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The Cyanation of Prochiral Aldehydes with Chiral Copper Complexes of R-(+)/S-(-) -α-Ethylphenyl Amine in Methanol

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Abstract: Interesting and unexpected results on the cyanation of prochiral aldehydes catalyzed by chiral copper complexes of R-(+)/(S)-(-) α-ethylphenyl amine (**I/II**) in anhydrous methanol are presented. The cyanation reaction with chiral copper complexes of R-(+)/S-(-) α-ethylphenyl amines, acetols in methanol perform to afford a series of chiral products such as amines and acetonitriles (compounds **4-6**, **8**, **10** and **11**). The obtained products are fully characterized by NMR, IR and X-ray analysis. The proposed mechanism for the formation of a series of chiral products can be concluded that methanol firstly promotes the decomposition of the copper complexes bearing R-(+)/S-(-) α-ethylphenyl amines to the ligand R-(+)/ S-(-)-α-ethylphenyl amine, which then conjugated with the initial TMS ether of the cyanohydrin or cyanohydrin to afford the chiral compounds **4-6**, **8**, **10** and **11**.

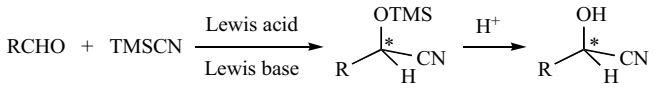
Keywords: Cyanation, chiral copper complexes, R-(+)/S-(-) -α-ethylphenyl amine, methanol, acetols, cyanohydrin.

INTRODUCTION

Cyanation has demonstrated significant utility in the synthesis of cyanohydrins. Cyanohydrins are generally precursors to α-hydro acids, β-amino alcohols and other valuable chiral building blocks, which are used as compoonents in pharmaceutials [1, 2]. Ions-based catalytic system that contains one or more metals such as B, Ti, V, Al, Mg, Mn, Co, Sn, Zr, Zn and Rh has recently demonstrated efficient catalysis in the cyanosilylation of prochiral aldehydes [3-6]. For example, our research group has synthesized 2-oxazolines in one–pot method from benzoylacetonitrile and β-aminoalcohols mediated by $ZnCl_2$. Our first goal is to obtain the novel oxazolinyl-zinc complexes with a large amount of Lewis acid, up to 140-172 mol% is used. Surprisingly, 2-oxazolines have shown good catalytic performances in cyanosilylation reactions [7]. The general approach for the cyanation reaction involves the catalysis of the aldehydes-trimethylsilylnitrile conjugated addition reaction with the derivative of chiral bdiamines, amino acids, and ionic liquids as shown in Scheme **1** [8]. Dichloromethane, THF or acetonitrile is usually selected as the solvent. Additionally, inspired by pioneering work [9-18], hereoin, we first reported the cyanation of prochiral aldehydes catalyzed by chiral copper complexes of R-(+)/S-(-)-α-ethylphenyl amines in methanol. The flexibility of the methodology will be demonstrated by the synthesis of acetols and a series of chiral products that are important in organic, carbohydrate and drug chemistry.

RESULTS AND DISCUSSION

First, we have synthesized the novel family of complexes **I and II** by reacting R-(+)/S(-)-α-phenylethylamine with copper acetate hydrate in the molar ratio of 2.1:1 in THF. The crystals were obtained after recrystallized from hexane [18] (Scheme **2**). These complexes were then used as catalysts for the cyanation of prochiral aldehydes in anhydrous methanol to produce compounds **2-6**, **8**, **10** and **11**, as presented in Scheme **3**.



Scheme 1. Common method for the cyanation of prochiral of aldehydes.

The following yields were obtained by reacting aldehydes with TMCN at room temperature for 3 days in anhydrous methanol using catalysts **I** or **II**: an approximately 30% yield of compound **2**, a 25% yield of compound **4**, a 25% yield of compound **5**, a 30% yield of compound **6**, 40% yields of compound **8** and 30% and 20% yields of compounds **10** or **11**, respectively.

In general, the synthesis of acetols requires protic or Lewis acidic catalysts, [19-20] in this paper, chiral copper complexes bearing R-(+)/S-(-)- α-ethylphenyl amines (**I/II**) have also demonstrated good catalytic activity in the condensation of aldehydes with the methanol. For example, the condensation of the aldehydes (**1a-1i**) with methanol yields compound **2**, which is attributed to the nucleophilic addition of the methanol to the carbonyl group in the presence of **I or II**.

