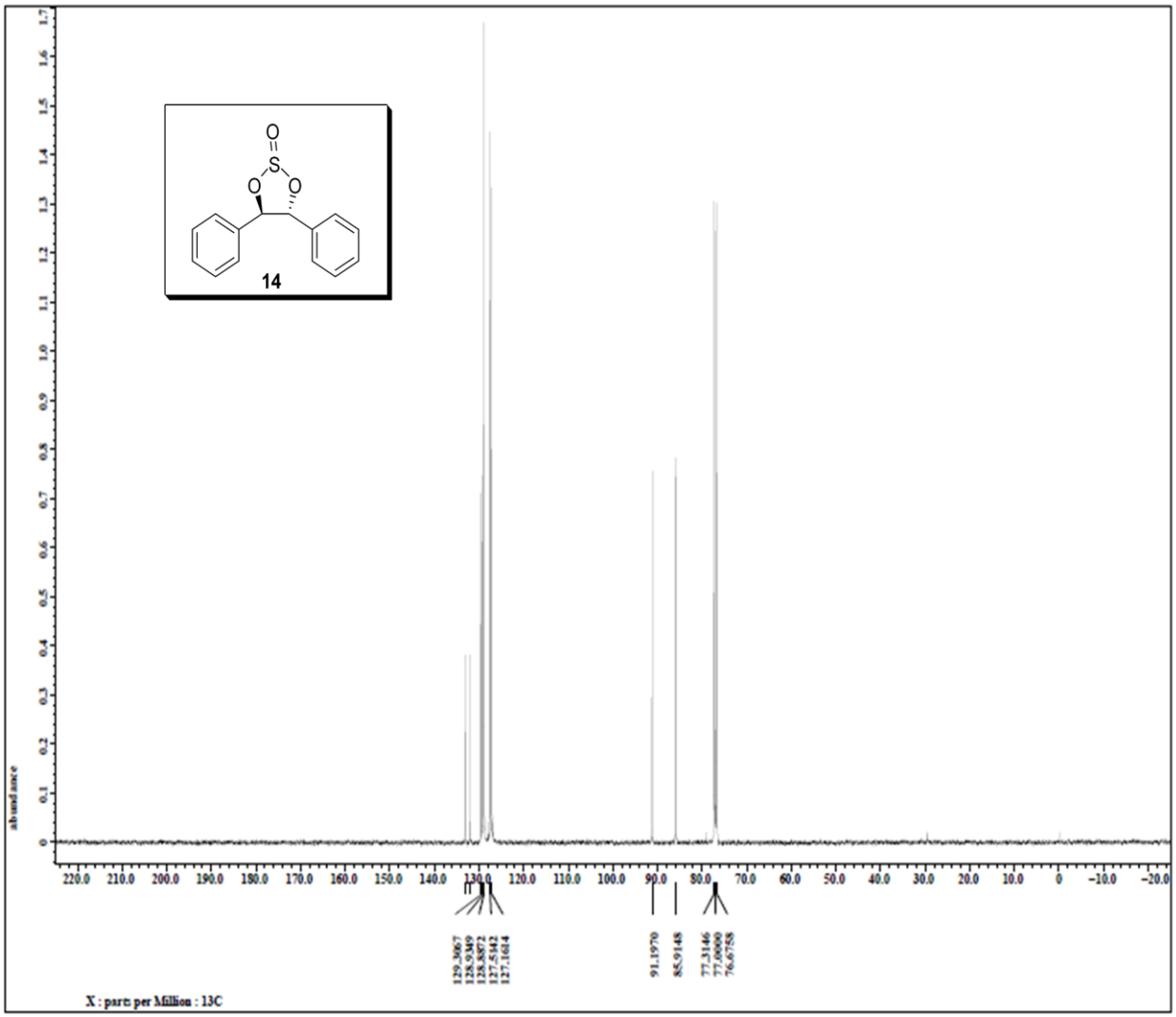
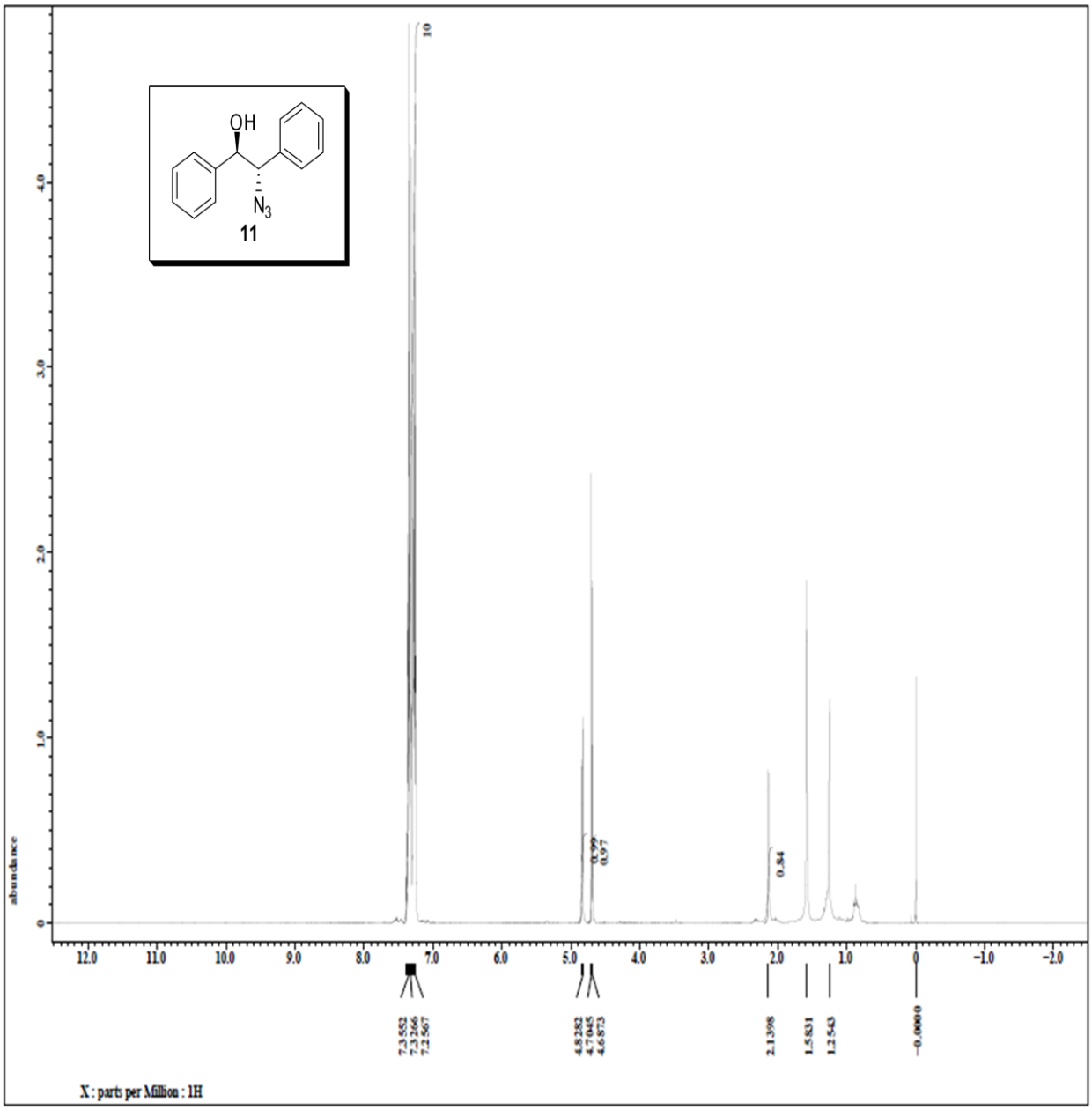
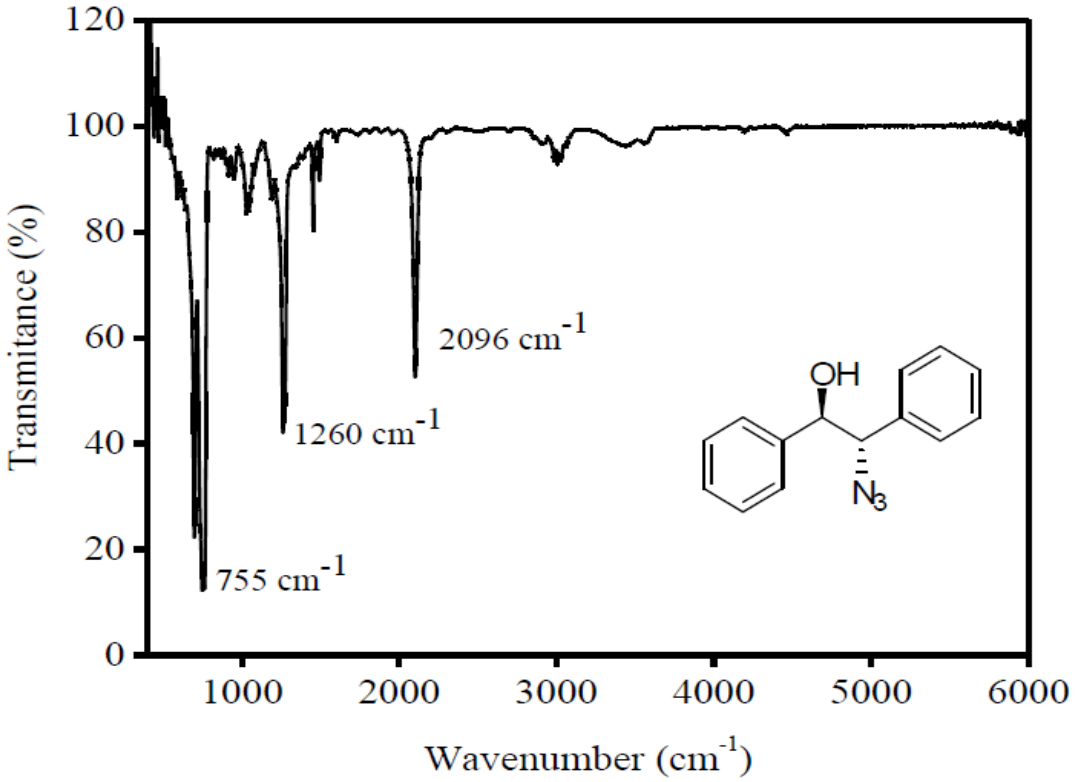


