A new NCN pincer ruthenium complex and its catalytic activity for enantioselective hydrogenation of ketones†

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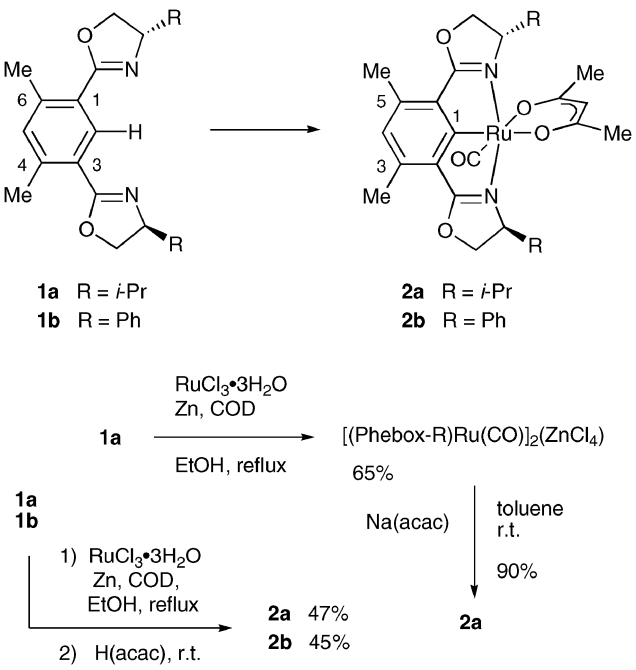
New bis(oxazolinyl)phenyl–ruthenium(II) complexes, which were synthesized by C–H bond activation with $RuCl_3 \cdot 3H_2O$ in zinc powder and 1,5-cyclooctadine followed by ligand exchange reaction with sodium acetylacetonate or acetylacetone, exhibited enantioselective hydrogenation of ketones in up to 90% ee.

Chiral nitrogen-based pincer-type ligands such as NNN, NCN, NNC, NPN, NNP *etc*. have successfully been applied to ruthenium catalysed enantioselective hydrogenation and transfer hydrogenation reactions of ketones.[1,2] As we reported that rhodium and platinum catalysts with bis(oxazolinyl)phenyl (= Phebox) ligand of NCN type pincers have been applied for highly enantioselective reactions,[3] for example, allylation of aldehydes,[4] Michael addition,[5] conjugate reduction,[6] reductive aldol reactions,[7] and direct aldol reaction,[8] we were encouraged to synthesise a ruthenium complex of Phebox for enantioselective hydrogenation of carbonyl compounds. It is of note that the bis(oxazolinyl) moiety of Phebox, which provides a C_2-symmetric and meridional environment around the metal center, would create a suitable catalyst to distinguish prochiral faces of substrates. To our best knowledge, only one example of an *in situ* ruthenium catalyst bearing a bis(oxazolinyl)benzene moiety was demonstrated for enantioselective cylcopropanation as disclosed by Iwasa and co-workers.[9] We report here the first synthesis and structural characterization of a Phebox–ruthenium(II) complex [abbreviated as (Phebox)-Ru] and its application for enantioselective hydrogenation and transfer hydrogenation.

We started by choosing the 4,6-dimethyl derivative of chiral 1,3-bis(oxazolinyl)benzene **1** as a precursor for complex formation with ruthenium atom *via* C–H bond activation at the 2-position.[10] The dimethyl substitution at 4- and 6-positions could block undesirable metallation by C–H bond activation at those positions. Simple heating of a mixture of $RuCl_3 \cdot 3H_2O$ and **1a** (R = *i*-Pr) in refluxing EtOH with Et_3N resulted in the formation of complicated solid mixtures to give no isolable ruthenium complexes. Reactions of **1a** with common ruthenium(II) complexes, such as $[RuCl_2(COD)]_2$ (COD = 1,5-cyclooctadiene) and $[RuCl_2(C_6H_6)]_2$, also failed. However, zinc powder in the presence of COD with $RuCl_3 \cdot 3H_2O$ and **1a** successfully afforded a ruthenium complex in 65% yield, which has a dimeric constitution of $[(Phebox\text{-}ip)Ru(CO)Cl]_2$-$(ZnCl_2)$ (Scheme 1).[11] The dimeric complex was in turn treated with sodium acetylacetonate [Na(acac)] at room temperature for 12 h to furnish (Phebox-*ip*)Ru(CO)(acac) **2a** in 90% yield. In place of Na(acac), acetylacetone can also be used. Alternatively, direct addition of acetylacetone at room temperature to a reaction mixture of $RuCl_3 \cdot 3H_2O$ and **1a** in EtOH and further stirring for 20 h produced the complex **2a** in 47% total yield in two steps. Similarly, phenyl-substituted complex **2b** could be synthesized in 45% yield from **1b** by the sequential method with acetylacetone.‡

The molecular structure of **2a** was confirmed by X-ray diffraction (Fig. 1). The Ru center is described to have a distorted octahedral geometry with meridionally coordinated Phebox-*ip* ligand and bidentate acetylacetonato ligand. The CO ligand is perpendicular to the Phebox plane.

