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Preliminary Communication

Synthesis and structure of a novel tridentate chiral-NHC ligand precursor

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Abstract

A novel tridentate chiral imidazolium hexafluorophosphate, a precursor for *N*-heterocyclic carbene (NHC) ligand, was synthesized from (S)-proline in five steps in 24% overall yield. The compound was characterized by NMR and elemental analysis. Its molecular structure was determined by X-ray diffraction analysis. This chiral compound has two stereogenic centers which are within two chelating side chains and its specific rotation is -19.6°.

Keywords: chiral; imidazolium salt; NHC ligand; (S)-proline; X-ray structure.

Introduction

N,*N*′-Disubstituted imidazolium salts are important precursors to *N*-heterocyclic carbenes (NHCs) (Kuehl, 2007; Wüertz and Glorius, 2008; Díez-González et al., 2009; Nolan, 2011). These electron-rich ligands have been widely employed in organometallic catalysis, such as olefin metathesis (Weskamp et al., 1998; Hoveyda and Schrock, 2001; Trnka and Grubbs, 2001), carbon-carbon and carbon-nitrogen cross-coupling (Hillier et al., 2002), hydrogenation, and hydrosilylation (Lee et al., 2001). A large number of chiral NHC ligands for asymmetric catalysis has been developed (Cesar et al., 2004; Snead et al., 2008). Most chiral NHC ligands are monodentate and bidentate systems, and only few are tridentate.

Results and discussion

To explore new efficient chiral NHC ligands for asymmetric catalysis, we prepared a novel chiral imidazolium salt **5** which is a tridentate chiral-NHC ligand precursor. Compound **5** was synthesized in five steps from (S)-proline in 24% overall yield (Scheme 1).

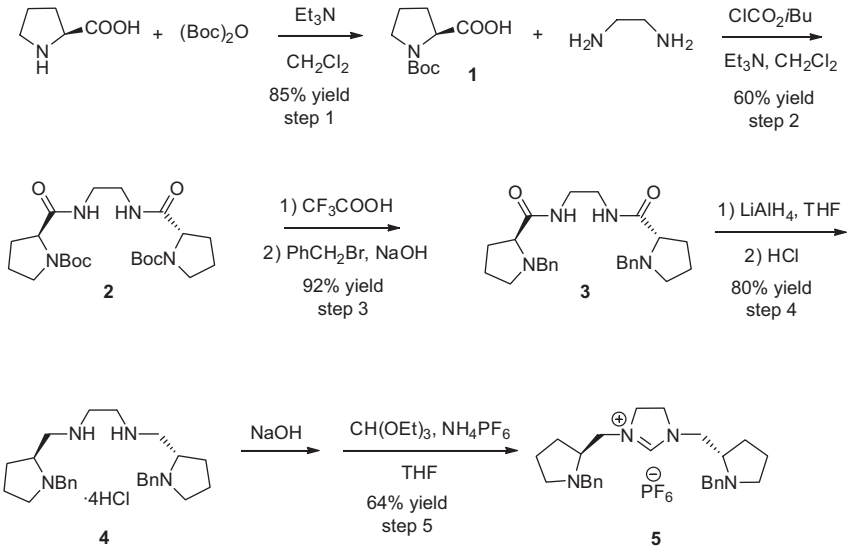
Compounds **1** (Kelleher et al., 2010) and **2** (Da Silva et al., 2002) were prepared from (S)-proline according to the literature procedures. The known compound **3** (Alcon et al., 2000) was prepared by using a modified procedure to avoid chromatography for purification. The NH function on (S)-proline was first protected by *tert*-butoxycarbonyl (Boc) group to give compound **1** in 85% yield. After formation of diamide **2** in 60% yield (step 2), the Boc groups were removed and replaced by benzyl (Bn) groups to give **3** in 92% yield. It is worth noting that in step 3, NaOH and dichloromethane were used as base and solvent, respectively, instead of Et_3N and tetrahydrofuran (THF) used in the literature to simplify the workup. This modification allowed the resultant product **3** to be purified by crystallization. The amide **3** was reduced by $LiAlH_4$ in step 4 to give amine **4**, which is a direct precursor to the desired final product **5**. Cyclization of **4** in the presence of $CH(OEt)_3$ and NH_4PF_6 in step 5 yielded **5**. However, it was surprising that an attempted reaction with NH_4Cl or NH_4Br instead of NH_4PF_6 did not furnish the corresponding cyclization product. Compound **5** was fully characterized by NMR and gave satisfactory elemental analysis results. Its molecular structure was determined by means of X-ray diffraction analyses (Figure 1).