The proposed mechanism for the formation of the compounds **3-6**, **8**, **10 and 11** involves methanol as the solvent (Scheme **4**). The solvent firstly promotes the decomposition of the copper complexes bearing R-(+)/S-(-) -α-ethylphenyl amines to the ligand R-(+)/ S-(-)-α-ethylphenyl amines, which then conjugated with the initial TMS ether of the cyanohydrin or cyanohydrin to afford the chiral compounds **4-6**, **8**, **10** and **11**. For example, condensing (R)/(S) -α-phenethylamine with the nucleophilic addition products *i.e.* trimethylsilyl ether or hydroxy acetonitriles, which are obtained from the reaction of 4-bromobenzaldehyde, 2-bromobenzaldehyde or 2-methoxybenzaldehyde with TMSCN, and eliminating trimethylsilanol or water afforded compounds **4**, **6**, **10** and **11**. The condensation of 4 -fluorobenzoic acid, an oxidization product fluorobenzaldehyde with (R)-(+)-α–phenethylamine generated 4- fluorobenzoic acid - (R)-(+)-α-phenethylamine salt (compound **5**).

Accordingly, condensation of the cinnamic aldehyde with (R)-(+)-α-phenethylamine afforded compound **8** after eliminating two equivalences of water.

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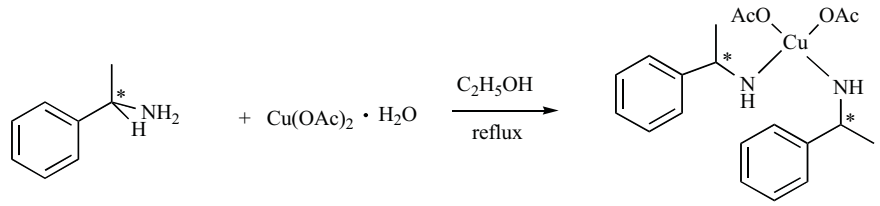
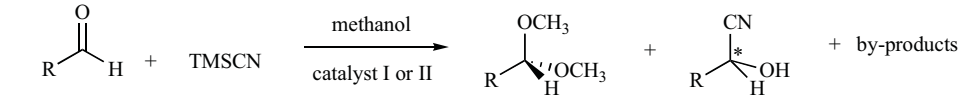


I-R =(+)α-ethylphenyl amines copper acetate complex
II-S = (-) α-ethylphenyl amines copper acetate complex

Scheme 2. The synthetic routes to the catalysts **I** and **II**.



1

R: a:2-bromophenyl
b:4-fluorophenyl
c:4-bromophenyl
d: allylphenyl
e: 2-methoxyphenyl
f: 2-methylphenyl
g: 4-chlorophenyl
h:2-fluorophenyl
i:4-methylphenyl
j:4-methoxyphenyl

2 **3**

4
5
6
8
10 and 11

Scheme 3. The synthetic routes to the compounds **2-6**, **8**, **10** and **11**.

Table 1. Cyanation of various aldehydes.

Aldehydes	Catalyst	Yield (2)[a]	Yield (%, 3)	Yield (%), by Products	Config[b]
1a	I	34	30	25(**4**)	**S**, **R**
1b	I	34		25(**5**)	**R**
1c	II	35	30	30(**6**)	**S** , **S**
1d	I			40(**8**)	**R**, **R**, **S**
1e	II			30(**10**),20(**11**)	**S(10)**, **R**,**S**, **R(11)**
1f	I	32			
1g	I/II	34			
1h	I/II	35			
1i	I/II	28			
1j	I/II	30			

[a]:isolated yield, which were performed from the silica gel,; [b]:configuration was determined by X-ray analysis.

