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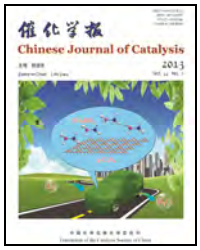

Article

Ru(II) pyridyl-based NNN complex catalysts for (asymmetric) transfer hydrogenation of ketones at room temperature

DU Wangming, WANG Qingfu, YU Zhengkun *

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China

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ABSTRACT

Ru(II) complexes bearing pyridyl-based benzimidazolyl-imidazolinyl tridentate NNN ligands were synthesized and structurally characterized. Their molecular structure was confirmed by X-ray crystallography. These complexes demonstrated good to excellent catalytic activity in the asymmetric transfer hydrogenation of ketones at room temperature, achieving up to 99% yields and 97% ee values.

1. Introduction

Asymmetric syntheses aim to provide versatile strategies for direct access to chiral products and have been extensively studied and applied in organic chemistry and the pharmaceutical industry [1]. Among these, asymmetric transfer hydrogenation (ATH) catalyzed by transition metals has gradually become a reliable method for the reduction of ketones and imines [2–8]. Ruthenium complexes have proved to be the most promising catalysts for this purpose, and among the best results reported so far have been Ru(II) complexes containing a monotosylated 1,2-diamine ligand [9,10]. These have been demonstrated to be powerful catalysts for the enantioselective reduction of ketones and imines. Recently, Baratta and co-authors [11] found that 2-(aminomethyl) pyridine (ampy) accelerated the transfer hydrogenation (TH) of ketones [12–14] in Ru(II) and Os(II) complex catalysts. Very recently, Morris group [15,16] reported that chiral NNPP ligands and their iron(II) complexes were effective in the ATH of ketones under mild conditions, representing a rare case of using inexpensive iron as the active metal. Although new ligands and their transition metal complexes have been established in this area [17–20], the desire for more highly active catalytic systems with better stereoselectivity and broader substrate scopes under mild conditions is still strong. We have recently documented that highly active transition metal complex catalysts could be rationally constructed by introducing a benzimidazolyl or pyrazolyl coordinating arm on a pyridyl-based ligand framework [21–30]. A series of highly active Ru(II) complexes have been obtained for the transfer hydrogenation of ketones [31,32], achieving >99% yield and final TOFs up to 720 000 h^{-1} at 82 °C, and 99% ee and final TOFs up to 55 800 h^{-1} at 28 °C in ATH (Scheme 1).

Chiral imidazolines have been used in a number of applications in asymmetric synthesis [33], among which bidentate phosphine imidazolines have been used in the enantioselective

*Corresponding author. Tel/Fax: +86-411-84379227; E-mail: zkyu@dicp.ac.cn
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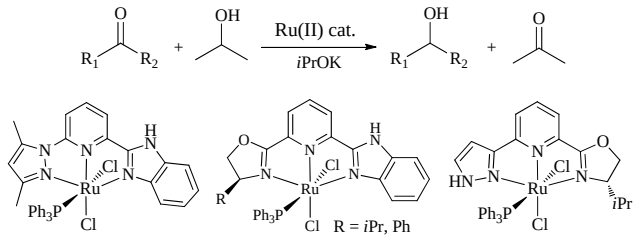
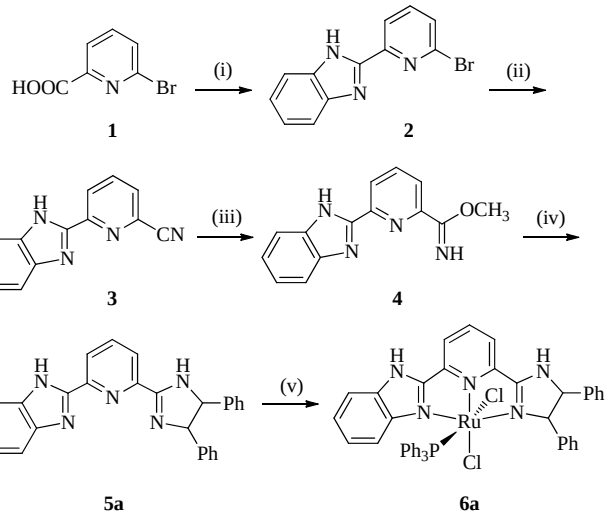
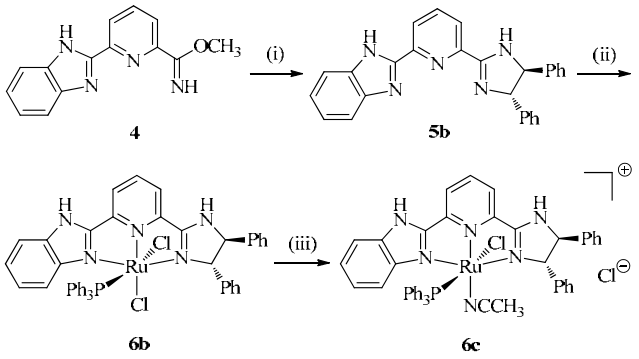


