1-Benzyl-2-methylindole (10g). ^{1}H NMR δ 2.31 (s, 3 H), 5.19 (s, 2H), 6.71-7.61 (m, 10H); ^{13}C NMR δ 49.7, 54.2, 100.4, 109.1, 119.5, 119.7, 120.7, 125.9, 126.7, 127.2, 128.1, 128.7, 136.7, 137.9; MS m/z (relative intensity) 221 (M^+, 41), 92 (100), 91 (73).

Acknowledgment. The authors are grateful to KOSEF-OCRC and Ministry of Education (BSRI-96-3408) for financial support.

References

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. Robinson, B. *Chem. Rev.* **1963**, *63*, 373; **1969**, *69*, 227.
3. Remers, W. A. *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, p 317.
4. (a) Remers, W. A. *Heterocyclic Compounds*; Houlihan, W. J., Ed.; Wiley-Interscience: New York, 1972; Vol. 25, p 385. (b) Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S.; Koletar, G. *J. Org. Chem.* **1973**, *38*, 3004.
5. Jpn. Kokai, 72-33355; *Chem. Abst.* **1972**, *77*, 164472w.
6. (a) Jpn. Kokai, 81-63958; *Chem. Abst.* **1981**, *95*, 150441v. (b) Jpn. Kokai, 83-32863; *Chem. Abst.* **1983**, *99*, 55378d. (c) U.S. Patent 1984, 4436917; *Chem. Abstr.* **1984**, *101*, 7024y.
7. Jpn. Kokai, 81-61353; *Chem. Abst.* **1981**, *95*, 115293b.
8. (a) Isomura, K.; Uto, K.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1977**, 664. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800. (c) Harrington, P. J.; Hegedus, L. S. *J. Org. Chem.* **1984**, *49*, 2657. (d) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (e) Etkin, N.; Babu, S. D.; Fooks, C. J.; Durst, T. *J. Org. Chem.* **1990**, *55*, 1093. (f) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (g) Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* **1994**, *59*, 3375.
9. (a) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *Tetrahedron Lett.* **1986**, *27*, 377. (b) Tsuji, Y.; Huh, K.-T.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 1673.
10. Preliminary communication of this work: Shim, S. C.; Youn, Y. Z.; Lee, D. Y.; Kim, T. J.; Cho, C. S.; Uemura, S.; Watanabe, Y. *Synth. Commun.* **1996**, *26*, 1349.
11. Murahashi, S.; Yano, T. *J. Am. Chem. Soc.* **1980**, *102*, 2456.
12. Murahashi, S.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229.
13. Watanabe, Y.; Tsuji, Y.; Ohsugi, Y. *Tetrahedron Lett.* **1981**, *22*, 2667.
14. Huh, K.-T.; Tsuji, Y.; Kobayashi, M.; Okuda, F.; Watanabe, Y. *Chem. Lett.* **1988**, 449.
15. Watanabe, Y.; Morisaki, Y.; Kondo, T.; Mitsudo, T. *J. Org. Chem.* **1996**, *61*, 4214.
16. Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.
17. Tsuji, Y.; Huh, K.-T.; Ohsugi, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1365.
18. Hallmann, P. S.; Stephenson, T. A.; Wilkinson, G. *Inorg. Synth.* **1970**, *12*, 237.

Chiral β-Amino Thiol Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

Jahyo Kang*, Jeong Whan Kim, Jun Won Lee, Dong Soo Kim, and Joo In Kim

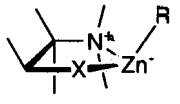
Department of Chemistry, Sogang University, Seoul 121-742, Korea

Received August 12, 1996

Reaction of diethylzinc with α-branched aldehydes in the presence of a catalytic amount (5 mol %) of various β-amino thiols in toluene or ether provided the corresponding secondary alcohols in outstanding ee. Detailed preparative procedure for the β-amino thiols are presented.

Introduction

The discovery of catalytic asymmetric addition of alkyl groups of dialkylzinc reagents to carbonyl carbon of aldehyde in the presence of β-amino alcohols[1] has given an explosive impetus to the highly successful development of synthetic methodologies of optically active secondary alcohols.[2] The β-amino alcohols behave as a ligand, forming an oxazazincolidine species **1** which is an active catalyst upon the interaction of dialkylzinc.[2] In search of a catalyst which would give *non-substrate-specifically* the absolute optical purity, we have found that chiral amino thiols containing cyclic amines could be employed as the ligand to form such a catalyst. And those chiral amino thiols were supposed to have the following features: 1) enhanced polarizability of sulfur (thiol) as compared to oxygen (alcohol), 2) the heterocyclic nature of the ligand ring as a face blocker, 3) high affinity of thiol and thiolate toward metals, especially for zinc, and 4) less tendency of



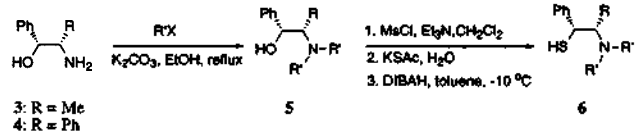
1: X = O

2: X = S

metal thiolates to diminish the Lewis acidity of the metal as compared to metal alcoholate.[3] Herein are reported the preparations of various β-amino thiols and the effects of their structures on the catalytic behavior.

Results and Discussion

Preparation of Chiral β-Amino Thiol Ligands. As shown in Scheme 1, chiral β-amino thiols, **6**, were synthesized from (1*R*,2*S*)-(−)-norephedrine **3** or (1*R*,2*S*)-(−)-1,2-diphenyl-2-amino-1-ethanol **4**, which were alkylated with 2 equiv. alkyl bromide.[4] The resulting (1*R*,2*S*)-(−)-1-phenyl-2-(dialkylamino)-1-ethanols **5** were mesylated, which was followed by displacement of the mesylate with potassium thioacetate to give the corresponding thioacetate with *retention of configuration*. Subsequent treatment of the thioacetate with DIBAH gave the β-amino thiols **6**. The amino thiols **6** were stored under nitrogen atmosphere in benzene below 0 ℃ due to their sensitivity toward air oxidation to the corresponding disulfide.



Scheme 1.

Thus, various β-amino thiols were synthesized by following this standard procedure as illustrated in Chart 1.

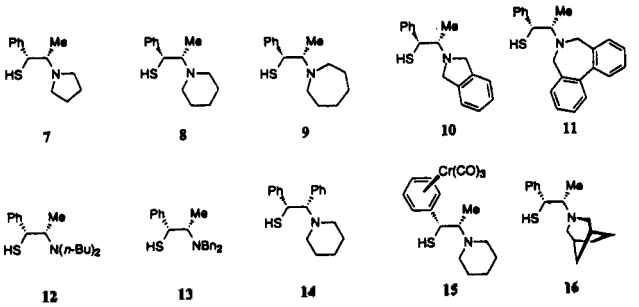
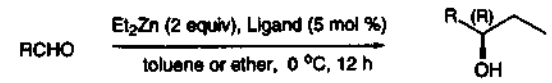


Chart 1.

