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Tetrahedron Letters 46 (2005) 2223–2226
Tetrahedron Letters

An efficient catalytic asymmetric addition of trimethylsilyl cyanide to aldehydes at room temperature

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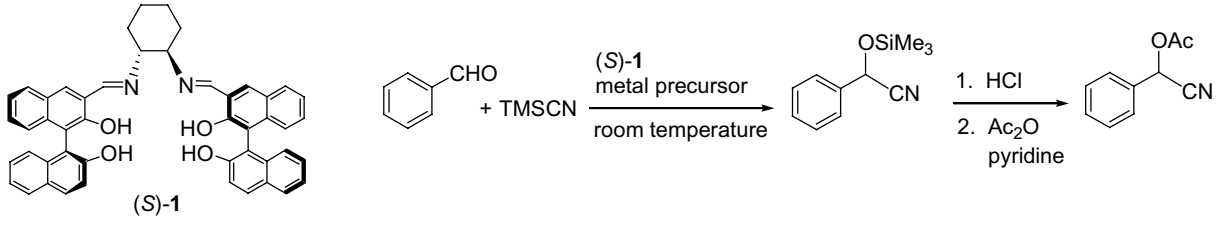
Received 30 December 2004; revised 3 February 2005; accepted 4 February 2005

Abstract—The BINOL–salen compound (*S*)-**5c** in combination with $Ti(O^iPr)_4$ is found to catalyze the addition of TMSCN to aldehydes to form chiral cyanohydrins with very good enantioselectivity (75–85% ee). The reactions are carried out in one-pot at room temperature without the need to isolate the chiral Lewis acid catalyst.

The asymmetric syntheses of cyanohydrins have attracted considerable research activity because these compounds are versatile starting materials for many functional organic molecules such as α-hydroxyacids, α-hydroxyketones, α-amino acids, and β-amino alcohols.[1] Among the methods developed for the asymmetric cyanohydrin syntheses, use of the titanium complexes derived from the chiral Schiff base of salicylaldehydes (salen) as catalysts has given very good results in a number of cases.[1,2] However, most of the reactions require the pre-preparation of the catalysts or/and low temperature reaction conditions.[1,2] It is highly desirable if the asymmetric reaction could be conducted by simply combining the chiral ligand, the metal precursor, the substrate and the reagent in one-pot at room temperature to form the cyanohydrin product with high enantioselectivity. Herein, we wish to report our progress toward this objective by using chiral 1,1′-bi-2-naphthol (BINOL)–salen ligands in combination with a Lewis acid metal precursor for the asymmetric reaction of aldehydes with trimethylsilyl cyanide (TMSCN). Very good enantioselectivity has been achieved.

Recently, we reported that the BINOL–salen compound (*S*)-**1**[3] could catalyze the addition of both aryl and alkyl alkynes to aromatic aldehydes at room temperature to form propargylic alcohols with high enantioselectivity (up to 97% ee).[4] We also explored the use of this ligand for the asymmetric cyanohydrin synthesis at room temperature (Scheme 1). We initially employed a two-step process for this reaction.[5] A chiral metal complex was first isolated from the reaction of (*S*)-**1** with a Lewis acid metal precursor. It was then used to catalyze the reaction of TMSCN with benzaldehyde. The resulting cyanohydrin was converted to the corresponding acetate for ee measurement by using GC-chiral column. The results of these reactions are summarized in Table 1. In entries 1–8 of Table 1, $Ti(O^iPr)_4$ was used as the Lewis acid. Various solvents including methylene chloride, toluene, THF and diethyl ether were examined among



Scheme 1. Asymmetric cyanohydrin synthesis catalyzed by (*S*)-**1** in combination with Lewis acids.

