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New chiral bis(oxazoline) Rh(I)-, Ir(I)- and Ru(II)-complexes for asymmetric transfer hydrogenations of ketones

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Abstract—Chiral bis(oxazoline)-based Rh(I)-, Ir(I)- and Ru(II)-complexes have been prepared and used for asymmetric transfer hydrogenation of prochiral ketones. The presence of a free hydroxyl group on the ligand is necessary for high enantioselectivity. With acetophenone, up to 50% conversion and 89% ee were achieved.

The synthesis of chiral nonracemic secondary alcohols from prochiral ketones by catalytic reduction remains one of the preferred methods in organic synthesis.[1] Asymmetric transfer hydrogenation using 2-propanol as the hydrogen source represents a very attractive route that requires inexpensive reagents, is easy to perform and is selective.[2] During the last decade, considerable effort has been devoted to the development of new efficient chiral catalysts and rapid progress has been made increasing the knowledge of the reaction mechanism, leading to rational design of the catalytic systems.[3] The best catalysts reported so far are usually Ru(II)-complexes bearing chiral diamino or amino-alcohol ligands. Chiral N-tosylated 1,2-diphenylethylenediamine Ru(II)-complexes reduce acetophenone to give (*S*)-1-phenylethanol with good yield (>85%) and very high ee (typically 90% to >99%) in boiling 2-propanol. Generally, the reaction rate and the enantioselectivity are dependent on the electronic properties of the substituents on the aromatic ring as well as the steric environment of the carbonyl group.[2b,3a,4] Ru(II)-complexes with chiral phosphino-oxazoline ligands were highly active towards hydrogen transfer reduction of prochiral alkyl aromatic ketones; the optical purity tends to increase with increasing steric bulk of the alkyl moiety (86% and 93% ee for acetophenone and isobutyrophenone at 74% conversion, respectively).[5] Recently Kim et al. reported the efficient chiral transfer hydrogenation of alkyl phenylketones using chiral imidazolidine Ru(II)-catalysts (81–99% yield and 53–93% ee).[3b] While chiral bis(oxazoline) Ir(I)-catalysts were described by Pfaltz and co-workers for transfer hydrogenation of ketones in 1991,[6] the successful use of bis(oxazoline) Ru(II)-complexes for this reaction was only reported in 1999 by Zhang and co-workers using a tridentate amine-bridged bis(oxazoline) ligand.[7] However, the use of chiral bis(oxazoline) Ru(II)-complexes for hydrogen transfer reduction of ketones is a relatively undeveloped area. With the aim of exploring the domain offered by the bis(oxazoline) ligands, we synthesised new chiral Rh(I)-, Ir(I)- and Ru(II)-complexes based on optically active bis(oxazoline) ligands. Herein we report their preparation, as well as the results obtained during their application as catalysts for the hydrogen transfer reduction of acetophenone derivatives.

Chiral bis(oxazoline) ligands **1** and **2** were synthesised from chiral amino alcohols and diethyl malonimidate dihydrochloride in CH_2Cl_2 according to a procedure reported by Aggarwal et al.[8] in acceptable yields. The OH-protected bis(oxazoline) **3** was obtained by treatment of the bis(oxazoline) **2** with TMSCl in THF/Et_3N in 94% yield (Scheme 1).

The Rh(I)-complex **4** was prepared from the cationic $[Rh(I)(COD)(THF)_2]^+[BF_4^-]$ complex (prepared from $[Rh(I)(COD)Cl]_2$ by treatment with $AgBF_4$ in dry THF) and the bis(oxazoline) **2** in dry THF at room temperature under argon in 99% isolated yield.[9] Similarly, the Ir(I) complex **5** was prepared from $[Ir(I)(COD)Cl]_2$ in

