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Synthesis of Novel Oxazolines and Application in Cyanosilylation of Prochiral Ketones

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ABSTRACT: *A new family of oxazolines was synthesized in high yields and was characterized by NMR, IR, and MS. Oxazoline–lanthanide complexes, as the novel Lewis acid catalysts, were applied to the asymmetric cyanosilylation of ketones that gave the corresponding cyanohydrin trimethylsilyl ethers in moderate yields and enantioselectivities under mild conditions.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:679–683, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20374

INTRODUCTION

The cyanosilylation reaction catalyzed by organometallic complexes has been developed for many years. The products are chiral cyanohydrins, which are precursors to the chiral α-hydroxyacids, α-amino acids, and β-amino alcohols. Shibasaki and coworkers [1–5], Ryu and Corey [6], Keith and Jacobsen [7], Deng and coworkers [8], Snapper and Hoveyda [9], and Feng and coworkers [10–13] have developed many catalysts for this field.

Oxazoline ligands, with a great deal of structural diversity, have been proved as good auxiliaries in the asymmetric cyanosilylation of aliphatic and aromatic aldehydes [14,15]. Inspired by the pioneering work, we also devised the novel oxazolines (**S-1** and **S-2**), which contain piperidino and an amine N-atom, through complexation with the metal ions. These could form bidentate complexes, binding as a planar unit. Their steric effect can be turned by the choice of different substrates.

Generally, the synthesis of the oxazolines involves two steps: (1) condensation of aminoalcohol with diethyl carboxylates to form hydroxyl amide derivatives and (2) treatment of these amides with $SOCl_2$ to form the chloride derivatives, which when exposed to a base furnished the oxazolines in good yields.

In this paper, we adopted one-pot, efficient method to synthesize five oxazolines [16]. The ligands (Scheme 1) selected were prepared from 3-(1-piperidino)propionitrile, 3-(1-piperidino)nitrile, and L-amino alcohol in chlorobenzene under water-free and oxygen-free conditions; 60–90 mg of $ZnCl_2$ was dried under vacuum, and it acted as the Lewis acid catalyst in this reaction. The synthesis route is shown in Scheme 2. The structures of these compounds, **S-1** and **S-2a–2d**, were characterized by NMR, IR, and MS (see Experimental).

NMR spectra of **S-1**, **S-2a–2d** clearly showed the protons of oxazol and piperidino heterocycles.

IR spectra of **S-1**, **S-2a–2d** showed characteristic bands at 1468–1668 cm^{-1} (C=N), 1353–1360 cm^{-1}

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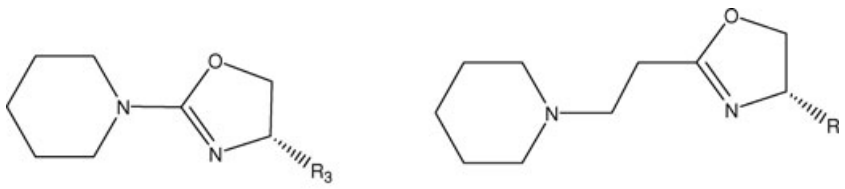
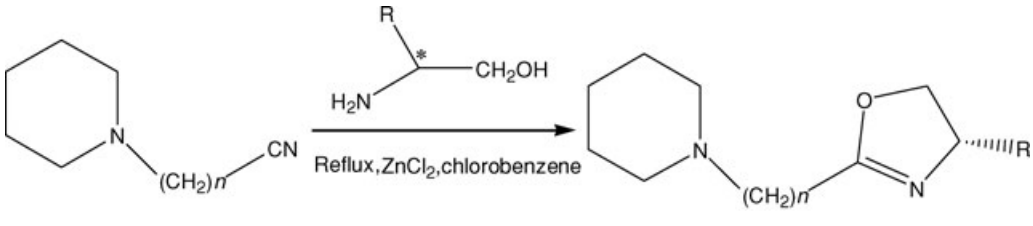


SCHEME 1



SCHEME 2

(C—N), and 1155–1174 cm^{-1} (C—O—C). HRMS of **S-1**, **S-2a–2d** proved the exact structures of the ligands.

To assess the catalytic reactivity of **S-1**, **S-2a–2d** and their complexes, $DyCl_3$ was used to investigate the enantioselective addition of trimethylsilyl cyanide (TMSCN) to acetophenone. It was found that the steric hindrance of different R groups (phenyl, benzyl, *i*-butyl, and isopropyl) in oxazol heterocycle played an important role in the enantioselectivity. A phenyl-substituted catalyst (entry 3) showed better enantioselectivity than did alkyl-substituted catalysts.

