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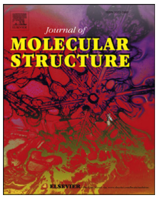

Orientation towards asymmetric transfer hydrogenation of ketones catalyzed by (pyrazolyl)ethyl)pyridine Fe(II) and Ni(II) complexes

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ABSTRACT

Compounds 2-[1-(3,5-dimethylpyrazol-1-yl)ethyl]pyridine (**L1**) and 2-[1-(3,5-diphenylpyrazol-1-yl)ethyl]pyridine (**L2**) were obtained in a three-step procedure which involved the reduction of acetylpyridine using $NaBH_4$, chlorination of the alcohol intermediate using $SOCl_2$ and subsequent reaction with appropriate pyrazoles. Reactions of **L1** and **L2** with Ni(II) and Fe(II) halides produced the respective complexes Ni(**L1**)Br_2 (**1**), Ni(**L1**)Cl_2 (**2**), Fe(**L1**)Cl_2 (**3**) and Ni(**L2**)Br_2 (**4**) as racemic mixtures in moderate yields. The molecular structures of complexes **1** and **4** are dinuclear and mononuclear respectively. All the complexes (**1**–**4**) formed active catalysts for the transfer hydrogenation of ketones (THK) in 2-propanol at 82 °C affording conversions of 58%–84% within 48 h. The influence of catalyst structure, reaction conditions and identity of ketone substrates in the TH reactions have been successfully established.

1. Introduction

Asymmetric transfer hydrogenation of ketones (ATHK) is a well-established method used to achieve enantiomerically enriched secondary alcohols [1,2]. Optically active alcohol products are useful intermediates in the manufacture of fine chemicals especially pharmaceuticals and pesticides [3,4]. Noyori and co-workers [1] first reported the Ru(II) complex [RuCl(η6-arene)(N-arylsulfonyl-DPEN)] as a catalyst in the transfer hydrogenation of ketones [5] to afford optically active products with high stereoselectivity. Since this discovery, there has been an extraordinary chiral catalyst development and applications in the asymmetric transfer hydrogenation reactions of ketones [6].

Currently, we have been working on the design and development of ruthenium, nickel and iron metal complexes as catalysts in the transfer hydrogenation of ketones [7]. In this current contribution, we originally aimed to design chiral (pyrazolyl)pyridine ligands and their Ni(II) and F(II) complexes as possible stereoselective catalysts for asymmetric transfer hydrogenation of ketones. However, out attempts to isolate the chiral ligands using Corey-Bakshi-Shibata (CBS) as the reducing agent have been so far unsuccessful. Other reports on the challenges of stereoselective reduction of acetylpyridine [8,9] have also been published. Herein, we thus report the syntheses of racemic mixtures of these pyrazolyl compounds, their respective Ni(II) and Fe(II) complexes and applications as catalysts in the transfer hydrogenation of various ketones.

2. Experimental

2.1. Materials and methods

The chemicals $NiCl_2$, $NiBr_2$, $FeCl_2\cdot 4H_2O$, 2-acetylpyridine, $SOCl_2$, $NaBH_4$ were obtained from Sigma-Aldrich and used as received. The solvents; dichloromethane, isopropanol, absolute ethanol and deuterated solvents were bought from Merck Chemicals, distilled and dried using conventional methods. NMR spectra were recorded on a Bruker 400 MHz (^1H) and a 100 MHz (^{13}C) spectrometer. Elemental analyses were performed on Thermal Scientific Flash 2000 and mass spectra were recorded on LC Premier micro-mass Spectrometer. Magnetic moment measurements were performed in an Evans balance.