The bond length of C1-N1 [1.275(5) Å] lies in the expected range of C=N double bond, and the distance of C1-N2 lies in the range of C-N single bond. The five atoms of the imidazolium ring are co-planar in the first approximation. The torsion angle of C1, N2, C3, C2 is 1.56° and the torsion angle of N1, C2, C3, N2 is 1.96°. The molecular structure also shows that the configuration of the two chiral carbons (C5 and C17) are S. Compound **5** exhibits two stereogenic centers, and each of them is within one of two chelating side chains. Its specific rotation in dichloromethane is -19.6°.

Experimental section

General

All reagents were commercially available and used without further purification. The ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz)



Scheme 1 Synthesis of compound **5**.

spectra were recorded on a Bruker DPX 400 spectrometer in $CDCl_3$ at room temperature. Elemental analyses were performed on a EuroVektor Euro EA-300 elemental analyzer. Optical rotation was measured with an Autopol IV automatic polarimeter in acetone solution. Melting points were determined on a microscope melting point apparatus. Compounds **1** and **2** are known and their ^{1}H NMR spectra were essentially identical with those of authentic samples were obtained by using published procedures (Da Silva et al., 2002; Kelleher et al., 2010). Compound **3** was obtained by using the procedure given below, which is a modification of the published method (Alcon et al., 2000). Compound **4** was used without characterization. New compound **5** was characterized by ^{1}H NMR, ^{13}C NMR, elemental analysis, and X-ray crystallographic analysis.

(2S,2′S)-*N,N′*-(Ethane-1,2-diyl)bis(1-benzylpyrrolidine-2-carboxamide) (3)

To diamide **2** (0.454 g, 1 mmol) cooled at 0°C was added trifluoroacetic acid (2 mL, 26 mmol) dropwise with stirring, and the resulting mixture was warmed up to room temperature and stirred for 30 min. After removal of the acid, the residue was treated with dichloromethane (15 mL) and aqueous NaOH (pH 12, 1 mL). Benzyl bromide (0.25 mL, 2.1 mmol) was added dropwise with vigorous stirring, and the mixture was stirred for 6 h at room temperature. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2×10 mL). The extract was washed with brine, dried over magnesium sulfate, concentrated, and treated with petroleum ether (5 mL). The resultant white precipitate of **3** was collected: yield 92%; mp 98.3–99.1°C; ^{1}H NMR: δ 1.64–1.76 (4H, m), 1.79–1.86 (2H, m), 2.13–2.23 (2H, m), 2.31–2.38 (2H, m), 3.00–3.04 (2H, m), 3.11–3.19 (4H, m), 3.30–3.37 (2H, m), 3.48 (2H, d, J=12.0 Hz), 3.77 (2H, d, J = 12.0 Hz), 7.24–7.32 (10H, m), 7.58 (2H, br s).

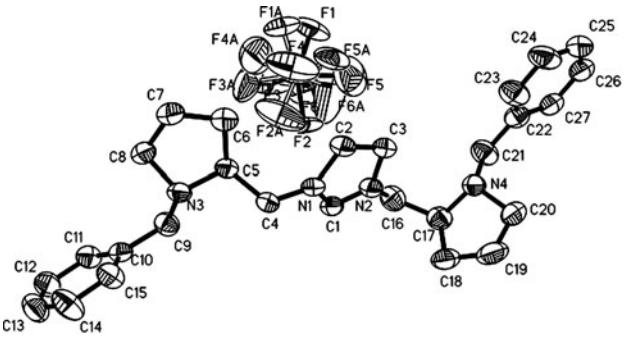


Figure 1 Molecular structure of compound **5**.

1,3-Bis(((S)-1-benzylpyrrolidin-2-yl)methyl)-4,5-dihydro-1*H*-imidazol-3-ium hexafluorophosphate (5)

The diamine **3** (0.44 g, 1 mmol) was added in portions over 30 min to a rapidly stirred suspension of $LiAlH_4$ (0.304 g, 8 mmol) in dry THF (15 mL) at 0°C. The mixture was allowed to warm to room temperature over 30 min and then heated under reflux for 24 h. A saturated solution of NH_4Cl (0.3 mL), a 15% solution of NaOH (0.3 mL) and a saturated solution of NH_4Cl (0.6 mL) were added successively to the above mixture at 0°C. The solid material was removed by filtration and thoroughly washed with dichloromethane. The combined organic solutions were dried over anhydrous Na_2SO_4 and then concentrated on a rotatory evaporator to give a yellow oil. This oil was dissolved in absolute ethanol (2 mL) and the solution was treated with concentrated HCl (0.3 mL). After removing most of the water and ethanol, the residue was crystallized from absolute ethanol to give the presumed product **4** as hydroscopic white solid.