Scheme 1. Representative Ru(II) complexes for the asymmetric transfer hydrogenation developed in our laboratory.



Scheme 2. Synthesis of ligand **5a** and Ru(II) complex **6a**. (i) *o*-phenylenediamine, polyphosphoric acid, 160 °C, 4 h, 45%; (ii) CuI, $K_4[Fe(CN)_6]$, *N*-methylimidazole, 160 °C, 16 h, 61%; (iii) Na, MeOH, 65 °C, 14 h, 85%; (iv) (+/−)-1,2-diphenylethane-1,2-diamine, CH_2Cl_2, 40 °C, 12 h, 90%; (v) $RuCl_2(PPh_3)_3$, toluene, 110 °C, 3 h, 82%.



Scheme 3. Synthesis of chiral ligand **5b** and complexes **6b** and **6c**. (i) (*S*,*S*)-1,2-diphenylethane-1,2-diamine, CH_2Cl_2, 40 °C, 12 h, 90%; (ii) $RuCl_2(PPh_3)_3$, toluene, 110 °C, 3 h, 82%; (iii) Recrystallization from CH_3CN/Et_2O (1/3, *V*/*V*).

hydrogenation of olefins [34] and allylic substitutions [35], tridentate benzene-bis(imidazolinyl) palladium complexes in asymmetric aza-Morita-Baylis-Hillman reactions [36] and Friedel-Crafts alkylations [37], and pyridinebisimidazoline NNN ligands in ATH [38], asymmetric epoxidation [39] and Henry reactions [40]. Herein, we report the synthesis of Ru(II) complexes bearing a tridentate NNN ligand containing benzimidazolyl and imidazolinyl moieties.

2. Experimental

2.1. Materials

6-Bromopicolinic acid, *o*-phenylenediamine, polyphosphoric acid, (+/−)-1,2-diphenylethane-1,2-diamine, (*S*,*S*)-1,2-diphenylethane-1,2-diamine, and *N*-methylimidazole were commercially available. $K_4[Fe(CN)_6]$ was dried at 60 °C for 6 h under reduced pressure prior to use. Acetonitrile, 2-propanol, and dichloromethane were dried by refluxing over CaH_2, and toluene and diethyl ether were dried by refluxing over sodium with benzophenone as indicator before being distilled. Other chemicals were used as received.

2.2. Preparation of NNN ligands and Ru(II)-NNN complexes

Heating a mixture of 6-bromopicolinic acid (**1**) and *o*-phenylenediamine in polyphosphoric acid afforded the intermediate compound **2** in 45% yield (Scheme 2). Copper(I)-catalyzed cyanation of **2** with $K_4[Fe(CN)_6]$ gave **3**. Treatment of **3** with NaOMe in refluxing methanol formed the imidate **4**, which was then condensed with the racemic diamine in CH_2Cl_2 to give the racemic tridentate NNN ligand **5a**. Refluxing ligand **5a** with $RuCl_2(PPh_3)_3$ in toluene produced the Ru(II)-NNN complex **6a** as a red-brown powder in 82% yield.

