Practical Synthesis of Chiral *N,N′*-Bis(2′-pyridinecarboxamide)-1,2-cyclohexane Ligands

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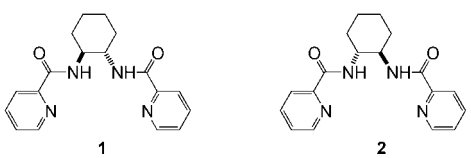
Received August 9, 2000; Accepted October 16, 2000

Asymmetric catalysis by transition metal complexes has emerged as an important tool for the synthesis of optically active compounds for both academia and industry. The study of asymmetric catalysis and subsequent utility in organic synthesis requires that the chiral catalysts and/or ligands be available in sufficient quantities. This is especially true for the pharmaceutical industry, since large quantities are often needed to prepare a drug candidate to support clinical trials. Accordingly, the development of practical syntheses of these chiral catalysts and/or ligands becomes of great importance.

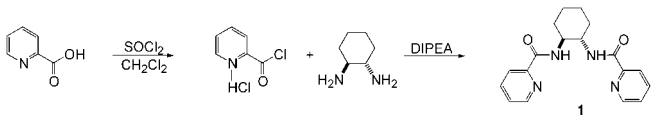
Transition metal-catalyzed allylic alkylations using chiral ligands is an elegant method for inducing asymmetry into achiral compounds.[1] Enantioselective alkylation of unsymmetrically substituted allylic substrates is a challenging problem, due to regioselectivity issues.[2] Trost has recently reported exceptional results with a chiral molybdenum catalyst prepared from ligand **2**[3] which gave a branched-to-linear ratio of 49:1 and an ee of 99% in the alkylation of methyl (*E*)-1-phenylallyl carbonate with dimethyl sodiomalonate. In order to further investigate a molybdenum-catalyzed asymmetric alkylation reaction for the preparation of a key intermediate in the synthesis of a new drug candidate, we needed to prepare multigram quantities of **1** and **2**.



Scheme 1.

A survey of the literature indicated that there was no straightforward, high yielding method capable of preparing these ligands with the high purity required for catalytic reactions. The racemic compound was first prepared from 1,2-diaminocyclohexane via triphenyl phosphite activation of 2-picolinic acid in 47% yield.[4] (*R,R*)-*N,N′*-Bis(2-pyridinecarboxamide)-1,2-cyclohexane (**2**) was prepared by this method, however, the yield was not reported.[5]

Initially, we prepared both **1** and **2** from the corresponding *trans*-1,2-diaminocyclohexane and 2-picolinoyl chloride hydrochloride.[6] Picolinoyl chloride was prepared in 87% yield from picolinic acid and thionyl chloride.[7]



Scheme 2.

Addition of picolinoyl chloride to a solution of *trans*-1,2-diaminocyclohexane and diisopropylethylamine, followed by an aqueous work up and concentration gave **1** and **2** in 44–85% yield. This procedure was very exhothermic, generated HCl gas during the acid chloride addition, and the aqueous washes were difficult to separate due to the extremely dark color of both layers.

An improved process was developed which offered several advantages over this procedure. In this process 2-picolinic acid is activated with 1,1′-carbonyldiimidazole (CDI) in THF followed by the addition of 1,2-diaminocyclohexane. After stirring overnight, the excess CDI is reacted with water and the reaction solvent is switched to ethanol. The ligand crystallizes from ethanol as a white solid in an 84–92% yield. This is a simpler reaction with a very mild exotherm during the diaminocyclohexane addition and is readily amenable to large-scale synthesis.

Keywords: allylic substitution; asymmetric catalysis; homogeneous catalysis; N ligands; transition metals

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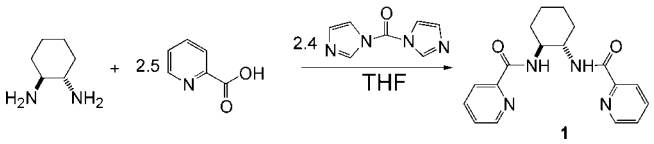

Scheme 3.

Using this procedure, 2.5 kg of **1** were prepared in 86% yield with a >99% ee. Easy access to these ligands will allow further exploration of other enantioselective transition metal-catalyzed allylic alkylation reactions.

Experimental Section

General Remarks

(1*S*, 2*S*)-(+)-1,2-Diaminocyclohexane and (1*R*, 2*R*)-(−)-1,2-diaminocyclohexane were purchased from Arran Chemical Company Limited. All other materials were obtained from commercial suppliers and used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer.

(*S,S*)-*N,N'*-Bis(2-pyridinecarboxamide)-1,2-cyclohexane (1)

A 22-L flask was charged with 1,1′-carbonyldiimidazole (1.70 kg, 10.48 mol) and anhydrous THF (KF < 50 μg/mL; 7.5 L). Solid picolinic acid (1.36 kg, 11 mol) was added to the slurry at room temperature. The resulting clear solution was stirred for 1 h at 18–20 °C and molten (1*S*, 2*S*)-(+)-1,2-diaminocyclohexane (0.5 g, 4.38 mol)[8] was added over 1 h while keeping the temperature below 50 °C. Additional 2.5 L of THF were added as a rinse. The reaction mixture was stirred at room temperature for 15 h. Water (0.5 L) was added to the mixture and the solution was stirred for 1 h at room temperature. The reaction mixture was concentrated to an orange semi-solid by rotary evaporation. The semi-solid residue was slurried in 5 L of ethanol and concentrated by rotary evaporation. The resulting solid was dissolved in ethanol (5 L) at 64–65 °C. The solution was allowed to slowly cool to –8 °C and the resulting white crystals were isolated by filtration on a sintered glass funnel, washed with 5 L of cold ethanol (−8 to −10 °C) and dried in a vacuum oven (35 °C). The title compound **1** was isolated as a white crystalline solid; yield: 1.23 kg (86.6%; 99.0% ee); mp 172–175 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.50–8.49 (m, 2H), 8.23 (d, J = 6.5 Hz, 2H), 8.02–7.99 (m, 2H), 7.69–7.64 (m, 2H), 7.29–7.24 (m, 2H), 4.03 (bs, 2H), 2.18–2.15 (m, 2H), 1.79 (bs, 2H), 1.42–1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 149.8, 148.1, 136.9, 125.8, 122.0, 53.2, 32.6, 24.8; HPLC (ChiralPak AD-RH 4.6×250 mm, flow rate = 0.5 mL/min, water : acetonitrile, 1 : 1, detection at 210 nm); t_R = 7.4 min (*S,S*-), t_R = 10.3 min (*R,R*-); anal. calcd. for $C_{18}H_{20}N_4O_2$: C, 66.65; H, 6.12; N, 17.27; found: C, 66.63; H, 6.24; N, 17.43.

Acknowledgments

We are grateful to Dr. Bing Mao of our Analytical Research Department for chiral HPLC analyses.

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[8] (1*S*, 2*S*)-(+)-1,2-Diaminocyclohexane is a low melting solid (mp = 40–43 °C). For ease of handling, the diamine was melted in a beaker on a hot plate and used as a melt.