

Notes

Ruthenium(II) Complexes Bearing a Pyridyl-Supported Pyrazolyl–N-Heterocyclic Carbene (NNC) Ligand and Their Catalytic Activity in the Transfer Hydrogenation of Ketones

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Summary: Ruthenium(II) complexes bearing a pyridyl-supported pyrazol-3-yl–N-heterocyclic carbene (NNC) ligand were synthesized from the reactions of $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ with pyridyl-supported pyrazol-3-yl–imidazolium salts in the presence of carbon monoxide. These Ru(II) complexes have exhibited good to excellent catalytic activity in the transfer hydrogenation of ketones in refluxing 2-propanol. Formation of a coordinatively unsaturated Ru(II) center in the precatalyst is attributed to the high catalytic activity of the Ru(II) complexes.

The development of ligands bearing donors other than phosphorus has been arousing much interest in coordination chemistry, homogeneous catalysis, and organic synthesis. N-heterocyclic carbenes (NHCs) have attracted considerable attention as a very useful class of ligands over the past decade.¹ Transition metal complex catalysts have been well documented in catalytic C–C and C–N bond coupling reactions² and olefin metathesis.³ However, only a few Ru(II) complexes bearing “pincer”-type N-heterocyclic carbene (CNC) ligands, i.e., 2,6-bis(N-heterocyclic carbene)pyridine ligands, have been reported.⁴ Ruthenium(II) complexes bearing aliphatic chain-linked bis- and mono-NHC ligands were also obtained by transmeta-

lation of their silver carbene complexes.⁵ Although some attention was paid to the synthesis of Ru(II) CNC complexes, only very limited work has been directed toward their catalytic activity. Exploration of their application as catalysts in the transfer hydrogenation of cyclohexanone and acetophenone in refluxing 2-propanol revealed only poor to moderate catalytic activity for them.^{4a,b,5b} Mixed-donor ligands have been widely used due to the versatility arising from the different stereoelectronic properties of the multiple coordination sites, providing unique reactivity of their metal complexes.^{6,7} We have been interested in new pyridyl-based 2,6-(mixed N-heterocycles) ligands which can potentially provide a dynamic “on and off” chelating effect for the metal center during catalysis.^{8,9} Very recently, we reported the synthesis of a new class of pyridyl-supported pyrazolyl–NHC ligands (NNC ligands) and their highly active palladium(II) complex catalysts for Suzuki coupling,⁸ pyridyl-based bis-pyrazoles,⁹ and pyrazolyl–imidazolyl ligands¹⁰ and their efficient Ru(II) complex catalysts for transfer hydrogenation of ketones, respectively. Herein, we report on the synthesis of a new unsymmetrical “pincer”-type pyridyl-based (pyrazol-3-yl)–N-heterocyclic carbene (NNC) ligand and the catalytic activity of its ruthenium(II) complexes in the transfer hydrogenation of ketones.

Results and Discussion

Transmetalation has proved to be a promising procedure to obtain transition-metal NHC complexes, because many ligands may be degraded under the harsh conditions for preparation of a free NHC ligand.^{11,12} However, treatment of $\text{RuCl}_2(\text{PPh}_3)_3$ or $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ with a stoichiometric amount of the silver

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(1) For recent reviews, see: (a) Diez-Gonzalez, S.; Nolan, S. P. *Coord. Chem. Rev.* **2007**, *251*, 874. (b) Mataa, J. A.; Poyatos, M.; Peris, E. *Coord. Chem. Rev.* **2007**, *251*, 841. (c) Pugh, D.; Danopoulos, A. A. *Coord. Chem. Rev.* **2007**, *251*, 610.

(2) (a) Lee, D.-H.; Kim, J.-H.; Jun, B.-H.; Kang, H.; Park, J.; Lee, Y.-S. *Org. Lett.* **2008**, *10*, 1609. (b) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101.

(3) For selected recent papers, see: (a) Vougioukalakis, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2008**, *130*, 2234. (b) Chen, J. R.; Li, C. F.; An, X. L.; Zhang, J. J.; Zhu, X. Y.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2489. (c) Debleds, O.; Campagne, J.-M. *J. Am. Chem. Soc.* **2008**, *130*, 1562.