Catalytic Asymmetric Addition. The optimum reaction condition for the application of the β-amino thiols **6** as a catalyst for enantioselective addition of diethylzinc to aldehydes was the one at 0 ℃ in the presence of 5 mol % of the chiral ligand in toluene or ether. Especially, the inclusion of ether as one of the preferred solvents makes it possible to utilize other commercially unavailable dialkylzinc reagents, which can be prepared from alkyllithium, Grignard reagents or alkyl iodides.[5] Consequently, enantioselective addition of diethylzinc to four representative aldehydes using 5 mol % of the ligands, **7-14**, **15**,[6] and **16** at 0 ℃ was studied to find out the best ligand in the series. And the ligands- **7**, **8**, **10**, **12**, and **14**- were found to be the best ligands for the operation, which gave consistently optically active carbinol with high enantiomeric purity (Table 1).

Table 1. Enantiomeric Excesses[a] of the Product Alcohol in the Reaction of Diethylzinc with Representative Aldehydes in the Presence of 5 mol % of Ligand in Toluene at 0 ℃

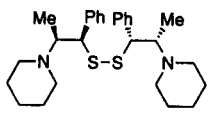


Ligands	PhCHO	*trans*-PhCH=CHCHO	ChCHO	2-NpCHO
7	99	78	99	99
8	100	79	100	99
9	86	74	97	96
10	97	72	96	97
11	73	66	97	96
12	99	81	100	98
13	72	72	97	95
14	100	79		100
15		69		
16		75		

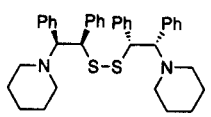
[a] Ee's were determined by chiral HPLC or GC of alcohol. For detailed condition, see footnotes of Table 2.

Consequently, enantioselective addition of diethylzinc to aldehydes using 5 mol % of the ligand **8** at 0 ℃ was studied (Table 2).[3] Under the standard condition (ether or toluene, 5 mol % of the ligand **8**, 0 ℃), all the aromatic aldehydes examined afforded the corresponding secondary alcohols with *R* configuration in high optical purity (more than 99 : 1). Similarly, some aliphatic aldehydes with exceptions of hexanal and *trans*-cinnamaldehyde were ethylated in 100% ee. Consequently, for an excellent asymmetric reaction with the present system, the aldehyde should be α-branched. Thus the steric factor seems to dominate over the electronic one. Nevertheless, to the best of our knowledge, the asymmetric induction to such a degree has not been achieved with other ligand system.

Thiol *vs.* Disulfide. During the above studies it was found that the thiol **8** contaminated with the corresponding disulfide **17** gave inferior reaction rate and enantioselectivity. Thus, the disulfides somehow interfered the reaction. However it was later reported enlighteningly by Kellogg that disulfides could be converted in part to thiols by the reaction with diethylzinc, which would form the same thiazazincolidine catalyst.[14] This finding was important. But contrary to our results, disulfides were claimed to be better than thiols.



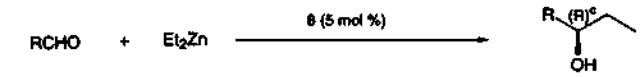
17



18

As shown in Scheme 2, the chiral β-amino thiol disulfide **18** was synthesized as a white crystal in 83% yield. Consequently, the asymmetric addition of diethylzinc to aldehydes in the presence of a catalytic amount of the β-amino thiol **14** or the corresponding disulfide **18** was carried out with two objectives; whether the amino thiol ligands derived from

Table 2. Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of Ligand 8



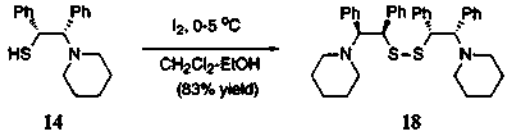
R in RCHO	Temp (℃)	Time (h)	Yield (solvent)[a] (%)	Analysis Method[b]	ee[c] (%)
Ph	0	12	94(tol), 92(eth)	A, B	100[d]
2-$MeOC_6H_4$	0	12	96(tol), 90(eth)	A	100[d]
4-$MeOC_6H_4$	0	12	95(tol), 96(eth)	A	100[d]
4-ClC_6H_4	0	12	99(tol), 89(eth)	A	100[h]
4-FC_6H_4	0	12	92(tol), 91(eth)	A	100[d,i]
2-naphthyl	0	12	98(tol)	B	99[k]
1-naphthyl	0	12	100(tol), 93(eth)	B	99[l]
ferrocenyl	20	12	98(tol)	D	98[m]
t-Bu	0	12	94[d](tol), 90(eth)	E	100
cyclohexyl	0	12	97(tol)	E	100
n-pentyl	−10 or 0		92-6(tol)	F	62-65
trans-PhCH=CH	−50 or 0		92-8(tol)	C	68-77

[a]Solvent (tol: toluene, eth: ether). [b]Enantiomeric excess was determined by chiral HPLC or chiral GC of alcohol formed unless specified otherwise. [A, Chiraldex B-PH (GC); B, Daicel Chiralcel OB (HPLC); C, Daicel Chiralcel OD (HPLC); D, Daicel Chiralcel OF (HPLC); E, Chiraldex B-PH of benzoate ester of the alcohol, GC; F, Chiraldex B-PH of MTPA ester of the alcohol, GC]. [c]Isolated yields. [d]Determined by GC using *n*-dodecane as an internal standard. [e]$[\alpha]_D^{25}=+46.0$ (5.2, $CHCl_3$), [lit. for S isomer $[\alpha]_D^{25}=-45.45$ (5.2, $CHCl_3$)].[7] [f]$[\alpha]_D^{25}=+53.3$ (3.0, Toluene), [lit. $[\alpha]_D^{25}=+47.0$ (1.2, Toluene) for 87% ee].[8] [g]$[\alpha]_D^{25}=+35.5$ (4.14, Benzene), [lit. for S isomer of 51% ee, $[\alpha]_D^{25}=-17.2$ (5, Benzene)].[9] [h]$[\alpha]_D^{25}=+28.0$ (5.0, Benzene), [lit. for S isomer of 43% ee, $[\alpha]_D^{2}=-10.4$ (5, Benzene)].[9] [i]$[\alpha]_D^{25}=+51.2$ (2.5, $CHCl_3$).[10] [j]Configuration presumed. [k]$[\alpha]_D^{25}=+29.8$ (4.7, Benzene), [lit. for S isomer of 97% ee, $[\alpha]_D^{25}=-26.6$ (3.35, Benzene)].[11] [l]$[\alpha]_D^{25}=+55.6$ (2.4, $CHCl_3$), [lit. $[\alpha]_D^{25}=+36.3$ (2.14, $CHCl_3$) for 62% ee].[12] [m]$[\alpha]_D^{25}=-57.5$ (1.1, Benzene), [lit. $[\alpha]_D^{25}=-57.5$ (1.0, Benzene) for 96% ee].[13]

Table 3. Enantioselective Addition of Diethylzinc in the Presence of Thiol 14 or Disulfide 17