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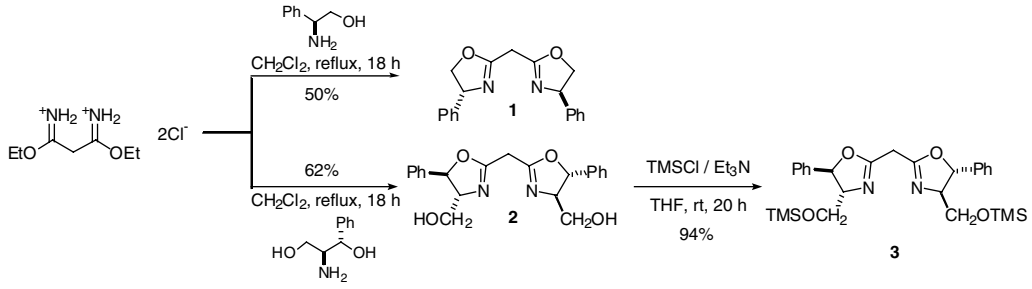
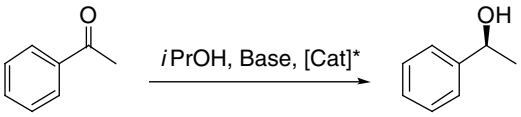


Scheme 1. Preparation of the chiral bis(oxazoline) ligands **1**–**3**.

CH_2Cl_2 in 96% isolated yield (Scheme 2).[6] The Ru(II)-catalysts **6**–**8** were prepared from $[Ru(II)(p\text{-cymene})Cl_2]_2$ in methanol at room temperature under argon in 90–99% isolated yields depending on the bis(oxazoline) ligand used (Scheme 3).[10] All the complexes were fully characterised.[11]

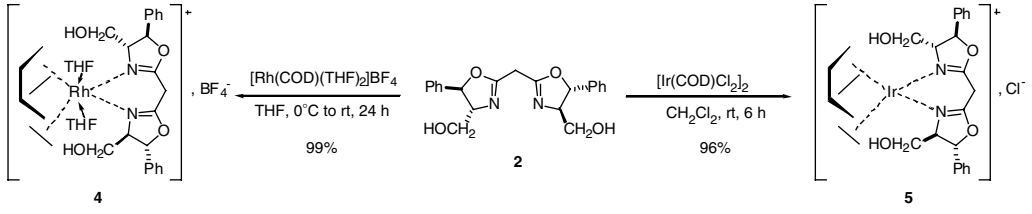
To examine the catalytic activity of the chiral complexes **4**–**8**, the transfer hydrogenation of acetophenone in 2-propanol was studied (Scheme 4). All catalytic tests were conducted under an argon atmosphere over 24 h at 50 °C using 1 mol% catalyst. The starting point of the reaction was defined by the addition of the base (15 mol%) to the reaction mixture.[12] As shown in Table 1, the reaction with Rh(I)- and Ir(I) complexes proceeded with low conversions (ca. 20%) and poor enantioselectivities (typically 16–20%). In contrast, the Ru(II)-based catalyst **7** exhibited good activity with 50% conversion after 24 h and high enantioselectivity (89%). The activity and the enantioselectivity of the Ru(II)-based catalysts were found to be highly dependent on the structure of the ligand: the replacement of the CH_2OH substituent at the 4-position in the oxazoline ring (ligand **2**) by a phenyl group (ligand **1**) or the



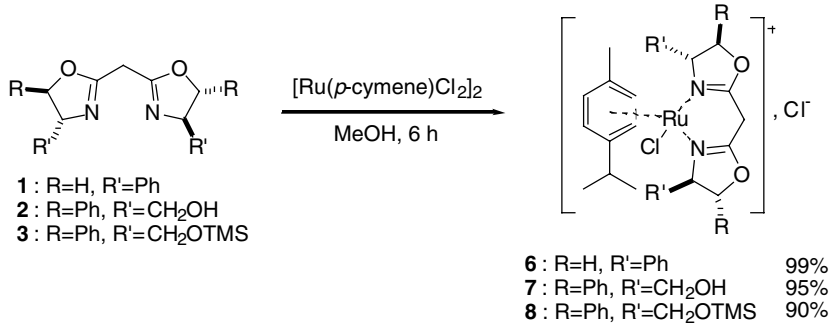
Scheme 4. Transfer hydrogenation of acetophenone. Reaction conditions: 1.7 mmol acetophenone, 1 mol% [Cat]*, 15 mol% *t*BuOK, 10 mL *i*PrOH, Ar, 50 °C, 24 h.

