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A ruthenium catalyst that does not require an N–H ligand to achieve high enantioselectivity for hydrogenation of an alkyl-aryl ketone

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Received (in Cambridge, UK) 20th December 2002, Accepted 12th February 2003
First published as an Advance Article on the web 25th February 2003

Ruthenium catalysts of the form *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)L_2 where L_2 = pyridine or 1,2-diamine, have been synthesized that display high catalytic activity towards the hydrogenation of 1′-acetonaphthone.

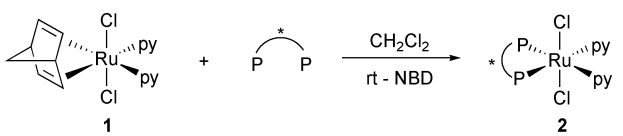
We report a Ru(diphosphine)bis(amine)(dichloride) compound that hydrogenates an alkyl-aryl ketone with high enantiomeric excess (ee) without the aid of a protic hydrogen bonded to nitrogen. The most active and generally the most selective catalyst systems for the enantioselective hydrogenation of simple ketones are the well-known complexes of the general form Ru(diphosphine)(diamine)(dihalide) discovered by Noyori *et al.*[1] A key element of the metal–ligand bifunctional mechanism for ketone hydrogenation proposed by Noyori is the presence of a protic hydrogen on nitrogen that hydrogen bonds to the ketone oxygen, thereby activating the ketone towards reduction, and directs the face selectivity of hydride addition by forming a six-membered, pericyclic transition state.[1,2] Noyori's mechanism is substantiated by mechanistic studies on transfer hydrogenations catalysed by ruthenium(II) complexes.[3] The mechanism has been investigated by Morris[4] and Chen,[5] and Casey has studied related systems.[6] We now report a ruthenium(diphosphine) catalyst that hydrogenates 1′-acetonaphthone with useful rates and high ee in the absence of an N–H bond in the ligands, and we report an improved, practical synthesis of the versatile ruthenium(diphosphine) catalyst synthon *trans*-$RuCl_2(NBD)(py)_2$ (**1**) (NBD = 2,5-norbornadiene, and py = pyridine).

We recently reported that **1** is a versatile ruthenium chiral-diphosphine catalyst synthon, reacting cleanly with a wide variety of structurally diverse chiral diphosphine ligands to generate the catalyst precursors *trans*-$RuCl_2$(diphosphine)$(py)_2$ (**2**) by displacement of NBD (Scheme 1).[7] The James group has prepared and studied a series of compounds related to **2**.[8] We showed that the catalyst precursors **2** react with trace amounts of aqueous HBF_4 (4 eq. HBF_4/Ru) in MeOH to generate active catalysts for low-pressure hydrogenations of β-keto esters, α-(acylamino)cinnamates, and related substrates.[9] The precursors **2** are also active catalysts for hydrogenations of α,β-unsaturated acids in the presence or absence of Et_3N.[7a] **2** Also reacts with (1*R*,2*R*)- or (1*S*,2*S*)-dpen (dpen = diphenylethylenediamine) to generate the Noyori catalysts *trans*-$RuCl_2$(P–P*)(N–N*). The utility of **1** as a general catalyst synthon was limited, however, by a synthesis involving long reaction times and a tedious workup.

The original preparation of **1** required stirring a mixture of $Ru(NBD)Cl_2/_n$ in pyridine for eight days at room temperature. Heating the mixture for shorter times resulted in formation of *trans*-$RuCl_2(py)_4$ as a side product. In accord with the results of Pannetier, reaction of $Ru(NBD)Cl_2/_n$ with five equiv. of piperidine at rt required only 16 h to form *trans*-$RuCl_2$(NBD)-$(pip)_2$ (pip = piperidine) (**3**) in near quantitative yields without evidence of NBD displacement by piperidine.[10] We unexpectedly found, however, that unlike the pyridine complex **1**, displacement of the NBD ligand in the piperidine complex **3** was difficult. For example, there was no reaction between (*R*)-BINAP and **3**, even after heating for 18 h in CH_2Cl_2. We also attempted to utilize *trans*-$RuCl_2$(NBD)(dpen) (**4**) as a catalyst precursor. Complex **4** was easily prepared by reaction of **1** and dpen in CH_2Cl_2, but the NBD ligand in **4** was also difficult to displace by diphosphine ligands. The origins of the differences in the rate of NBD displacement between the pyridine (**1**), piperidine (**3**), and dpen (**4**) complexes are unknown. The amine ligands in complexes **3** and **4** are more basic than pyridine, and they do not act as π-acids. As a result, the NBD ligand may be more strongly bonded to ruthenium in complexes **3** and **4** than in complex **1**. Alternatively, displacement of NBD may occur by prior dissociation of an amine ligand, and pyridine dissociates more readily from ruthenium than piperidine or dpen in these complexes. Regardless, we found that reaction of **3** with 180 equiv. of pyridine at rt for 2 h displaces piperidine to form **1** in 80% yield after recrystallization. Our improved synthesis of **1**† thus involves stirring $Ru(NBD)Cl_2/_n$ in piperidine for 16 h at rt to form **3** in 90% yield, which is then followed by reaction of **3** with excess pyridine for another 2 h to give **1** in 80% yield.

