

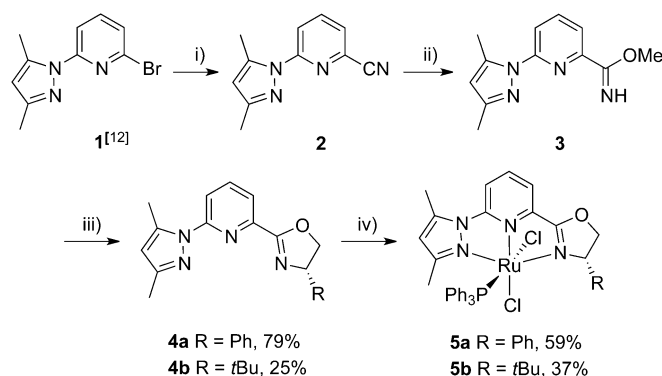
## Ruthenium(II) Pyrazolyl–Pyridyl–Oxazolinyll Complex Catalysts for the Asymmetric Transfer Hydrogenation of Ketones

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Asymmetric transfer hydrogenation (ATH) is an attractive synthetic method for the reduction of ketones to form enantiopure alcohols.<sup>[1]</sup> Ruthenium(II) complexes have been found to be the most powerful catalysts for this purpose. The Noyori Ru<sup>II</sup> complexes containing a monotosylated 1,2-diamine<sup>[2]</sup> or aminoalcohol ligand<sup>[3]</sup> can offer high catalytic activity and selectivity in the ATH of ketones. Baratta and co-workers<sup>[4]</sup> have reported the highly efficient ruthenium(II) 2-(aminomethyl)pyridine (ampy) phosphane complexes for which the ampy ligand clearly accelerates the reaction rate of the ATH of ketones. The well-established “N–H” effect is rationalized in terms of an outer-sphere mechanism involving the concerted transfer of hydrogen from the intermediate of type [(H)Ru–NHR] to the ketone substrate.<sup>[5]</sup> PP<sup>[6]</sup> and PN,<sup>[7]</sup> symmetric NNN,<sup>[8]</sup> NNPP,<sup>[9]</sup> and tethered ligands<sup>[7,10]</sup> have also been reported for constructing transition-metal-complex catalysts in this area.

Recently, we have reported versatile unsymmetrical pyridyl-based NNN ligands and their exceptionally active Ru<sup>II</sup> complexes for the transfer hydrogenation (TH) and ATH of ketones.<sup>[11]</sup> These complex catalysts were constructed by means of the following strategy: two different N-donor coordinating arms are tethered to the 2,6 positions of the pyridyl backbone of the ligand. When one of the coordinating arms contains a convertible NH moiety, the resultant Ru<sup>II</sup> complex catalysts usually exhibit very high catalytic activity for the TH or ATH of ketones due to easy in situ generation of coordinatively unsaturated 16-electron Ru<sup>II</sup> precatalysts. Herein, we report the synthesis of ruthenium(II) NNN complexes containing a chiral pyrazolyl–pyridyl–oxazolinyll ligand, featuring a pyrazolyl NH functionality and their application as catalysts for the ATH of ketones.

Copper-catalyzed C–N coupling was employed to synthesize the intermediate compound **2**. The reaction of **1**<sup>[12]</sup> with K<sub>4</sub>[Fe(CN)<sub>6</sub>] in *N*-methylimidazole in the presence of CuI formed the cyanation product **2**, which was then transformed into imidate **3** by use of sodium and methanol. Condensation of compound **3** with a chiral aminoalcohol in chlorobenzene yielded tridentate ligands **4**. Treatment of compounds **4a** and **4b** with [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] in toluene heated at reflux afforded Ru<sup>II</sup> complexes **5a** (59%) and **5b** (37%), respectively (Scheme 1). Compounds **2–5** were characterized by NMR spectroscopy, HRMS, and elemental analysis, which were consistent with the stated compositions.



