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 amine amides, 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 amine amides 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, cyanohydrid.

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 components in pharmaceuticals [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-aminoacohols mediated by ZnCl2. Our first goal is to obtain the novel oxazolylzinc 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-trimethylsililnitrile conjugated addition reaction with the derivative of chiral biamine, 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 amine amides 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 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 proic 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-11) with methanol yields compound 2, which is attributed to the nucleophilic addition of the methanol to the carbonyl group in the presence of 1 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 amine, which then conjugated with the initial TMS ether of the cyanohydrin or cyanohydrid 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 oxidation product fluorobenzaldehyde with (R)-(+) -α-phenethylamine generated 4- fluorobenzoic acid - (R)-(+) -α-phenethylamine salt (compound 5).

Accordingly, condensation of the cinnamon aldehyde with (R)-(+)-α-phenethylamine afforded compound 8 after eliminating two equivalences of water.
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. Cyanation of various aldehydes.

| Aldehydes | Catalyst | Yield (2) | Yield (%), by Products | Configa |
|-----------|----------|-----------|------------------------|---------|
| 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 novelty of this paper can be summarized as following: using methanol as solvent, R-(+)/S-(−)-α-phenylethylamine copper acetate could be
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.

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

Materials and Measurements

Benzaldehydes, R-(+)/S(-)/g1/1-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), 1H and 13C NMR and 31PNMR 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 (CDCl3, δ 7.26 ppm). The following abbreviations were used to designate chemical shift multiplicities: 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 El ion source. Optical rotations were measured on WZZ-1 automatic polarimeter with a 2 cm cell at the sodium D-line.

Structure Determination

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 MoKα radiation (λ=0.71073Å). A total of 3020 reflections were collected in the range 4.16 < 0 < 62.65° by using “phi and omega scans” techniques at 290(2) K, C16H15BrN2, 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) Å³, Z = 2, Dcalc = 1.432 g/m³, the final R factor was R 1 = 0.0421, 1729 for reflections with I0 > 2γ(I0), R =0.1154b for all data. The structures were solved by full-matrix least-squares on F² using the SHELXTL PROGRAM.

The colorless crystal of the title compound 3a of approximately 0.40 x 0.35 x 0.32 mm was selected for the data collection on a “graphite” diffractometer with mirror monochromated CuKα radiation (λ=0.71073Å). A total of 3257 reflections were collected in the range of 3.35 < 0 < 62.52 º by using “phi and omega scans” techniques at 290 (2) K, C8H6BrNO, 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 = 728.84(3) Å³, Z = 2, Dcalc = 1.432 g/m³, the final R factor was R1 = 0.0421, 1729 for reflections with I0 > 2σ(I0), R =0.0776 for all data. The structures were solved by full-matrix least-squares on F² using the SHELXTL PROGRAM.

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 CuKα radiation (λ=0.71073Å). A total of 13229 reflections were collected in the range of 2.99 < 0 < 30.62 º by using “phi and omega scans” techniques at 133 (2) K, C15H16FNO2, 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 = 90°, V = 1348.1(3) Å³, Z = 4, D_{calc} = 1.287 g/cm³, the final R factor was R₁ = 0.0474, 4119 for reflections with I > 2σ(I), R_{wp} = 0.1079 for all data. The structures were solved by full matrix least-squares on F² using the SHELXTL PROGRAM.

The prismatic crystal of the title compound 6 of approximately 0.24x 0.32 x 0.30 mm was selected for the data collection on a "graphite" diffractometer with mirror monochromated CuKα radiation (λ = 0.71073 Å). A total of 4347 reflections were collected in the range of 1.50 < 0 < 25.08° by using "phi and omega scans" technique at 291 (2) K, C₨H₧BrNO, monoclinic, P 2(1)(1/2)(1), a = 10.892(4) Å, a = 90°, b = 5.652(14) Å, β = 117.6°, c = 11.363(7) Å, γ = 90°, V = 619.0(4) Å³, Z = 2, D_{calc} = 1.728 g/cm³, the final R factor was R₁ = 0.0694, 2009 for reflections with I > 2σ(I), R_{wp} = 0.1579 for all data. The structures were solved by full-matrix least-squares on F² using the SHELXTL PROGRAM.