Table 1. Influence of the catalyst on the transfer hydrogenation of acetophenone (Scheme 4)

Catalyst (metal)	Conversion (%)	Ee (%)
4 (Rh^I)	22	16 (*S*)
5 (Ir^I)	22	20 (*S*)
7 (Ru^{II})	50	89 (*S*)
6 (Ru^{II})	32	10 (*R*)
8 (Ru^{II})	20	30 (*S*)



Scheme 2. Preparation of the chiral bis(oxazoline) Rh(I)- and Ir(I)-complexes **4** and **5**.



Scheme 3. Preparation of the chiral bis(oxazoline) Ru(II)-complexes **6**–**8**.

protection of the OH function by a trimethylsilyl substituent (ligand **3**) dramatically decreased both the conversion (typically 20–30%) and the enantiomeric excess (typically 10–30%). These results are to be compared with those reported by Noyori et al.[1b,2b] Zhang and co-workers[7] and Lemaire and co-workers.[4,13] They noted that the NH moiety present in the chiral ligands (diamino-diphosphines, amino-bridged bis(oxazoline) and diamines, respectively) may promote the hydrogen transfer reaction through a cyclic transition state by hydrogen bonding with the ketone substrate. In our case, by analogy to those systems, the CH_2OH substituent present on the oxazoline ring could promote the reaction by formation of a six-membered transition state (Fig. 1) similar to that suggested earlier by Noyori and Hashiguchi.[2b]

In order to improve the reactivity of our catalytic system, we examined the influence of the base. With the organic bases pyridine and Et_3N no conversion was observed (Fig. 2). Using the inorganic bases K_2CO_3, NaOH, KOH and *t*BuOK, the conversion was strongly dependent upon the base strength: the stronger the base, the higher the conversion ($K_2CO_3 \ll NaOH < KOH <$ *t*BuOK). On the other hand, the nature of the base did not significantly affect the enantioselectivity (89–96% ee).

A range of arylketones was reduced to the corresponding secondary alcohols. Table 2 shows that both the electronic nature of the substituents on the aromatic ring and the steric hindrance around the carbonyl moiety played an important role towards the activity and enantioselectivity. In the presence of the electron-withdrawing substituent CF_3, the conversion decreased slightly; however the enantiomeric excess was maintained (entries 1–2). When the carbonyl moiety was strongly hindered, no conversion could be observed (compare entries 1 and 3).

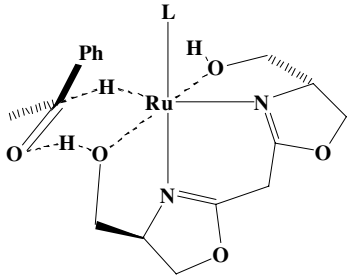


Figure 1. Proposed transition state for the transfer hydrogenation of prochiral ketones.

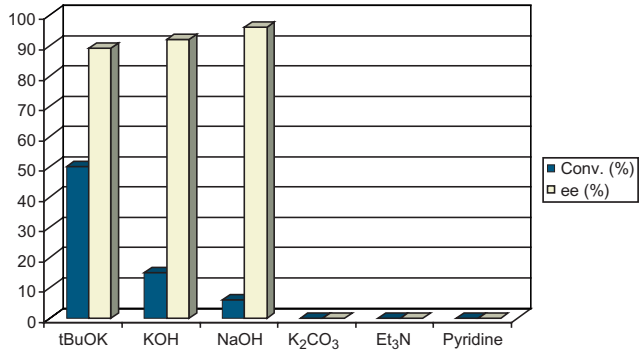
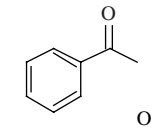
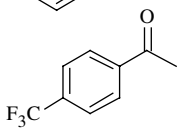
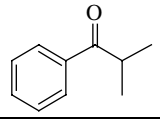


Figure 2. Influence of the base on the transfer hydrogenation of acetophenone using catalyst **7**.