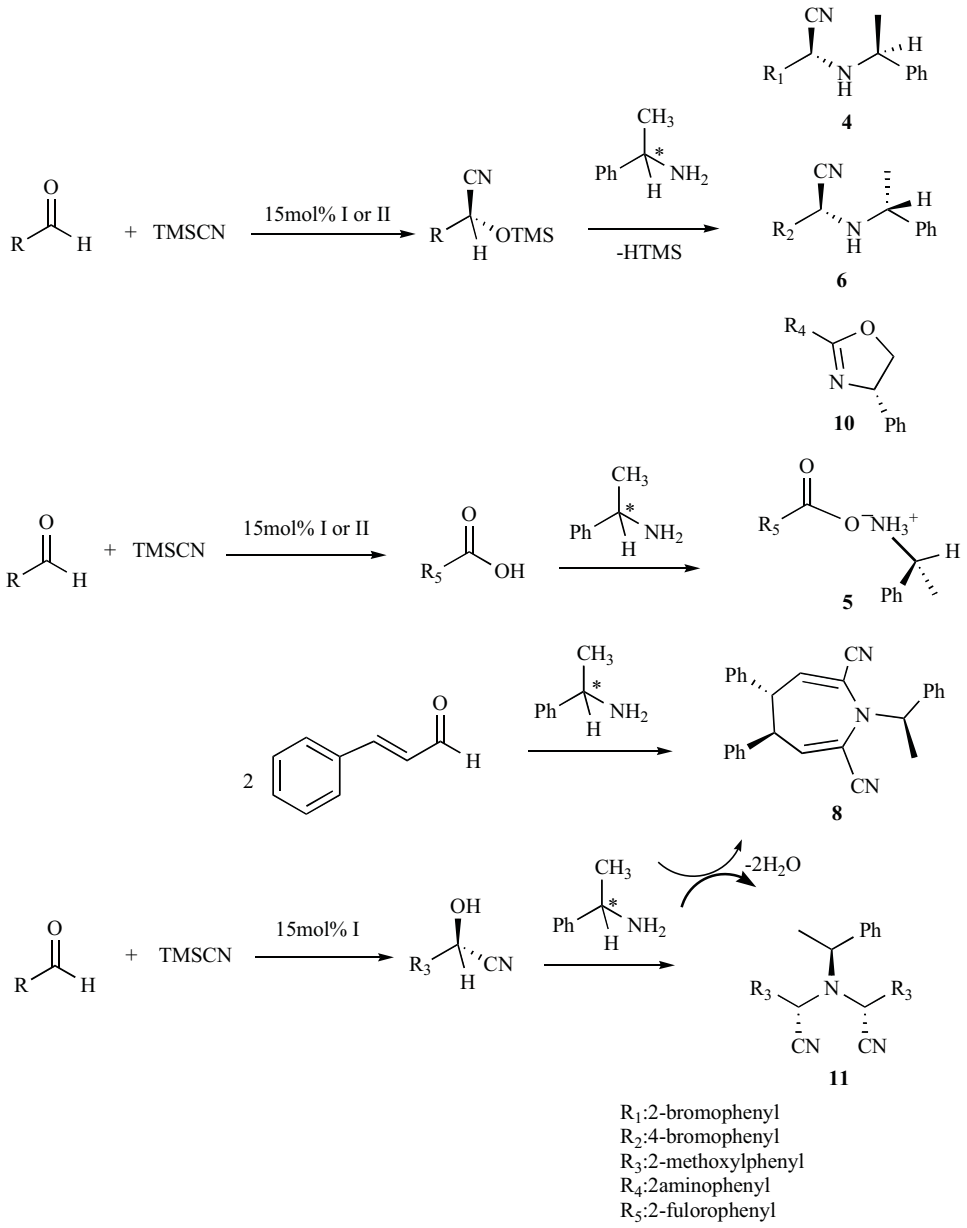
Unfortunately, only the target products of the compounds **3a** and **3c** were obtained by reacting 2-bromobenzaldehyde and 4-bromobenzaldehyde separately with TMSCN, the crystals were obtained by slowly evaporating the last component from the saturated solution in ethanol and dichloromethane. However, in the parallel conditions, the crystal structures of the cyanohydrins were not given from the aromatic aldehydes and aliphatic aldehydes. Table **1** lists the yields from compounds **2-6**, **8**, **10** and **11** from different aldehydes.

Compounds **2-6**, **8**, **10** and **11** were separated using silica gel column chromatography, eluting with petroleum ether and dichloromethane. The eluate containing the product was collected, and evaporation of the first fraction yielded compound **2**, evaporation of the second fraction yielded compounds **4-6**, **8**, **10** and **11**, and evaporation of the last fraction afforded compound **3** (Figs. **1-8**).

Scheme **4** presents the proposed mechanism for the compounds **4-6**, **8**, **10** and **11**.

CONCLUSION

In conclusion, we have developed a simple, and direct method to synthesize silylcyanohydrines, acetols (compound **2**) and a series of chiral products using methanol as the reaction solvent and copper complexes of chiral α-ethylphenyl amine as the reagents. The novelity of this paper can be summarized as following: using methanol as solvent, R-(+)/S-(-)-α-phenylethylamine copper acetate could be



Scheme 4. The proposed mechanism to the compounds **4-6**, **8**, **10** and **11**.