To the aqueous solution of salt **4** (1.1 g, 2 mmol), a 15% solution of NaOH was added until the pH reached 11–12. The free amine was recovered by extracting the aqueous solution with diethyl ether (10 mL×2), and evaporating the solvent. The solution of the free amine in dry THF (15 mL) was treated with triethyl orthoformate (0.6 g, 4 mmol) and NH_4PF_6 (0.33 g, 2 mmol). The mixture was heated at 80°C for 2 h. After cooling to room temperature, the solids were removed and diethyl ether was added to the filtrate. The white precipitate of **5** was collected, washed with diethyl ether, and dried under reduced pressure: yield 0.7 g (51% from **3**); mp 119.0–120.3°C (from THF-ether); $[\alpha]^{25}_D$=-19.6° [c=1.0, DCM (dichloromethane)]; ^{1}H NMR: δ 1.43–1.51 (2H, m), 1.59–1.68 (2H, m), 1.70–1.79 (2H, m), 1.94–2.04 (2H, m), 2.37 (2H, m), 2.84–2.89 (2H, m), 2.97–3.02 (2H, m), 3.21–3.32 (4H, m), 3.49 (2H, d, J=12.0 Hz), 3.63–3.70 (2H, m), 3.74–3.86 (4H, m), 7.23–7.32 (10H, m), 7.78 (1H, s);

^{13}C NMR: δ 23.4 (CH_2), 27.9 (CH_2), 49.8 (CH_2), 51.0 (CH_2), 54.5 (CH_2), 59.7 (CH), 61.2 (CH_2), 127.2 (CH), 128.5 (CH), 128.9 (CH), 139.2 (C), 158.0 (CH). Anal. calcd for $C_{27}H_{37}F_6N_4P$: C, 57.64; H, 6.63; N, 9.96. Found: C, 57.28; H, 6.32; N, 10.19%.

X-Ray crystallographic analysis of 5

The crystal for the solid state structure of compound **5** was obtained by slow diffusion of ether into THF solution. Preliminary examination and data collection were carried out on a Rigaku Mercury CCD device at the window of a sealed X-ray tube with graphite-monochromated Mo Kα radiation (λ=0.71073 Å). Absorption correction was performed by the SADABS program. The structure was solved by directed methods using the SHELXS-97 program and refined by full-matrix least squares techniques on F^2. The single-crystal of **5** is monoclinic, space group P2(1) with a=6.0816(12) Å, b=32.899(7) Å, c=14.360(3) Å, α=90°, β=90.56(3)°, γ=90°, Mr=2250.30, V=2873.0(10) Å^3. The formula is $C_{108}H_{148}F_{24}N_{16}P_4$, Z=1, μ (Mo Kα)=0.157 mm^{-1}, -7≤h≤7, -39≤k≤39, -17≤l≤17, total number of reflection=9845, number of independent reflections=5254, R=0.0538, the largest difference peak and hole of electron density are 0.178 and -0.145 Å^{-3}, respectively. Selected bond lengths (Å) and angles (°): N(1)-C(1) 1.275(5), N(1)-C(2) 1.453(5), N(1)-C(4) 1.448(5), N(2)-C(1) 1.316(5), N(2)-C(3) 1.464(5), N(2)-C(16) 1.446(6), C(2)-C(3) 1.534(6), C(4)-C(5) 1.519(5), C(16)-C(17) 1.505(6), N(1)-C(1)-N(2) 115.6(4), C(1)-N(1)-C(4) 125.1(4), C(1)-N(1)-C(2) 109.5(3), C(2)-N(1)-C(4) 125.4(3), C(1)-N(2)-C(16) 125.8(4), C(1)-N(2)-C(3) 108.7(3), C(3)-N(2)-C(16) 124.9(4), N(1)-C(2)-C(3) 103.7(3), N(2)-C(3)-C(2) 102.4(3), C(4)-C(5)-C(6) 114.1(4), C(4)-C(5)-N(3) 109.0(3), C(16)-C(17)-C(18) 115.1(4), C(16)-C(17)-N(4) 112.3(4). CCDC-825945 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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