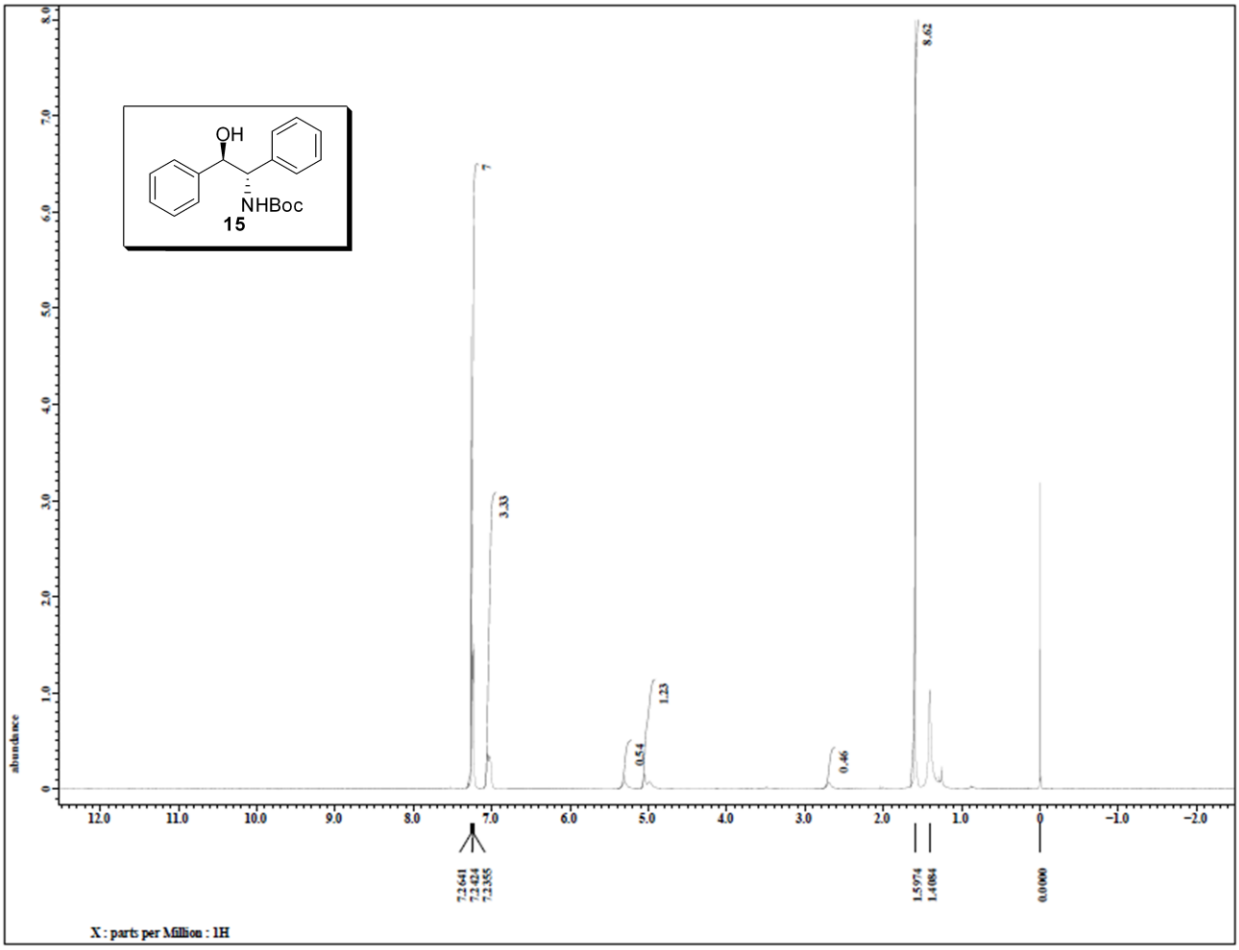
^{1}H-NMR of (*1R,2S*)-2-azido-1,2-diphenylethanol



IR spectra of (*1R,2S*)-2-azido-1,2-diphenylethanol



^{1}H-NMR of tert-butyl (*1S,2R*)-2-hydroxy-1,2-diphenylcarbamate



^{1}H-NMR of (*1R,2S*)-2-(methylamino)-1,2-diphenylethanol