

A Highly Active Ruthenium(II) Pyrazolyl–Pyridyl–Pyrazole Complex Catalyst for Transfer Hydrogenation of Ketones

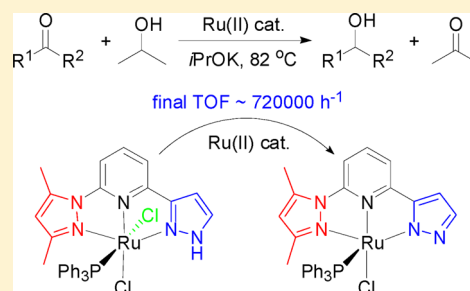
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Supporting Information

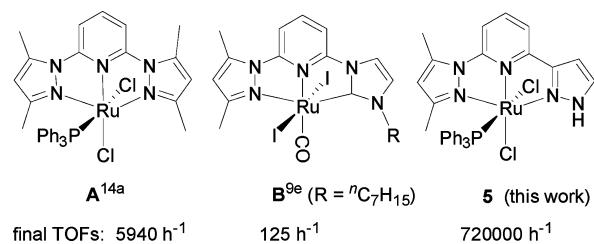
ABSTRACT: Ruthenium(II) complexes bearing a pyrazolyl–pyridyl–pyrazole ligand were synthesized and exhibited exceptionally high catalytic activity in the transfer hydrogenation of ketones in refluxing isopropyl alcohol, reaching final TOFs up to 720 000 h⁻¹. The β -NH functionality of the pyrazole arm in the ligand demonstrated a remarkable acceleration effect on the reaction rate. The unsymmetrical nature (hemilability) and presence of the convertible NH group of the ligand is attributed to the high catalytic activity of the complex catalyst.



NNN ligands have been extensively applied in materials science, coordination chemistry, and homogeneous catalysis,¹ among which pyridyl-based tridentate NNN ligands such as pybox,² 2,6-bis(imino)pyridines,³ and terpyridines⁴ have attracted much more attention due to their tunable properties and potential applications. Although these NNN ligands as well as other symmetrical polydentate ligands⁵ have been reported to establish catalytic systems for diverse purposes,^{6,7} unsymmetrical polydentate ligands are still strongly desired. NNN ligands can be readily prepared and structurally and electronically modified, and their transition-metal complexes are usually stable during preparation and storage and are more reactive than their analogues bearing a phosphine ligand.^{8–10} In addition, the construction of refined transition-metal complexes as catalysts has been applied as a potentially straightforward way to probe the reaction mechanism.

Ketone reduction is a straightforward route to alcohols, and transfer hydrogenation of ketones by using isopropyl alcohol as the hydrogen donor has been considered as a reliable method under mild conditions.¹¹ Noyori et al. developed the efficient ruthenium(II) *N*-tosylethylenediamine complex catalysts for asymmetric transfer hydrogenation of ketones.¹² Baratta and co-workers reported highly active ruthenium(II) NNC complexes containing a NH₂ group as catalysts for transfer hydrogenation of ketones.¹³ Our group¹⁴ and that of Karam et al.¹⁵ used pyrazolyl-containing pyridyl-based NNN ligands for the first time to make transition-metal complex catalysts for the transfer hydrogenation of ketones and polymerization of olefins, respectively. In our hands,^{14a} a complex bearing a symmetrical NNN ligand, i.e., RuCl₂(PPh₃)L (**A**; L = 2,6-bis(3,5-dimethylpyrazol-1-yl)pyridine), was synthesized and structurally characterized and exhibited good catalytic activity in the transfer hydrogenation of ketones in refluxing isopropyl

alcohol, reaching final TOFs up to 5940 h⁻¹. However, ruthenium(II) complex **B**,^{9c} supported by an unsymmetrical NNC ligand, only exhibited a poor catalytic activity for the same process (final TOF = 125 h⁻¹), due to the strong σ -donor ability of the NHC coordinating arm in the ligand, which renders complex **B** less labile during the catalytic reaction. Thus, the structural and electronic properties of a polydentate ligand should be compatible in order to construct a highly active complex catalyst. During our ongoing investigation on transition-metal complex catalysts,^{9,14} the NH group of an *N*-heterocycle has been found to act as an acceleration functionality in the complex catalysts. Herein, we report a highly active ruthenium(II) complex catalyst (**5**) bearing an unsymmetrical pyridyl-based bis-pyrazole ligand for the transfer hydrogenation of ketones.