2.2. Syntheses2-[1-(3,5-dimethylpyrazol-1-yl)ethyl]pyridine (*L1*)

Compound **L1** was prepared by dissolving 2-(1-chloroethyl)

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pyridine, initially prepared by reduction of acetyl pyridine using $NaBH_4$ and subsequent reaction with $SOCl_2$, (2.02 g, 14.20 mmol) and 3,5-dimethylpyrazole (1.37 g, 14.20 mmol) in toluene (30 mL), 40% aqueous NaOH (10 mL) and 40% aqueous tetrabutylammonium bromide (5–6 drops). The reaction mixture was refluxed for 120 h. The organic layer was then separated from the aqueous layer and washed three times with deionised water, then dried over anhydrous Na_2SO_4 and solvent removed under vacuum. Purification of the crude product by column chromatography using a solution of hexane and diethyl ether mixture (3:2) gave a chrome yellow liquid. Yield: 1.43 g (49%). ^1H NMR ($CDC1_3$): δ 2.14 (s, 3H, CH_3, pz); 2.30 (s, 3H, CH_3, pz); 1.96 (d, 3H, CH_3, $^3J_{HH} = 8$); 5.46 (q, H, CH_3); 5.87 (s, 1H, pz); 6.82 (d, ^1H, py, $^3J_{HH}$ = 7.61 Hz); 7.15 (t, ^1H, py, $^3J_{HH}$ = 7.8 Hz); 7.58 (t, ^1H, py, $^3J_{HH}$ = 7.8 Hz); 8.54 (d, ^1H, py, $^3J_{HH}$ = 7.8 Hz).^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.71, 14.05, 20.19, 59.17, 105.64, 120.25, 122.13, 137.07, 139.49, 147.50, 148.77, 162.10. (ESI-MS) *m*/*z* (%) 201 (M^+, 35%).

2.3. Synthesis of 2-[1-(3,5-diphenylpyrazol-1-yl)ethyl]pyridine (**L2**)

Compound **L2** was prepared following the same method described for **L1** using 2-(1-chloroethyl)pyridine (2.00 g, 14.30 mmol) and 3,5-diphenylpyrazole (3.14 g, 14.30 mmol). Light red semi-solid. Yield: 1.68 (36%). ^1H NMR ($CDC1_3$): δ 2.02 (d, 3H, CH_3); 5.67 (q, 1H, CH); 6.67 (s, 1H, CH, pz); 7.16 (d, 1H, py, $^3J_{HH}$ = 7.61 Hz); 7.93 (d, 1H, py, $^3J_{HH}$ = 7.8 Hz); 7.61 (t, 2H, py, $^3J_{HH}$ = 7.73 Hz), 7.36–7.45 (m, 10H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.04, 59.57, 103.63, 120.93, 122.19, 125.61, 125.63, 125.69, 127.61, 128.40, 128.57, 128.65, 128.69, 128.94, 129.05, 130.50, 133.74, 137.18, 145.69, 148.56, 150.80, 161.95. (ESI-MS) *m*/*z* (%) 348 (M^++Na, 75%).

2.4. Synthesis of complex [Ni_2(**L1**)$_2Br_2(\mu$-Br)$_2$] (**1**)

To a mixture of $NiBr_2$ (0.11 g; 0.50 mmol) in CH_2Cl_2 (10 mL) was added a solution of **L1** (0.10 g; 0.50 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 24 h at room temperature to give a purple solution. Slow evaporation of the solution afforded purple crystals suitable for single crystal X-ray analyses. Yield = 0.15 g (73%). ESI-MS), *m*/*z* (%) 339 (1/2 M^+ – Br, 15%), 259 (1/2 M^+ – Br_2, 5%). μ_{eff} = 2.96 BM. Anal Cald. $C_{24}H_{30}Br_4$N6Ni_2. C, 34.34; H, 3.60; N, 10.01. Found: C, 34.11; H, 3.80; N, 10.32.

Complexes **2**–**4** were prepared following the protocol described for **1**.

2.5. Synthesis of complex [Ni_2(**L1**)$_2Cl_2(\mu$-Cl)$_2$] (**2**)

$NiCl_2$ (0.06 g; 0.50 mmol) and **L1** (0.16 g; 0.50 mmol). Orange solid. Yield = 0.12 g (65%). (ESI-MS), *m*/*z* (%) 295 (1/2 M^+ – Cl, 75%). μ_{eff} = 2.95 BM. Anal. Cald for $C_{24}H_{30}Cl_4N_6Ni_2$: C, 43.56; H, 4.57; N, 12.70. Found: C, 43.29; H, 4.78; N, 12.97.

