Ultrasound-Mediated Synthesis of Camphoric Acid-Based Chiral Salens for the Enantioselective Trimethylsilylcyanation of Aldehydes

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ABSTRACT New chiral salen ligands were prepared by the ultrasound-irradiated condensation of optically active (1*R*, 3*S*)-1,2,2-trimethyl-1,3-diaminocyclopentane with aromatic 1-hydroxyaldehydes. The ultrasound-mediated process is more convenient due to shorter reaction times, energy economy, and easier isolation of the products. The in situ formed Ti(IV)(salen) complexes, evaluated as catalysts in the enantioselective trimethylsilylcyanation of benzaldehyde, were found to be efficient for this process, originating the corresponding product in high yields (72–99%) and selectivities of up to 79%. The lowest energy transition states were determined by computational studies. These results were in qualitative agreement with the experimentally observed ones. *Chirality 22:425–431, 2010.* © 2009 Wiley-Liss, Inc.

KEY WORDS: salens; camphoric acid; ultrasound; enantioselective; trimethylsilylcyanation; benzaldehyde

INTRODUCTION

The enantioselective trimethylsilylcyanation of aldehydes to give optically active cyanohydrins is a versatile and useful synthetic method. The products of this reaction are of great interest because of their use as precursors of molecules with other important functional groups, namely, α-hydroxyacids, α-hydroxyketones, primary and secondary β-hydroxyamines, α-aminonitriles, and α-hydroxyesters, among others. Chiral ligand–metal complexes have been used as Lewis acid catalysts in the enantioselective trimethylsilylcyanation of aldehydes. The metals used include titanium, vanadium, and aluminum and the nature of chiral ligands which have proven efficient in this process are diverse.[1–6] Since Oguni's initial studies,[7–9] many tridentate and tetradentate Schiff bases have been used and found very efficient in the enantioselective trimethylsilylcyanation of aldehydes.[10–16]

Extending our studies on enantioselective catalysis,[17–19] we undertook the synthesis of optically active salen ligands derived from (1*R*, 3*S*)-1,2,2-trimethyl-1,3-diaminocyclopentane, (1*R*, 3*S*)-**1**, a diamine which is readily obtained from natural camphoric acid, (1*R*, 3*S*)-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid, (1*R*, 3*S*)-**2**. The structural characteristics of these salens seemed appropriate for their application in the enantioselective trimethylsilylcyanation of aromatic aldehydes. The usual synthetic procedure for obtaining this type of ligands is the reaction of a diamine with 2 equiv of a 1-hydroxyaldehyde in ethanol or toluene reflux, usually in the presence of a water sponge such as silica, sodium sulfate, alumina, and triethylorthoformate, among others, to favor the formation of the diimine. This procedure requires reaction times which may go from 2 to 24 h or more, depending on the specific reagents and are therefore time and energy consuming. It is well known that ultrasound irradiation is a form of speeding up many synthetic transformations, having advantages such as shorter reaction times, energy conservation, and simpler workup, which make it an attractive alternative to classical synthetic procedures. Accordingly, we chose to study the application of ultrasound irradiation to the synthesis of several chiral salen ligands (Scheme 1), to be subsequently tested in the enantioselective trimethylsilylcyanation of benzaldehyde.

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EXPERIMENTAL

General

All solvents were dried before use following standard procedures. Titanium tetraisopropoxide was obtained from Aldrich, and trimethylsilylcyanide from Fluka. Benzaldehyde was distilled before use and stored over 4 Å molecular sieves. All other reagents were used as commercially acquired.

Melting points were determined using a Leitz-Wetzler 799 microscope with a heated plate (values are uncor-

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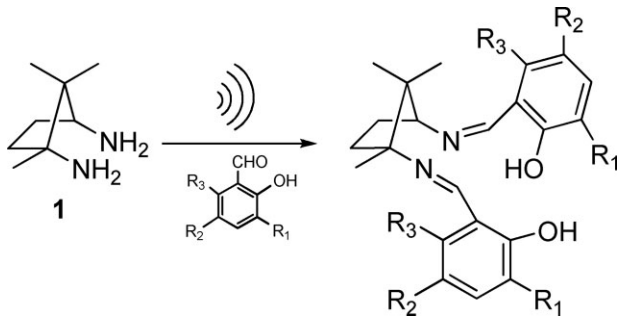


Scheme 1. Ultrasound-mediated synthesis of chiral salens.