To improve the catalyst activity, different metal ions, La^{3+}, Sm^{3+}, Pr^{3+}, Nd^{3+}, Zn^{2+}, and Cu^{2+}, were evaluated when the reaction time was extended to 83 h. Although La and Sm catalysts showed remarkable reactivities, they gave a low- enantiomeric excess (ee) (Table 2, entries 1 and 2). These results are summarized in Table 2.

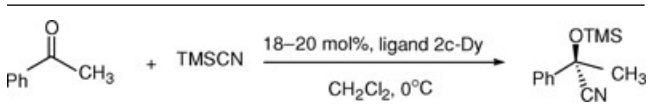
During the experiment, because $DyCl_3$ was used and the catalytic activity of 2c-La was nearly the same as that of 2c-Dy, we employed 2c-La as the catalyst in the latter study.

By comparing the effect of solvents on this reaction, it was found that CH_2Cl_2 provided a relatively good enantioselectivity, lowered the reaction temperature, and resulted in relative enhancement in enantioselectivity, although it did decrease the reactivity relatively (Table 3, entry 4).

Different ketones were investigated by using the novel catalyst 2c-La under the present optimum conditions (as shown in Table 4). Substrates bearing electron-donating groups (entries 5 and 6) were more active than those with electron-withdrawing groups after 120 h, but curiously, they afforded the relatively lower enantioselectivites.

In summary, the first novel oxazoline–lanthanide catalysts have been reported for

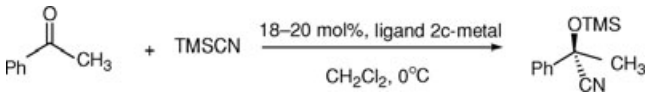
TABLE 1 The Effect of Different Ligands on the Cyanosilylation of Acetophenone[a] [10]



Entry	*Ligand*	*Time (h)*	*Conversion (%)[b]*	*ee (%)[c]*
1	R:$CH_2CH(CH_3)_2$	48	30	6
2	R:$CH(CH_3)_2$	48	29	5
3	R:Ph	48	32	10
4	R:CH_2Ph	48	31	7
5	S-1	48	42	4

[a]Reaction was carried out with 2c-Dy complex 2:1 at 0°C and CH_2Cl_2 solvent.
[b]The yield (%) was given by ^1H NMR ($CDCl_3$).
[c]Determined by HPLC on a Chiralcel OD column.

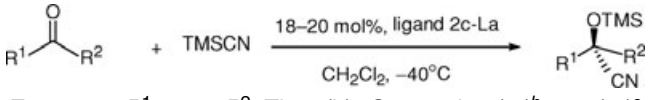
TABLE 2 The Effect of Different Ln^{3+} on Cyanosilylation of Acetophenone[a] [10]



Entry	*Ion*	*Time (h)*	*Conversion (%)[b]*	*ee (%)[c]*
1	La^{3+}	83	>99	4
2	Sm^{3+}	83	>99	3
3	Pr^{3+}	83	60	4
4	Nd^{3+}	83	65	2
5	Zn^{2+}	83	48	4
6	Cu^{2+}	83	27	3

[a]Reaction was carried out with 2c-metal complex 2:1 at −40°C, 18 mol%, and CH_2Cl_2 solvent.
[b]The yield (%) was given by ^1H NMR ($CDCl_3$).
[c]Determined by HPLC on a Chiralcel OD column.

TABLE 4 The Cyanosilylation of Ketones Catalyzed by Rare Earth Complex 2c-La [10]



Entry	R^1	R^2	*Time (h)*	*Conversion (%)[b]*	*ee (%)[c]*
1	C_6H_5	CH_3	95	35	8
2	2-$OCH_3C_6H_4$	CH_3	120	40	9
3	2-$CH_3C_6H_4$	CH_3	120	38	10
4	4-$CH_3C_6H_4$	CH_3	120	31	6
5	4-BrC_6H_4	CH_3	120	25	12
6	4-ClC_6H_4	CH_3	120	29	16

[a]Reaction was carried out with 2c-La complex 2:1 at −40°C, 18–20 mol%, and CH_2Cl_2 solvent.
[b]The yield (%) was given by ^1H NMR ($CDCl_3$).
[c]Determined by HPLC on a Chiralcel OD column.

