The Novel Application of Chiral α-Ethylphenyl Amine Tartaric Acid Salts-Cyanosilylation of Prochiral Aldehydes

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Abstract: The α-ethylphenylamine tartaric acid salts 1a-1d were synthesized from R- (+)/(S-) -α-ethylphenylamine by reacting with (2S,3S)-(+)/(2R,3R)-(-) dihydrobutanedioic acid. They were used as the catalysts in cyanosilylation of prochiral aldehydes to give the corresponding cyanohydrin trimethylsilyl ethers in moderate conversion at room temperature.

Keywords: α-ethylphenylamine tartaric acid salts, R- (+)/(S-) -α-ethylphenyl amine, (2S,3S)-(+)/(2R,3R)-(-) dihydrobutanedioic acid, cyanosilylation of prochiral aldehydes, cyanohydrin trimethylsilyl ethers.

INTRODUCTION

Many chiral catalysts provide good catalysis for the cyanosilylation, including Al-O [1] Ti-N [2], Mg-N complexes [3], basic cinchona alkaloid [4] chiral oxazaborolidinium ions [5], thiourea catalysts [6], and chiral amino acid salts [7]. But the scope and limitation of this reaction often makes it difficult for large scale syntheses. For example, generally, asymmetric cyanosilylation must be conducted with very little acid or base. Furthermore, the yields for the cyanosilylation of prochiral ketones are less than for cyanosilylation of prochiral aldehydes. The reported asymmetric cyanosilylation reactions were all conducted with base catalysts or bi-functional catalysts which are not easily synthesized [8].

Metal-ligands as lewis acid catalysts have been used widely in organic reactions and polymerization [9-11]. However, Brønsted acids catalysts have not been reported to date. In this paper we report for the first time, a novel application of chiral (R)-(+)/(S)-(-) -ethylphenyl amine, (2S,3S)-(+)/(2R,3R)-(-) dihydrobutanedioic acid in methanol (Fig. 1).

In addition, the crystal structure of S(-)-α-ethylphenylamine (2R,3R)-(-) dihydrobutanedioic acid salt (Fig. 2) was obtained.

EXPERIMENTAL SECTION

General Procedures

All cyanosilylation reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel coated glass plates (60F-254) using UV light to visualize the course of reaction. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.02 – 0.03 mm). Chemical conversion were obtained by 1HNM,13CNMR,H and 13C NMR spectra were obtained using a Bruker AM-300, Bruker AM-400 spectrometer. The following abbreviations were used to designate chemical shifts multiplicities: s = singlet, d = doublet, t = triplet, m =multiplet, Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 Spectrometer. High resolution mass spectra were obtained on Micro GCT-MS, Optical rotations were measured on WZZ-1 automatic polarimeter.

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Fig. (1). Synthetic routes of the catalysts 1a-1h.
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The Open Catalysis Journal, 2010, Volume 3  89

Fig. (2). Crystal structure of 1c.

program and refined isotropically in the riding mode with fixed thermal factors. The final cycle of refinement gave rise to $R=0.0331$ and $w=1.023$, $\langle \Delta/\sigma \rangle_{\text{max}}=0.000$, and $\langle \Delta/\sigma \rangle_{\text{mean}}=0.000$. The molecular graphics were drawn with the Brucker SHELXTL program package [12, 13].

1a: Preparation of R-(+)-α-Ethylphenyl Amine -(2R,3R)-(-)-2,3-Dihydroxybutanedioic Acid Salt

6.3g of (-)-tartaric acid was dissolved in 90ml methanol, and 5g R-a-phenylethylamine was slowly added in a dry 250ml cone bottle, motionless above 24h, the single crystals were obtained 3.5g, 31% in yield melting point: 66-68 ºC, $[\alpha]_D^{25}=-13.9^\circ$ (c=1.72, CH 3OH); 1HNMR (300MHz,CD 3OD, 27), (ppm)= 7.38~7.48(m, 5H), 4.89(s, 5H),4.43~4.48(m, 1H), 4.40 (s, 2H), 1.62~1.64(d, J=5.16,3H), 13CNMR: 20.80(x2), 52.27,74.20,127.69,130.04,130.24,139.89,177.07,IR:3274,3193,2950,2867,2838,1710,1597,1436,1354,1309,165,1089,920,898,813,754,706,669,548,577,532; HRMS(EI): m/z(%): calcd for C14H26N2O:271.1056; found: 271.1053.