rected). Optical rotations were measured with an optical activity AA-5 polarimeter. NMR spectra were recorded on a Bruker AMX 300. TMS was used as the internal standard, chemical shifts are referred in δ, and coupling constants, *J*, in Hz. Infrared spectra were recorded on a Perkin-Elmer 1720X FTIR or Thermo Scientific Nicolet 6700 FTIR (liquids and oils were processed as films and solids as KBr pellets). Elemental analyses were carried out on a Fisons Instruments EA 1108 CHNS-O elemental analyzer. GC analyses were recorded on a HP 5890A instrument coupled to an HP 3396A integrator using a capillary column (Supelcowax 10, 30 m, 0.25 i.d., 0.25 μm). Mass spectra were recorded on a HP 5973 MSD chromatograph with 70 eV (EI), Agilent 6890 series, equipped with an HP-5MS column (30 m × 0.25 mm × 0.25 μm) or on a Fisons Instruments-Platform with an APCI probe coupled to a Thermo Separation Spectra Series P200 chromatograph. Sonication was performed in a Bandelin Sonorex RK100H cleaning bath with a frequency of 35 Hz and a nominal power of 80/160 W.

Trimethylsilylcyanation reactions were carried out in an inert atmosphere using standard Schlenk-type techniques. Reaction products were identified by GC/MS analysis and NMR. Catalytic experiments were repeated to confirm the results. Enantiomeric excesses were determined using a chiral γ-cyclodextrin capillary column (FS-Lipodex-E, 25 m, 0.25 i.d.) from Machery-Nagel on an HP 5890A instrument coupled to an HP 3396A integrator. The absolute configuration of the major enantiomer was determined by comparison of the optical rotation with literature values.[14,20]

For the computational studies, calculations were carried out with MOPAC2007.[21] The geometry of the transition state was optimized with MOPAC2007, and a subsequent Hessian calculation was performed to assess the rank of the critical point obtained. All the calculations in MOPAC2007 used the PM6 Hamiltonian,[22] and the localization of the transition state geometry was performed until the gradient was less than 0.01 kcal/Å.

(1R, 3S)-1,3-Diamino-1,2,2-trimethylcyclopentane (1)

To a two-necked round-bottomed flask, 10.15 g (50 mmol) of (1*R*, 3*S*)-camphoric acid, 30 mL concentrated sulfuric acid, and 100 mL chloroform were added, and the reaction was placed at 55–60°C with stirring. Sodium azide (9.3 g, 143 mmol) was added in small portions at intervals. The reaction mixture was stirred at the same temperature until gas evolution ceased, usually overnight. Subsequently, the mixture was poured into a water/ice mixture, and solid NaOH was added to pH 14. The product was extracted several times with chloroform, and the combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. After filtering and evaporating the solvent, the diamine was vacuum dried to give a pale yellow oil (62%), which is used directly. $[\alpha]_D^{25} = +30$ (c1, ethanol) [+35.3 (c1, ethanol)].[23]

An analytical sample of the dihydrochloride was obtained by treating the diamine with HCl. The resulting product was recrystallized from methanol/ether and fully characterized. m.p.: 240°C (dec.). ^{1}H NMR (CD_3OD): 1.11 (s, 3H); 1.20 (s, 3H); 1.38 (s, 3H); 1.76–2.01 (m, 2H); 2.13–2.34 (m, 2H); 3.55 (t, 1H, J = 8.8). ^{13}C NMR (CD_3OD): 17.92, 21.34, 22.77, 25.73, 34.47, 46.11, 59.22, 64.28. IR (cm^{-1}): 3427, 3404, 3322, 3049, 3028, 2988, 2970, 2933, 2903, 2885, 2866, 2842, 2812, 1600, 1522. *m/z* (ES+): 143 [$(M+1)^+$], 126.

General Procedure for the Synthesis of Chiral Salens

In a 25-mL Erlenmeyer flask, diamine (1*R*, 3*S*)-**1** (1.5 mmol, 0.139 g) was dissolved in 5 mL of dry dichloromethane, and then the aldehyde (3 mmol) and silica (0.900 g) were added. The mixture was placed in an ultrasound bath until the reaction was complete, as monitored by TLC, approximately 30 min. The silica was filtered off, the solvent was evaporated, and the product was isolated by crystallization as described later.

(1R, 3S)-N′,N″-Bis[salicylidene]-1,3-diamino-1,2, 2-trimethylcyclopentane (4a)