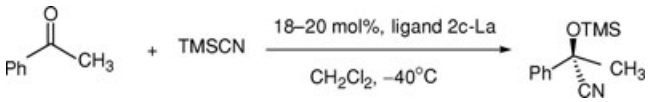
cyanosilylation of ketones, and they gave stable cyanotrimethylsilyl ethers in moderate yields with a certain enantioselectivity. Further efforts are underway to cultivate single crystals, improve the catalysis, get better ee data, and clarify the reaction mechanism.

EXPERIMENTAL

General Procedures

All cyanosilylation reactions were performed using dichloromethane as solvent. Ligands and lanthanum complexes were synthesized, and the reactions were monitored by thin layer chromatography. Flash column chromatography was performed using E. Merck silica gel (60, particle size 0.02–0.03 mm). Chemical conversions were obtained by ^1H NMR, Qinf Dao, China ^{13}C NMR, ^1H, and ^{13}C NMR spectra obtained using a Bruker AM-300 spectrometer. The following abbreviations were used to designate chemical shift multiplicities: s, singlet; d, doublet; t, triplet; and m, multiplet. Infrared spectra were recorded on a Mattson Galaxy series FTIR 3000 spectrometer. High-resolution mass spectra were obtained on Micro GCT-MS spectrometer. Optical rotations were measured on WXG-4 polarimeter. The ee was determined by the HPLC analysis, and HPLC was performed on Chuangxin Tonghang system consisting of the following: pump, UV, Daicel Chiracel OD; mobile phase hexane.

TABLE 3 The Effect of Different Solvents on Cyanosilylation of Acetophenone[a]



Entry	*Solvent*	*Time (h)*	*Conversion (%)[b]*	*ee (%)[c]*
1	THF	95	28	9
2	Ether	95	76	2
3	Hexane	95	17	6
4	Dichloromethane	95	35	8
5	Toluene	95	74	4

[a]Reaction was carried out with 2c-La complex 2:1 at −40°C, 18–20 mol%, and CH_2Cl_2 solvent.
[b]The yield (%) was given by ^1H NMR ($CDCl_3$).
[c]Determined by HPLC on a Chiralcel OD column.

Preparation of 1-[2-(4S)-4-i-Butyl-4,5-dihydro-oxazol-2-yl-ethyl]-piperidine (**S-2a**). Sixty milligrams of dry $ZnCl_2$, 1 g (8.0 mmol) of 3-(1-piperidino)propionitrile, and 2 g (12.8 mmol) of L-leucinol were added under water-free and oxygen-free conditions in a dry 100-mL Schlenk flask. These were dissolved in 30 mL of dry chlorobenzene, and the reaction mixture was refluxed for 48 h. The solvent was removed under vacuum. The residue was dissolved in 15 mL H_2O and was extracted with 10 × 3 mL of dichloromethane. The solvent was removed under vacuum and gave 1.2 g. of crude red oil. Further purification was performed by silica gel (petroleum/dichloromethane/ether: 1/4/2). The title compound was obtained as a red oil (1.68 g, yield 72%); $[\alpha]^5_D = -50.2^\circ$ ($c = 0.828$, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$, 27°C), δ (ppm) = 4.18–4.24 (t, $J = 7.95$ Hz, 1H), 3.99–4.04 (m, 1H), 3.67–3.70 (t, $J = 0.12$ Hz, 1H), 2.56–2.61 (m, 2H), 2.33–2.42 (m, 6H), 1.63–1.70 (m, 4H), 1.35–1.39 (m, 2H), 1.14–1.24 (m, 1H), 0.84–0.88 (m, 6H). ^{13}C NMR, 22.58 (×2), 22.62, 24.17, 25.21, 25.81 (×2), 45.50, 54.07 (×2), 55.20, 64.38, 72.59, 165.89. IR: 3290, 3076, 2936, 2867, 2854, 2810, 1644, 1553, 1469, 1444, 1367,

1275, 1255, 1155, 1116, 1041, 1071; HRMS (EI): *m/z* (%): calcd for $C_{14}H_{26}N_2O$: 238.2045; found 238.2036.