(4) (a) Danopoulos, A. A.; Winston, S.; Motherwell, W. B. *Chem. Commun.* **2002**, 1940, 1376. (b) Poyatos, M.; Mata, J. A.; Falomir, E.; Crabtree, R. H.; Peris, E. *Organometallics* **2003**, *22*, 1110. (c) Son, S. U.; Park, K. H.; Lee, Y.-S.; Kim, B. Y.; Choi, C. H.; Lah, M. S.; Jang, Y. H.; Jang, D.-J.; Chung, Y. K. *Inorg. Chem.* **2004**, *43*, 6896. (d) Wright, J. A.; Danopoulos, A. A.; Motherwell, W. B.; Carroll, R. J.; Ellwood, S. J. *Organomet. Chem.* **2006**, *691*, 5204.

(5) (a) Arnold, P. L.; Scarisbrick, A. C. *Organometallics* **2004**, *23*, 2519. (b) Chiu, P. L.; Lee, H. M. *Organometallics* **2005**, *24*, 1692.

(6) Bianchini, C.; Meli, A. *Coord. Chem. Rev.* **2002**, *225*, 35.

(7) (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1113. (b) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.

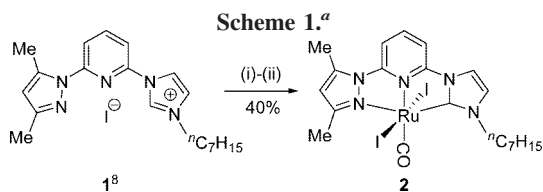
(8) Zeng, F. L.; Yu, Z. K. *J. Org. Chem.* **2006**, *71*, 5274.

(9) (a) Sun, X. J.; Yu, Z. K.; Wu, S. Z.; Xiao, W.-J. *Organometallics* **2005**, *24*, 2959. (b) Deng, H. X.; Yu, Z. K.; Dong, J. H.; Wu, S. Z. *Organometallics* **2005**, *24*, 4110.

(10) Zeng, F. L.; Yu, Z. K. *Organometallics* **2008**, *27*, 2898.

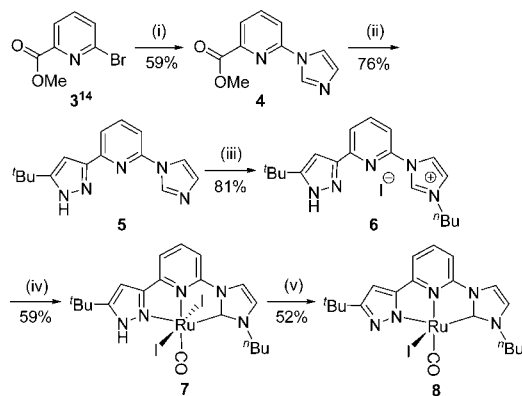
(11) Wang, H. M. J.; Lin, I. J. B. *Organometallics* **1998**, *17*, 972.

(12) Garrison, J. C.; Youngs, W. J. *Chem. Rev.* **2005**, *105*, 3978.



^a Legend: (i) RuCl₃ · 3H₂O, CO (1.0 atm), ethylene glycol, 190 °C, 1 h; (ii) KI, CH₂Cl₂, room temperature, 2 h.

Scheme 2. Synthesis of Complexes 7 and 8^a



^a Legend: (i) imidazolotopassium, diglyme, 100 °C, 60 h; (ii) (1) pinacolone, *t*BuOK, PhMe, room temperature, 24 h, (2) N₂H₄ · H₂O, ethanol, reflux, 15 h; (iii) ^tBuI, acetonitrile, reflux, 48 h; (iv) (1) RuCl₃ · 3H₂O, CO (1.0 atm), ethylene glycol, 190 °C, 1 h, (2) KI, DCM, room temperature, 2 h; (v) K₂CO₃, CH₂Cl₂, 7 days.

complex of imidazolium iodide **1** in dichloromethane failed to afford the desired ruthenium(II) NNC complex. Reaction of **1** with 1.0 equiv of KN(SiMe₃)₂ or NaH in THF followed by treatment with RuCl₂(PPh₃)₃ or [Ru(*p*-cymene)Cl₂]₂ also did not form the desired Ru(II) complex. A one-pot reaction of **1** and RuCl₂(PPh₃)₃ in the presence of a base such as LiOtBu, NaAcO, Na₂CO₃, or Et₃N did not produce the desired Ru(II) complexes of type **2**. Unexpectedly, compound **1** reacted with 1.0 equiv of RuCl₃ · 3H₂O and carbon monoxide in ethylene glycol at 190 °C formed complex **2** in 40% isolated yield under the optimized conditions¹³ (Scheme 1). When the *n*-heptyl group in the imidazolium salt **1** was replaced by a *n*-propyl or *n*-butyl group, the desired complex could not be obtained. Presumably, the poor solubility of the ligands with a short alkyl chain affected reduction of the Ru(III) precursors to the Ru(II) species. It should be noted that anion exchange should be carried out to convert the possible Ru(II)–Cl species to the desired product in order to ease the isolation procedure. The present method employs the easily accessible RuCl₃ · 3H₂O as the Ru(II) source, exhibiting much better efficiency than Peris' procedure.^{4b}