The product was crystallized in ethyl acetate to yield 85% of the title compound. m.p.: 156–157°C. $[\alpha]_D^{25} = +35$ (c2, $CHCl_3$) [+34 (c2, $CHCl_3$)].[23,24] ^{1}H NMR ($CDCl_3$): 0.96 (s, 3H); 0.98 (s, 3H); 1.32 (s, 3H); 1.82–1.88 (m, 1H); 1.98–2.08 (m, 1H); 2.14–2.24 (m, 1H); 2.29–2.36 (m, 1H); 3.60 (approx. t, 1H, J = 8.62); 6.89 (t, 2H, J = 7.40); 6.96 (d, 2H, J = 8.20); 7.28–7.34 (m, 4H); 8.35 (s, 2H). ^{13}C NMR ($CDCl_3$): 18.89, 20.70, 24.50, 28.14, 33.90, 48.33, 70.73, 76.31, 117.01, 117.12, 118.40, 118.56, 118.74, 119.01, 131.22, 131.36, 132.14, 132.26, 161.22, 161.34, 161.44, 163.82. IR (cm^{-1}): 1629, 1496, 1413, 1282, 1167, 1120, 1030, 988, 757. Elemental Analysis for ($C_{22}H_{22}N_2O_2 \cdot 0.5$ CH_3CH_2OH): calculated, N: 7.8; C: 75.39; H: 7.48; found, N: 8.08; C: 75.67; H: 7.61. GC-MS: *m/z* (EI): 350 (M+, 79%), 162 (40), 148 (100), 122 (42), 107 (21).

(1R, 3S)-N′,N″-Bis[3-methoxysalicylidene]-1, 3-diamino-1,2,2-trimethylcyclopentane (4b)

The product was crystallized in ethyl acetate/hexane to yield 65% of the title compound. m.p.: 173–175°C. $[\alpha]_D^{25} = +95$ (c1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.97 (s, 3H); 0.99 (s, 3H); 1.32 (s, 3H); 1.83–1.89 (m, 1H); 1.99–2.03 (m, 1H); 2.16–2.23 (m, 1H); 2.28–2.36 (m, 1H); 3.62 (approx. t, 1H, J = 8.67); 3.90 (s, 3H); 3.91 (s, 3H); 6.77–6.84 (m, 3H); 6.88–6.94 (m, 6H); 8.33 (s, 1H); 8.34 (s, 1H); 14.26 (s, 1H); 14.85 (s, 1H). ^{13}C NMR ($CDCl_3$): 18.78, 20.31, 24.59,

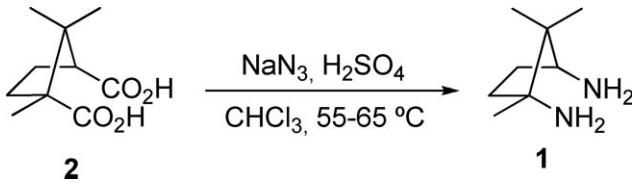
28.00, 33.74, 48.33, 55.95, 56.01, 70.41, 75.54, 113.43, 113.74, 117.45, 117.82, 118.38, 118.41, 122.70, 122.84, 148.56, 148.73, 152.17, 152.92, 161.36, 163.86. IR (cm^{-1}): 1626, 1461, 1420, 1255, 1092, 1080, 1000, 973, 745. Elemental Analysis for ($C_{24}H_{30}N_2O_4$): calculated, N: 6.82; C: 70.22; H: 7.37; found, N: 6.70; C: 70.21; H: 7.04. LC-MS: *m/z* 411 [$(M+1)^+$], 394, 260, 152.

(1R, 3S)-N′,N″-Bis[6-bromo-3-methoxysalicylidene]-1, 3-diamino-1,2,2-trimethylcyclopentane (4c)

To the resulting oil, hexane was added and the product crystallized to yield 65% of the title compound. m.p.: 213–214°C. $[\alpha]_D^{25}$ = +50 (c1, $CHCl_3$). ^1H NMR ($CDCl_3$): 1.02 (s, 3H); 1.05 (s, 3H); 1.41 (s, 3H); 1.92–2.07 (m, 2H); 2.26–2.39 (m, 2H); 3.74 (approx. t, 1H, J = 8.55); 3.87 (s, 6H); 6.67 (d, 1H, J = 8.46); 6.71 (d, 1H, J = 8.52); 6.87 (d, 1H, J = 8.46); 6.92 (d, 1H, J = 8.52); 8.69 (s, 2H); 15.48 (s, 1H); 16.10 (s, 1H). ^{13}C NMR ($CDCl_3$): 18.71, 20.16, 24.21, 27.85, 34.19, 48.38, 55.90, 56.01, 69.94, 74.27, 113.51, 113.97, 114.66, 114.92, 115.07, 115.23, 119.62, 120.50, 149.35, 149.88, 157.73, 159.85, 161.96, 164.50. IR (cm^{-1}): 1618, 1460, 1249, 1085, 971, 892, 813, 758. Elemental Analysis for ($C_{24}H_{28}N_2O_4Br_2$): calculated, N: 4.91; C: 50.88; H: 4.99; found, N: 4.81; C: 50.86; H: 4.89. LC-MS: *m/z* 569 [$(M+1)^+$], 338, 232.