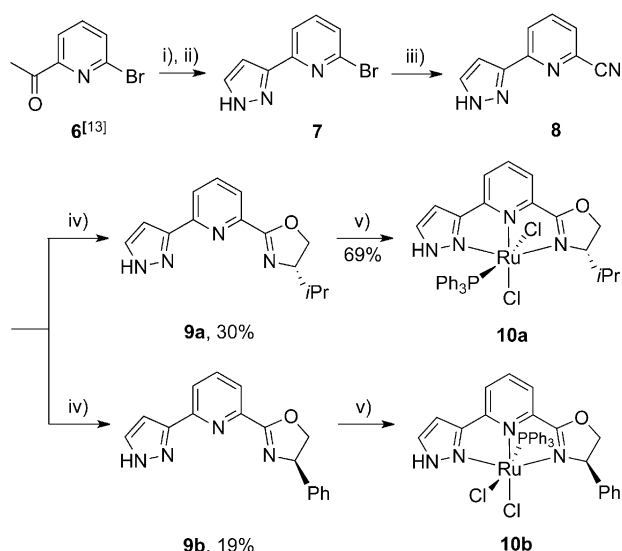
Scheme 1. Synthesis of chiral Ru<sup>II</sup> NNN complexes **5**. i) CuI, K<sub>4</sub>[Fe(CN)<sub>6</sub>], *N*-methylimidazole, 160 °C, 16 h, 91%; ii) Na, MeOH, 40 °C, 24 h, 40%; iii) 1,2-aminoalcohol, HCl (37%), chlorobenzene, 80 °C, 12 h; iv) [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], toluene, N<sub>2</sub> (0.1 MPa), reflux, 2 h.

Heating a mixture of **6**<sup>[13]</sup> and *N,N*-dimethylformamide dimethyl acetal at reflux, followed by reacting with hydrazine hydrate, produced **7** in 63% yield. Cyanation of **7** led to the formation of compound **8**, which was treated with chiral 1,2-aminoalcohols to give ligands **9**, containing a pyrazolyl NH functionality. Complexes **10a** (69%) and **10b** (<30%) were synthesized in a similar fashion to the preparation of complexes **5** (Scheme 2). The NMR analysis of **10a** in solution is consistent with its composition. Its <sup>31</sup>P{<sup>1</sup>H} NMR spectrum revealed a singlet at 46.8 ppm, suggesting one PPh<sub>3</sub> ligand is present in the complex. The molecular structure of **10a** was further confirmed by X-ray crystallographic determination (Figure 1). In the solid state, complex **10a** exhibits a neutral molecular structure with a nearly planar tridentate NNN ligand and the ruthenium atom is surrounded by one PPh<sub>3</sub>

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Scheme 2. Synthesis of chiral Ru<sup>II</sup> NNN complexes **10**. i) *N,N*-Dimethylformamide dimethyl acetal, reflux, 12 h; ii) NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O, EtOH, reflux, 12 h, 63 %; iii) CuI, K<sub>4</sub>[Fe(CN)<sub>6</sub>], *N*-methylimidazole, 160 °C, 16 h, 63 %; iv) 1,2-aminoalcohol, ZnCl<sub>2</sub>, chlorobenzene, reflux, 60 h; v) [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], toluene, reflux, 8 h.

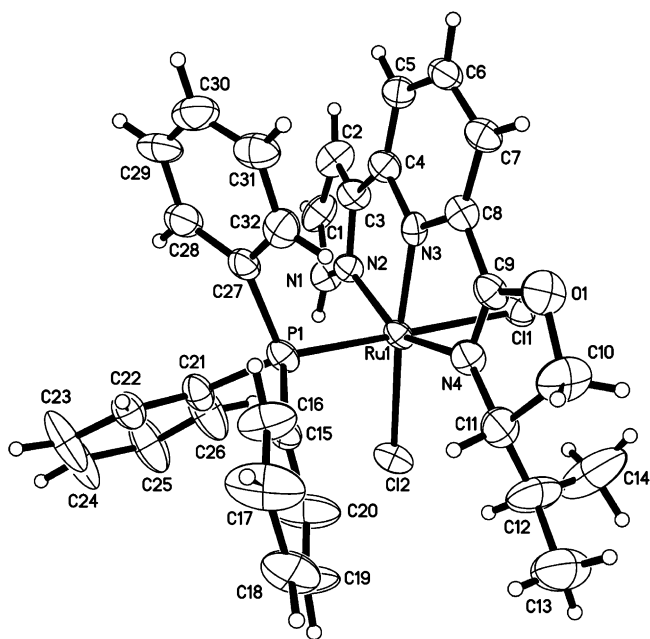


Figure 1. The molecular structure of complex **10a**.<sup>[14]</sup>

ligand, the three pyridyl, pyrazolyl, and oxazolinyll nitrogen donor atoms, and one chloride atom. The PPh<sub>3</sub> ligand is positioned *trans* to and far from the isopropyl group to reduce the steric hindrance. The Ru–N(2), Ru–N(3), and Ru–N(4) bond lengths are 2.101, 1.960, and 2.120 Å, respectively, demonstrating that **4a** is a tridentate ligand. The three P–Ru–N angles are in the range 91.6–94.5°, and the P–Ru–Cl(1) and N(2)–Ru–N(4) angles are 178.8° and 155.3°, respectively, revealing that the metal atom is situated in a dis-

torted bipyrimidal environment. It should be noted that the single-crystal structure of complex **10b** was preliminarily determined although it was not successfully purified by column chromatography and recrystallization (see the Supporting Information).