R in RCHO	With Disulfide (**18**) Time (h)[a]	Yield (%)[b]	ee (%)[c]	With Thiol (**14**) Time (h)[a]	Yield (%)[b]	ee (%)[c]	Analysis Method[d]
Ph	30	92	99	12	90	100	A, B
4-ClC_6H_4	28	93	99	12	92	100	A
2-$MeOC_6H_4$	28	92	98	12	92	99	A
4-$MeOC_6H_4$	28	91	99	12	91	99	A
2-naphthyl	28	93	98	12	98	100	B
ferrocenyl	18[e]	89	98	12[e]	89	100	C
t-Bu	24	63[f]	99	12	83[f]	100	D
cyclohexyl	24	92	98	12	87	100	D
n-pentyl	20	89	87	12	88	79	E
t-PhCH=CH	20[e]	93	83	12[e]	88	80	F

[a]Reactions were carried out in toluene at 0 ℃ in the presence of 5.0 mol % of thiol **14** or 2.5 mol % of disulfide **18** unless specified otherwise. [b]Isolated yields after the reaction unless specified otherwise. [c]Absolute configuration (*R*) was determined by comparison with the known optical rotation and chromatographic retention values. [d]Enantiomeric excess was determined by chiral HPLC or chiral GC of alcohol formed unless specified otherwise. [e]Reaction at room temperature. [f]Determined by GC using *n*-dodecane as an internal standard.



14 18

Scheme 2.

the readily available *erythro*-1,2-diphenyl-2-amino-1-ethanol would function as effective ligands and which form, thiols or disulfides, would be the better ligand.

The reaction with the disulfide ligand **18** was slower than that with the corresponding thiol ligands **8** or **14**. Thus, regardless of solvent, more than 28 h was required to complete reaction at 0 ℃. And, the enantioselectivity with this disulfide in the reaction with α-branched aldehydes was acceptable but slightly inferior to that with the thiol ligands, **8** or **14**.

Even with the excellent results with the disulfide, the choice between the β-amino thiol and the corresponding disulfide compounds as a ligand for the addition of organozinc

reagents especially to α-branched aldehydes is certainly dictated by the convenient reaction rates and higher enantioselectivity. In this regard, the thiols are better. However, the disulfides which have better chemical stability can also be used even with some sacrifice of reaction rate and enantioselectivity.

Conclusion. Even though β-amino thiols are chemically labile toward air oxidation to the corresponding disulfides, the reactions of dialkylzinc with α-branched aldehydes in the presence of a catalytic amount (5 mol %) of a β-amino thiol or the corresponding disulfide in toluene or ether provided secondary alcohols in outstanding ee. Additionally, the actual catalyst, thiazazincolidine complex, was found to catalyze enantioselective reduction of *meso* *N*-phenylimides to the corresponding hydroxy lactam in high ee.[15] The physicochemical characteristics of the present catalytic system will be reported shortly.[16]

Experimental

General. All reactions involving organometallic reagents were carried out under an inert atmosphere of nitrogen. Tetrahydrofuran and diethyl ether were freshly distilled from sodium benzophenone ketyl and DMF from calcium hydride prior to use. Solvents and liquid reagents were transferred using hypodermic syringes. Alkyllithium solution (Aldrich) were assayed for active alkyl by titration with 2-butanol in tetrahydrofuran using 1,10-phenanthroline as an indicator. All other reagents and solvents used were reagent grade. Small and medium-scale purifications (20 mg-2 g) were performed by radial chromatography by using a Harrison Research Chromatotron on plates of 1-, 2-, or 4-mm thickness made with Merck silica 60 PF_{254} containing gypsum. Flash chromatography was performed on a Tokyo Rikagikai EF-10 with Merck 230-400 mesh silica gel. TLC data were obtained on Merck TLC with silica gel 60 F_{254}. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and all melting points were uncorrected. ^{1}H NMR spectra were obtained on a Varian Gemini 200 (200 MHz) or a Varian Gemini 300 (300 MHz) spectrometer. NMR Spectra were recorded in ppm (δ) relative to tetramethylsilane (δ 0.00) as an internal standard unless stated otherwise and are reported as follows: chemical shift, multiplicity (br= broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant and integration. Infrared spectra were obtained on a Mattson Galaxy 2000 spectrometer. Mass spectra were taken on a VG Trio 2000 (low resolution) spectrometers with an electron beam energy of 70 eV (EI or CI) and elemental analysis by Carlo Erba EA 1180 elemental analyzer. Optical rotations were obtained on a Rudolph Autopol III. digital polarimeter. Data are reported as follow: $[\alpha]_D^{25}$ (concentration g/100 mL, solvent). Optical purities (% ee) were determined by HPLC analyses using chiral column (Chiralcel, Daicel Chemical Co. Ltd.) and GC analyses using capillary chiral column (Chiraldex, Advanced Separation Technologies Inc.).

Preparation of (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl) propan-1-ol. A mixture of (1*R*,2*S*)-norephedrine (10 g, 66.1 mmol), 1,5-dibromopentane (18 mL, 132.9 mmol) and potassium carbonate (45.7 g, 330.7 mmol) in EtOH (70 mL) was refluxed for 24 h. The reaction mixture was hot-filtered through Celite pad and the resulting solution was cooled to room temperature. The filtrate was concentrated under reduced pressure. The precipitated product was collected by filtration. The solid was washed with cold *n*-hexane : ether (1 : 1) solution to give a white solid. Recrystallization from toluene gave the title compound as a white solid (11.1 g, 83%). mp 103-104 ℃. TLC (50% MeOH/EtOAc) R_f 0.4. IR (KBr) 3028, 1692 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, J=7.1 Hz, 3H), 1.44-1.48 (m, 2H), 1.55-1.62 (m, 4H), 2.47-2.52 (m, 4H), 2.68-2.72 (m, 1H), 4.83 (d, J=7.1 Hz, 1H), 7.23-7.33 (m, 5H). $[\alpha]_D^{25}$ −7.5 (c 4.1, MeOH). MS (m/z) 219 (M^+), 201, 186, 112, 77.

Preparation of (1*R*,2*S*)-1-Acetylthio-1-phenyl-2-(1-piperidinyl)propane. To a stirred solution of 1.6 g (7.3 mmol) of (1*R*,2*S*)-1-(phenyl-2-(1-piperidinyl))propan-1-ol and 1.52 mL (10.9 mmol) of triethylamine in 15 mL methylene chloride at −78 ℃ was added dropwise 0.62 mL (8.0 mmol) of methanesulfonyl chloride. The solution was stirred for 30 min at −78 ℃. The reaction mixture was evaporated under reduced pressure and the resulting residue was dissolved in 8 mL H_2O. To this solution potassium thioacetate (2.5 g, 21.9 mmol) was added in one portion. After stirring for 2 h at rt, the aqueous solution was extracted with methylene chloride (20 mL×3) and the organic layer was dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed to give 1.9 g (92%) of the thioacetate. TLC (20% EtOAc/*n*-Hexane) R_f 0.35. IR (neat) 3028, 2934, 1692 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.15-7.41 (m, 5H), 4.72 (d, J=7.0 Hz, 1H), 2.98 (m, 1H), 2.20-2.55 (m, 4H), 2.30 (s, 3H), 1.18-1.35 (m, 6H), 1.12 (d, J=7.0 Hz, 3H). MS (m/z) 277 (M^+).