Keywords: Cyanohydrin; Enantioselective; Trimethylsilyl cyanide addition; Aldehydes; Salen; BINOL.
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doi:10.1016/j.tetlet.2005.02.028

Table 1. Asymmetric addition of trimethylsilyl cyanide to benzaldehyde in the presence of (*S*)-**1**

Entry	(*S*)-**1** (%)	TMSCN (equiv)	Lewis acid complex	Solvent	Time (h)	Ee (%)
1	20	4	$Ti(O^iPr)_4$ (20%)	CH_2Cl_2	22	46
2	20	4	$Ti(O^iPr)_4$ (20%)	Toluene	22	14
3	20	4	$Ti(O^iPr)_4$ (20%)	THF	22	14
4	20	4	$Ti(O^iPr)_4$ (20%)	Ether	22	15
5	10	4	$Ti(O^iPr)_4$ (10%)	CH_2Cl_2	22	66
6	10	4	$Ti(O^iPr)_4$ (10%)[a]	CH_2Cl_2	22	48
7	0.5	4	$Ti(O^iPr)_4$ (0.5%)	CH_2Cl_2	36	69
8	0.05	4	$Ti(O^iPr)_4$ (0.05%)	CH_2Cl_2	60	26
9	10	4	$TiCl_4$ (10%)	CH_2Cl_2	22	45
10	0.5	4	$TiCl_4$ (0.5%)	CH_2Cl_2	36	34
11	10	4	$AlMe_2Cl$ (10%)	CH_2Cl_2	22	15
12	0.5	4	$AlMe_2Cl$ (0.5%)	CH_2Cl_2	36	40
13	10	4	$ZrCl_4$ (10%)	CH_2Cl_2	18	2
14	10	4	$CeCl_3$ (10%)	CH_2Cl_2	22	17
15	10	4	$O{=}VSO_4$ (10%)	CH_2Cl_2	20	52

[a] 10% $O{=}P(Ph)_3$ was added.

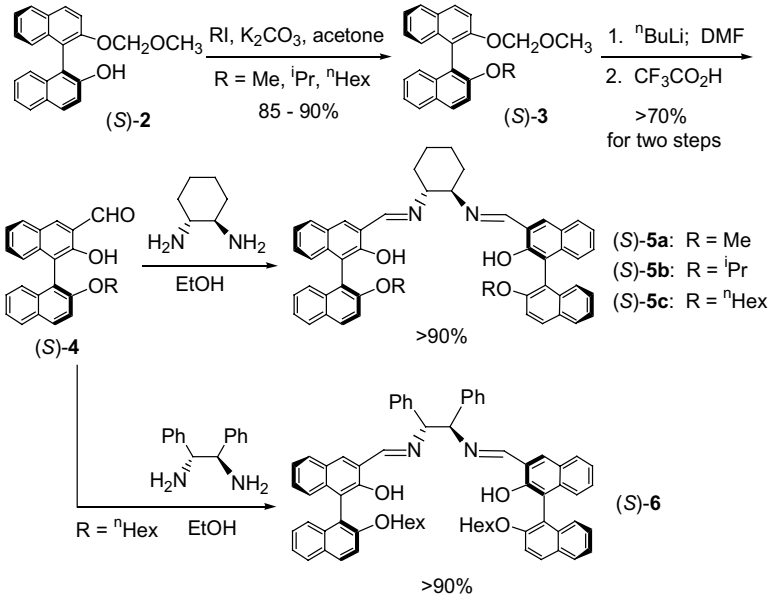
which methylene chloride was found to be the best (Table 1, entries 1–4). Decreasing the catalyst loading to 10 mol % improved the ee (Table 1, entry 5). Addition of a Lewis base reduced the enantioselectivity (Table 1, entry 6). Further decreasing the catalyst loading to 0.5 mol % slightly improved the ee, but gave much lower reaction rate (Table 1, entry 7). At an even lower catalyst loading of 0.05 mol %, the enantioselectivity was significantly decreased (Table 1, entry 8). Other Lewis acids besides $Ti(O^iPr)_4$ were also tested but no improvement was observed (Table 1, entries 9–15).