(1R, 3S)-N′,N″-Bis[3-t-butylsalicylidene]-1, 3-diamino-1,2,2-trimethylcyclopentane (4d)

The product was crystallized from ether/water, yielding 71% of the title compound. m.p.: 69–70°C. $[\alpha]_D^{25}$ = +70 (c1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 0.99 (bs, 6H); 1.32 (s, 3H); 1.43 (s, 9H), 1.45 (s, 9H); 1.84–1.89 (m, 1H); 2.08–2.37 (m, 3H); 3.58 (approx. t, 1H, J = 8.13); 6.82 (t, 2H, J = 7.65); 7.11–7.16 (m, 2H); 7.32 (d, 2H, J = 7.74); 8.34 (s, 1H); 8.36 (s, 1H); 14.04 (s, 1H); 14.44 (s, 1H). ^{13}C NMR ($CDCl_3$): 19.05, 20.83, 24.53, 28.22, 29.32, 34.07, 34.83, 48.37, 70.65, 76.56, 117.53, 117.71, 118.64, 118.93, 129.09, 129.29, 129.60, 129.74, 137.38, 137.43, 160.54, 160.69, 161.95, 164.43. IR (cm^{-1}): 2959, 2872, 1628, 1436, 1384, 1269, 1200, 1144, 1088, 750. Elemental Analysis for ($C_{30}H_{42}N_2O_2 \cdot 0.5\ H_2O$): calculated, N: 5.94; C: 76.39; H: 9.19; found, N: 5.96; C: 76.21; H: 8.78. LC-MS: *m/z* 463 [$(M+1)^+$], 286, 178.



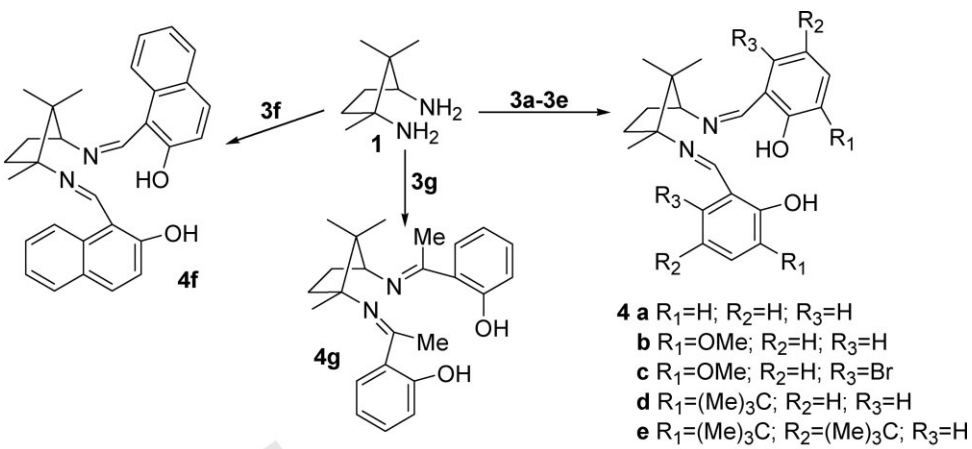
Scheme 2. Synthesis of (1*R*, 3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane from camphoric acid.

(1R, 3S)-N′,N″-Bis[3,5-di-t-butylsalicylidene]-1, 3-diamino-1,2,2-trimethylcyclopentane (4e)

The product was crystallized by concentrating the solution and adding several drops of water, yielding 70% of the title compound. m.p.: 181–183°C. $[\alpha]_D^{25}$ = +25 (c1, CH_2Cl_2).[25] ^1H NMR ($CDCl_3$): 0.97 (s, 3H); 0.99 (s, 3H); 1.30 (s, 3H); 1.31 (s, 9H); 1.32 (s, 9H); 1.43 (s, 9H); 1.44 (s, 9H); 1.79–1.88 (m, 1H); 2.02–2.23 (m, 2H); 2.28–2.38 (m, 1H); 3.56 (approx. t, 1H, J = 8.5) 7.11–7.13 (m, 2H); 7.38–7.39 (m, 2H); 8.35 (s, 1H); 8.36 (s, 1H); 13.86 (bs, 1H); 14.22 (bs, 1H). ^{13}C NMR ($CDCl_3$): 19.02, 20.79, 24.71, 28.23, 29.41, 31.51, 31.53, 34.02, 34.13, 35.04, 35.05, 48.31, 70.65, 117.82, 118.09, 125.80, 125.94, 126.63, 126.83, 136.70, 136.76, 139.74, 139.92, 158.20, 158.31, 162.28, 164.74. IR (cm^{-1}): 2961, 1628, 1465, 1391, 1170, 1069, 873. Elemental Analysis for ($C_{38}H_{58}N_2O_2 \cdot 0.5\ CH_3CH_2OH$): calculated, N: 4.87; C: 79.39; H: 10.17; found, N: 4.69; C: 78.34; H: 10.28. LC-MS: *m/z* 575 [M^+], 519, 342, 234.