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 evaporating 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%; 1HNMR (500MHz, CDCl₃, 27°C), δ (ppm) = 7.55–7.62 (dd, J=8Hz, 8Hz, 2H), 7.20–7.22 (3.2d, J=7.5Hz, 1H), (1H), 5.57(s, 1H), 3.93(s, 6H); 13CNMR (125MHz, CDCl₃, 27°C) 136.4, 132.5, 127.9, 126.8, 122.6, 102.5, 53.5(x2).

2b: yield%: 34%; 1HNMR (500MHz, CDCl₃, 27°C), δ (ppm) = 7.401 (J=8Hz, 5.5Hz, 2H), 7.03(t, 2H), 5.73 (s, 1H), 3.29(s, 6H); 13CNMR (125MHz, CDCl₃, 27°C) 128.4(x2), 115.1(x2), 114.9(x2), 102.4, 52.2(x2).

2c: yield%: 35%; 1HNMR (500MHz, CDCl₃, 27°C), δ (ppm) = 7.49(d, J=8Hz, 2H), 7.31 (d, J=8Hz, 2H), 5.34(s, 1H), 3.29(s, 6H); 13CNMR(125MHz, CDCl₃, 27°C) 128.0, 127.8, 101.9, 52.2(x2).

2e: yield%: 32%; 1HNMR (500MHz, CDCl₃, 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); 13CNMR(125MHz, CDCl₃, 27°C) 126.4, 135.8, 130.6, 128.5, 126.7, 125.5, 109.1, 53.1(x2), 19.0, HRMS(ELI): m/z (%): calcd for C₁₉H₁₆O₂: 315.20, experimental, 315.20.

2f: yield%: 28%; 1HNMR (500MHz, CDCl₃, 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); 13CNMR(125MHz, CDCl₃, 27°C) 128.5, 128.1, 127.8, 126.6, 126.3, 102.7, 52.3(x2), 24.5.

2g: yield%: 30%; 1HNMR (500MHz, CDCl₃, 27°C), δ (ppm) = 7.35(d, J=8Hz, 2H), 6.88(d, J=8Hz, 2H), 5.32(s, 3H), 3.79(s, 3H), 3.29(s, 6H); 13CNMR(125MHz, CDCl₃, 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-bromophenyl]acetonitrile (4)

yield%: 25%; [α]D = -100.44° (c=0.0448 CH₂Cl₂): 1HNMR (300MHz, CDCl₃, 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, 3H); 13CNMR(100MHz, CDCl₃, 27°C) 143.5, 136.0, 135.0, 131.9, 130.6, 129.9, 129.5, 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) 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; elemental analysis C₁₆H₁₅BrN₂: calculated: C : 60.97%; H : 4.80%; N : 8.89%; found: C : 60.47%; H : 4.69% ; N : 8.66%.

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

A colorless crystals were obtained, yield%: 30%; 1HNMR (300MHz, CDCl₃, 27°C), δ (ppm) = 7.73–7.75(dd, J=1.6Hz, 1H), 7.62–7.65(dd, J=0.8, 0.8Hz, 1H), 7.42–7.46 (m, 1H), 7.26–7.34 (m, 1H), 5.87(s, 1H), 2.01 (br, 1H).

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

A colorless crystals were obtained, yield%: 25%; [α]D = +21.92° (c=0.02, CH₂Cl₂); 1HNMR (500MHz, CDCl₃, 27°C), δ
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CONFLICT OF INTEREST
The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS
This work was supported by Hefei University of Technology. The authors acknowledge University of Science and Technology of China for providing the spectral measurements conditions.

SUPPLEMENTARY MATERIAL
Supplementary material is available on the publisher’s web site along with the published article.

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