Since the highest ee observed with the use of (*S*)-**1** was only 69% (Table 1, entry 6), modification of the chiral ligand was conducted. Scheme 2 shows the synthesis of a series of BINOL–salen ligands. The mono-protected BINOL (*S*)-**2**[6] was reacted with various alkyl iodides to give (*S*)-**3**. *ortho*-Metallation[7] of (*S*)-**3** by reaction with ^{n}BuLi followed by addition of DMF and deprotection with trifluoroacetic acid gave the binaphthyl aldehyde (*S*)-**4**. Condensation of (*S*)-**4** with chiral diamines in ethanol gave the BINOL–salen ligands (*S*)-**5a**–**c** and (*S*)-**6**.[8,9] In these ligands, various sizes of alkyl groups were introduced in order to modify both the steric and electronic environments of (*S*)-**1**.

Compounds (*S*)-**5a**–**c** and (*S*)-**6** in combination with $Ti(O^iPr)_4$ were used to catalyze the reaction of benzaldehyde with TMSCN at room temperature and the results are summarized in Table 2. Compound (*S*)-**5a** that con-

Table 2. Reactions of TMSCN with benzaldehyde in the presence of ligands (*S*)-**5a**–**c** and (*S*)-**6**

Entry	Ligand (12%)	TMSCN (equiv)	$Ti(O^iPr)_4$ (%)	Solvent	Time (h)	Ee (%)
1	(*S*)-**5a**	4	10	CH_2Cl_2	22	52
2	(*S*)-**5b**	4	10	CH_2Cl_2	4	66
3	(*S*)-**5c**	4	10	CH_2Cl_2	4	84
4	(*S*)-**6**	4	10	CH_2Cl_2	4	32
5	(*S*)-**6**	4	10	Toluene	6	18



Scheme 2. Synthesis of the BINOL–salen ligands (*S*)-**5a**–**c** and (*S*)-**6**.

Table 3. Reactions of TMSCN with benzaldehyde in the presence of (*S*)-**5c** and $Ti(O^iPr)_4$

Entry	Ligand (%)	TMSCN (equiv)	Lewis acid	Solvent	Temperature	Time (h)	Ee (%)
1	10	4	$Ti(O^iPr)_4$ (10%)[a]	CH_2Cl_2	Rt	4	84
2	10	4	$Ti(O^iPr)_4$ (10%)	CH_2Cl_2	Rt	4	85
3	10	4	$AlMe_2Cl$ (10%)	CH_2Cl_2	Rt	18	3
4	10	4	$Ti(O^iPr)_4$ (15%)	CH_2Cl_2	Rt	2.5	55
5	10	4	$Ti(O^iPr)_4$ (8%)	CH_2Cl_2	Rt	3	82
6	25	4	$Ti(O^iPr)_4$ (20%)	CH_2Cl_2	Rt	4	80
7	12	4	$Ti(O^iPr)_4$ (10%)	CH_2Cl_2	Rt	3	85
8	12	4	$Ti(O^iPr)_4$ (10%)[b]	CH_2Cl_2	Rt	3	85
9	12	4	$Ti(O^iPr)_4$ (10%)[c]	CH_2Cl_2	Rt	3	86
10	12	2	$Ti(O^iPr)_4$ (10%)	CH_2Cl_2	Rt	4	85
11	12	2	$Ti(O^iPr)_4$ (10%)[b]	CH_2Cl_2	−20 °C	4	89

[a] The isolated BINOL–salen–Ti(IV) complex was used.
[b] 10% $O{=}PPh_3$ was added.
[c] 4 Å molecular sieves were added.

tains a methyl group in each of the two BINOL units showed lower enantioselectivity than (*S*)-**1** (Table 2, entry 1). Increasing the size of the methyl group of (*S*)-**5a** to the isopropyl group of (*S*)-**5b** improved the enantioselectivity but it was still lower than that of (*S*)-**1** (Table 2, entry 2). Surprisingly, replacing the methyl and isopropyl groups of (*S*)-**5a**,**b** with the hexyl groups in (*S*)-**5c** led to very good ee (Table 2, entry 3). Changing the diamine unit from the more rigid cyclohexanediamine of (*S*)-**5a**–**c** to the more flexible 1,2-diphenylethylenediamine of (*S*)-**6** gave greatly decreased enantioselectivity (Table 2, entries 4 and 5). These studies demonstrate that ligand (*S*)-**5c** is the best in the catalytic asymmetric reaction with very good enantioselectivity.