*Preparation of 1-[2-(4S)-4-Isopropyl-4,5-dihydro-oxazol-2-yl-ethyl]-piperidine (***S-2b***).* Following the procedure already described, yield 64%; $[\alpha]_D^5 = -46.9^\circ$ ($c = 0.677$, CH_2Cl_2); δ (ppm) = 4.08–4.13 (m, 1H), 3.79–3.87 (m, 2H), 2.55–2.61 (m, 2H), 2.33–2.42 (m, 6H), 1.63–1.70 (m, 2H), 1.47–1.55 (m, 4H), 1.35–1.39 (m, 2H), 1.14–1.24 (m, 1H), 0.86–0.88 (d, J = 6.81, 3H), 0.78–0.81 (d, J = 6.76, 3H). ^{13}C NMR: 17.84, 18.58, 24.21, 25.77 (×2), 25.85, 32.36, 53.77, 54.10, 55.32, 69.53, 71.92, 166.01. IR: 3306, 2935, 2854, 2809, 2775, 2248, 1668, 1548, 1469, 1444, 1379, 1352, 1302, 1229, 1156, 1116, 1042, 991, 913, 862, 748, 401; HRMS (EI): *m/z* (%): calcd for $C_{13}H_{24}N_2O$: 224.1889; found, 224.1896.

*Preparation of 1-[2-(4S)-4-Phenyl-4,5-dihydro-oxazol-2-yl-ethyl]-piperidine (***S-2c***).* Following the procedure already described, yield 74%; $[\alpha]^5{}_D = -44.0^\circ$ ($c = 0.170$, CH_2Cl_2); δ (ppm) = 7.26–7.37 (m, 5H), 5.12–5.18 (t, J = 0.309 Hz, 1H), 4.55–4.61 (m, 1H), 4.04–4.10 (t, J = 0.93 Hz, 1H), 2.74–2.79 (m, 2H), 2.58–2.69 (m, 2H), 2.47 (m, 6H), 1.47–1.63 (m, 4H), 1.45–1.47 (m, 2H), 0.92–0.96 (m, 2H); ^{13}C NMR: 24.29, 25.90, 25.94, 54.27 (×2), 55.30, 69.61, 74.54, 126.64 (×2), 127.46, 128.62 (×2), 142.52, 167.65. IR: 2934, 2852, 2802, 2773, 1667, 1493, 1469, 1454, 1443, 1379, 1353, 1302, 1270, 1226, 1171, 1156, 1122, 1116, 991, 961, 913, 759, 700; HRMS (EI): *m/z* (%): calcd for $C_{16}H_{22}N_2O$: 258.1732; found 258.1727.

*Preparation of 1-[2-(4S)-4-Benzyl-4,5-dihydro-oxazol-2-yl-ethyl]-piperidine (***S-2d***).* Following the procedure described earlier, yield 82%; $[\alpha]_D^5 = -50.7^\circ$ ($c = 0.148$, CH_2Cl_2); δ (ppm) = 7.18–7.32 (m, 5H), 4.35 (m, 1H), 4.11–4.16 (t, J = 3.66 Hz, 1H), 3.91–3.96 (m, 1H), 3.05–3.11 (dd, J = 5.07, 2.07, 2H), 2.62–2.67 (m, 3H), 2.38–2.49 (m, 5H), 1.43–1.62 (m, 6H). ^{13}C NMR: 24.42, 25.99, 26.07, 41.84 (×2), 54.37 (×2), 55.41, 67.31, 71.58, 126.60, 128.61 (×2), 129.38 (×2), 138.04, 167.05. IR: 3306, 3085, 3061, 3026, 2933, 2852, 2802, 2782, 1740, 1668, 1632, 1603, 1583, 1496, 1454, 1442, 1380, 1360, 1306, 1261, 1225, 1174, 1156, 1116, 1040, 988, 942, 924, 862, 802, 750, 700. HRMS (EI): *m/z* (%): calcd for $C_{17}H_{24}N_2O$: 272.1889; found 272.1885.

*Preparation of 1-[2-(4S)-4-Phenyl-4,5-dihydro-oxazol-2-yl]-piperidine (***S-1***).* Following the procedure described earlier, yield 56% $[\alpha]_D^5 = -43.6^\circ$ (c = 0.385, CH_2Cl_2); δ (ppm) = 7.22–7.41 (m, 5H), 4.88–4.93 (t, J = 1.34 Hz, 1H), 4.72–4.83 (t, J = 0.187 Hz, 1H), 3.99–4.17 (m, 1H), 2.54–2.56 (m, 2H), 2.29–2.36 (m, 3H), 1.57–1.58 (m, 3H), 1.41–1.45 (m, 2H); ^{13}C NMR: 24.31, 25.4, 46.8, 52.7 (×2), 55.41, 67.31, 71.58, 126.06, 127.51, 128.21, 128.38, 138.04, 167.05. IR: 3272, 3061, 3029, 2934, 2853, 2805, 1758, 1693, 1644, 1602, 1563, 1494, 1453, 1443, 1353, 1302, 1272, 1257, 1155, 1116, 1110, 1040, 1028, 1073, 995, 757, 700. HRMS (EI): *m/z* (%): calcd for $C_{14}H_{18}N_2O$: 231.1402; found 231.1497.