In a similar preparation to **6a**, chiral ligand **5b** was reacted with $RuCl_2(PPh_3)_3$ to afford the chiral Ru(II) complex **6b** (Scheme 3). Unexpectedly, the neutral complex **6b** was transformed into the ionic complex **6c** during recrystallization from CH_3CN-Et_2O. In **6c**, an acetonitrile molecule replaced coordinated Cl ion at the metal center.

2.3. Procedure for transfer hydrogenation of ketones

A typical procedure for the catalytic asymmetric transfer hydrogenation of ketones was as follows. Under a nitrogen atmosphere, a mixture of 2 mmol ketone, 18.6 ml *i*-PrOH, and 1 ml of the chiral catalyst solution containing 4 μmol of the Ru(II) complex in *i*-PrOH was stirred at 28 °C for 10 min. A 0.4 ml of 0.1 mol/L *i*-PrOK solution in *i*-PrOH was then introduced to initiate the reaction. During the reaction, 0.1 ml of the reaction mixture was sampled and immediately diluted with 0.5 ml *i*-PrOH pre-cooled at 0 °C for GC analysis on a chiral *β*-DEX 225 (supelco) column. After the reaction was complete, the remaining reaction mixture was condensed under reduced pressure and purified by silica gel column chromatography to afford the corresponding alcohol product. This was then identified by comparison with the authentic sample by ^1H NMR and/or GC analysis.

3. Results and discussion

3.1. Structural characterization of compounds **5** and **6**

All new compounds were characterized by NMR spectroscopy and either HRMS or elemental analysis, giving results that are consistent with their proposed compositions. The benzimidazolyl and imidazolinyl N-H functionalities in complexes **6a** and **6b** showed a singlet resonance at δ = 15.03 and 9.40 in the ^{1}H NMR spectra, respectively, revealing the presence of the N-H moieties. The molecular structure of complex **6c** was confirmed by X-ray crystallography (Fig. 1), and the two distinctive N-H moieties remained unchanged. In the solid state, the ruthenium atom in **6c** is coordinated by the tridentate NNN ligand **5b**, one PPh_3 ligand, one CH_3CN molecule, and one Cl ion. The PPh_3 ligand is *trans* to the bonded Cl ion and *anti* to one of the phenyl groups of the chiral imidazolinyl moiety. This reduces the steric interactions in the complex. The P-Ru-N angles are in the range of 89.9°–96.6°, and P-Ru-Cl(1) and N(3)-Ru-N(6) angles are 178.6° and 170.2°, respectively, suggesting that the Ru atom is situated at the center of a distorted bipyramidal environment with the CH_3CN molecule and N(3) atom of the pyridyl backbone *trans* to each other.

3.2. Transfer hydrogenation of ketones

Following the procedure previously reported from our laboratory [21–32], complex **6a** was tested as a catalyst for the transfer hydrogenation of acetophenone in the presence of *i*-PrOK. To our surprise, **6a** exhibited excellent catalytic activity for the reduction of acetophenone in 2-propanol even at room temperature (28 °C). With a loading of 0.2% (molar fraction) **6a** as catalyst, acetophenone was converted to 1-phenylethanol in 96% yield within 5 min, giving a final TOF value of 5760 h^{-1} (entry 1, Table 1). This catalytic system was applied to the transfer hydrogenation of a variety of ketones, including substituted acetophenones, aliphatic cyclic and acyclic ketones, generating the corresponding alcohols as the sole products. In most of the cases, the ketone substrates reached >98% conversions within 10 min with final TOF values up to 59 400 h^{-1} within 30 s (entry 13), demonstrating a rare example of a highly active transition metal complex catalyst for the transfer hydrogenation of ketones [29]. Acetophenones containing an electron-withdrawing substituent such as a halo atom, a CF_3 or methyl group reacted the fastest (entries 3–15), while electron-donating methoxy group-bearing acetophenones required longer reaction times (entries 16 and 17). To our delight, all the fluoro- and trifluoromethyl-bearing acetophenones could be smoothly reduced to the desired alcohols (entries 9–13). Other ketones such as benzophenone, 2-acetylnaphthalene, and aliphatic ketones also exhibited high reactivity (entries 18, 19, 21, and 22), but indanone only showed moderate reactivity (entry 20).