In the fashion shown in Scheme 2, the 1*H*-pyrazol-3-yl-containing imidazolium iodide **6** was prepared and its corresponding 18-electron Ru(II) pyridyl-supported 1*H*-pyrazol-3-yl–*N*-heterocyclic carbene complex **7** and 16-electron analogue **8** were synthesized, respectively. Heteroarylation of imidazole with methyl 6-bromo-2-pyridinecarboxylate (**3**)¹⁴ afforded methyl 6-(imidazol-1-yl)-2-pyridinecarboxylate (**4**). 2-(Imidazol-1-yl)-6-(5-*tert*-butyl-1*H*-pyrazol-3-yl)pyridine (**5**) was easily

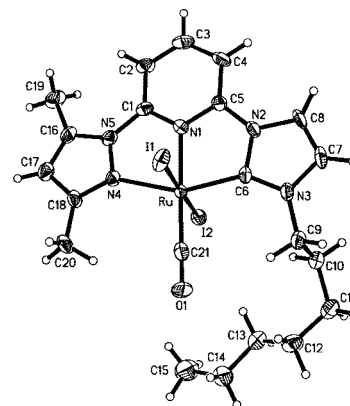


Figure 1. Molecular structure of complex **2**.

obtained by Claisen condensation of **4** with 3,3-dimethyl-2-butanone followed by reacting with hydrazine hydrate. The ligand precursor **6** was efficiently prepared by the reaction of **5** with 1-iodobutane in refluxing acetonitrile. When the *tert*-butyl group in **5** was substituted by a methyl group, the corresponding imidazolium iodide could not be successfully made, due to the easy alkylation of the pyrazole moiety under the reaction conditions, suggesting that the sterically hindered *tert*-butyl can block alkylation of the pyrazole moiety during the alkylation of the imidazole moiety in **5**. It is noteworthy that the intermediate **5** did not react with 1-iodoheptane to form *N*-*n*-heptylimidazolium iodide. In a fashion similar to the preparation of the 16-electron ruthenium(II) complex of a pyridyl–pyrazolyl–imidazolyl ligand,¹⁰ complex **7** was successfully transformed to its 16-electron analogue **8** by using K₂CO₃ as the base.

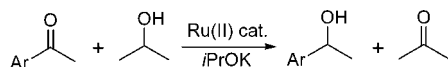
All of the complexes are stable in air, even at its melting point for **2** and at temperatures above 300 °C for **7** and **8**. Complex **2** exhibited NMR features similar to those of its palladium(II) analogues,⁸ while the ¹³C resonance of its Ru=C group appeared at 192.5 ppm in solution. The ¹H NMR signals of the NH and pyrazolyl CH moieties in **7** were shifted downfield by about 1.04 and 0.21 ppm, respectively, as compared with those of the ligand precursor **6** (δ_{NH} , 12.95 ppm; $\delta_{\text{pyrazolyl CH}}$, 6.87 ppm). The proton resonances of the imidazolyl CH in **7** appeared at 8.41 and 7.53 ppm, shifting upfield by 0.25 and 0.58 ppm, respectively, as compared with those of the ligand precursor. The ¹³C NMR resonances of the carbonyl and Ru–carbene carbon of **7** were found at 206.3 and 192.6 ppm, respectively. These results suggest that all the imidazolyl, pyrazolyl, and carbonyl moieties in complex **7** are coordinated to the metal center. The ¹H NMR signals of the corresponding pyrazolyl, imidazolyl, and pyridyl CH groups in complex **8** were shifted upfield about 0.1 ppm, and the ¹³C NMR signals of the carbonyl and Ru=C (203.7 and 189.6 ppm) were shifted upfield by 2.6 and 2.9 ppm, respectively, as compared to those of the 18-electron complex **7**.







The solid-state molecular structure of complex **2** was further confirmed by an X-ray crystallographic study (Figure 1).¹⁵ In the complex molecule, the ruthenium atom is in a distorted-octahedral environment with the two iodine ligands trans to each other on the two sides of the NNC ligand plane. The unsymmetrical “pincer”-type NNC ligand occupies the three meridional sites with the three *N*-heterocyclic rings in a quasi-planar disposition, and the carbonyl ligand is positioned trans to the

(13) Ziesel, R.; Grosshenny, V.; Hissler, M.; Stroh, C. *Inorg. Chem.* **2004**, *43*, 4262.