We recently reported that *trans*-$RuCl_2$((*S*,*S*)-Skewphos)$(py)_2$ ((*S*,*S*)-Skewphos = (2*S*,4*S*)-(−)-2,4-bis(diphenylphosphino)-pentane) is a hydrogenation catalyst for acetophenone with useful rates (500 turnovers, 60 °C, 4 atm. H_2, 4 equiv. KO^{t}Bu/Ru, 24 h, unoptimized) but with moderate ee (48 % (*R*)) despite the absence of a nitrogen ligand bearing a NH bond.[7a] Fogg *et al.* recently reported that [*fac*-RuH_3(CO)(dcypb)]$^-$ (dcypb = 1,4-bis(dicyclohexylphosphino)butane) is a very active catalyst for the reduction of benzophenone.[11] Although the complexes *trans*-$RuCl_2$(diphosphine)$(py)_2$ (**2**) are active for ketone hydrogenations under our conditions, the N–H groups in the Noyori catalysts, Ru(diphosphine)(diamine)(dihalide) (*e.g.* diamine = dpen), help direct the stereoselectivity of the enantiodetermining hydride addition to the prochiral ketone.[2–4] It thus seemed unlikely that the complexes *trans*-$RuCl_2$(diphosphine)$(py)_2$ would obtain high ee for hydrogenation of an alkyl-aryl ketone. As we reported previously, **1** reacts with (*R*)-(*S*)-Josiphos ((*R*)-(−)-1-[(*S*)-2-(diphenylphosphino)ferrocenyl]ethyldicyclohexylphosphine) to generate *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)$(py)_2$ (**5**).[7a] Fig. 1 shows the solid-state structure of **5** as obtained by X-ray diffraction.‡

We found that **5** catalyzes the hydrogenation of 1′-acetonaphthone (60 °C, 4 atm. H_2, 4 equiv KO^{t}Bu/Ru) in 98% ee (*S*).§ Table 1 summarizes the hydrogenation results we obtained for this study. Catalyst **5** achieved 2 400 turnovers under our conditions after 48 h (Table 1, entry 1). 1 000 turnovers were achieved after the first 24 h, while 1 400 were achieved after the second 24 h, suggesting there is an activation period for the reaction. In comparison, *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)((1*R*,2*R*)-dpen) (**6**) (Table 1, entry 2) and *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)((1*S*,2*S*)-dpen) (**7**) (Table 1, entry 3) were at least twice as active as the pyridine catalyst **5**. The dpen



Scheme 1

DOI: 10.1039/b212544g

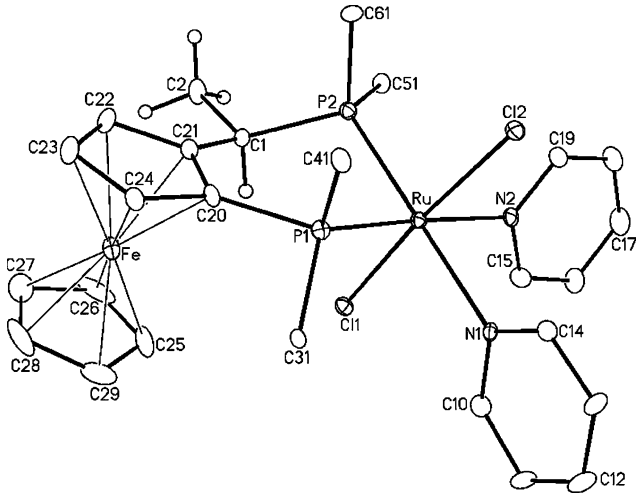


Fig. 1 Crystal structure of *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)$(py)_2$ (**5**) as determined by X-ray diffraction. Hydrogen atoms on C(1) and C(2) are shown with arbitrarily small thermal parameters in idealized positions. All other hydrogen atoms have been omitted. Only the *ipso* carbons of the phenyl and cyclohexyl groups are shown. Selected bond distances [Å] and bond angles [°] are as follows. Ru–Cl(1) 2.4310(16), Ru–Cl(2) 2.4170(15), Ru–P(1) 2.2878(18), Ru–P(2) 2.3309(18), Ru–N(1) 2.233(5), Ru–N(2) 2.224(5), Cl(1)–Ru–Cl(2) 173.51(6), P(1)–Ru–P(2) 88.56(6), N(1)–Ru–N(2) 83.87(19).