Next, asymmetric hydrogenation of several simple ketones was attempted with chiral (Phebox)Ru complexes **2a** and **2b**. An initial reaction was carried out using *para*-methoxyphenyl methyl ketone **3a** in isopropyl alcohol (IPA) with 1 mol% of **2** and 20 mol% of NaOMe at 40 °C for 24 h under 30 atm of hydrogen pressure.‡ The corresponding alcohol **4a**, (*S*)-1-(*para*-methoxyphenyl)-1-ethanol, was successfully obtained



Scheme 1 Synthesis of (Phebox)Ru complexes.

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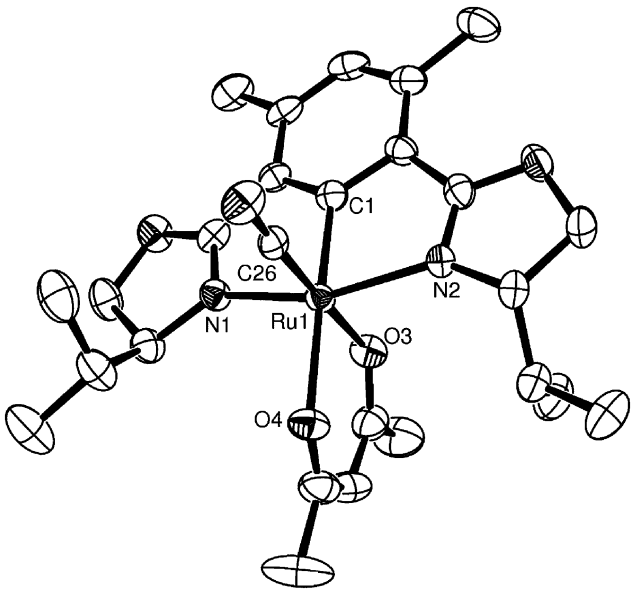
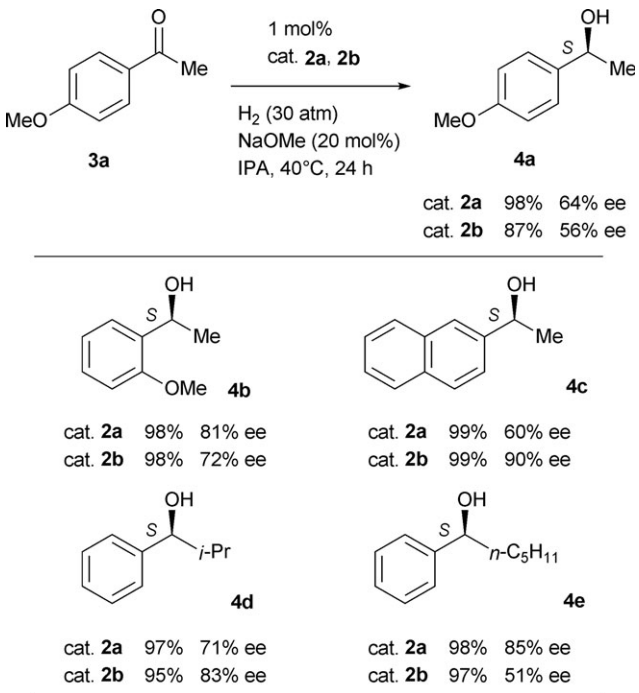
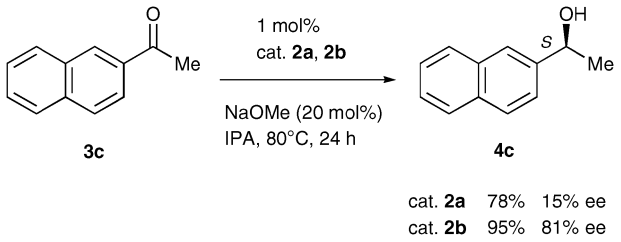


Fig. 1 ORTEP diagram of **2a** with 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angle (°): Ru1–C1 1.976(3), Ru1–C26 1.813(5), Ru1–N1 2.095(3), Ru1–N2 2.126(3), Ru1–O3 2.125(3), Ru1–O4 2.201(3); N1–Ru1–N2 156.52(11).