(1R, 3S)-N′,N″-Bis[naphthylidene]-1,3-diamino-1,2, 2-trimethylcyclopentane (4f)

The product was crystallized in ethyl acetate/hexane to yield 50% of the title compound. m.p.: 250–251°C. $[\alpha]_D^{25}$ = −75 (c1, CH_2Cl_2). ^1H NMR ($CDCl_3$): 1.08 (s, 3H); 1.14 (s, 3H); 1.53 (s, 3H); 2.02–2.14 (m, 2H); 2.37–2.47 (m, 2H); 3.79 (m, 1H); 6.97 (approx. t, 2H, J = 9.5); 7.23–7.30 (m, 2H); 7.44–7.49 (m, 2H); 7.65 (approx. t, 2H, J = 6.8); 7.72 (dd, 2H, J = 5.5; 9.2); 7.92 (dd, 2H, J = 8.4; 13.7); 8.84 (s,



Scheme 3. Synthesis of chiral salens derived from (1*R*, 3*S*)-1,3-diamino-1,2,2-trimethylcyclopentane.

TABLE 1. Classical versus ultrasound method in the synthesis of Salens (1*R*, 3*S*)-4(a–g)

	Classical method		Ultrasound method	
Salen	Yield (%)	Time (h)	Yield (%)	Time (h)
(1*R*, 3*S*)-**4a**	62	4	74	0.5
(1*R*, 3*S*)-**4b**	65	5	63	0.5
(1*R*, 3*S*)-**4c**	68	3	59	0.5
(1*R*, 3*S*)-**4d**	–	–	71	0.5
(1*R*, 3*S*)-**4e**	81	24	69	0.5
(1*R*, 3*S*)-**4f**	59	48	51	0.5
(1*R*, 3*S*)-**4g**	68	14	80	0.5

1H); 8.87 (s, 1H); 14.93 (s, 1H); 15.39 (s, 1H). ^{13}C NMR ($CDCl_3$): 18.53, 20.27, 23.80, 27.76, 34.68, 48.21, 67.96, 72.43 106.74, 107.08, 117.68, 118.07, 122.76, 122.95, 123.63, 124.65, 126.29, 126.57, 127.92, 129.30, 129.35, 133.34, 133.71, 136.73, 137.13, 154.23, 157.78, 173.42, 175.60. IR (cm^{-1}): 1625, 1523, 1492, 1427, 1314, 834. Elemental Analysis for ($C_{30}H_{30}N_2O_2 \cdot 0.5\ CH_3CH_2OH$): calculated, N: 6.22; C: 79.97; H: 6.71; found, N: 5.91; C: 78.62; H: 7.02. LC-MS: *m/z* 451[M^+], 307, 280.

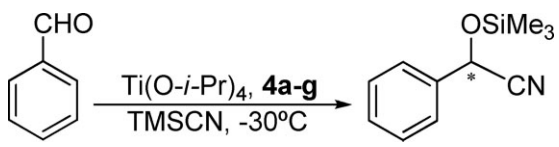
(1R, 3S)-N′,N″-Bis[2-hydroxyphenoylidene]-1, 3-diamino-1,2,2-trimethylcyclopentane (4g)

The product crystallized by the addition of ether to yield 59% of the title compound. m.p.: 225–227°C. $[\alpha]_D^{25} = +215$ (c1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.13 (s, 3H); 1.21 (s, 3H); 1.41 (s, 3H); 1.87–1.94 (m, 1H); 2.12–2.28 (m, 3H); 2.41 (s, 3H); 2.47 (s, 3H); 4.03–4.10 (m, 1H); 6.72–6.81 (m, 2H); 6.91 (dd, 1H, J = 1.2, 5.0); 6.94 (dd, 1H, J = 1.2, 5.0); 7.26–7.33 (m, 2H); 7.52 (approx. t, 1H, J = 1.53); 7.55 (approx. t, 1H, J = 1.53); 16.72 (s, 1H); 17.14 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.56, 18.45, 18.93, 20.57, 24.10, 28.44, 35.92, 49.84, 63.67, 68.96, 116.61, 116.93, 118.85, 118.93, 119.25, 119.63, 127.80, 128.12, 132.61, 132.74, 164.33, 164.64, 169.76, 171.21. IR (cm^{-1}): 1610, 1502, 1447, 1303, 1252, 839, 760, 753, 635. Elemental Analysis for ($C_{24}H_{30}N_2O_2$): calculated, N: 7.40; C: 76.16; H: 7.99; found, N: 7.62; C: 76.57; H: 7.59. LC-MS: *m/z* 397 [$(M+1)^+$], 244, 227.