Preparation of (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl) propan-1-thiol (8). DIBAH (1.4 M in toluene, 69 mL, 96.6 mmol) was added to toluene (100 mL) solution of thioacetate (13.4 g, 48.3 mmol) at −10 ℃. After being stirred for 2 h at −10 ℃, the reaction mixture was diluted with 100 mL ether. The reaction was quenched with H_2O with caution. The solution was warmed up to rt and allowed to stir for 2 h. The solution was filtered through Celite pad under inert atmosphere. The filtrate was dried over Na_2SO_4 and the solvent was evaporated. The crude oil was short path column on silica gel to give 11.2 g (97%) of amino thiol. This amino thiol was purified by distillation under reduced pressure (105 ℃, 0.1 mmHg) to afford **26** as a clear oil. TLC (20% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 3061, 2933, 2793, 2643 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.40 (m, 5H), 4.16 (d, J=6.9 Hz, 1H), 2.87 (m, 1H), 2.32-2.54 (m, 4H), 2.19 (br, 1H), 1.26-1.49 (m, 6H), 1.11 (d, J=6.9 Hz, 3H). $[\alpha]_D^{25}$ −66.9 (c 2.25, $CHCl_3$). MS (m/z) 202 (M^+-33), 121, 112.

Likewise, the following compounds were prepared.

Bis[(1*R*,2*S*)-1-phenyl-2-(1-piperidinyl)-1-propyl] Disulfide (17). TLC (20% EtOAc/*n*-Hexane) R_f 0.4. IR (naet) 2934, 1726 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, J=6.7 Hz, 6H), 1.16 (m, 12H), 2.05-2.40 (m, 8H), 2.90 (m, 2H), 3.26 (d, J=8.8 Hz, 2H), 6.95-7.30 (m, 10H). MS (m/z) 468 (M^+), 359.

(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-ol. Yield 42%, bp 108 ℃/0.2 mmHg., TLC (50% EtOAc/*n*-Hexane) R_f 0.35. IR (neat) 3420 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$)

δ 7.15-7.50 (m, 5H), 5.00 (d, J=3.2 Hz, 1H), 2.40-2.90 (m, 5H), 1.80-2.00 (m, 4H), 0.79 (d, J=6.6 Hz, 3H). $[\alpha]_D^{25}$ +13.1 (c 2.04, $CHCl_3$). MS (m/z) 205 (M^+).

(1*R*,2*S*)-1-Acetylthio-1-phenyl-2-(1-pyrrolidinyl)propane. Yield 70%. TLC (30% EtOAc/*n*-Hexane) R_f 0.35. IR (neat) 1692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, J=6.6 Hz, 3H), 1.80 (m, 4H), 2.34 (s, 3H), 2.40-2.90 (m, 5H), 5.50 (d, J=3.7 Hz, 1H), 7.2-7.5 (m, 5H). MS (m/z) 263 (M^+).

(1*R*,2*S*)-1-Phenyl-2-(1-pyrrolidinyl)propan-1-thiol (7). Yield 69%. bp 106 ℃/0.2 mmHg. TLC (30% EtOAc/*n*-Hexane) R_f 0.35. IR (neat) 3027, 2967, 2787, 2710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.17-7.50 (m, 5H), 4.54 (d, J=4.0 Hz, 1H), 2.40-2.90 (m, 5H), 2.35 (br, 1H), 2.35 (br, 1H), 1.70-1.90 (m, 4H), 0.98 (d, J=6.6 Hz, 3H). $[\alpha]_D^{25}$ −99.5 (c 1.0, $CHCl_3$). MS (m/z) 221 (M^+).

(1*R*,2*S*)-2-(1-Azepino)-1-phenylpropan-1-ol. Yield 60% (colorless oil). bp 124 ℃ (0.2 mmHg). TLC (50% Ethyl acetate/*n*-Hexane) R_f 0.2. IR (neat) 3419 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, J=6.9 Hz, 3H), 1.61 (br s, 8H), 2.66-2.68 (m, 4H), 2.95-3.07 (m, 1H), 4.76 (d, J=4.8 Hz, 1H), 7.22-7.35 (m, 5H). $[\alpha]_D^{25}$ −7.50 (c 2.2, $CHCl_3$). MS (m/z) 233 (M^+), 215, 126, 77.

(1*R*,2*S*)-1-Acetylthio-1-phenyl-2-(1-azepino)propane. Yield 88%. TLC (20% Ethyl acetate/*n*-Hexane) R_f 0.4. IR (neat) 1692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (d, J=6.5 Hz, 3H), 1.28 (br s, 8H), 2.30 (s, 3H), 2.42-2.71 (m, 4H), 3.14-3.22 (m, 1H), 4.68 (d, J=9.9 Hz, 1H), 7.19-7.29 (m, 5H). MS (m/z) 291 (M^+).

(1*R*,2*S*)-1-Phenyl-2-(1-azepino)-1-propan-1-thiol (9). Yield 70%. bp 118 ℃ (0.1 mmHg). TLC (20% EtOAc/*n*-Hexane) R_f 0.4. IR (neat) 2540 cm^{-1}. ^1H-NMR (200 MHz, $CDCl_3$) δ 1.20 (d, J=4.6 Hz, 3H), 1.31 (br s, 8H), 1.99 (s, 1H), 2.35-2.66 (m, 4H), 3.09-3.17 (m, 1H), 4.00 (d, J=8.9 Hz, 1H), 7.09-7.30 (m, 5H). $[\alpha]_D^{25}$ −107.1 (c 2.7, $CHCl_3$). MS (m/z) 249 (M^+).

(1*R*,2*S*)-2-(2-(1,3-Dihydroindolino))-1-phenylpropan-1-ol. Yield 55%. mp 92 ℃. TLC (20% EtOAc/*n*-Hexane) R_f 0.2. IR (CH_2Cl_2) 3387 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J=6.6 Hz, 3H), 2.83-2.88 (m, 1H), 3.68 (s, 1H), 4.08 (d, J=11.1 Hz, 2H), 4.16 (d, J=11.1 Hz, 2H), 5.06 (d, J=2.8 Hz, 1H), 7.2-7.4 (m, 9H). MS (m/z) 235 (M^+-18).

(1*R*,2*S*)-1-Acetylthio-2-(2-(1,3-dihydroindolino))-1-phenylpropane. Yield 85%. TLC (20% EtOAc/*n*-Hexane) R_f 0.50. IR (neat) 1692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (d, J=6.2 Hz, 3H), 2.33 (s, 3H), 3.03-3.08 (m, 1H), 4.06 (s, 4H), 5.11 (d, J=4.4 Hz, 1H), 7.18-7.43 (m, 9H). MS (m/z) 310 (M^+-1).

(1*R*,2*S*)-2-(2-(1,3-Dihydroindolino))-1-phenylpropan-1-thiol (10). Yield 73%. mp 101.5 ℃. TLC (20% EtOAc/*n*-Hexane) R_f 0.55. IR (KBr) 2540 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (d, J=7.9 Hz, 3H), 2.45 (s, 1H), 2.90-2.96 (m, 1H), 4.04 (d, J=11.2, 2H), 4.14 (d, J=11.2, 2H), 4.61 (d, J=3.7 Hz, 1H), 7.22-7.47 (m, 9H). $[\alpha]_D^{25}$ −23.8 (c 1.0, $CHCl_3$). MS (m/z) 267 (M^+-2), 146.