We further explored the conditions for the reaction of TMSCN with benzaldehyde catalyzed by (*S*)-**5c** in combination with $Ti(O^iPr)_4$. We attempted to simplify the reaction procedure by mixing ligand (*S*)-**5c** with $Ti(O^iPr)_4$ in methylene chloride followed by the addition of benzaldehyde and TMSCN in one-pot at room temperature without the pre-preparation and isolation of the titanium complex.[11] As shown in Table 3, this simplified procedure (entry 2) gave the same enantioselectivity as that used the isolated catalyst (entry 1). All the other entries in Table 3 used this simplified procedure. Replacement of $Ti(O^iPr)_4$ with $AlMe_2Cl$ gave diminished enantioselectivity (Table 3, entry 3). Increasing the amount of $Ti(O^iPr)_4$ significantly reduced the ee (Table 3, entry 4) and decreasing the amount of $Ti(O^iPr)_4$ also slightly decreased the ee (Table 3, entry 5). Increasing the amount of the chiral ligand, reducing the ratio of $Ti(O^iPr)_4$ versus (*S*)-**5c**, adding a Lewis base, reducing the amount of TMSCN, or using molecular sieves all could not further improve the enantioselectivity (Table 3, entries 6–9). Lowering the reaction temperature to −20 °C only led to a small increase in ee (Table 3, entry 11). The configuration of the cyanohydrin product in the reaction catalyzed by (*S*)-**5c** and $Ti(O^iPr)_4$ was determined to be *S* by comparing the optical rotation of the product with that in the literature.

The reaction conditions in entry 2 of Table 3 were applied to the reaction of various aldehydes with TMSCN. The following results were obtained for the TMSCN addition to several aromatic and aliphatic aldehydes in the presence of (*S*)-**5c** and $Ti(O^iPr)_4$: 85% ee and 78% yield for benzaldehyde; 80% ee and 68% yield for *p*-methoxybenzaldehyde; 85% ee and 70% yield for *p*-methylbenzaldehyde; and 75% ee and 64% yield for octyl aldehyde.

In summary, we have found that the BINOL–salen compound (*S*)-**5c** in combination with $Ti(O^iPr)_4$ can catalyze the addition of TMSCN to aldehydes to form chiral cyanohydrins with very good enantioselectivity. The reactions can be carried out in one-pot at room temperature without the need to isolate the chiral Lewis acid catalyst.

Acknowledgements

We thank the National Institute of Health (R01GM58454/R01EB002037) for support of this research.