1b: Preparation of R-(+)–Ethylphenyl Amine -(2S,3S)-(+)-2,3-Dihydroxybutanedioic Acid Salt

The same procedure described 1a, $[\alpha]_D^{25}=+13.1^\circ$ (c=1.42, CH3OH).

1c: Preparation of S-(-)-Ethylphenyl Amine -(2R,3R)-(-)-2,3-Dihydroxybutanedioic Acid Salt

6.3g of (-)-tartaric acid was dissolved in 90ml methanol, and 5g a-ethylphenyl amine was slowly added in a dry 250ml cone bottle, motionless above 0.5h, concentrated in vacuo, recrystallized in hexane, white solid was obtained 4.5g, melting point:66-68 ºC, $[\alpha]_D^{25}=-15.2^\circ$ (c=0.88, H2O).

1f: Preparation of α-Ethylphenyl Amine-(2S,3S)-(+)-2,3-Dihydroxybutanedioic Acid Salt

The same procedure described 1e, melting point: 66-68 ºC, $[\alpha]_D^{25}=15.4^\circ$ (c=1.03, H2O).

1g: Preparation of R-(+)-α-Ethylphenyl Amine-2,3-Dihydroxybutanedioic Acid Salt

The same procedure described 1e, melting point: 64-66 ºC, $[\alpha]_D^{25}=16.9^\circ$ (c=0.8, H2O).

1h: Preparation of S-(-)-α-Ethylphenyl Amine-2,3-Dihydroxybutanedioic Acid Salt

The same procedure described 1e, melting point: 68-70 º C, $[\alpha]_D^{25}=14.8^\circ$ (c=0.8, H2O).

1i: Preparation of R-(+)-α-(Trimethylsilyloxyl)-Phenylacetonitrile

0.15g(0.55mmol) was dissolved in 5ml hexane, benzaldehyde 0.2ml (1.98 mmol) and TMSCN (0.4 ml,3.00mmol)were successively added at room temperature. After 40h, the reaction were quenched. and the mixture was extracted with dichloromethane (3x10ml), the combined organic layers was dried over Na2SO4,concentrated in vacuo, further purification was performed by silica gel (petroleum/dichloromethane 4/1).

The title compound was obtained as a colorless oil, conversion =78 %, $^1$HNMR (300MHz, CDCl3) 7.56–7.59 (m, 0.9 Hz, 2H), 7.31–7.34 (m, 3H), 5.43 (s, 1H),0.16 (s, 9H). 13C NMR (75 MHz, CDCl3) 136.1, 128.8(x2), 126.2(x2), 119.1, 63.5, -0.39(x3). HRMS(EI): m/z(%)=:calcd for C11H15NOSi: 205.0923; found: 205.0922.

1j: R-(+)-2-(2-Furyl-Phenyl)-2-(Trimethylsilyloxy)Acetonitrile

The same procedure described 1i, the title compound was obtained as a colorless oil, conversion =78 %, $^1$HNMR (300MHz, CDCl3) 7.56–7.59 (m, 0.9 Hz, 2H), 7.31–7.34 (m, 3H), 5.43 (s, 1H),0.16 (s, 9H). $^1$C NMR (75 MHz, CDCl3) 136.1, 128.8(x2), 126.2(x2), 119.1, 63.5, -0.39(x3). HRMS(EI): M-15/z calcd for C10H11NOSiF:208.0594, Found:205.0583.

1k: R-(+)-2-(4-Methoxyphenyl)-2-(Trimethylsilyloxy)Acetonitrile

The same procedure described 1i, the title compound was obtained as a colorless oil, conversion =34%, $^1$HNMR (300MHz, CDCl3) 7.38–7.40 (m, 2H), 6.91-6.93 (m, 2H), 5.44(s, 1H), 3.81(s,0.2), 0.21(s, 9H). $^1$C NMR (75 MHz, CDCl3) 160.4,128.6,127.9,119.4,114.3,63.4,55.3,-0.45(x3). HRMS(EI):M-15/z calcd for C12H17NO2Si:235.1029 Found:235.1024.
5.48 (s, 1H), 2.38 (s, 3H), 0.24 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) 139.3, 133.5, 129.6, 126.4, 63.6, 31.6, 22.6, 21.2, 14.1, -0.23 (x3). HRMS (EI) calcd for C$_{12}$H$_{17}$NOSi: 219.1079, Found: 219.1084

1m: (+)-2-(Trimethylsilyloxy)Pentanenitrile

The same procedure described in 1i, the title compound was obtained as a colorless oil, conversion = 77%, $^1$HNMR (300 MHz, CDCl$_3$) 4.35-4.39 (t, J = 0.042 Hz, 1H), 1.70-1.74 (m, 2H), 1.43-1.49 (m, 2H), 0.89-0.95 (m, 3H), 0.17 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$) 120.0, 61.2, 38.2, 16.8, 13.3, -0.50 (x3). HRMS (EI): m/z(%): calcd for C$_8$H$_{17}$NOSi: 171.1079; found: 171.1081.