(14) Asberom, T.; Zhao, Z. Q.; Bara, T. A.; Clader, J. W.; Greenlee, W. J.; Hyde, L. A.; Josien, H. B.; Li, W.; McPhail, A. T.; Nomeir, A. A.; Parker, E. M.; Rajagopalan, M.; Song, L. X.; Wong, G. T.; Zhang, L. L.; Zhang, Q.; Pissarnitskia, D. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 511.

(15) Crystal data for **2**: C₂₁H₂₇I₂N₅ORu, monoclinic, *Cc*, $a = 14.925(3)$ Å, $b = 17.760(3)$ Å, $c = 9.3659(18)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 99.702(3)^\circ$, $V = 2447.0(8)$ Å³, $Z = 4$, $T = 293(2)$ K, $D_{\text{calcd}} = 1.955$ g cm⁻³, $R(F) = 5.70\%$ for 4665 observed reflections ($3.60 \leq 2\theta \leq 53.98^\circ$).

Table 1. Screening of the Catalysts for the Transfer Hydrogenation of Ketones^b

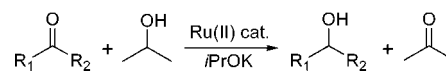
entry	ketone	cat.	time (h)	yield (%) ^a
1		2	4	98
2		7	2	98
3		8	2	97
4		2	24	90
5		7	1/4	97
6		8	1/4	98



















^a GC yield of the corresponding alcohol. ^b Reaction conditions: ketone/*i*PrOK/cat. = 500/1/20; ketone, 2.0 mmol (0.1 M in 20 mL of *i*PrOH); 0.1 MPa; 82 °C.

pyridyl nitrogen atom. The average bond lengths of Ru=C (carbene carbon), Ru-N_{pyridyl}, Ru-N_{pyrazolyl}, and Ru-C (carbonyl carbon) in **2** are 1.971(9), 2.038(8), 2.148(7), and 1.841(13) Å, respectively. The pyridyl N-Ru-CO bond angle is close to 180° (average 178.4(4)°), and the average pyrazolyl N-Ru-C (carbene carbon) bond angle is 153.9(3)°.

Transfer hydrogenation (TH) of acetophenone and 4-bromoacetophenone in refluxing 2-propanol was carried out to test the catalytic activity of complexes **2**, **7**, and **8**. Using 0.1 M ketone solution, 0.2 mol % of the complex as catalyst, and 4 mol % of *i*PrOK as the base, complex **2** acted as an efficient catalyst for the TH of acetophenone, reaching 98% conversion for the ketone within 4 h (Table 1, entry 1). Under the same conditions, complexes **7** and **8** nearly exhibited the same catalytic activity, reaching 97–98% conversions for acetophenone over a period of 2 h and 97–98% conversions for 4-bromoacetophenone with a final TOF up to 1940 h⁻¹ within 15 min. Presumably due to the instant transformation of the 18-electron complex **7** to the 16-electron species **8** under the reaction conditions, the two complexes exhibited the same catalytic activity. The coordinatively unsaturated Ru(II) center in the precatalyst **8** may prompt coordination of the ketone substrate through an inner-sphere TH mechanism,¹⁰ accelerating reduction of the ketone, and thus complexes **7** and **8** demonstrated a catalytic activity much higher than that of the coordinatively saturated complex **2**.

Under the same conditions, transfer hydrogenation of various ketones was carried out by using complex **7** as the catalyst (Table 2). With a 0.2 mol % loading, complex **7** exhibited excellent catalytic activity for the TH of 3-chloroacetophenone, 3-bromoacetophenone, 4-chloroacetophenone, and 4-bromoacetophenone (entries 4, 5, 8, and 9), reaching >97% conversions for the ketones with final TOFs up to 1940 h⁻¹ within 15–30 min. The reduction of 2-chloroacetophenone was slow, achieving 98% conversion within 12 h (entry 3). Other 2-substituted acetophenones, i.e., 2-methylacetophenone, and 2-methoxyacetophenone, reacted much more quickly than 2-chloroacetophenone, but they underwent the TH reactions slowly as compared with their 3- and 4-substituted analogues (entries 4–15). 2-Acetonaphthone was also reduced to its corresponding alcohol in 94% yield within 2 h (entry 16). For the reduction of aliphatic