2.6. Synthesis of complex [Fe_2(**L1**)$_2Cl_2(\mu$-Cl)$_2$] (**3**)

3: $FeCl_2$ (0.10 g; 0.50 mmol) and **L1** (0.10 g; 0.50 mmol). Dark brown solid. Yield = 0.08 g (51%). (ESI-MS), *m*/*z* (% abundance) 464 (1/2 M^+ – Cl, 8%). μ_{eff} = 5 0.00 BM. Anal. Cald for $C_{24}H_{30}Cl_4Fe_2N_6$: C, 43.94; H, 4.61; N, 12.81. Found: C, 43.49; H, 4.90; N, 13.02.

2.7. Synthesis of complex [Ni_2(**L2**)Br_2] (**4**)

$NiBr_2$ (0.10 g; 0.46 mmol) and **L1** (0.15 g; 0.46 mmol) were used. Purple solid. Yield = 0.17 g (67%). (ESI-MS), *m*/*z* (% abundance) 464 (M^+ – Br, 11%), 384 (M^+ – Br_2, 5%), 325 (M^+ – $NiBr_2$, 10%), 311 (M^+ – $NiBr_2$,-CH_3, 18%) μ_{eff} = 3.62 BM. Anal. Cald for $C_{22}H_{19}Br_2N_3Ni$: C, 48.58; H, 3.52; N, 7.73. Found: C, 48.78; H, 3.21; N, 7.48.

2.8. Crystal data collection and structure refinement

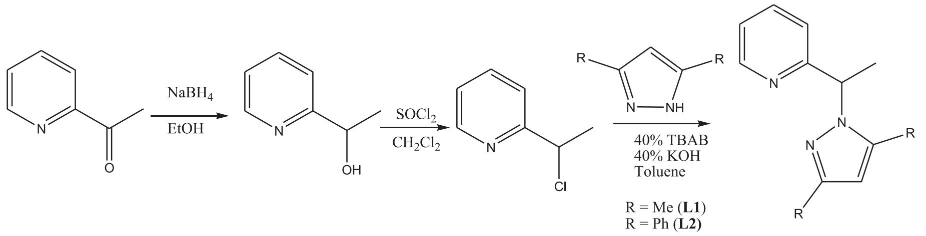
Single crystal X-ray diffraction data collection and refinement for complex **1** and **4** were recorded on a Bruker Apex Duo equipped with an Oxford Instruments Cryo jet operating at 100 (2) K and an Incoatec micro source operating at 30 W power. The data were collected with Mo Kα (λ = 0.71073 Å) radiation at a crystal-to-detector distance of 50 mm. The following conditions were used for the data collection: omega and phi scans with exposures taken at 30 W X-ray power and 0.50° frame widths using APEX2 [10]. The data were reduced with the programme SAINT [10] using outlier rejection, scan speed scaling, as well as standard Lorentz and polarization correction factors. A SADABS semi-empirical multi-scan absorption correction was applied to the data. Direct methods, SHELXS-2014 [11] and WinGX [12] were used to solve all three structures. All non-hydrogen atoms were located in the difference density map and refined anisotropically with SHELXL-2014 [11]. All hydrogen atoms were included as idealized contributors in the least squares process. Their positions were calculated using a standard riding model with C-$H_{aromatic}$ distances of 0.93 Å and U_{iso} = 1.2 Ueq.

3. Results and discussion

3.1. Syntheses and spectroscopic characterization of the compounds

The pyrazolyl ligands **L1** and **L2** were prepared following a conventional method for the reduction of ketones using $NaBH_4$ as shown in Scheme 1. Purification of the crude products using column chromatography and hexane:diethyl ether (3:2) solvent system afforded **L1** and **L2** as analytically pure compounds in low yields. ^1H NMR spectra of both **L1** and **L2** showed a quartet at 5.46 ppm and 5.67 ppm respectively which were assigned to the methine protons. All the expected signals were observed in the ^1H NMR spectra of both compounds **L1** and **L2** (Fig. S1).

Treatment of compounds **L1** and **L2** with the relevant Ni(II) or Fe(II) salts afforded the corresponding complexes **1**–**4** in moderate



Scheme 1. The synthetic route for ligands **L1** and **L2** using $NaBH_4$ as the reducing agent.