Pergamon

Tetrahedron Letters 43 (2002) 3821–3823

TETRAHEDRON LETTERS

Novel chiral Schiff base ligands from amino acid amides and salicylaldehyde

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Received 21 March 2002; revised 2 April 2002; accepted 8 April 2002

Abstract—A novel type of symmetric chiral Schiff base ligands has been synthesized in good yield using an easy and good yielding stepwise approach from *o*-phenylenediamine, amino acids and salicylaldehyde.

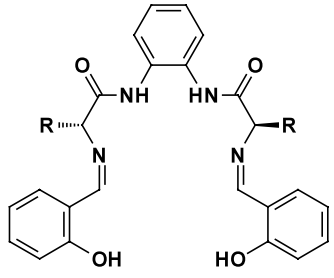
1. Introduction

The synthesis of new kinds of chiral ligands represents one of the most important factors in the field of asymmetric catalysis. The major part of the most common ligands are bidentate and neutral, like DIOP and BINAP,[1] or dianionic, like TADDOL[2] and BINOL.[3] Among higher denticity ligands are the tetradentate salen ligands, used for example in asymmetric epoxidation,[4] epoxide ring opening[5] and aziridination.[6,7]

Salen-type chiral Schiff base ligands have received considerable attention during the last decades, mainly because their steric and electronic properties can be easily adapted by choosing the right chiral amine and aldehyde precursors. In this context, for example, Jacobsen catalyst and other similar transition metal complexes with symmetric or unsymmetric ligands have been developed and used as catalysts for many kinds of processes.[8]

An interesting class of salen analogue transition metal complexes is that one having *N*-salicylaldehyde chiral aminoacidatos as ligands; studied as non-enzymatic models for pyridoxal-amino acid system.[9] To this aim several copper(II),[10] zinc(II)[10] and vanadium(IV) or (V)[11] salicylaldehyde aminoacidatos have been synthesized and structurally characterized.

As a part of our ongoing studies on using lanthanide salts as catalysts in synthetic organic chemistry,[12–14] we report in the present work the synthesis and spectroscopic characterization of novel symmetric *N*-salicylaldehyde ligands based on chiral amino acid-derived subunits of general structure **1**.



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Complexes of trivalent lanthanides aminoacidato complexes have been the subject of several physicochemical studies,[15] but very few reports on the catalytic activity of such complexes have been found in the literature.[16] Ligand **1** contains from four up to six coordination sites; its core is based upon two nitrogen imine atoms and two hydroxyl functions, which are known to coordinate strongly to transition metal centers,[10] and two amide moieties. The synthesis was carried out in three easy steps, each with excellent or good yields, as outlined in Scheme 1.

Starting from *N*-Boc-protected amino acids, prepared by standard methods,[17] the coupling reaction with *o*-phenylenediamine (2:1 ratio) was made by using 2 equiv. of dicyclohexyl carbodiimide (DCC) as condensating agent in EtOAc at room temperature. Employing *N*-Boc protected L-phenylalanine, D-phenylglycine and L-valine as starting materials, the corresponding diamide adduct **4** was obtained in 90% (R = -CH_2Ph,

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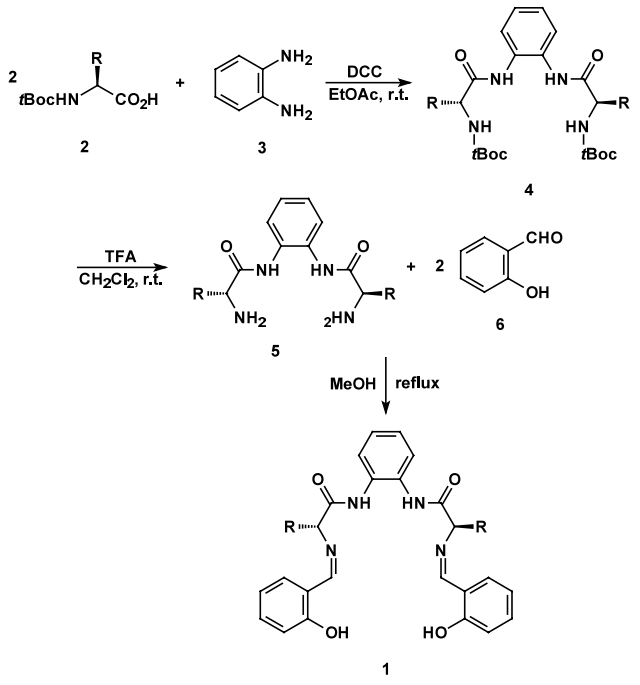
PII: S0040-4039(02)00687-1



Scheme 1.