General Procedure for the Trimethylsilylcyanation Reactions

To a solution of the chiral salen ligand (0.44 mmol) in dry dichloromethane (5 mL), Ti(O-*i*-Pr)$_4$ (0.40 mmol, 0.12 mL) was added under an inert atmosphere at room temperature. The resulting mixture was stirred overnight and subsequently cooled to −30°C. Benzaldehyde (2 mmol, 0.2 mL) and trimethylsilylcyanide (4 mmol, 0.54 mL) were added and the reaction stirred for 24 h at −30°C.

At the end of the reaction, hexane was added and the precipitated solids were filtered off. Conversions were determined by GC, and the ee of the resulting cyanosilylethers were determined by chiral GC analysis.



Scheme 4. Trimethylsilylcyanation of benzaldehyde.

RESULTS AND DISCUSSION

Synthesis of Chiral Salen Ligands

Diamine (1*R*, 3*S*)-**1** was obtained directly from (1*R*, 3*S*)-**2** by refluxing with sodium azide and sulfuric acid in chloroform, according to a slightly modified literature procedure[23] (Scheme 2).

To prepare the salen derivatives of (1*R*, 3*S*)-**1** (Scheme 3), we started off by using the classical method, refluxing the diamine with the appropriate aldehydes in ethanol and controlling the reaction by TLC. Using salicylaldehyde (**3a**), 3-methoxysalicylaldehyde (**3b**), 6-bromo-3-methoxysalicylaldehyde (**3c**), 3-*t*-butylsalicylaldehyde (**3d**), 3,5-di-*t*-butylsalicylaldehyde (**3e**), and 1-hydroxynaphthaldehyde (**3f**), the corresponding salens (1*R*, 3*S*)-**4(a–f)** were obtained in moderate to good yields (Table 1). The reaction of (1*R*, 3*S*)-**2** with 1-hydroxyacetophenone **3g** gave (1*R*, 3*S*)-**4g** in moderate yield. The synthesis of salens **4a** and **4e** by the aforementioned method has been previously described.[23–26] The reaction times varied for the different aldehydes used, and consequently, reactions were stopped after complete conversion or when no further evolution was observed.

Stefani and coworkers[27] achieved the efficient condensation of simple amines with aromatic aldehydes in dichloromethane under ultrasound irradiation and in the presence of silica as a promoter. We decided to try these conditions for the synthesis of our salen ligands. The condensation of diamine (1*R*, 3*S*)-**1** with 2 equiv of salicylaldehyde (**3a**) under ultrasound irradiation for 15 min at room temperature gave (1*R*, 3*S*)-**4a** in low yield, about 30%. We increased the amount of promoter and irradiation times as well, resulting in the formation of (1*R*, 3*S*)-**4a** in 74% yield after 30 min.

The condensation of (1*R*, 3*S*)-**1** with other aromatic aldehydes originated the corresponding salens (1*R*, 3*S*)-

TABLE 2. Enantioselective trimethylsilylcyanation of benzaldehyde[a]

Entry	Salen	Conversion[b] (%)	ee[c] (%)
1	(1*R*, 3*S*)-**4a**	97	43 (*R*)
2	(1*R*, 3*S*)-**4b**	72	8 (*S*)
3	(1*R*, 3*S*)-**4c**	89	22 (*S*)
4	(1*R*, 3*S*)-**4d**	98	56 (*S*)
5	(1*R*, 3*S*)-**4e**	93	79 (*S*)
6	(1*R*, 3*S*)-**4f**	95	59 (*S*)
7	(1*R*, 3*S*)-**4g**	92	6 (*S*)

[a]Reaction was carried out on a 2 mmol scale in 5 ml of dry CH_2Cl_2 at −30°C, using a molar ratio of Ti:ligand:aldehyde:TMSCN of 1:1.1:5:10.
[b]Determined by GC.
[c]Of the silylether, determined by chiral GC.