Complexes **5** and **10** were then tested as catalysts for the ATH reactions of acetophenone, 3'-bromoacetophenone, and 3'-chloroacetophenone in the presence of the *i*PrOK base in 2-propanol (Table 1). At 40 °C, acetophenone was

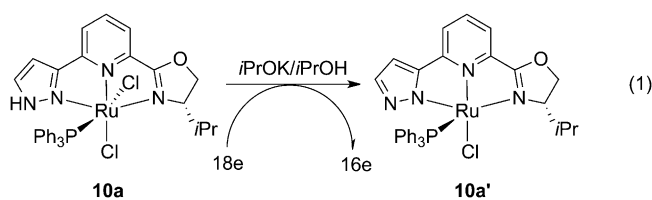
Table 1. The ATH of ketones catalyzed by complexes **5** and **10**.<sup>[a]</sup>

Ketone	Catalyst [mol %]	<i>T</i> [°C]	<i>t</i> [min]	Conv. <sup>[b]</sup> [%]	<i>ee</i> <sup>[b]</sup> [%]
1	<b>5a</b> (0.5)	40	60	98	36 ( <i>R</i> )
2	<b>5b</b> (1.0)	40	120	94	27 ( <i>R</i> )
3	<b>10a</b> (0.3)	40	8	96 <sup>[c]</sup>	93 ( <i>S</i> )
4	<b>10a</b> (0.4)	30	10	93	90 ( <i>S</i> )
5	<b>10b</b> (0.4)	40	15	97	23 ( <i>R</i> )
6	<b>10a</b> (0.3)	40	5	99	84 ( <i>S</i> )
7	<b>10a</b> (0.4)	30	10	98 <sup>[c]</sup>	85 ( <i>S</i> )
8	<b>10a</b> (0.4)	30	20	97 <sup>[c]</sup>	84 ( <i>S</i> )

[a] Conditions: ketone (2.0 mmol; 0.1 M in 20 mL *i*PrOH), *i*PrOK/cat. = 20:1; N<sub>2</sub> (0.1 MPa). [b] Determined by GC analysis using a chiral column β-DEX 225 (supelco). [c] *i*PrOK/cat. = 10:1.

exclusively reduced to the corresponding alcohol in 98 % yield with 36 % *ee* within 60 min by using 0.5 mol % **5a** as the catalyst, whereas **5b** exhibited a much lower catalytic activity (Table 1, entries 1 and 2). Complex **10a** showed a decent catalytic activity, reaching 93–96 % yields and 90–93 % *ee* over a period of 8–10 min at 30–40 °C (Table 1, entries 3 and 4). Although **10b** also exhibited good catalytic activity, the desired product was only formed with a poor enantiopurity (23 % *ee*) presumably due to the low purity of the catalyst (Table 1, entry 5). These results suggest that the convertible NH group in the ligand has a remarkable enhancing effect on the catalyst activity (Table 1, entries 1–5). We assume that complexes **10** could be easily converted into the coordinatively unsaturated 16-electron complexes in situ under the basic conditions [Eq. (1)],<sup>[11a,f]</sup> which were then transformed into the catalytically active RuH species and thus facilitated the catalytic reaction. Screening of the ATH of 3'-bromoacetophenone and 3'-chloroacetophenone revealed the optimal reaction conditions to be 30–40 °C with 0.3–0.4 mol % **10a** as the catalyst.

Next, the ATH reactions of various aromatic ketones were explored under the optimized conditions (Table 2). At 40 °C and with 0.3 mol % **10a** as the catalyst, propiophenone, 3'-methylacetophenone, and 2'-bromoacetophenone

Table 2. The ATH reactions of ketones catalyzed by complex **10a**.<sup>[a]</sup>

$\text{R}^1\text{C(=O)R}^2 + \text{CH}_3\text{CH(OH)CH}_3 \xrightarrow[\text{iPrOK, 30 }^\circ\text{C}]{\text{cat. } \mathbf{10a}}$		$\text{R}^1\text{CH(OH)R}^2 + \text{CH}_3\text{C(=O)CH}_3$			
Ketone	<i>t</i> [min]	Conv. <sup>[b]</sup> [%]	<i>ee</i> <sup>[b]</sup> [%]	final TOF [h <sup>-1</sup> ]	
1		8	96 <sup>[c]</sup>	93	2400
2		40	96 <sup>[c]</sup>	94	480
3		5	97	98	2910
4		45	95 <sup>[c]</sup>	90	423
5		30	91 <sup>[c]</sup>	90	303
6		5	99 <sup>[c]</sup>	97	3960
7		10	98	85	1470
8		20	98	80	735
9		20	98	96	735
10		20	97	84	728
11		20	98	73	735
12		30	96 <sup>[d]</sup>	67	320
13		30	94	86	485