Table 1 Hydrogenation of 1′-acetonaphthone catalyzed by *trans*-$RuCl_2$((*R*)-(*S*)-Josiphos)L_2[a]

Catalyst	S/C	Time/h	% Conversion	% ee
5	2 500	24	40	98 (*S*)
		48	96	98 (*S*)
6	2 500	24	100	98 (*S*)
7	2 500	24	90	99 (*S*)

[a] Hydrogenations done in 2-propanol at 60 °C under 4 atm. dihydrogen, in the presence of 4 equiv. of KO^{t}Bu per Ru, where [ketone] = 1 M.

catalysts **6** and **7**, containing the opposite enantiomers of dpen, both produced 1-(1-naphthyl)ethanol in nearly the same ee as **5**, showing that the asymmetric induction of the Josiphos ligand dominates the enantioselectivity of this catalytic hydrogenation. Only 5% conversion was obtained after 24 h using **5** as catalyst in the absence of hydrogen.

Noyori *et al.*'s discovery and development of Ru(diphosphine)(diamine) catalysts incorporating amine ligands with N–H bonds has revolutionized the field of enantioselective catalytic hydrogenation of ketones. The catalysts incorporating ligands with N–H groups are more active and are generally more selective than *trans*-$RuCl_2$(diphosphine)$(py)_2$. The results presented in this paper do show, however, that useful rates and high enantioselectivities can be obtained in the absence of ligands with N–H groups.[12] As such, they add flexibility to the design of catalyst precursors for such hydrogenations. Consistent with this premise is our direct observation that addition of hydrogen and ruthenium across the ketone double bond is quite rapid in the absence of N–H groups for certain catalyst–ketone combinations.[13] Finally, the new synthesis of **1** facilitates its use as a general synthon for ruthenium-diphosphine catalysts.

Notes and references

† Preparation of *trans*-$RuCl_2(NBD)(py)_2$ (**1**) *via trans*-$RuCl_2(NBD)(pip)_2$ (**3**): $Ru(NBD)Cl_2/_n$ (0.51 g, 1.9 mmol) and piperidine (0.81 g, 9.6 mmol) were suspended in 2.3 mL of acetone and the mixture stirred rapidly under N_2 at rt for 16 h. Hexanes (30 mL) was added to complete the precipitation of **3** from the dark reaction mixture with a yellow precipitate. The supernatant was filtered, the mustard-yellow solid was washed with hexanes, and dried *in vacuo*. Yield: 0.78 g (90%). (Anal. Calc.: C, 47.00; H, 6.96; N, 6.45. Found: C, 46.57; H, 6.76; N, 6.31%). **3** (0.12 g, 0.28 mmol) was dissolved in 1 mL CH_2Cl_2 and stirred under N_2 at rt for 10 min. Pyridine (4.0 g, 50 mmol) was added to the yellow solution and stirred for 2 h. Hexanes (100 mL) were added to precipitate the product (**1**), then filtered, washed with hexanes and dried *in vacuo*. Yield: 0.094 g (80%). The NMR data of **1** matches that reported in ref. 7*a*. We found that some batches of $Ru(NBD)Cl_2/_n$ produced **1** containing small amounts (~3%) of *trans*-$RuCl_2(pip)_4$. If required, this impurity is easily removed by recrystallization from CH_2Cl_2–hexanes. The impurity is substantially less soluble than **1** in this solvent mixture.

‡ *Crystal data* for **5**: $C_{46}H_{54}Cl_2FeN_2P_2Ru{\cdot}0.5C_2H_4Cl_2$, M = 974.15, orthorhombic, a = 22.663(3), b = 13.3050(15), c = 14.5132(16) Å, V = 4376.2(8) Å^3, T = 193 K, space group $P2_12_12$ (no. 18), Z = 4, μ (Mo Kα) = 0.969 mm^{-1}, 24 602 reflections measured, 9 008 unique (R_{int} = 0.0985), R_1 (F) = 0.0565 for 6545 observed data [$F_o^2 \geq 2\sigma(F_o^2)$], wR_2 (F^2) = 0.1107 for all unique data, Flack parameter x = −0.02(3).

CCDC 199753. See http://www.rsc.org/suppdata/cc/b2/b212544g/ for crystallographic data in .cif or other electronic format.

§ The ee's were determined as described in ref. 7*a*.

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