Preparation of (1*R*,2*S*)-(−)-1-phenyl-2-(5,7-dihydro-6*H*-dibenz[*c*,*e*]azepino)-1-propanol. (1*R*,2*S*)-Norephedrine (3.1 g, 20.5 mmol), 2,2′-Bis(bromomethyl)-1,1′-biphenyl (8.4 g, 24.7 mmol) and K_2CO_3 (16.0 g, 115.8 mmol) were placed in 20 mL of MeCN at rt. The reaction mixture was stirred for 8 h at rt. After filtering off inorganic salt, the filtrate was concentrated and purified by flash column chromatography to give the desired amino alcohol (5.8 g, 86%). TLC (20% Ethyl acetate/*n*-Hexane) R_f 0.25. IR (KBr) 3422 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.95 (d, J=6.7 Hz, 3H), 2.99-3.04 (m, 1H), 3.6 (s, 4H), 5.16 (d, J=3.4 Hz, 1H), 7.26-7.55 (m, 13H). $[\alpha]_D^{25}$ +14.03 (c 1.8, $CHCl_3$). MS (m/z) 330 (M^++1), 222, 179, 77.

Preparation of (1*R*,2*S*)-(−)-1-Phenyl-2-(5,7-dihydro-6*H*-dibenz[*c*,*e*]azepino)-1-propanthioacetate. To a solution of (1*R*,2*S*)-(−)-1-phenyl-2-(5,7-dihydro-6*H*-dibenz[*c*,*e*]azepino)-1-propanol (6.0 g, 18.2 mmol) in CH_2Cl_2 (36 mL) was added triethylamine (3.6 g, 36.1 mmol) at −78 ℃. Then to the reaction mixture was added methanesulfonyl chloride (2.5 g, 21.8 mmol) at −78 ℃, stirred for 2 h and allowed to warm up to −10 ℃. The reaction mixture was concentrated and dissolved in 36 mL of water. To the reaction mixture was added potassium thioacetate (4.2 g, 36.4 mmol) at rt, and stirred for 4 h at rt. The mixture was extracted with methylene chloride, dried over anhydrous sodium sulfate, concentrated, and purified by flash column chromatography to give the desired thioacetate (6.3 g, 89%). mp 190 ℃. TLC (20% EtOAc/*n*-Hexane) R_f 0.52. IR (KBr) 1689 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22 (d, J=6.6 Hz, 3H), 2.35 (s, 3H), 3.24-3.30 (m, 1H), 3.42 (d, J=12.5 Hz, 2H), 3.55 (d, J=12.5 Hz, 2H), 4.99 (d, J=6.3 Hz, 1H), 7.21-7.47 (m, 13H). MS (m/z) 388 (M^++1), 342, 312.

Preparation of (1*R*,2*S*)-(−)-1-Phenyl-2-(5,7-dihydro-6*H*-dibenz[*c*,*e*]azepino)-1-propanthiol, 11. To a solution of (1*R*,2*S*)-(−)-1-phenyl-2-(5,7-dihydro-6*H*-dibenz[*c*,*e*]azepino)-1-propanethioacetate (5.4 g, 13.9 mmol) in toluene (30 mL) was added diisobutylaluminum hydride (28 mL, 1.0 M solution in hexane) dropwise and stirred for 3 h at −30 ℃. The reaction mixture was diluted with diethyl ether (30 mL) and quenched with water (15 mL) over 30 min period at −30 ℃, allowed to warm up to rt, and stirred for 30 min. The reaction mixture was dried over sodium sulfate, then filtered. After inorganic salt filtered off, filtrate was concentrated, and purified by flash column chromatography to give the desired amino thiol (4.0 g, 84%). TLC (20% EtOAc/*n*-Hexane) R_f 0.61. IR (KBr) 2521 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (d, J=6.5 Hz, 3H), 3.17 (m, 1H), 2.43 (s, 1H), 3.53 (d, J=12.4 Hz, 2H), 3.68 (d, J=12.5 Hz, 2H), 4.60 (d, J=5.2 Hz, 1H), 7.24-7.58 (m, 13H). $[\alpha]_D^{25}$ −26.3 (c 0.93, $CHCl_3$). MS (m/z) 345 (M^+), 222, 179.

(1*R*,2*S*)-2-(*N*,*N*-Di-*n*-butylamino)-1-phenylpropan-1-ol. Yield 81% (colorless oil). bp 170 ℃ (2 mmHg) TLC (50% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 3425, 2950 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.70-1.10 (m, 9H), 1.10-1.60 (m, 8H), 2.10-2.70 (m, 4H), 3.0 (m, 1H), 3.6 (br s, 1H), 4.65 (d, J=5.0 Hz, 1H), 7.25 (s, 5H). $[\alpha]_D^{25}$ +18.9 (c 2.17, *n*-hexane). MS (m/z) 218 (M^+-45), 156.

(1*R*,2*S*)-1-Acetylthio-2-(*N*,*N*-di-*n*-butylamino)propane. Yield 90% (colorless oil). TLC (3% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 1694 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.70-1.35 (m, 17H), 2.10-2.45 (m, 4H), 2.28 (s, 3H), 3.15 (m, 1H), 4.64 (d, J=9.7 Hz, 1H), 7.10-7.30 (m, 5H). MS (m/z) 322 (M^++1).

(1*R*,2*S*)-2-(*N*,*N*-Di-*n*-butylamino)-1-phenylpropan-1-thiol (12). Yield 75% (colorless oil). TLC (10% EtOAc/*n*-Hexane) R_f 0.25. IR (neat) 3028, 2957, 2870, 2811 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.65-1.30 (m, 14H), 1.15 (d, J=6.6 Hz, 3H), 2.10-2.40 (m, 4H), 3.10 (m, 1H), 4.00 (d, J=8.9 Hz, 1H), 7.05-7.40 (m, 5H). $[\alpha]_D^{25}$ −3.25 (c 1.4, $CHCl_3$). MS (m/z) 279 (M^+).

(1*R*,2*S*)-(−)-1-Phenyl-2-(*N*,*N*-dibenzylamino)-1-propanol. Yield 68%. TLC (10% EtOAc/*n*-Hexane) R_f 0.37. IR (neat) 3445 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (d, J=7.0 Hz, 3H), 2.57 (s, 1H), 3.11 (m, 1H), 3.48 (d, J=13.8 Hz, 2H), 3.73 (d, J=13.8 Hz, 2H), 4.76 (d, J=6.2 Hz, 1H), 7.13-7.33 (m, 15H). MS (m/z) 331 (M^+).

(1*R*,2*S*)-(−)-1-Phenyl-2-(*N*,*N*-dibenzylamino)-1-propyl thioacetate. Yield 85%. mp 105 ℃. TLC (10% EtOAc/*n*-Hexane) R_f 0.47. IR (KBr) 1690 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.25 (d, J=6.6 Hz, 3H), 2.25 (s, 1H), 3.15-3.25 (m, 1H), 3.29 (d, J=13.6 Hz, 2H), 3.73 (d, J=13.6 Hz, 2H), 4.78 (d, J=10.6 Hz, 1H), 6.90-7.25 (m, 15H). MS (m/z) 375 (M^+-14), 346 (M^+-43).