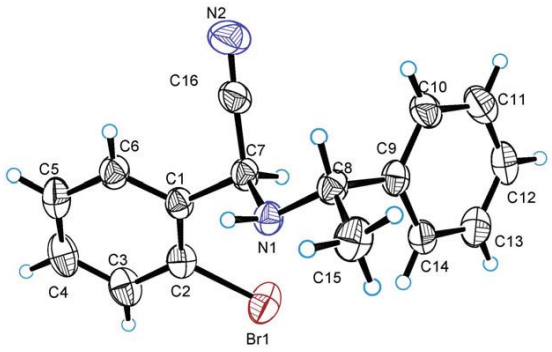


Fig. (1). The crystal structure of compound **4**.

induced in the decomposition of R-(+)/S-(-)-α-phenylethylamine copper complexes to the ligand R-(+)/S-(-)-α-phenylethylamine, which is involved in the cyanosilylation, thus affording a series of compounds such as amines and acetonitriles.

Further efforts should be directed towards scaling up experiments, and further investigating the efficacy of the organometallic complexes in other organocatalytic reactions.

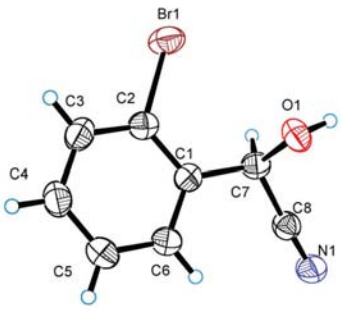


Fig. (2). The crystal structure of compound **3c**.

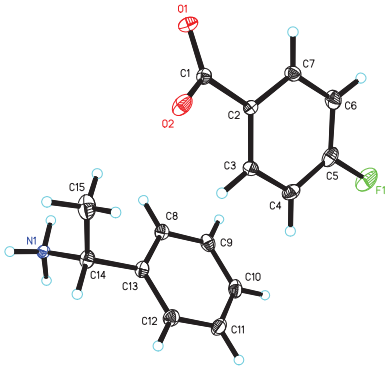


Fig. (3). The crystal structure of compound **5**.

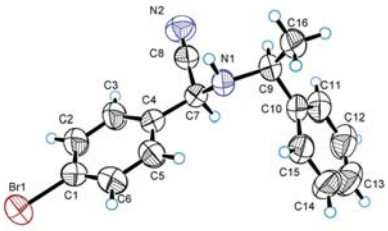


Fig. (4). The crystal structure of compound **6**.

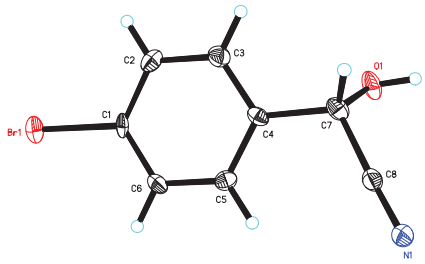


Fig. (5). The crystal structure of compound **3h**.

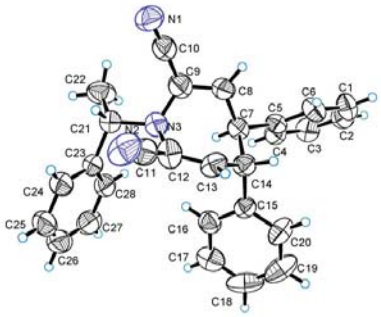


Fig. (6). The crystal structure of compound **8**.

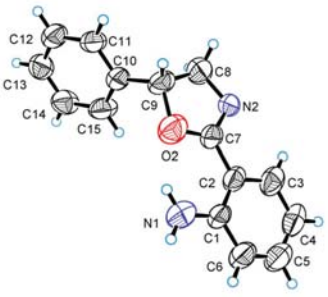


Fig. (7). The crystal structure of compound **10**.

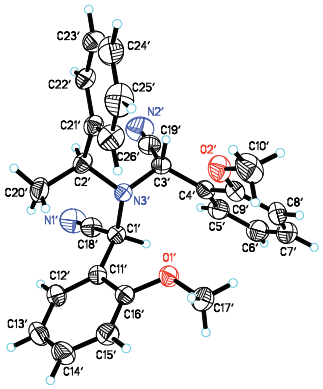


Fig. (8). The crystal structure of compound **11**.