2-(Trimethylsilyoxy)-(2-phenyl)propanenitrile. 0.1 g (0.387 mmol) of **S-2c** and 40 mg of $LaCl_3$ (0.164 mmol) were dissolved in 1 mL of CH_2Cl_2. 0.1 mL (0.833 mmol) of acetophenone and 0.2 mL (1.50 mmol) of TMSCN were successively added at −40°C. After 95 h, the reaction was quenched. Further purification was performed by silica gel (petroleum/dichloromethane: 4/1). The title compound was obtained as a colorless oil, conversion = 35%, ^{1}H NMR (300 MHz, $CDCl_3$): 7.44–7.47 (m, 3H), 7.24–7.32 (m, 2H), 1.76 (s, 3H), 0.079 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 0.98 (×3), 22.56, 33.51, 71.53, 121.54, 124.53 (×2), 128.57 (×2), 141.92. ee: 8%, HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.5 mL/min, t_R (minor) = 16.579, t_R(major) = 18.027.

2-(Trimethylsilyoxy)-(2′-methyloxylphenyl)propanenitrile. The title compound was obtained as a colorless oil, conversion = 40%. ^{1}H NMR (300 MHz, $CDCl_3$): 7.44–7.48 (m, 1H), 7.23–7.29 (m, 1H), 6.85–6.95 (m, 2H), 3.83 (s, 3H), 1.83 (s, 3H), 0.229 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.28 (×3), 30.09, 55.53, 68.53, 111.63, 120.56, 125.72, 129.80 (×2), 157.9; HRMS: calcd for $C_{13}H_{19}SiNO_2$: 249.11851, found 249.11720. ee: 9%, HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.35 mL/min, t_R (minor) = 48.611, t_R (major) = 53.068.

2-(Trimethylsilyoxy)-2-(2′-methylphenyl)propanenitrile. The title compound was obtained as a colorless oil, conversion = 38%, ^{1}H NMR (300 MHz, $CDCl_3$): 7.53–7.58 (m, 1H), 7.18–7.27 (m, 3H), 2.55 (s, 3H), 1.94 (s, 3H), 0.077 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.09 (×3), 20.68, 30.51, 71.68, 121.62, 125.29, 125.97, 128.66, 132.64, 135.50, 138.41; ee: 10%, HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.35 mL/min, t_R (minor) = 25.985, t_R (major) = 28.390.

2-(Trimethylsilyoxy)-2-(4′-methylphenyl)propanenitrile. The title compound was obtained as a colorless oil, conversion = 31%; ^{1}H NMR (300 MHz, $CDCl_3$): 7.33–7.37 (m, 2H), δ (ppm) = 7.09–7.17 (m, 2H), 2.28 (s, 3H), 1.18 (s, 3H), 0.068 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): 1.00 (×3), 20.98, 33.45, 71.44, 121.67, 124.51 (×2), 129.19 (×2), 138.43, 139.03. ee: 6%; HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.35 mL/min, t_R (minor) = 22.778, t_R (major) = 24.012.

2-(Trimethylsilyoxy)-2-(4′-bromophenyl)propanenitrile. The title compound was obtained as the yellow solid, conversion = 25%; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.42–7.46 (d, J = 13.5 Hz, 2H), 7.31–7.35 (d, J = 12.6 Hz, 2H), 1.74 (s, 3H), −0.002 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 1.00 (×3), 33.42, 71.02, 115.87, 121.07, 122.66, 126.30 (×2), 131.73 (×2), 141.19; ee: 12%; HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.35 mL/min, t_R (minor) = 25.358, t_R (major) = 27.717.

2-(Trimethylsilyoxy)-2-(4′-chlorophenyl)propanenitrile. The title compound was obtained as a colorless oil, conversion = 29%; the physical and spectral data were identical to those previously reported for this compound. ^{1}H NMR (300 MHz, $CDCl_3$): 7.61–7.64 (m, 2H), 7.33–7.36 (m, 2H), 1.75 (s, 3H), 0.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): 0.96 (×3), 33.42, 70.96, 121.12, 126.00, 128.75 (×2), 134.5 (×2), 140.64. ee: 16%; HPLC (Chiralcel OD), mobile phase: hexane; flow = 0.35 mL/min, t_R (minor) = 29.850, t_R (major) = 32.291.

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