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5. The general procedure: (1) Catalyst preparation. Under nitrogen, to a solution of the ligand, a Lewis acid complex was added. The resulting mixture was stirred at room temperature for 2 h. The solvent was then removed under vacuum. The residue was washed with the dry solvent and then dried under vacuum for another hour. (2) Asymmetric catalysis. Benzaldehyde and TMSCN were added to the solution of the catalyst under nitrogen at room temperature. The reaction was monitored by TLC. After the reaction was complete, 1 N HCl was added and the resulting mixture was stirred for 1 h. CH_2Cl_2 was added for extraction. The organic layer was combined with Ac_2O (5 equiv) and pyridine (1 equiv), and the mixture was stirred for another hour. This gave an acetate product, which was purified on a short silica gel column eluted with hexane/ethylacetate (20:1). The ee of the product was determined by GC analysis. The instrument and conditions: HP 6890 series GC, Supelco Beta-Dex 120 fused silica capillary column (30 m length × 0.25 mm ID × 0.25 mm film thickness). Flow rate: 1.0 mL/min. Inlet temperature: 250 °C. FID detector: 280 °C. Isothermal at 160 °C for cyano(phenyl)methyl acetate.
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8. The general procedure for the ligand synthesis: To a solution of (*S*)-**4** in ethanol, the chiral diamine (0.5 equiv) was added. The mixture was heated at reflux under nitrogen for 1 h and then stirred at room temperature for additional 18 h. The product was obtained as a yellow solid, which could be further purified by recrystallization from ethanol and hexane.
9. Characterization of the ligands. For (*S*)-**5a**:[10] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.04 (s, 2H), 8.50 (s, 2H), 8.00–7.67 (m, 8H), 7.46–7.02 (m, 14H), 3.53 (s, 6H), 3.35 (m, 2H), 2.01–1.32 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.6, 154.6, 134.0, 133.5, 129.9, 129.7, 128.9, 128.5, 128.3, 127.6, 126.7, 125.3, 125.0, 123.9, 123.3, 117.3, 114.9, 73.1, 57.1, 33.0, 24.3. Mp 194–195 °C. $[\alpha]_D$ −554.6 (*c* 0.50, THF). For (*S*)-**5b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 13.02 (s, 2H), 8.48 (s, 2H), 7.96–7.60 (m, 8H), 7.44–7.02 (m, 14H), 4.27 (m, 2H), 3.34 (m, 2H), 2.02–1.26 (m, 8H), 0.74 (m, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 154.2, 134.2, 133.4, 130.0, 129.6, 128.9, 128.8, 128.5, 128.3, 127.4, 126.5, 125.6, 125.3, 124.0, 123.3, 120.5, 118.9, 73.4, 72.8, 33.1, 24.3, 22.5. Mp 162–164 °C. $[\alpha]_D$ −392.0 (*c* 0.50, THF). MS Calcd for $C_{54}H_{51}N_2O_4$ (MH^+): 791.4. Found: 791.5. For (*S*)-**5c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (s, 2H), 8.02 (d, 2H, J = 9 Hz), 7.92 (m, 2H), 7.75 (s, 2H), 7.69 (m, 2H), 7.52 (d, 2H, J = 9 Hz), 7.93–7.34 (m, 2H), 7.30–7.19 (m, 8H), 7.13 (m, 2H), 4.07–3.93 (m, 4H), 3.37 (m, 2H), 2.02 (m, 2H), 1.86 (m, 2H), 1.74–1.71 (m, 2H) 1.47–1.34 (m, 6H), 0.70 (t, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 154.6, 154.4, 135.4, 133.8, 133.1, 129.5, 128.5, 128.0, 127.8, 127.2, 126.3, 125.3, 125.2, 124.9, 123.6, 122.9, 120.5, 119.7, 117.3, 116.0, 72.2, 69.7, 32.7, 31.1, 29.1, 25.2, 23.9, 22.4, 13.9. Mp 112–113 °C. $[\alpha]_D$ −413.0 (*c* 0.50, THF). MS Calcd for $C_{60}H_{63}N_2O_4$ (MH^+): 875.5. Found: 875.1. For (*S*)-**6**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.77 (s, 2H), 8.51 (s, 2H), 8.03-7.87 (m, 4H), 7.66 (s, 2H), 7.56–7.49 (m, 4H), 7.33–7.05 (m, 22H), 4.69 (s, 2H), 3.91 (m, 4H), 2.18 (s, 2H), 1.91–0.90 (m, 14H), 0.69 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 154.6, 139.1, 136.0, 134.1, 129.8, 128.9, 128.6, 128.4, 127.9, 126.7, 125.6, 125.2, 123.9, 123.3, 120.8, 119.9, 117.8, 116.5, 81.0, 70.1, 31.6, 29.5, 25.5, 22.8, 14.3. $[\alpha]_D$ −64.2 (*c* 0.50, THF). MS Calcd for $C_{68}H_{65}N_2O_4$ (MH^+): 973.5. Found: 973.4.
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11. The general procedure. Under nitrogen, to a solution of the chiral ligand, the Lewis acid metal precursor was added. The resulting mixture was stirred at room temperature for 2 h. An aldehyde and TMSCN were added into the solution directly. The reaction was monitored by TLC. The workup and the ee determination were the same as described in reference.[5]