EXPERIMENTAL PART

Materials and Measurements

Benzaldehydes, R-(+)/S(-) α-1-ethylphenyl amine, copper diacetate, TMSCN were purchased from Acros, Aldrich, Fluka. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.02-0.03 mm), ^{1}H and ^{13}C NMR and ^{31}PNMR spectra were obtained using Bruker AM-300, Bruker AM-400 and Bruker AM-500 spectrometer. Proton chemical shifts are reported in ppm (δ) with the solvent relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$, δ 7.26 ppm). The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrometer; peaks are reported in cm^{-1}. High resolution mass spectra (HRMS) were obtained on Micro GCT-MS equipped with an EI ion source. Optical rotations were measured on WZZ-1 automatic polarimeter with a 2 cm cell at the sodium D-line.

Structure Deterimination

The colorless crystal of the title compound **4** of approximately 0.32 x 0.25 x 0.24 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated MoK/α radiation (λ=0.71073Å). A total of 3020 reflections were collected in the range $4.16 < \theta < 62.65°$ by using "phi and omega scans" techniques at 290(2) K, $C_{16}H_{15}BrN_2$, M = 315.21, monoclinic, P 21, a = 9.4325(3) Å, α = 90º, b = 7.2774(10) Å, β =111.102(3) º, c = 11.3809(3) Å, γ = 90º, V = 728.84(3) $Å^3$, Z = 2, D_{calc} = 1.432 g/m^3, the final R factor was R_1 = 0.0421, 1729 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.1154b for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The colorless crystal of the title compound **3a** of approximately 0.40 x 0.35x 0.32 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated CuK/α radiation (λ=0.71073Å). A total of 3257 reflections were collected in the range of $3.35 < \theta < 62.52$ ° by using "phi and omega scans" techniques at 290 (2) K, C_8H_6BrNO, M = 212.05, orthorhombic, P 2(1)2(1)2(1), a = 4.0882 (3) Å, α = 90º , b = 7.4159(10) Å, β =90 º, c = 26.413(2) Å, γ = 90º , V = 800.79(14) $Å^3$, Z = 4, D_{calc} = 1.759 g/m^3, the final R factor was R_1 = 0.0302, 1267 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.0776 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The prismatic crystal of the title compound **5** of approximately 0.30 x 0.08 x 0.04 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated CuK/α radiation (λ=0.71073Å). A total of 13229 reflections were collected in the range of $2.99 < \theta < 30.62°$ by using "phi and omega scans" techniques at 133 (2) K, $C_{15}H_{16}FNO_2$, M = 261.29, orthorhombic, P 2(1)2(1)2(1), a = 6.1648 (9) Å, α = 90º , b = 6.9841(10) Å, β =90 º,

c = 31.310(5) Å, γ = 90º , V = 1348.1(3) Å^3, Z = 4, D_{calc} = 1.287 g/m^3, the final R factor was R_1 = 0.0447, 4119 for reflections with $I > 2\sigma(I)$, R_ω=0.1079 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The prismatic crystal of the title compound **6** of approximately 0.42x 0.32 x 0.30 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated CuK/α radiation (λ=0.71073Å). A total of 5363 reflections were collected in the range of 3.60 < θ < 69.80 ° by using "phi and omega scans" techniques at 291 (2) K, $C_{16}H_{15}BrN_2$, M = 315.20, monoclinic, P 2(1)2(1)2(1), a = 21.2191 (17) Å, α = 90º , b = 5.8501(8) Å, β =90 º, c = 12.2998(10) Å, γ = 93.767º, V = 1523.5(3) Å^3, Z = 4, D_{calc} = 1.374 g/m^3, the final R factor was R_1 = 0.0469, 2533 for reflections with $I > 2\sigma(I_0)$, R_ω=0.1598 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The colorless crystal of the title compound **3c** of approximately 0.15 x 0.08 x 0.01 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated MoK/α radiation (λ=0.71073Å). A total of 4989 reflections were collected in the range of 1.51 < θ < 25.08° by using "phi and omega scans" techniques at 153 (2) K, C_8H_6BrNO, M = 212.05 orthorhombic, P 2(1)2(1)2(1), a = 4.0735(10) Å, α = 90º , b = 7.2720(18) Å, β =90 º, c = 27.007(7) Å, γ = 90º , V = 800.0(3) Å^3, Z = 4, D_{calc} = 1.761 g/m^3, the final R factor was R_1 = 0.0451, 1410 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.0848 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The colorless crystal of the title compound **8** of approximately 0.32 x 0.32 x 0.30 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated MoK/α radiation (λ=0.71073Å). A total of 10458 reflections were collected in the range of 3.96 < θ < 62.87° by using "phi and omega scans" techniques at 291 (2) K, $C_{28}H_{23}N_3$, M = 401.49, orthorhombic, P 2(1)2(1)2(1), a = 8.9552(15) Å, α = 90º , b = 14.623(3) Å, β =90 º, c = 17.320(2) Å, γ = 90º , V = 2268.1(6) Å^3, Z = 4, D_{calc} = 1.176 g/m^3, the final R factor was R_1 = 0.0623, 3632 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.1740 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The colorless crystal of the title compound **10** of approximately 0.30x 0.20 x 0.20 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated CuK/α radiation (λ=0.71073Å). A total of 4347 reflections were collected in the range of 1.51 < θ < 25.08° by using "phi and omega scans" techniques at 293 (2) K, $C_{15}H_{14}N_2O$, M = 238.28, monoclinic P 2(1), a = 10.892(4) Å, α = 90º, b = 5.6521(14) Å, β =117.76 º, c = 11.363(7) Å, γ = 90º, V = 619.0(4) Å^3, Z = 2, D_{calc} = 1.278 g/m^3, the final R factor was R_1 = 0.0694, 2009 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.1579for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