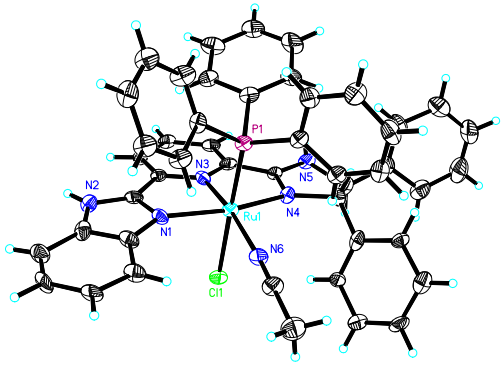
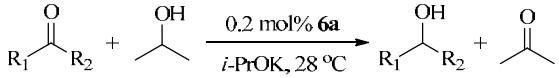


Fig. 1. Molecular structure of complex **6c**.

Table 1
Transfer hydrogenation of ketones.



Entry	Ketone	Time (min)	Yield [a] (%)	Final TOF (h^{-1})
1		5	96	5760
2		10	97	2910
3		5	96	5760
4		2	98	14700
5		1	99	29700
6		1	97	29100
7		1	98	29400
8		2	98	14700
9		1	99	29700
10		1	99	29700
11		2	98	14700
12		2	98	14700
13		0.5	98	59400
14		2	97	14500
15		5	93	2790
16		10	98	2940
17		20	86	2580
18		2	98	14700
19		5	97	5820
20		90	80	267
21		10	98	2940
22		5	97	5820

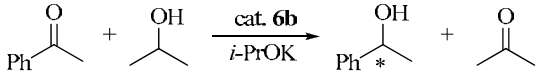
Reaction conditions: ketone 2.0 mmol (0.1 mol/L in 20 ml *i*-PrOH); ketone/*i*-PrOK/**6a** = 500/20/1; $p(N_2)$ = 0.1 MPa; 28 °C.
[a] Determined by GC analysis.

3.3. Asymmetric transfer hydrogenation of ketones

The chiral Ru(II) complex **6b** was then employed as the catalyst for the ATH of acetophenone under the same conditions as shown in Table 1. With a 0.2% loading of **6b** as catalyst, acetophenone was reduced to the corresponding chiral alcohol at room temperature (28 °C), achieving 96% yield and 85% ee within 5 min (entry 1, Table 2), and **6b** exhibited the same catalytic activity as the racemic catalyst **6a** (entry 1, Table 1). Increasing the reaction temperature accelerated the reaction, but the enantiomer excesses decreased from 85% to 26% (entries 3–5, Table 2). A base effect was observed that improved the product enantioselectivity. Lowering the base loading to 10 equivalents of the catalyst enhanced the enantioselectivity to 90% ee (entry 6, Table 2). Under the same conditions, chiral complex **6c** exhibited catalytic activity inferior to **6b** (entry 7, Table 2).

Under the optimized reaction conditions, a variety of ketones were tested as substrates to explore the generality of the protocol. As shown in Table 3, acetophenones with both electron-withdrawing and -donating substituents were tolerated to give the corresponding chiral alcohol products in very high yield. Acetophenone, propiophenone, and *ortho*-substituted acetophenones could be reduced to the chiral alcohols within 2–10 min, reaching 97% ee with final TOFs up to 14850 h^{-1} (entries 1–5, Table 3). The asymmetric reduction of *meta*-, *para*-, and 2′-methyl-substituted acetophenones was also accomplished, affording less enantioselective alcohol products (74%–84% ee, entries 6–11, Table 3). A strong steric effect resulted in the highest product enantioselectivity. 2′-Trifluoromethyl-substituted acetophenone was reduced to the corresponding alcohol in 97% ee (entry 3, Table 3). As the bulkiness of the substituents decreased from bromo to chloro, the resultant enantioselectivity decreased from 95% to 93% (entries 4 and 5, Table 3). We have previously shown that a benzimidazolyl N-H in a ligand can accelerate the TH and ATH of ketones [28–30], and an imidazolinyl N-H functionality has also been reported as improving the enantioselectivity in ATH [38]. In our case, the combination of the two N-H functionalities may provide the complex catalysts with high catalytic activity and good selectivity for ATH of ketones under mild conditions.