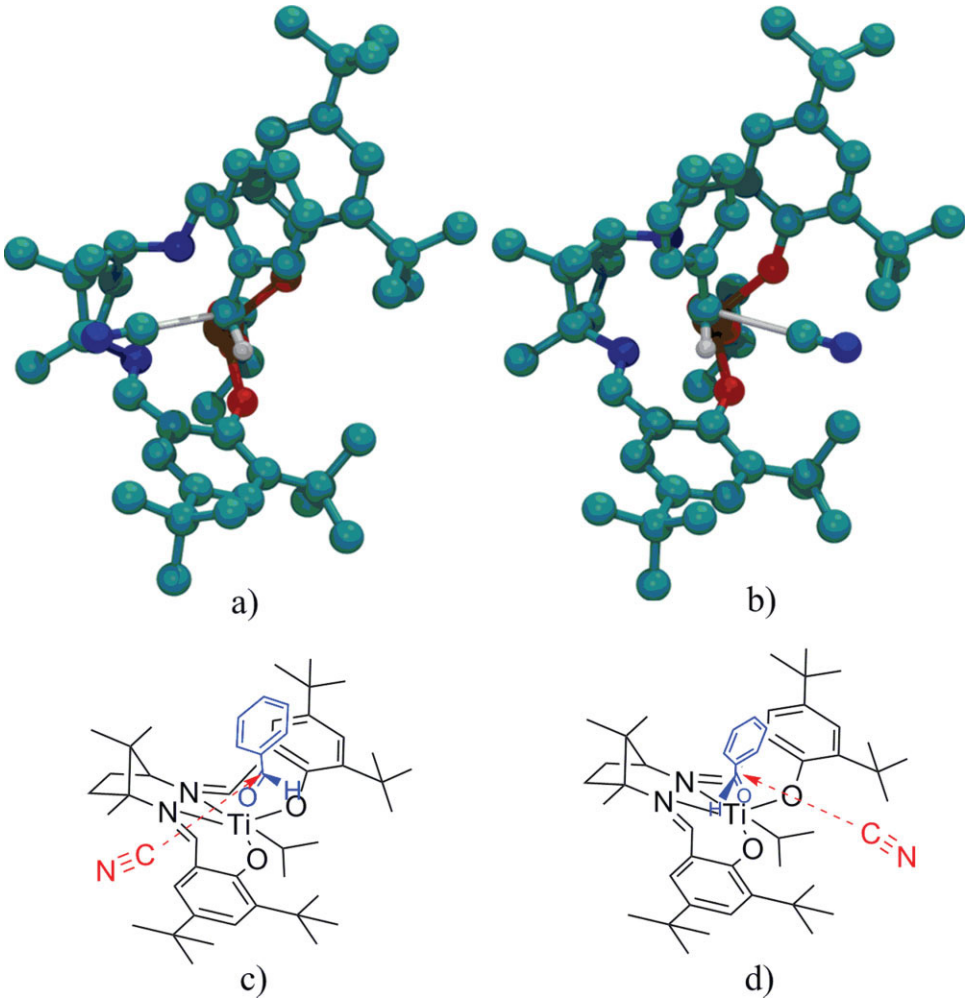


Fig. 1. The two transition states (not all hydrogen atoms are displayed so as not to hinder visibility): (**a**) TS1 and (**b**) TS2 (images produced using VMD[38]). The light blue corresponds to carbon atoms, brown to titanium, red to oxygen, dark blue to nitrogen, and white corresponds to hydrogen. Note that the "white" bond, corresponds to the cyano attack to the carbon. (**c**) and (**d**) schematic representations of TS1 and TS2, respectively. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

4(**b–g**) (Table 1). In all cases, even when yields are comparable with the classic method, the procedure is more convenient due to much shorter reaction times, energy economy, and a much simpler isolation of the product.

Enantioselective Trimethylsilylcyanation

The titanium(IV) complexes of chiral salens (1*R*, 3*S*)-**4**(**a–g**) were evaluated as catalysts in the enantioselective trimethylsilylcyanation of aldehydes, using benzaldehyde as model substrate (Scheme 4). All reactions were carried out in an inert atmosphere at −30°C for 24 h, using dichloromethane as solvent. The Ti:ligand:aldehyde:TMSCN ratio used was 1:1.1:5:10. The results of these catalytic experiments are summarized in Table 2.

All catalysts were found to be very active in promoting the trimethylsilylcyanation of benzaldehyde under the reaction conditions used. The ee of the products varied according to the ligand used. The most selective ligand was found to be (1*R*, 3*S*)-**4e**, which gave the corresponding cyanosilylether with an ee of 79%, followed by (1*R*, 3*S*)-**4f**, which gave the product with 59% ee. These results are in agreement with previous studies which have shown that bulky groups in C3 and C3′ of the aldehyde moieties are essential for high selectivity.[7–12,28] Also, bulky groups in C5 and C5′ have been described as important. The order of selectivity (1*R*, 3*S*)-**4e** > (1*R*, 3*S*)-**4f** > (1*R*, 3*S*)-**4d** of the most selective ligands can thus be explained. The low ee of the products obtained when (1*R*, 3*S*)-**4**(**a–c**) were used may be a consequence of both the presence of substituents with reduced steric bulk on the aldehyde moiety and of their electronic characteristics.

All cyanosilylethers obtained presented (*S*) absolute configuration except when ligand (1*R*, 3*S*)-**4a** was used, resulting in the product with (*R*) absolute configuration. As previously referred, this inversion of configuration may be attributed to the presence of bulky substituents on the aldehyde moieties.[13,29]

Computational Studies

Theoretical studies were carried out to illustrate the stereochemistry and enantiomeric excess of the product.