The colorless crystal of the title compound **11** of approximately 0.256x 0.211 x 0.142 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated MoK/α radiation (λ=0.71073Å). A total of 32112 reflections were collected in the range of 4.19 < θ < 67.47° by using "phi and omega scans" techniques at 273 (2) K, $C_{26}H_{25}N_3O_2$, M = 411.49, monoclinic P 2(1), a = 9.9611(4) Å, α = 90º, b = 16.5671(6) Å, β =99.979(2) º, c = 13.9107(5) Å, γ = 90º, V = 2260.90.0(15) Å^3, Z = 4, D_{calc} = 1.209 g/m^3, the final R factor was R_1 = 0.0377, 7779 for reflections with $I_0 > 2\sigma(I_0)$, R_ω=0.1086 for all data. The structures were solved by full-matrix least-squares on F^2 using the SHELXTL PROGREM.

General Procedure for the Preparation of Compounds 2-4, 6, 8,10 and 11

Aldehydes (1mmol) and TMSCN (3mmol) were added to a dry 25mL Schlenk flask under free-water and oxygen conditions. and dissolved in 2mL of dry methanol. Coordination with 20 mol% (S)-(-)-α-phenylethylamine copper acetate complex, or (R)-(+)-α-phenylethylamine copper acetate complex was accomplished at room temperature for 3 days, after slowly evapolating the ethanol and dichloromethane from the saturated solution, the first fraction was dried to afford 2a-2h; drying the second ingredient to afford **4-6**, **8** and **10**; drying the third ingredient to afford **11**; and drying the last ingredient to afford **3a** and **3c**.

2a: yield%: 34% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.55–7.62(dd, J=8Hz, 8Hz, 2H), 7.20–7.22 7.32 (d, J=7.5Hz, 1H), (t, 1H), 5.57(s, 1H), 3.39(s, 6H); ^{13}CNMR (125MHz, $CDCl_3$, 27°C) 136.4, 132.5, 129.7,127.9, 126.8, 122.6, 102.5, 53.5(x2).

2b: yield%: 34% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.40(t, J=8Hz, 5.5Hz, 2H), 7.03(t, 2H), 5.36 (s, 1H), 3.29(s, 6H); ^{13}CNMR (125MHz, $CDCl_3$, 27ºC) 128.4(x2), 115.1(x2), 114.9(x2), 102.4, 52.5(x2).

2c: yield%: 35% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.49(d, J=8Hz, 2H), 7.31(d, J=8Hz, 2H), 5.34(s, 1H), 3.29(s, 6H); 136.7(x2), 130.9(x2), 128.1(x2), 101.9, 52.2(x2).

2f: yield%: 32% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.54(t, 1H), 7.16–7.25(m, 3H), 5.46(s, 1H), 3.34(s, 6H), 2.38(s, 3H), ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 136.4, 135.8, 130.6, 128.5, 126.7, 125.5, 101.9, 53.1(x2), 19.0. HRMS(EI): m/z (%): calcd for $C_{10}H_{14}O_2$: 166.0994; found: 166.0992.

2g: yield%: 34% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.33–7.40(m, 4H), 5.38(s, 1H), 3.31(s, 6H); ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 128.0, 127.8, 101.8, 52.2.

2h: yield%: 35% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.54(t, 1H), 7.29(d, J=6Hz, 1H), 7.14(d, J=7.5Hz, 1H), 7.03(d, J=9.5Hz, 1H), 5.60(s, 1H), 3.36(s, 6H); ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 136.2, 133.8, 128.0(x2), 127.8(x2), 101.8, 52.2(x2).