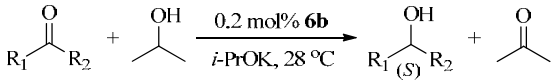
Table 2
Screening of conditions for asymmetric transfer hydrogenation of ketones catalyzed by **6b**.



Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield [a] (%)	ee [a] (%)
1	0.2	28	5	96	85 (*S*)
2	0.3	28	5	96	85 (*S*)
3	0.2	40	2	96	83 (*S*)
4	0.1	60	1	95	26 (*S*)
5	0.02	80	2	97	33 (*S*)
6 [b]	0.2	28	5	95	90 (*S*)
7 [c]	0.2	28	5	76	68 (*S*)

Reaction conditions: acetophenone 2.0 mmol (0.1 mol/L in 20 ml *i*-PrOH); *i*-PrOK/**6b** (or **6c**) = 20/1; $p(N_2)$ = 0.1 MPa.
[a] Determined by GC analysis on a chiral column β DEX 225, and absolute configuration was determined by comparing optical rotations with literature values. [b] *i*-PrOK/**6b** = 10/1. [c] **6c** as catalyst.

Table 3
Asymmetric transfer hydrogenation of ketones catalyzed by **6b**.



Entry	Ketone	Time (min)	Yield [a] (%)	ee [a] (%)	Final TOF (h^{-1})
1		5	95	90	5400
2		10	97	90	2910
3		5	96	97	5880
4		2	99	95	14850
5		10	96	93	2880
6		5	98	84	5880
7		2	98	74	14700
8		5	96	77	5760
9		5	98	75	5880
10		5	97	77	5820
11		5	95	74	5400

Reaction conditions: ketone 2.0 mmol (0.1 mol/L in 20 ml *i*-PrOH); ketone/*i*-PrOK/**6b** = 500/10/1; $p(N_2)$ = 0.1 MPa; 28 °C.
[a] The conversion and ee were determined by GC analysis on a chiral column β DEX 225. All the major secondary alcohols had the *S* configuration. Absolute configuration was determined by comparing optical rotations with literature values.

4. Conclusions

Pyridyl-based benzimidazolyl-imidazolinyl tridentate NNN ligands and their Ru(II) complexes were synthesized and structurally characterized. These complex catalysts feature two heterocyclic N-H functionalities and exhibit excellent catalytic activity and selectivity in the asymmetric transfer hydrogenation of ketones under mild conditions.

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Graphical Abstract

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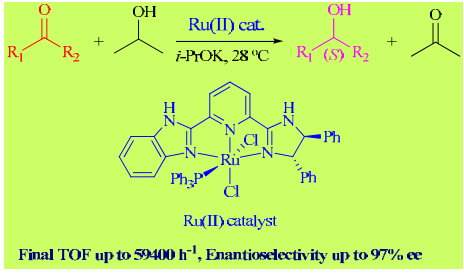
DU Wangming, WANG Qingfu, YU Zhengkun *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences

Ru(II) complexes bearing pyridyl-based benzimidazolyl-imidazolinyl tridentate NNN ligands exhibited excellent catalytic activity and selectivity in the asymmetric transfer hydrogenation of ketones at room temperature.



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钌(II)-吡啶基NNN配合物催化酮的室温(不对称)氢转移反应

杜旺明，王清福，余正坤*
中国科学院大连化学物理研究所，辽宁大连116023

摘要: 合成了一种基于吡啶骨架含有苯并咪唑和手性咪唑啉基团的三齿NNN配体及其二价钌(II)配合物,通过核磁共振波谱学和X射线单晶晶体结构测定确认了钌(II)配合物的分子结构. 这些配合物在室温下催化酮的氢转移反应,表现出了优异的催化活性,收率和ee值最高分别可达99%和97%.

关键词: 钌(II)配合物; 不对称氢转移; 手性咪唑啉; 苯并咪唑; 酮

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*通讯联系人. 电话/传真: (0411)84379227; 电子信箱: zkyu@dicp.ac.cn
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