(1*R*,2*S*)-(−)-1-Phenyl-2-(*N*,*N*-dibenzylamino)-1-propanthiol (13). Yield 88%. TLC (10% EtOAc/*n*-Hexane) R_f 0.47. IR ($CDCl_3$) 2569 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.38 (d, J=6.5 Hz, 3H), 1.91 (s, 1H), 3.68 (d, J=13.6 Hz, 2H), 3.32 (d, J=13.6 Hz, 2H), 4.09 (d, J=10.3 Hz, 2H), 6.95-7.32 (m, 15H). $[\alpha]_D^{25}$ −88.2 (c 1.51, $CHCl_3$). MS (m/z) 347 (M^+).

(1*R*,2*S*)-(−)-1,2-Diphenyl-2-(1-piperidinyl)-1-propanol. mp 100.5-101.5 ℃. TLC (50% EtOAc/*n*-Hexane) R_f 0.6. IR (KBr) 3298, 2980, 2796 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.07-7.15 (m, 6H), 6.96-7.01 (m, 4H), 5.35 (d, J=4.6 Hz, 1H), 3.35 (d, J=4.6 Hz, 1H), 2.53-2.63 (m, 2H), 2.43-2.50 (m, 2H), 1.40-1.67 (m, 6H). $[\alpha]_D^{25}$ −66.5 (c 1.2, EtOH). MS (m/z) 280 (M^+-1), 263 (M^+-18).

(1*R*,2*S*)-(−)-1-Acetylthio-1,2-diphenyl-2-(1-piperidinyl)-propane. TLC (10% EtOAc/*n*-Hexane) R_f 0.5. IR (KBr) 2935, 2850, 2802, 1687, 1452 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.31 (m, 8H), 7.09-7.13 (m, 2H), 5.30 (d, J=10.3 Hz, 1H), 3.8 (d, J=10.3 Hz, 1H), 2.37-2.44 (m, 2H), 2.12-2.18 (m, 5H), 1.17-1.35 (m, 6H). $[\alpha]_D^{25}$ −126.9 (c 1.3, $CHCl_3$). MS (m/z) 264 (M^+-75), 213, 174.

(1*R*,2*S*)-(−)-1,2-Diphenyl-2-(1-piperidinyl)-1-propanethiol (14). TLC (10% EtOAc/*n*-Hexane) R_f 0.5. IR (KBr) 3061, 3028, 2933, 2850, 2798, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.42 (m, 10H), 4.69 (d, J=9.5 Hz, 1H), 3.79 (d, J=9.5 Hz, 1H), 2.29-2.41 (m, 2H), 2.13-2.26 (m, 2H), 1.89 (s, 1H), 1.15-1.38 (m, 6H). $[\alpha]_D^{25}$ −81.95 (c 3.27, toluene). MS (m/z) 264 (M^+-33), 180, 174.

(1*R*,2*S*)-(−)-Bis[1,2-diphenyl-2-(1-piperidinyl)-1-propyl] disufide (18). mp 145.5-146.0 ℃. TLC (2% EtOAc/*n*-Hexane) R_f 0.25. IR (KBr) 3061, 3026, 2931, 2852, 2800, 1494, 1450 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.43 (m, 12H), 7.07-7.10 (m, 4H), 6.96-6.99 (m, 4H), 3.98 (d, J=10.6 Hz, 2H), 3.74 (d, J=10.6, 2H), 2.05-2.20 (m, 8H), 1.11-1.41 (m, 12H). $[\alpha]_D^{25}$ −343.14 (c 0.51, $CHCl_3$). MS: (m/z) 264 (M^+-328), 180, 174.

Preparation of Chromium Complex of (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl)propan-1-ol. (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl)propan-1-ol (0.4 g, 1.82 mmol) and chromium hexacarbonyl (2.0 g, 9.12 mmol) in 3 : 1 mixture of di-*n*-butyl ether : THF (24 mL) was heated to reflux under nitrogen for 24 h. The mixture was cooled to −40 ℃, warmed to room temperature, filtered through Celite pad and washed with ether. After removal of solvent, the residue was chromatographed to yield the chromium complex (0.14 g, 21.6%). TLC (20% EtOAc/*n*-Hexane) R_f 0.2. IR (neat) 3406, 2936, 1964, 1884 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, J=7.0 Hz, 3H), 1.30-1.70 (m, 6H), 2.40-2.70 (m, 5H), 3.60 (br s, 1H), 4.36 (d, J=5.1 Hz, 1H), 5.15-5.5.70 (m, 5H). MS (m/z) 355 (M^+).

Thioacetate of Arene Chromium Complex of (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl)propan-1-ol. Yield 79%. TLC (20% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 1964, 1871, 1698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, J=6.8 Hz, 3H), 1.30-1.50 (m, 6H), 2.20-2.60 (m, 4H), 2.40 (s, 3H), 2.72 (m, 1H), 4.35 (d, J=8.3 Hz, 1H), 5.05-5.60 (m, 5H). MS (m/z) 413 (M^+).

Arene Chromium Complex of (1*R*,2*S*)-1-Phenyl-2-(1-piperidinyl)propan-1-thiol (15). Yield 79%. TLC (20% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 1960, 1883 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (d, J=6.8 Hz, 3H), 1.25-1.60 (m, 6H), 2.20-2.70 (m, 5H), 3.85 (d, J=7.0 Hz, 1H), 5.15-5.50 (m, 5H). MS (m/z) 371 (M^+).

Preparation of *cis*-1,3-Bis(hydroxymethyl)cyclopentane. A solution of norbonene (10.3 g, 109.4 mmol) in 150 mL CH_2Cl_2 at −78 ℃ was ozonized until a faint blue color persisted (*ca.* 5 h), and the mixture was then purged with oxygen for 5 min. The ozonide was reduced with methyl sulfide (41.4 mL, 545 mmol) at −78 ℃ and the resulting mixture was allowed to warm up to rt slowly. The reaction was stirred for overnight. After evaporation of solvent, the crude aldehyde obtained. IR (neat) 1720 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.80-2.32 (m, 6H), 2.88 (m, 2H), 9.64 (s, 2H).

The crude aldehyde was dissolved in 100 mL MeOH and 8.25 g (218 mmol) $NaBH_4$ was added at 0 ℃. The reaction mixture stirred for 1 h at 0 ℃. After evaporation of MeOH, H_2O was added to the residue and the aqueous solution was extracted with ethyl acetate (×3). The organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed to give 7.5 g (49%) of diol. TLC (neat EtOAc) R_f 0.35. IR (neat) 3356.4 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.90-2.30 (m, 8H), 3.55 (d, J=6.6 Hz, 4H). MS (m/z) 112 (M^+-18), 94 (M^+-36).