2i: yield%: 28% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.32(d, J=8Hz, 2H), 7.15 (d, J=7.5Hz, 2H), 5.35(s, 1H), 3.30(s, 6H), 2.34(s, 3H); ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 128.5, 128.1, 127.8, 126.8, 126.6, 126.3, 102.7, 52.3(x2), 24.5.

2j: yield%: 30% ; ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.35(d, J=8Hz, 2H), 6.88(d, J=8Hz, 2H), 5.33(s, 1H), 3.79(s, 3H), 3.29(s, 6H); ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 160.3, 128.0(x2), 119.3(x2), 114.3, 110.0, 63.4, 55.4.

(S,R)-[2-(2-phenylethyl-2-amino)]-2-bromophenylacetonitrile (4)

yield%: 25% ; $[a]^5_D$=-100.44º (c=0.0448 CH_2Cl_2): ^{1}HNMR (300MHz, $CDCl_3$, 27°C), δ (ppm) = 7.56–7.63(m, 1H), 7.31-7.48 (m, 4H); 7.20-7.23(m, 4H); 4.19-4.26(m, 1H); 1.44(d, J=6.3Hz, 1H); ^{13}CNMR(100MHz, $CDCl_3$, 27°C) 143.5, 136.0, 135.0, 131.9, 130.6, 129.9, 129.5, 129.2, 128.7, 124.5, 119.7, 58.2, 53.7, 25.7. IR (KBr) : 3435, 3308, 3064, 3025, 2981, 2965, 2927, 2866, 2223, 1592, 1570, 1494, 129.9(x2); 129.2(x2) 1472, 1452, 1436, 1370, 1360, 1342 1310, 1291, 1275, 1210, 1189, 1114, 1085, 1059, 1050, 1027, 1003, 986, 967, 929, 836, 772, 751, 716, 705, 686, 633, 623, 592, 553, 463, 437; elemetal analysis C_{16} H_{15} Br N_2: calculated : C : 60.97% ; H : 4.80% ; N : 8.89% ; found: C : 60.47%; H : 4.69% ; N : 8.66%.

(S, R)-1-(2-bromophenyl)-1-hydroxy Acetonitrile (3a)

A colorless crystals were obtained, yield%: 30% ^{1}HNMR (300MHz, $CDCl_3$, 27°C), δ (ppm) = 7.73–7.75(dd, J=1.6, 1.6Hz, 1H), 7.62–7.65(dd, J=0.8, 0.8H, 1H), 7.42–7.46 (m, 1H), 7.26–7.34 (m, 1H), 5.87(s, 1H), 2.01 (br, 1H).

(R)-4 - Fluoro-benzoic Acid Phenylethylamine Hydrochloride (5)

A colorless crystals were obtained, yield%: 25% ; $[a]^5_D$= +21.92º (c=0.02, CH_2Cl_2): ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ

(ppm) = 7.87 (d, J=1 Hz, 2H), 7.51–7.56(m, 1H), 7.22–7.33 (m, 4H), 7.01–7.21(m, 2H), 4.73(s, 1H), 3.67(s, br, 3H), 1.57 (s, 3H); ^{13}CNMR(125MHz, $CDCl_3$, 27℃) 190.5, 158.1, 142.9, 132.3, 132.2, 128.9 , 128.8(x2), 127.8, 126.9, 120.3, 116.3, 160.0, 48.1, 27.8. IR (KBr) : 2970, 2546, 1607, 1527, 1457, 1394, 1368, 1228, 1149, 858, 785, 76 6, 698, 611; HRMS(EI):m-$C_8H_{11}N$/z (%): calcd for $C_7H_5O_2F$: 140.0274; found:140.0278.

(S,S)-[2-(2-phenylethyl-2-amino)]-4-bromophenylacetonitrile(6)

A colorless crystals were obtained. yield%: 30% ; $[a]^5_D$=-16.44º (c=0.0304 CH_2Cl_2): ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.52(d, J=6.5Hz, 2H), 7.26–7.40(m, 7H), 4.34 (s, 1H), 4.23(d, J=5Hz, 1H), 1.56 (s, 2H), 1.44 (d, J = 5 Hz, 3H), ^{13}CNMR(100MHz, $CDCl_3$, 27℃) 132.0(x2), 129.0(x2), 128.8(x3), 128.0(x2), 126.9(x2), 119.9, 118.5, 56.9, 51.8, 24.8. IR (KBr) : 3245, 2970, 2546, 1607, 1527, 1457, 1368, 1228, 1149, 1090, 856, 785, 766, 716, 698, 611; HRMS: m-CH_3/z (%):calcd for $C_{15}H_{12}N_2Br$, 301.0163; found: 301.0185.