Table 2. Transfer hydrogenation of different prochiral ketones using catalyst **7**

Entry	Substrate	Conversion (%)	Ee (%)
1		50	89
2		32	85
3		0[a]	—

Reaction conditions: 1.7 mmol, ketone 1 mol% [Cat]*, 15 mol% *t*BuOK, 10 mL *i*PrOH, Ar, 50 °C, 24 h.
[a] No conversion was observed even after 5 days of reaction.

In conclusion, chiral bis(oxazoline) Ru(II)-complexes are active and selective catalysts for hydrogen transfer reduction of arylketones to secondary chiral alcohols with up to 50% ee at 89% conversion. We are currently investigating other substrates and reactions catalysed by these chiral complexes and are improving the activity and enantioselectivity of such catalysts by fine tuning the chiral bis(oxazoline) ligands.

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11. Selected data for the bis(oxazoline) Ru(II)-complex **7**: ^{1}H NMR ($CDCl_3$, 250 MHz), δ (ppm): 1.19 (d, $^{3}J = 6.8$ Hz, 6H, CH_3CH); 2.30 (s, 3H, CH_3); 2.89 (m, 1H, CHCH$_3$); 3.60 (br d, $^{3}J = 10.0$ Hz, 2H, CH_2OH); 4.14 (br d, $^{3}J = 14.2$ Hz, 2H, CH_2OH); 4.36 (d, $^{2}J = 8.2$ Hz, NCCH_2CN); 5.77 (m, 6H, PhCHO, NCH and CH (C_6H_4)); 6.08 (br d, $^{3}J = 8.1$ Hz, 1H, NCH); 6.31 (d, $^{3}J = 5.2$ Hz, 1H, C$H_{(Ar)}$); 7.40 (m, 10H, C$H_{(Ar)}$). ^{13}C NMR ($CDCl_3$, 62.9 MHz), δ (ppm): 18.37 (*C*H$_3$); 22.04 (*C*H$_3$CH); 22.57 (*C*H$_3$CH); 28.60 (NC*C*H$_2$CN); 30.91 (*C*H(CH$_3$)$_2$); 59.37 (*C*H$_2$OH); 58.88 (*C*H$_2$OH); 75.59 (Ph*C*HO or *C*HN); 80.81 (*C*HN or Ph*C*HO or *C*H (C_6H_4)); 81.60 (*C*HN or Ph*C*HO or *C*H (C_6H_4)); 84.30 (*C*HN or Ph*C*HO or *C*H (C_6H_4)); 85.48 (*C*HN or Ph*C*HO or *C*H (C_6H_4)); 98.35 (*C*q$_{CH3}$ C_6H_4)); 107.91 (*C*q$_{CH}$ (C_6H_4)); 126.12 (*C*H (C_6H_5)); 127.36 (*C*H (C_6H_5)); 128.19 (*C*H (C_6H_5)); 128.99 (*C*H (C_6H_5)); 129.52 (*C*H (C_6H_5)); 141.67 (*C*q (C_6H_5)); 164.48 (*C*N); 166.82 (*C*N).
12. General procedure for the catalytic tests: Ketone (200 mg) was introduced under argon into a Schlenk tube. Catalyst (1 mol%) was dissolved in 2-propanol (10 mL deaerated by argon flow). The solution was added to the substrate followed by addition of 15 mol% of base (previously dried). The reaction was performed under vigorous stirring at 50 °C for 24 h.
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