RESULTS AND DISCUSSION

Our initial catalyst screening was done in THF solvent with a 28% mol catalyst (1a-1d) loading condition. It was found that catalyst 1a showed relatively good reactivity (Table 1). The reason for catalyst loading at 28%mol is that it allowed the catalyst to be measured at a weight (0.15 g) that could be done accurately. In order to get higher conversion, we prolonged the reaction time. However, after several experiments, we also found that according to the molar ratio of benzaldehyde/TMSCN (1:1.5), even if the reaction time was prolonged to 5 days, the $^1$HNMR showed not much improvement in conversion. The reason is probably closely connected with the structure of the catalyst, and is more important if the catalyst is a Bronsted acid. In fact, we were pleased to find that if α-ethylphenyl amine was used, the conversion was >99% within 24h.

Table 1. Catalysts Effect

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Catalyst</th>
<th>Conv. %</th>
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</thead>
<tbody>
<tr>
<td>1i</td>
<td>O</td>
<td>1a</td>
<td>67</td>
</tr>
<tr>
<td>1j</td>
<td>O</td>
<td>1a</td>
<td>78</td>
</tr>
<tr>
<td>1k</td>
<td>O</td>
<td>1a</td>
<td>34</td>
</tr>
<tr>
<td>1l</td>
<td>O</td>
<td>1a</td>
<td>33</td>
</tr>
<tr>
<td>1m</td>
<td>O</td>
<td>1a</td>
<td>77</td>
</tr>
</tbody>
</table>

Optimization of the solvents effects such as in hexane, ether, toluene, isopropanol, dichloromethane with 28mol% catalyst 1a and 1d, the results are summarized in Table 2, and hexane was the solvent of best choice, which gave the yield 67%.

Table 2. Solvents Effect

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Conv. %</th>
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<tbody>
<tr>
<td>1a</td>
<td>CH$_2$Cl$_2$</td>
<td>48</td>
</tr>
<tr>
<td>1a</td>
<td>Isopropanol</td>
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<tr>
<td>1d</td>
<td>Ether</td>
<td>36</td>
</tr>
<tr>
<td>1d</td>
<td>Isopropanol</td>
<td>18</td>
</tr>
</tbody>
</table>

**Table 3. Cyanosilylation of Aldehydes Catalyzed by 1a and 1da**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Catalyst</th>
<th>Conv.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1i</td>
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<td>1a</td>
<td>67</td>
</tr>
<tr>
<td>1j</td>
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<td>1a</td>
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<td>1k</td>
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<td>1a</td>
<td>77</td>
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</table>

$^*$The room temperature is around 10-20°C, $^b$The conversion (%) was given by $^1$HNMR (CDCl$_3$).
Encouraged by the results achieved in the presence of 28 mol % catalyst 1a in hexane at room temperature (around 10-20°C), the asymmetric cyanosilylation of aromatic aliphatic aldehydes was also investigated under the optimized reaction conditions. After screening, we obtained some results with moderate to excellent enantioselectivity as displayed in Table 3. The aromatic aldehydes and aliphatic aldehydes such as 2-FPhCHO, 4-OCH3PhCHO, 4-CH3 PhCHO, and C3H7CHO afforded the corresponding trimethylsilyl ethers in 78%, 34%, 33%, and 77% conversion respectively. To further improve the conversion, we found that when the molar ratio of aldehyde to TMSCN was changed to 1:5, after 3 days, the conversions were nearly all >99%.

A probable reaction mechanism that can be proposed is that the proton acid can greatly active the C=O bond, increasing the electrophilic reactivity of the carbon atom, which can then accept the nucleophilic attack of CN'.

CONCLUSIONS

In conclusion, the novel catalysts used in the cyanosilylation of prochiral aldehydes have been reported here for the first time with moderate yield and good enantioselectivity at room temperature. The use of these catalysts in other applications such as in Aldol reactions, the Henry ions, and allylation reactions are all in progress.

REFERENCES