Table 2. Transfer Hydrogenation of Ketones Catalyzed by Complex **7**^c

entry	ketone	time (h)	yield (%) ^a	final TOF (h ⁻¹)
1		2	98	245
2		2	98	245
3		12	98	41
4		1/2	98	980
6		1/3	98	1470
7		12	16	7
8		1/3	98	1470
9		1/4	97	1940
10		2	97	243
11		1.5	98	327
12		5	96	96
13		2	83	208
14		1.5	97	323 ^b
15		3	99	165
16		2	94	235
17		1.5	100	333
18		3	95	158
19		5	96	96

^a GC yield of the corresponding alcohol. ^b By ¹H NMR. ^c Reaction conditions: ketone/*i*PrOK/cat. = 500/1/20; ketone, 2.0 mmol (0.1 M in 20 mL of *i*PrOH); 0.1 MPa; 82 °C.

ketones, cyclohexanone was completely transformed to the alcohol product over a period of 1.5 h (entry 17), while cyclopentanone and 2-octanone were reduced to their corre-

sponding alcohols in 95–96% yields over a longer period (entries 18 and 19). In comparison with the catalytic activity of the known Ru(II) complex catalysts bearing “pincer” NHC and alkyl chain-linked bis(NHC) ligands for the TH of ketones (with 0.07–0.1 mol % catalyst, 60–100% conversions were reached for acetophenone and cyclohexanone over a period of 2–20 h),^{4a,b,5b} our catalyst system has exhibited comparable and, in most cases, better catalytic activity (Table 2) and demonstrated a wider scope of the ketone substrates. Complex catalyst **7** has also shown a catalytic activity much better than that of a rhodium(I) bis(NHC) complex catalyst (0.5 mol % catalyst, 93% conversion for acetophenone within 2 h).¹⁶ However, the present catalyst system is much less efficient for the TH of ketones than our recently reported Ru(II) complex catalysts bearing a pyridyl-based pyrazolyl–imidazol-2-yl ligand, which exhibited a final TOF up to 720 000 h⁻¹ and reached >99% conversion for ketones within 10 s.¹⁰ The relatively low catalytic efficiency of the present complex catalyst is attributed to the overly strong σ -donating ability of the NHC moiety in the ligand, which cannot bestow the newly formed complex catalyst suitable hemilability. An inner-sphere mechanism is proposed.^{10,17} The TH of a ketone is initiated from **2** or the in situ generated **8** from **7** by extrusion of 1 equiv of hydrogen iodide from **7** with *i*PrOK. **2** or **8** 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 **2** or **8** with EtONa or *i*PrOK in refluxing ethanol or 2-propanol. RuH species generated in situ from Ru–Cl complexes have been well-documented to act as the active catalysts for the TH of ketones.¹⁸

Conclusions

In conclusion, “pincer”-type Ru(II) NNC complexes bearing a pyridyl-supported pyrazol-3-yl–N-heterocyclic carbene (NNC) ligand have been synthesized and exhibited good to excellent catalytic activity in the TH of ketones under phosphine-free conditions. Formation of a coordinatively unsaturated Ru(II) center in the precatalyst is attributed to the high catalytic activity of these complexes. The present methodology has demonstrated an efficient route to rare Ru(II) NHC complexes.

Experimental Section

General Procedure for Catalytic Transfer Hydrogenation of Ketones. A catalyst solution was prepared by dissolving complex **7** (28.4 mg, 40.0 μ mol) in 2-propanol (30.0 mL) with stirring. Under a nitrogen atmosphere, the mixture of a ketone (2.0 mmol), 2-propanol (16.2 mL), and 3.0 mL of the catalyst solution containing 4.0 μ mol of complex **7** was stirred at 82 °C for 5 min. A 0.8 mL portion of a 0.1 M *i*PrOK solution in 2-propanol was then introduced to initiate the TH reaction. At the stated time, 0.05 mL of the reaction mixture was sampled and immediately diluted with 0.25–0.5 mL of 2-propanol at ambient temperature for GC analysis. After the reaction was complete, the reaction mixture was condensed under reduced pressure and subjected to purification by flash silica gel column chromatography to afford the alcohol product. All of the alcohol products were identified by comparison with the authentic samples and/or by proton NMR measurements.

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Supporting Information Available: Text and figures giving preparation details and characterization data for the compounds in this paper and a CIF file giving X-ray crystallographic data for **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Yang, L. R.; Krüger, A.; Neels, A.; Albrecht, M. *Organometallics* **2008**, *27*, 3161.

(17) Comas-Vives, A.; Ujaque, G.; Lledós, A. *Organometallics* **2007**, *26*, 4135.

(18) (a) Casey, C. P.; Clark, T. B.; Guzei, I. A. *J. Am. Chem. Soc.* **2007**, *129*, 11821.