Table 2. (Continued)

Ketone	<i>t</i> [min]	Conv. <sup>[b]</sup> [%]	<i>ee</i> <sup>[b]</sup> [%]	final TOF [h <sup>-1</sup> ]	
14		5	93	83	1395
15		10	99 <sup>[e]</sup>	99	743
16		20	99	77	743
17		10	97 <sup>[e]</sup>	89	728
18		20	75 <sup>[e]</sup>	78	281
19		20	96 <sup>[e]</sup>	86	360

[a] Conditions: ketone (2.0 mmol; 0.1 M in 20 mL *i*PrOH), *i*PrOK/cat. = 10:1; N<sub>2</sub> (0.1 MPa), 30 °C. [b] Determined by GC analysis using a chiral column β-DEX 225 (supelco). All the major secondary alcohol products had the *S* configuration. The absolute configuration was determined by comparing the optical rotations of the products with the literature values. [c] **10a** (0.3 mol %), 40 °C. [d] **10a** (0.6 mol %). [e] **10a** (0.8 mol %).

were reduced to the corresponding alcohols in 95–99% yields with 90–97% *ee* within 5–45 min, reaching final TOFs of up to 3960 h<sup>-1</sup> (Table 2, entries 2, 4, and 6). By using 0.6 mol% of the catalyst, the reaction of 4'-methylacetophenone gave the product in 91% yield and 90% *ee* (Table 2, entry 5). 2'-Methylacetophenone, 4'-bromoacetophenone, and chloro-substituted acetophenones reached 97–98% conversions with 73–98% *ee* for their reduction products over a period of 5–20 min (Table 2, entries 3 and 8–11). The ATHs of fluoro-substituted acetophenones were also accomplished, but afforded less enantioselective products (67–86% *ee*, Table 2, entries 12–14). Surprisingly, 2'-trifluoromethylacetophenone underwent the ATH reaction to give the desired product in 99% yield and 99% *ee* (Table 2, entry 15), whilst 3'-CF<sub>3</sub>-, 3'-MeO-, and 4'-MeO-substituted acetophenones and 2-acetylnaphthalene underwent the ATH reactions much less efficiently (Table 2, entries 16–19). It is noteworthy that all of the major alcohol products had an *S* configuration.

In summary, we have developed a strategy to construct highly active Ru<sup>II</sup> NNN complex catalysts containing a chiral pyridyl-based 1*H*-pyrazolyl-oxazolinyl ligand for the asymmetric transfer hydrogenation of ketones. These complex catalysts exhibited much higher catalytic activity than Ru<sup>II</sup> pyridyl-pyrazolyl-oxazolinyl complexes featuring no NH functionality.

## Experimental Section

**Typical procedure for the ATH of ketones:** Under a nitrogen atmosphere, a mixture of a ketone (2 mmol), *i*PrOH (18.2 mL), and the chiral catalyst solution (1 mL) containing the Ru<sup>II</sup> complex (8 μmol) in *i*PrOH was stirred at 30 °C for 15 min. Then, *i*PrOK (0.8 mL, 0.1 M) in *i*PrOH was introduced to initiate the reaction. During the reaction, 0.1 mL of the reaction mixture was sampled and immediately diluted with pre-cooled (0 °C) *i*PrOH (0.5 mL) for GC analysis by means of a chiral β-DEX 225 (supelco) column. After the reaction was complete, the reaction mixture was condensed under reduced pressure and subjected to purification by silica gel column chromatography to afford the corresponding alcohol product, which was identified by comparison with the authentic sample through <sup>1</sup>H NMR spectroscopy and/or GC analysis.

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**Keywords:** asymmetric catalysis • ketones • ligand design • ruthenium • transfer hydrogenation

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- [14] Crystal structure analysis of **10a**-(CH<sub>2</sub>Cl<sub>2</sub>)<sub>0.125</sub>(PhMe)<sub>0.2</sub>: *M<sub>r</sub>* = 719.59, triclinic (*P* $\bar{1}$ ); *a* = 11.9012(17), *b* = 17.788(3), *c* = 33.986(5) Å; *α* = *β* = *γ* = 90°; *V* = 7194.7(18) Å<sup>3</sup>; *Z* = 8; GOF = 1.074; *R*<sub>1</sub> = 0.0700; *wR*<sub>2</sub> = 0.1799.

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