Preparation of *cis*-1,3-Bis(bromomethyl)cyclopentane. To a diol (8.5 g, 60.7 mmol) at 0 ℃ was added PBr3 (16.4 mL, 60.7 mmol) slowly. The resulting solution was heated to reflux for 1 h. After cooling to 0 ℃, the reaction mixture was poured into cold ice water. The aqueous solution was extracted with ether (×3) and washed with brine. The combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was chromatographed to give 9.6 g (59%) of dibromide. TLC (10% EtOAc/*n*-Hexane) R_f 0.6. ^1H NMR (200 MHz, $CDCl_3$) δ 1.0-2.5 (m, 8H), 3.41 (d, J=6.6 Hz, 4H). MS (m/z) 175 (M^+-80).

(1*R*,2*S*)-1-Phenyl-2-(2-azabicyclo[3.2.1]octan-2-yl)propan-1-ol. Yield 58%. TLC (10% EtOAc/*n*-Hexane) R_f 0.3. IR (neat) 3441 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.78 (d, J=6.9 Hz, 3H), 1.25-3.0 (m, 13 H), 4.86 (d, J=4.6 Hz, 1H), 7.18-7.40 (m, 5H). MS (m/z) 231 (M^+-14).

(1*R*,2*S*)-1-Acetylthio-2-(2-azabicyclo[3.2.1]octan-2-yl) propane. Yield 92%. TLC (10% EtOAc/*n*-Hexane) R_f 0.6. IR (neat) 1692 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (d, J=6.5 Hz, 3H), 0.95-2.50 (m, 12H), 3.0 (m, 1H), 4.64 (d, J=10.7 Hz, 1H), 7.15-7.35 (m, 5H). MS (m/z) 303 (M^+).

(1*R*,2*S*)-2-(2-azabicyclo[3.2.1]octan-2-yl)-1-phenylpropan-1-thiol (16). Yield 86%. TLC (10% EtOAc/*n*-Hexane) R_f 0.5. IR (neat) 2570, 1599 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.0-2.5 (m, 12H), 1.14 (d, J=6.6 Hz, 3H), 2.00 (s, 1H), 2.90 (m, 1H), 4.00 (d, J=9.1 Hz, 1H), 7.15-7.35 (m, 5H). MS (m/z) 260 (M^+-1).

A Typical Procedure for Enantioselective Addition of Diethylzinc to Aldehydes in the Presence of β-Amino Thiols. Diethylzinc (1 M in *n*-hexane, 6.0 mmol) was added to a mixture of aldehyde (3.0 mmol) and chiral β-amino

thiol (0.15 mmol) in toluene (10 mL) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 12 h, after which the reaction was quenched at 0 ℃ by the addition of 1M HCl. The aqueous phase was extracted with CH_2Cl_2, and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/*n*-Hexane). The product was identified by comparing samples with authentic ones, and the optical rotation was measured.

Chromatographic Data

1-Phenylpropan-1-ol. $[\alpha]_D^{25}$ +46.0 (c 5.2, $CHCl_3$). HPLC resolution: Chiralcel OB; eluent 10% IPA/n-Hexane; flow rate (mL/min) 0.5; retention time (min) 13.1 (*S*), 15.7 (*R*). GC resolution: Chiradex-BPH; oven temp. 110 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 36.6 (*R*), 37.8 (*S*).

1-(*p*-Chlorophenyl)propan-1-ol. $[\alpha]_D^{25}$ +28.0 (c 5.0, Benzene). GC resolution: Chiradex-BPH; oven temp. 130 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 55.7 (*R*), 57.4 (*S*).

1-(*p*-Methoxyphenyl)propan-1-ol. $[\alpha]_D^{25}$ +35.5 (c 4.14, Benzene). GC resolution: Chiradex-BPH; oven temp. 130 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 69.2 (*R*), 71.1 (*S*).

1-(o-Methoxyphenyl)propan-1-ol. $[\alpha]_D^{25}$ +53.3 (c 3.0, Toluene). GC resolution: Chiradex-BPH; oven temp. 140 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 22.9 (*S*), 24.0 (*R*).

1-(*p*-Fluorophenyl)propan-1-ol. GC resolution: Chiradex-BPH; oven temp. 120 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 29.6 (major), 31.5.

1-(2-Naphthyl)propan-1-ol. $[\alpha]_D^{25}$ +29.8 (c 4.7, Benzene). HPLC resolution: Chiralcel OB; eluent 10% IPA/*n*-Hexane; flow rate (mL/min) 0.5; retention time (min) 21.7 (*S*), 25.0 (*R*).

1-(1-Naphthyl)propan-1-ol. $[\alpha]_D^{25}$ +55.6 (c 2.4, $CHCl_3$). HPLC resolution: Chiralcel OB; eluent 2.5% IPA/*n*-Hexane; flow rate (mL/min) 0.8; retention time (min) 33.2 (*S*), 40.5 (*R*).

1-Ferrocenylpropan-1-ol. $[\alpha]_D^{25}$ −57.5 (c 1.1, Benzene). HPLC resolution: Chiralcel OF; eluent 0.3% IPA/*n*-Hexane; flow rate (mL/min) 0.6; retention time (min) 114.1 (*S*), 125.8 (*R*).

***trans*-1-Phenylpent-1-en-3-ol.** HPLC resolution: Chiralcel OD; eluent 10% IPA/*n*-Hexane; flow rate (mL/min) 0.5; retention time (min) 17.0 (*R*), 25.0 (*S*).

Benzoate of 1-Cyclohexylpropan-1-ol. GC resolution: Chiradex-BPH; oven temp. 135 ℃; detector temp. 300 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1.02 mL/min; retention time (min) 95.7 (*R*), 96.7 (*S*).

Preparation of (*R*)-(+)-MTPA Ester of Octan-3-ol. (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (117 mg, 0.5 mmol) dissolved in $SOCl_2$ (1 mL) was refluxed for 48 h. The mixture was concentrated under reduced pressure. Benzene (2 mL×2) was added to the residue twice, condensed *in vacuo* to give a crude acid chloride. To an ice-cooled solution of alcohol (50 mg, 0.38 mmol) and pyridine (0.04 mL, 0.5 mmol) in CH_2Cl_2 (1 mL). The reaction mixture stirred at 0-5 ℃ for 4 h. The mixture was diluted with additional CH_2Cl_2 (10 mL) before washing with a sat. $NaHCO_3$ aqueous solution and water, drying ($MgSO_4$), and evaporation under reduced pressure. The resulting residue was chromatographed on silica gel (EtOAc/Hexane; 1 : 9) to yield the MTPA ester as an oil; yield 121 mg (92%). TLC (10% EtOAc/*n*-Hexane) R_f 0.24. IR (neat) 1744 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.78-0.97 (m, 6H), 1.21-1.30 (m, 6H), 1.52-1.72 (m, 4H), 3.57 (s, 3H), 5.02-5.08 (m, 1H), 7.27-7.56 (m, 5H). GC resolution: Chiradex-BPH; oven temp. 125 ℃; detector temp. 300 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 83.3 (*S*), 85.9 (*R*).

Benzoate of 2,2-Dimethylpentan-3-ol. GC resolution: Chiradex-BPH; oven temp. 105 ℃; detector temp. 250 ℃; injector temp. 250 ℃; split ratio 120 : 1; column flow 1 mL/min; retention time (min) 65.7 (*R*), 67.4 (*S*).