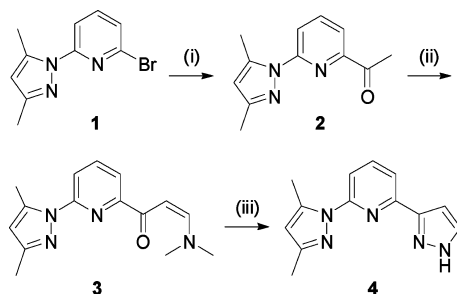
Ketone **2** was synthesized by lithiation of 2-bromo-6-(3,5-dimethylpyrazol-1-yl)pyridine (**1**) with *n*BuLi at -78 °C and then reacted with *N,N*-dimethylacetamide.¹⁶ Treatment of **2** with *N,N*-dimethylformamide dimethyl acetal with heating afforded the β -amino-substituted enone **3**,¹⁷ which was

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condensed with hydrazine hydrate to produce ligand **4** (Scheme 1). Reacting ligand **4** with an equivalent amount of

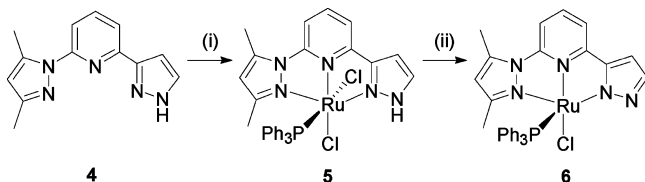
Scheme 1. Synthesis of Ligand **4**^a



^aLegend: (i) *n*BuLi, $-78\text{ }^{\circ}\text{C}$, *N,N*-dimethylacetamide, Et_2O , 65%; (ii) *N,N*-dimethylformamide dimethyl acetal, reflux, 14 h, 88%; (iii) hydrazine hydrate, EtOH, reflux, 1.5 h, 82%.

$\text{RuCl}_2(\text{PPh}_3)_3$ in refluxing toluene led to complex **5** in 85% yield (Scheme 2). Under basic conditions, the reaction of **5**

Scheme 2. Synthesis of Complexes **5** and **6**^a



^aLegend: (i) $\text{RuCl}_2(\text{PPh}_3)_3$, toluene, $110\text{ }^{\circ}\text{C}$, 2 h, 85%; (ii) K_2CO_3 , CH_2Cl_2 , room temperature, 10 h, 90%.

with K_2CO_3 base afforded the **16e** complex **6** in 90% yield. Both of the complexes were stable in air. The proton NMR spectrum of **5** in CDCl_3 revealed a broad peak at 14.55 ppm for the pyrazolyl NH group, which was shifted downfield by 3.39 ppm as compared to that of free ligand **4** (δ_{NH} 11.16 ppm). The CH resonance of the 3,5-dimethylpyrazolyl moiety in complex **5** appeared as a singlet at 6.11 ppm, shifting downfield by 0.10 ppm in comparison to that of the ligand. The broad N–H stretching vibration peak of the free ligand was sharpened and red-shifted by 88 cm^{-1} in the IR spectrum of **5**. These results reveal coordination of the pyrazolyl nitrogen donor atoms to the metal center in **5**. The ^{31}P NMR signals of complexes **5** and **6** in CDCl_3 appeared at 46.1 and 46.6 ppm, respectively, suggesting no obvious alteration of the environment around the PPh_3 ligand in these complexes. In the ^1H NMR spectrum of complex **6**, the resonance signal of the NH group disappeared, suggesting formation of a Ru–N σ bond, and the proton signal of 3,5-dimethylpyrazolyl CH was shifted downfield from 6.11 to 6.28 ppm. The ^{31}P NMR resonances of **5** and **6** in $\text{DMSO}-d_6$ appeared at 31.3 and 33.4 ppm, respectively, which are similar to the ^{31}P NMR features of complexes **C** and **D** ($\delta(^{31}\text{P})$ 31.5 and 33.8 ppm),^{9b,d} demonstrating that $\text{DMSO}-d_6$ was coordinated to the metal center and complexes **5** and **6** have structures similar to those of **C** and **D**, as we previously reported (Scheme 3).

Next, complexes **5** and **6** were tested as the catalysts for transfer hydrogenation of acetophenone in refluxing isopropyl alcohol (Table 1). By using 0.05–0.2 mol % of the complex catalyst, i.e., **5** or **6**, reduction of the ketone was completed within 10 s to 1 min, exclusively forming 1-phenylethanol as the

Scheme 3. Complexes **C** and **D**^{9b,d}

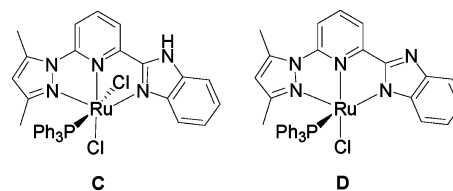
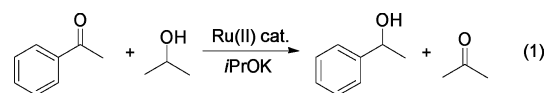