4a), 88% (R = -Ph, **4b**) and 87% (R = -*i*Pr, **4c**) yield, respectively, after SiO_2 gel column chromatography using CH_2Cl_2/MeOH (99:1) as eluent. The carbamate functions of **4** were cleaved (98% yield in all cases, R = -CH_2Ph, **5a**, R = -Ph, **5b**, R = -*i*Pr, **5c**) with a 50% solution of CF_3COOH (TFA) in CH_2Cl_2 at room temperature. This high yielding two-step synthesis of diamino diamides of structure like **5** needs to be pointed out as they represent useful synthons for tetra- and pentadentate macrocyclic tetramide ligands.[18] The synthesis of the desired ligands was then completed by condensation of chiral diamine **5** with salicylaldehyde in refluxing MeOH for 2 h, followed by crystallization of the corresponding Schiff base **1**. Yields were as follows: 57% (R = -CH_2Ph, **1a**), 58% (R = -Ph, **1b**), 53% (R = -*i*Pr, **1c**).

These ligands are insoluble at room temperature in apolar solvents such as *n*-hexane, benzene or toluene, but exhibit a very good solubility in slightly polar solvents such as dichloromethane, acetonitrile, acetone or tetrahydrofuran, for example; solubility tends to diminish with increasing solvent polarity (e.g. they are sparingly soluble in methanol and insoluble in water), but in such solvents, increases by raising the temperature. These compounds are also stable for several days at room temperature in the solid state.

In conclusion, we have developed a short synthesis of a new class of chiral polydentate Schiff base ligands, which contain mixed N,O donors. These ligands were easily prepared in good yield starting from low-cost commercially available materials. The work to obtain the corresponding transition metal complexes to provide new chiral Lewis acids to use in asymmetric catalytic processes and for possible use with lanthanides and for multimetallic application in general, is currently in progress in our laboratories. In fact coordinating our ligands to lanthanides would not only have great significance in the fundamental chemistry of these rare earth elements but could also have an important role in the field of MRI contrast agents, biological probes or NMR chiral shift reagents.

2. Experimental

2.1. Synthesis of diamide 4

To a stirred solution of *N*-*t*butoxycarbonyl amino acid **2** (2.44 mmol) and *o*-phenylenediamine **3** (1.22 mmol) in EtOAc (6 mL), a solution of DCC (2.44 mmol) in EtOAc (4 mL) was added dropwise over a period of 20 min at room temperature. After the addition was complete the mixture was stirred for 6 h, the white precipitate formed was filtered under reduced pressure, the filtrate was washed twice with a 5% solution of citric acid (10 mL) and evaporated. The residue was purified by SiO_2 gel column chromatography (eluent CH_2Cl_2/MeOH, 99:1) to give the desired compound **4**.

Data for compound 4a: Mp 222–224°C; $[\alpha]_D = +20.24$ ($c = 1.0$ g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 18H), 2.89–3.34 (m, 4H), 4.39–4.64 (m, 2H), 7.06–7.49 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 38.1, 56.2, 80.5, 125.3, 126.4, 126.9, 128.6, 129.4, 130.0, 136.7, 155.9, 170.9 ppm. IR (neat) 3300 (br), 1674 cm^{-1}.

Data for compound 4b: Mp 202–203°C; $[\alpha]_D = -60.93$ ($c = 1.0$ g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 18H), 5.25 (d, 2H, $J = 6.9$ Hz), 5.81 (d, 2H, $J = 6.9$ Hz), 6.90–7.48 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.3, 59.0, 80.2, 125.2, 126.4, 127.3, 128.5, 129.0, 130.0, 137.7, 155.2, 170.0 ppm. IR (neat) 3300 (br), 1672 cm^{-1}.

Data for compound 4c: Mp 176–178°C; $[\alpha]_D = +15.38$ ($c = 1.0$ g/mL, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, 6H, $J = 6.8$ Hz), 1.01 (d, 6H, $J = 6.8$ Hz), 1.42 (s, 18H), 2.09–2.30 (m, 2H), 4.04–4.24 (m, 2H), 5.51 (d, 2H, $J = 8.2$ Hz), 7.02–7.14 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.8, 19.3, 28.5, 30.9, 60.4, 79.8, 125.2, 126.0, 129.9, 155.9, 171.2 ppm. IR (neat) 3300 (br), 1670 cm^{-1}.