Acknowledgment. This research is supported by OCRC-KOSEF and Korea Research Foundation.

References

1. (a) Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1978**, 601. (b) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. *J. Am. Chem. Soc.* **1979**, *101*, 1455. (c) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.
2. (a) For reviews on catalytic addition of organozinc reagents to carbonyl compounds, see Noyori, R.: Kitamura, M. *Angew. Chem. Int. Ed.* **1991**, *30*, 49 and Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (c) Hones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 649. (d) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (e) Soai, K.; Okawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.
3. (a) Kang, J.; Lee, J. W.; Kim, J. I. *J. Chem. Soc., Chem. Commun.* **1994**, 2009. (b) Kang, J.; Kim, D. S.; Kim, J. I. *Synlett* **1994**, 842. (c) After completion of our study, but prior to publication of our first report on this matter,[3a] Professor Kellogg has reported thiol analogs of N-alkylephedrine as ligands for the present reaction. However, the best ligands in their case were the corresponding disulfides of N-methyl and N-isopropyl analogs, which gave the corresponding alcohol of only 90% ee. Hof, R. P.; Poelert, M. A.; Peper, N. C. M. W.; Kellogg, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 31.
4. Soai, K.; Okudo, M.; Okamoto, M. *Tetrahedron Lett.* **1991**, *32*, 95.
5. (a) Boersma, J. in *Comprehensive Organometallic Chemistry*; wilkinson, G. W. ed., Vol. 2, Pergamon, 1982, pp 863-978. (b) Seebach, D.; Behrendt, L.; Felix, D. *Angew. Chem. Int. Ed.* **1991**, *30*, 1008. (c) Stadm ller, H.; Lentz, R.; Tucker, C. E.; Stüdenmann, T.; Dörner, W.; Knochel, P. *J. Am. Chem. Soc.* **1993**, *115*, 7027.
6. For catalytic behavior of the corresponding alcohol, see Jones, G. B.; Heaton, S. B. *Tetrahedron: Asymmetry* **1993**, *4*, 261.
7. Richard, R. H.; Kenyon, J. *J. Chem. Soc.* **1914**, 1115.
8. Capillon, J.; Guette, J. *Tetrahedron* **1979**, *35*, 1817.
9. Smaardijk, A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135.

10. Soai, K.; Hirose, Y.; Niwa, S. *J. Fluorine Chem.* **1992**, *59*, 5.
11. Watanabe, M.; Araki, S.; Butsugan, Y.; Uemura, M. *J. Org. Chem.* **1991**, *56*, 2218.
12. (a) Soai, K.; Nishi, M.; Yuhki, I. *Chem. Lett.* **1987**, 2405. (b) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2717.
13. Natsumoto, Y.; Ohno, A.; Lu, S.; Hayashi, T. *Tetrahedron: Asymmetry* **1993**, *4*, 1763.
14. (a) Fitzpatrick, K.; Hulst, R.; Kellog, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1861. (b) Kellog, R. M.; Hof, R. P. *J. Chem. Soc. Perkin Trans I*, **1996**, 1651.
15. Kang, J.; Lee, J. W.; Kim, J. I.; Pyun, C. *Tetrahedron Lett.* **1995**, *36*, 4265.
16. Kang, J.; Kim, J. B.; Kim, J. W.; Lee, D. *J. Chem. Soc., Perkin 2*, in press.

Differential Pulse Voltammetric Determination of Copper(I) Ion with a Rubeanic Acid-Modified Carbon Paste Electrode

Mi-Sook Won†, Hyun-Jeong Kim, and Yoon-Bo Shim*

†*Pusan Branch, Korean Basic Science Research Institute, Pusan 609-735, Korea*
Department of Chemistry, Pusan National University, Pusan 609-735, Korea
Received September 1, 1996

A copper(I) ion-sensitive modified electrode was constructed by incorporating rubeanic acid into a carbon paste mixture composed of graphite powder and Nujol oil. By simple immersing of the modified electrode into the measuring solution, the test ion was chemically deposited on the electrode *via* a complex formation. The resulting surface was characterized by cyclic voltammetry and differential pulse voltammetry. The exposure of the used modified electrode to a 0.1 M nitric acid and the potential cycling, beyond more positive and negative potential than the redox potential of the copper complex, led to the reuse of the electrode more than three times. A linear calibration plot was obtained over the concentration range of 5.0×10^{-6} to 1.0×10^{-7} M with 5.6% relative standard deviation. The detection limit for Cu(I) ion are found to be 5.0×10^{-8} M using differential pulse voltammetry at 15 min of the deposition. Ag(I), Hg(II), Ni(II), Co(II), Cd(II), Pb(II), Cr(II), Al(III), As(IV), Be(II), Mg(II), Ca(II), Pt(IV), Se(IV), Zn(II), Tl(I), Hg(II), and Fe(II) ions did not interfere. After the reduction of Cu(II) ion to Cu(I) with hydroxylamine in the sample solution, satisfactory results were obtained for the determination of copper in the certified standard urine reference material, SRM's 2670 (trace elements in the urine).

Introduction

The chemically modified electrode (CME) can be applied to the voltammetric analysis of heavy metal ions, which are selectively preconcentrated at the electrode through chemical reactions with a modifier.[1~5] Modification of an electrode with appropriate compounds can be used to pre-concentrate an analyte on the electrode bypassing interference of electroactive substances that easily disturb the analysis of target species or the electrode reaction. Thus, the voltammetric method coupled with the CME gives a variable preconcentration range with little interferences compared to the conventional method.[2] In general, the characteristics of the CME are dependent on the chemical reaction between the modifier and analyte rather than the redox potential of the analyte; therefore, it is important to develop the modifier in the CME study. Of the CMEs, carbon paste electrodes (CPEs) were often used to analyze the ions in the sample solution because of their unique advantages.[6~9]

Rubeanic acid (or dithiooxamide, $H_2NC(=S)C(=S)NH_2$) (Rba) has been known as a flexidentate ligand.[10] A certain group of rubeanic acids is a typical polyfunctional ligand that ligate with the transition metal ions in various ways. Therefore, the Rba was used to detect some metal ions with spectrometry.[11~13] As well as this, sulfur and nitrogen atoms of Rba react with some metal ions to form a stable polymeric metal complex,[14] it will be expected to capture the metal ions strongly. Thus, we tested the interaction of the Rba modified CPE with heavy metal ions and found that the modified CPE captures Cu(I) ion of the other metal ions selectively, so that we made the determination of Cu(I) ion using CPE containing Rba. Various studies for the determination of copper employing the modified CPEs were reviewed by Kalcher *et al.*[6,9] However, there are few studies for the determination of Cu(I) ion with organic modifiers except Nafion/2, 2'-biquinoline[15] and di(2-iminocyclopentylidine mercaptomethyl) disulfide.[16] Thus, we aimed at the selective determination of the Cu(I) ion with CPE containing the ligand forming the polymeric metal complex.

In the present study, to verify the formation of the complexes on the electrode surface, the Cu(I)-Rba complex was prepared and the CV of the complex was recorded in the aqueous solution. This study characterized the analytical performance of the CPE and optimized various analysis para-