For these studies, we used our most selective system, the Ti-(1*R*, 3*S*)-**4e** system.

The details of the structure of the catalysts in trimethylsilylcyanations are not yet completely known. While some studies point to a dimeric titanium species, others point to a monomeric one. The studies of Belokon and North support the existence of a dimeric titanium species, with the two titanium atoms connected through two oxygen bridges.[5,15,30–32] The involvement of a monomeric titanium species is suggested by others[10,33–36] and is said to be favored when there are large substituents, such as *t*-butyl, on the aldehyde moiety. It has been referred that the catalyst structure (monomeric, dimeric, or a mixture of both) is probably related to some reaction conditions such as molar ratios, solvents, and ligand structures.[33]

Concerning the reaction mechanism, another question arises with respect to the reactive nucleophile and whether it is TMSCN or HCN. Results of several studies indicate HCN as the actual reactive nucleophile, possibly generated from the reaction of TMSCN and ^{i}PrOH.[12,36,37]

In our calculations, we considered the existence of a monomeric titanium species and of the cyanide ion as the attacking agent, assumptions which have previously been used by others. Also, in our calculations, solvent effects were not considered. The computational studies were carried out to predict the lower energy transition states and the mode of attack of cyanide to benzaldehyde. To establish the transition state, a search for the minimum of the charged species was first carried out. Subsequently, cyanide ion was added to the minimized structure in the appropriate position. These structures were then allowed to relax to their minimum energy configurations.

A transition state search was then performed and some care was taken in following the path from the minimum to the transition state: the Hessian (matrix of the second derivatives of the energy to the nuclear coordinates) was calculated at every point so as to provide a suitable guide for finding the transition state. Small enough trust radii (0.05 Å or 0.05 radian) were imposed in order to not overshoot the saddle point.

After the localization of the putative saddle point, the respective character was confirmed by inspecting the corresponding Hessian matrix, in which only one imaginary frequency should be present. We noted that the normal mode associated with the imaginary frequency corresponds to the attack of the cyanide ion to the carbon atom in both transition states.

3D representations[38] of the lowest energy transition states, as well as the corresponding schematic drawings, are presented in Figure 1. Some relevant parameters concerning the two transition states are found in Tables 3 and 4.

TABLE 3. Energetics and structural parameters for the two transition states depicted in Figure 1

	TS1	TS2
Heat of formation (kcal/mol)	−230.92	−209.78
r(CC) (Å)	2.266	2.674
r(CN) (Å)	1.150	1.155
Angle (C—C—N)	178.9°	179.6°
Imaginary frequency (cm^{-1})	−318.6	−161.70

TABLE 4. Charges and bond orders for the atoms involved in the transition state

	TS1	TS2
q(N)	−0.45 (0.56)	−0.53 (0.52)
q(C)	−0.25 (−0.15)	−0.36 (−0.25)
q′(C)	0.54 (0.53)	0.54 (0.52)
q(Ti)	0.88 (1.35)	0.90 (1.37)
B.O. (C—C)	0.363	0.123
B.O (C—N)	2.896	2.881

The values in parenthesis are the Mulliken charges and the others are MOPAC charges.

From the proposed transition states, the cyanide can attack both from the diamine side of the molecule, TS1, and from the salicylaldehyde moiety of the molecule, TS2. The calculated heats of formation (Table 3) indicate that the attack from the diamine side constitutes the predominant pathway for these reactions. The process therefore involves the intermolecular attack of the cyanide ion to the Si-face of the aldehyde giving rise to *O*-trimethylsilyl-(*S*)-mandelonitrile as the major reaction product. It can therefore be concluded that there is qualitative agreement between the theoretical predictions and the observed experimental results.

To clarify the inversion of configuration observed when ligand (1*R*, 3*S*)-**4a** was used, similar computational studies were carried out for this ligand. These studies confirm that preferential attack of the cyanide occurs to the Re-face of the aldehyde, originating *O*-trimethylsilyl-(*R*)-mandelonitrile as the major product in this case, confirming the experimental results.

CONCLUSIONS

In conclusion, we have prepared chiral salen ligands (1*R*, 3*S*)-**4(a–f)** by ultrasound mediated condensation in good yields with short reaction times and easy isolation of the products.

Our studies demonstrated that the Ti(IV)(salen) complexes of these ligands are very active in the trimethylsilylcyanation of benzaldehyde, where conversions of up to 97% were observed. A selectivity of 79% was obtained in the presence of (1*R*, 3*S*)-**4f** with two sterically demanding *t*-butyl substituents on each aldehyde moiety of the salen ligand. The computational studies carried out for this ligand are in qualitative agreement with the observed results.

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