in 98% yield and 65% ee with **2a** and in 87% yield and 56% ee with **2b**, respectively (Scheme 2). Other base sources such as NaOEt, NaO*t*-Bu, KO*t*-Bu, and LiOMe provided similar results, 98–99% yields and 51–63% ees, whereas use of K_2CO_3 and Cs_2CO_3 resulted in low yields (3–11%) and low selectivity (22–37% ees). The hydrogenation did not proceed in the absence of the bases. Under the same reaction condition, several ketones, *o*-$MeOC_6H_4COMe$ **3b**, 2-NaphCOMe **3c**, PhCO*i*-Pr **3d**, and PhCO*n*-C_5H_{11} **3e**, were examined to give



Scheme 2 Enantioselective hydrogenation of ketones.



Scheme 3 Asymmetric transfer hydrogenation of ketone.

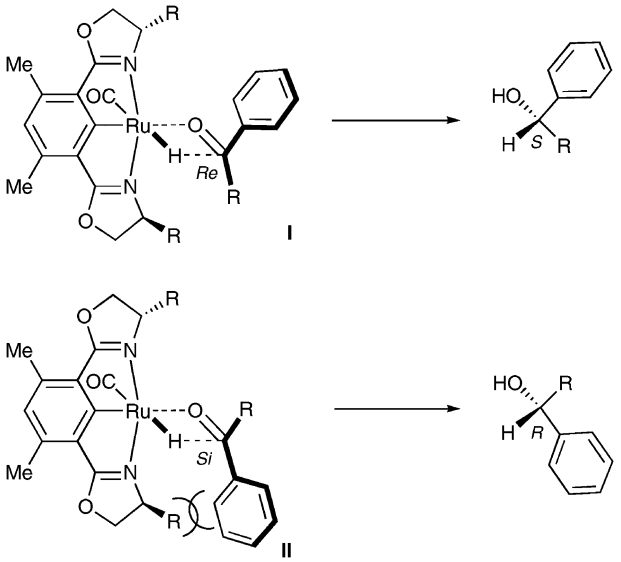


Fig. 2 Hypothetical stereochemical course.

the corresponding secondary alcohols, **4b–4e** in 81–90% ees. The enantioselectivity thus changed depending on the combination between the substituents of ketones and substituents of the ligands.

In the absence of hydrogen, the transfer hydrogenation of the ketone **3c** with catalyst **2b** (1 mol%) at 80 °C was found to proceed giving the alcohol (*S*)-**4c** in 95% yield with 81% ee (Scheme 3). However, use of catalyst **2a** drastically decreased the ee to 15%.

The hydrogenation and the transfer hydrogenation with (Phebox)Ru catalysts afforded alcohols with the same *S*-absolute configuration. We propose a hypothetical reaction course for the hydrogenations as follows: the monohydride species (Phebox)Ru(H)(CO) may be formed by elimination of acac ligand from **2**, followed by activation of molecular hydrogen by a base. Alternatively, β-H elimination of a Ru–$OCH(CH_3)_2$ intermediate, which is generated by exchange of the acac ligand with NaO*i*Pr, may provide the hydride intermediate in the case of transfer hydrogenation. Judging from the *S*-absolute configuration of the product alcohols, the transition state **I** that apical hydride attacks *Re*-face of ketone could be proposed (Fig. 2).

In summary, the first synthesis of ruthenium complexes with the bis(oxazolinyl)phenyl moiety has been described *via* C–H activation using commercially available ruthenium chloride in the presence of zinc powder. It was also found that the (Phebox)Ru complex catalyses the enantioselective hydrogenation of ketones in isopropyl alcohol with NaOMe to afford

the corresponding *S*-alcohols with enantioselectivity up to 90% ee. We are now studying on the scope and limitations of the hydrogenations and further applications of the (Phebox)Ru complex as a potential catalyst for a variety of enantioselective reactions.

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Notes and references

‡ Procedure of the hydrogenation. To a stainless steel autoclave were added **2** (0.010 mmol), NaOMe (0.20 mmol), isopropyl alcohol (10 mL) and ketone (1.0 mmol) under an argon atmosphere. After purging with H_2, the H_2 pressure was adjusted to 30 atm. The mixture was stirred at 40 °C for 24 h, and then the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 10 : 1) to yield white solids of the alcohol. The enantioselectivity was determined using HPLC with a suitable chiral column; see ESI.†

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11 The constitution of the complex was determined by elemental analysis. The ^{1}H NMR spectrum indicates an unsymmetric structure.