2.2. Boc deprotection

Compound **4** (3.4 mmol) was added to a stirred solution of CF_3COOH (5.0 mL) in CH_2Cl_2 (10 mL) at room temperature; the mixture was allowed to react for 30 min, diluted with CH_2Cl_2 (30 mL), basified with 0.5N NaOH and the organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to give the desired diamine **5**.

Data for compound 5a: Mp 265–266°C; $[\alpha]_D = -22.43$ ($c = 1.0$ g/mL, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.76 (dd, 2H, $J_{1-2} = 8.8$ Hz, $J_{1-3} = 14.6$ Hz), 3.33 (dd, 2H, $J_{1-2} = 4.2$ Hz, $J_{1-3} = 14.6$ Hz), 3.74 (dd, 2H, $J_{1-2} =$

4.2 Hz, $J_{1-3}=8.8$ Hz) 7.14–7.64 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 40.7, 56.5, 124.6, 125.9, 126.9, 128.7, 129.3, 129.9, 137.9, 173.5 ppm. IR (neat) 3300 (br), 1682 cm^{-1}.

Data for compound 5b: Mp 226–228°C; $[\alpha]_D=-101.42$ ($c=1.0$ g/mL, MeOH); ^1H NMR ($CDCl_3$, 200 MHz) δ 4.48 (s, 2H), 7.12–7.58 (m, 14H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 60.0 124.8, 126.2, 126.2, 126.9, 128.1, 128.9, 130.0, 140.8, 172.1 ppm. IR (neat) 3300 (br), 1680 cm^{-1}.

Data for compound 5c: Mp 185–187°C; $[\alpha]_D=+97.37$ ($c=1.0$ g/mL, MeOH); ^1H NMR ($CDCl_3$, 200 MHz) δ 0.86 (d, 6H, $J=7.5$ Hz), 1.00 (d, 6H, $J=7.5$ Hz), 2.05–2.48 (m, 2H), 3.25–3.36 (m, 2H), 7.03–7.65 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3, 19.7, 31.1, 60.6, 124.4, 125.6, 130.0, 173.7 ppm. IR (neat) 3300 (br), 1682 cm^{-1}.

2.3. Schiff base synthesis

To a stirred solution of compound **5** (0.91 mmol) in MeOH (4 mL), salicylaldehyde (1.82 mmol) was added and the mixture was allowed to react at reflux for 2 h, then cooled; the white precipitate formed was filtered under reduced pressure, washed with a little cold MeOH and collected to give the Schiff base **1**.

Data for compound 1a: Mp 275–276°C; $[\alpha]_D=-36.98$ ($c=1.0$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.24 (dd, 2H, $J_{1-2}=8.9$ Hz, $J_{1-3}=13.3$ Hz), 3.49 (dd, 2H, $J_{1-2}=3.6$ Hz, $J_{1-3}=13.3$ Hz), 4.20 (dd, 2H, $J_{1-2}=3.6$ Hz, $J_{1-3}=8.9$ Hz), 6.78–7.49 (m, 22H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 41.2, 76.2, 117.0, 118.3, 119.2, 125.0, 126.4, 127.0, 128.5, 128.7, 129.5, 129.8, 132.2, 133.3, 136.6, 160.5, 167.9, 169.9 ppm. IR (neat) 3300 (br), 1660, 1628 cm^{-1}.

Data for compound 1b: Mp 268–269°C; $[\alpha]_D=-121.41$ ($c=1.0$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 5.23 (s, 2H), 6.95–7.60 (m, 22H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 76.4, 116.9, 119.4, 125.8, 127.6, 127.9, 128.4, 128.6, 128.8, 129.2, 130.9, 132.0, 133.4, 139.5, 160.0, 166.5, 169.6 ppm. IR (neat) 3300 (br), 1665, 1627 cm^{-1}.

Data for compound 1c: Mp 275–276°C; $[\alpha]_D=+158.34$ ($c=1.0$ g/mL, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 1.01 (d, 6H, $J=6.4$ Hz), 1.07 (d, 6H, $J=6.4$ Hz), 2.40–2.62 (m, 2H), 3.76 (d, $J=3.8$ Hz), 6.90–7.55 (m, 12H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.8, 19.6, 32.4, 80.4, 117.0, 118.6, 119.2, 125.1, 126.3, 129.8, 132.2, 133.2, 160.5, 167.8, 170.7 ppm. IR (neat) 3300 (br), 1660, 1628 cm^{-1}.

Acknowledgements

Financial support from MIUR (Rome, Italy) is gratefully acknowledged.

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