1-(4-bromophenyl)-1-hydroxy acetonitrile (3c)

A colorless crystals were obtained. Yield% : 30% ; ^{1}HNMR (600MHz, $CDCl_3$, 27°C), δ (ppm) = 7.59(d, J=8.4Hz, 2H), 7.42(d,J=8.4Hz, 2H), 5.51(s, 1H), 2.85 (br, 1H).

Chiral Azacycloheptane Compound (8)

A colorless crystals were obtained. Yield%: 40% ; $[a]^5_D$ = +81.16 º (c=0.35, $CHCl_3$): ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.40–7.58(m, 4H), 6.83–7.14(m, 9H), 6.51–6.53 (d, J=9Hz, 1H), 6.17(s, 1H), 4.76–4.78(m, 1H), 4.59–4.62 (m,1H), 3.66–3.72(m, 1H), 3.02–3.03(m, 1H), 1.67–1.76(dd, J=11.5Hz, 11.0Hz, 3H). ^{13}CNMR (100MHz, $CDCl_3$, 27°C) 143.0, 142.1, 141.3, 139.8, 135.9, 129.4, 128.9, 128.5(x2), 128.4(x3), 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 126.9, 126.7, 126.6, 119.3, 118.6, 115.5, 60.9, 41.5, 38.3, 19.0. IR (KBr) : 3439, 3060, 3028, 3005, 2984, 2937, 2845, 2210, 1632, 1604, 1493, 1453, 1382, 1370, 1348, 1321, 1279, 1255, 1220, 1204, 1176, 1133, 1090, 1029, 967, 930, 914, 880, 789, 776, 706, 603, 591, 583, 527, 465; HRMS(EI):m/z (%): calcd for $C_{26}H_{23}N_3$ $(M\text{-}2CN)^+$: 351.1861; found:351.1872.

(R)-2-(4,5-dihydro-5-phenyl-2-oxazolyl)benzeneamine(10)

A colorless crystals were obtained. Yield%: 30% ; $[a]^5_D$= +178.57º (c=0.35, $CHCl_3$): ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.77 ~ 7.80(dd, 2Hz, 2.5Hz, 1H), 7.24–7.41(m, 6H), 6.68–6.76 (m, 2H), 6.17(s, 1H), 5.48(t, J=11.5Hz, 1H), 4.74(t, J=6Hz, 1H), ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 165.09, 148.86, 142.80, 132.32, 129.83, 128.74, 127.57, 126.64, 116.07, 115.76, 108.78, 73.12, 70.26, 29.73. IR (KBr) : 3417, 3275, 3029, 2922, 2851, 1633, 1597, 1563, 1489, 1465, 1452, 1363, 1313, 1262, 1249, 1161, 1094, 1059, 1040, 979, 953, 760, 748, 699, 680, 528, 483; HRMS(EI):m/z (%): calcd for $C_{13}H_{18}N_2O$: 238.1106; found: 238.1100.

Chiral (S, R)-N,N-bis(2-methoxyphenylcyanomethyl)-1(R)-phenylethylamine (11)

A colorless crystals were obtained. Yield%: 20 % ; $[a]^5_D$= +55.9° (c=0.098 CH_2Cl_2): ^{1}HNMR (500MHz, $CDCl_3$, 27°C), δ (ppm) = 7.66–7.68(m, 3H), 7.41–7.42 (m, 4H), 6.98-7.06(m, 4H), 6.88(d, J=7.5Hz, 2H), 4.33-4.54(m, 1H), 3.75 (s, 2H), 3.38(s, 6H), 2.02-2.04(d, J=6.5Hz, 3H); ^{13}CNMR(125MHz, $CDCl_3$, 27°C) 157.3(x2), 142.3, 131.2, 131.0, 130.3, 129.0(x2), 128.6 (x2), 128.5(x2), 128.1(x3), 127.4, 120.7(x2), 111.2(x2), 60.6, 55.2, 54.9, 50.2, 47.4, 13.9; IR (KBr) : 2917, 2848, 1601, 1590, 1494, 1463, 1438, 1382, 1326, 1292, 1257, 1190, 1113, 1051, 1028, 792, 756, 700; HRMS: calcd for $C_{26}H_{25}N_3O_2$, 411.1947; found: 411.1976.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

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