Table 1. Screening of Conditions for the Transfer Hydrogenation of Acetophenone^c






















entry	cat./amt (mol %)	amt of <i>i</i> PrOK (mol %)	temp ($^{\circ}\text{C}$)	time (min)	conversion ^a (%)
1	5/0.2	4	82	1/6	98
2	5/0.1	4	82	1/2	97
3	5/0.1	1	82	1/2	97
4	5/0.05	1	82	1	95
5	5/0.05	1	r.t.	1	10 (24) ^b
6	6/0.05	1	82	1	95

^aBy GC analysis. ^bYield at 60 min in parentheses. ^cConditions: ketone, 2.0 mmol (0.1 M in 20 mL of *i*PrOH); 0.1 MPa N_2 .

product. Both **5** and **6** exhibited the same catalytic activity (Table 1, entries 4 and 6), reaching 95% conversion for the ketone substrate within 1 min. Complex **5** underwent instantaneous conversion to form **6** through dehydrochlorination under basic conditions; thus, they exhibited the same catalytic activity for transfer hydrogenation of ketones. By means of the conditions for entries 4 and 6 in Table 1 as the optimal conditions, reduction of a variety of ketones was performed by using complex **5** (0.05 mol %) as the catalyst (Table 2). For most of the substrates, their reactions were very fast, achieving $\geq 96\%$ conversion within 10 s. In particular, 2-bromoacetophenone was quantitatively reduced to the corresponding alcohol within 10 s and the catalyst reached the highest final TOF value of $7.2 \times 10^5\text{ h}^{-1}$ (Table 2, entry 4). Thus, complexes **5** and **6** are among the few most active complex catalysts for transfer hydrogenation of ketones to date.^{9,10,13} In other cases, the reactions were finished over a period of 1/2 min, reaching 95–99% conversion for the ketone substrates. Electron-donating and -withdrawing substituents such as chloro, bromo, methyl, and methoxy were tolerated. 4-Methoxy substitution deteriorated the substrate reactivity (entry 12), causing the reaction not to proceed after the initiation period. With an N-heterocyclic substrate, the catalyst loading should be increased to promote the reaction (entry 16).

The present transfer hydrogenation reactions may follow an inner-sphere mechanism.¹⁸ Reduction of a ketone is initiated directly from **6** or in situ generated **6** by extrusion of 1 equiv of hydrogen chloride from **5** with *i*PrOK. Complex **6** interacts with the base to form a Ru(II) alkoxide which undergoes β -H elimination to form a RuH species that is presumably considered as the catalytically active species, although it was not successfully isolated by reacting **5** or **6** with EtONa or *i*PrOK in refluxing ethanol or isopropyl alcohol. Formation of RuH complexes from RuCl precursors has been documented in our laboratory^{9a} and by others,¹⁹ and in situ formed RuH species have been known to act as the active catalysts for the transfer hydrogenation of ketones.^{11,18,20}

Table 2. Transfer Hydrogenation of Ketones Catalyzed by Complex 5^d

entry	ketone	time (min)	conversion (%) ^a	final TOF (h ⁻¹)
1		1	95	114000
2		1	98	117600
3		1/6	96	691200
4		1/6	100	720000
5		1/2	98	235200
6		1/2	95	228000
7		1/6	99	712800
8		1/2	95	228000
9		1/6	98	705600
10		1/6	98	705600
11		1/6	96	691200
12		1/6	90	648000
13		1/6	97	698400
14		1/2	98 ^b	235200
15		1/6	98 ^b	705600
16		10	10	1200
		15	95 ^c	1900
17		1/6	98	705600
18		1/6	98	705600
19		1/6	99	712800

^aBy GC analysis. ^bBy ¹H NMR analysis. ^c0.2 mol % 5 was used. ^dConditions: ketone, 2.0 mmol (0.1 M in 20 mL of *i*PrOH); catalyst, 0.05 mol % 5; ketone/*i*PrOK/S = 2000:20:1; 0.1 MPa N₂; 82 °C.

In summary, Ru(II) complexes bearing a unsymmetrical pyrazolyl–pyridyl–pyrazole ligand were successfully synthesized and exhibited exceptionally high catalytic activity in the transfer hydrogenation of ketones at 82 °C, demonstrating rare examples of highly active Ru(II) NNN complex catalysts that

do not feature an ancillary N–H functionality.²¹ The hemilability of the ligand and easy convertibility from the coordinately saturated complex to the coordinately unsaturated precatalyst under the reaction conditions are attributed to the exceptionally high catalytic activity of these complexes.

■ ASSOCIATED CONTENT

📄 Supporting Information

Text and figures giving experimental procedures, analytical data, and NMR and HRMS spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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