Hydrogenation of Aldehydes, Esters, Imines, and Ketones Catalyzed by a Ruthenium Complex of a Chiral Tridentate Ligand

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Summary: A novel ruthenium complex prepared from a chiral tridentate amine functionalized phosphine has been characterized by X-ray crystallography and been found to be active in the hydrogenation of an unprecedented range of C═O and C═N double bonds, including the enantioselective hydrogenation and transfer hydrogenation of normally unreactive bulky ketones with up to 90% ee.

Reduction of C═O and C═N double bonds using molecular hydrogen is, due to its low cost and complete atom efficiency, a very important process in industrial organic syntheses.[1−3] There has consequently been a massive research effort aimed at developing homogeneous catalysts that can carry out this goal with high efficiency, chemoselectivity, and, in the case of prochiral ketones, enantioselectivity. Asymmetric hydrogenation of β-keto esters and related substrates has been an industrial process for some time.[3] Homogeneous hydrogenation of unfunctionalized ketones could not be carried out with sufficient efficiency or chemoselectivity until Noyori's pioneering research on ruthenium complexes containing both diphosphine and diamine ligands.[4] These catalysts are highly chemoselective for C═O bonds,[5] show industrially relevant turnover numbers, and if the catalyst shown in Figure 1 is used, extremely high enantioselectivity for a range of acetophenone derivatives. Since Noyori's publications, several other catalysts have appeared that are based on the same design blueprint and have also given excellent results for reduction of acetophenone derivatives.[6−10] The key to the massively enhanced reactivity relative to that of simple Ru−phosphine catalysts is proposed to be the unique mechanism in which the substrate hydrogen bonds to the NH functionality in the diamine ligand.[11,12]

However, [Ru(BINAP)(DAIPEN)Cl_2] and related catalysts do have some important limitations and are far less effective for the hydrogenation of tetralones, dialkyl ketones, bulky ketones, and some heterocyclic ketones and imines. We therefore initiated a project aimed at successfully hydrogenating these difficult substrates, with the general impression that a departure from the [Ru(diphosphine)(diamine)Cl_2] blueprint would be required. In this communication, we report preliminary results showing the promise of ruthenium complexes of chiral tridentate ligands as hydrogenation catalysts. Phosphine−amine ligands have provided some interesting niche applications in catalysis,[13−15] and given the absence of data on hydrogenation catalysis using tridentate ligands,[16,17] ruthenium complexes of tridentate P^N^NH_2 type ligands seemed worthy of investigation. This type of ligand could form octahedral ruthenium complexes with a more open coordination environment, thus increasing substrate scope or reactivity in hydrogenation. Another feature of interest was applying a single ligand to play the roles carried out by both diphosphine and diamine ligands in Noyori catalysts.[18−20]

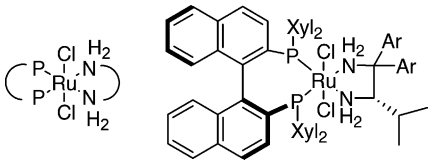

Figure 1. General structure of Noyori catalysts and the most selective catalyst known.

Ligand **1** is readily available in both racemic and enantiomerically pure forms from cheap starting materials. After some optimization, we found that heating ligand **1**[21,22] with [Ru(dmso)$_4$$Cl_2$] in THF at 120 °C in a microwave oven gave a quantitative yield of ruthenium complex **2** in sufficient purity (∼90−95%) for the applications described here (Scheme 1). Complexation reactions carried out using conventional heating always gave a significant amount of side products. Pure **2** can be obtained by column chromatography or by recrystallization

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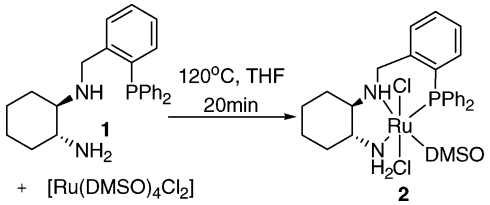
Scheme 1. Synthesis of the Novel Ruthenium Catalyst



from acetonitrile as a solvate (all samples behaved the same in catalysis). Samples of complex **2** have remained unchanged in air for extended periods of time, which is a desirable feature for a catalyst.

We were not able to unambiguously determine the exact structure of this complex spectroscopically but eventually obtained a crop of high-quality crystals (MeCN, slow evaporation) which were analyzed by X-ray diffraction. The crystal structure of the complex is shown in Figure 2. Complex **2** is an octahedral Ru(II) complex in which ligand **1** acts as a tridentate neutral ligand. The secondary amine part of the ligand, which is chiral at nitrogen, becomes configurationally stable (*S* configuration) within the complex. A sulfur-bound DMSO ligand occupies the site trans to the secondary amine part of the ligand. With the structurally characterized precatalyst in hand, we investigated its potential in hydrogenation of a range of substrate classes.

Reduction of aldehydes with molecular hydrogen has attracted considerable attention as a cleaner alternative to $NaBH_4$. There are several catalysts available for this process, but some catalysts suffer from a competing decarbonylation reaction, and few show complete chemoselectivity for C═O over C═C bonds.[23−26] Complex **2** (0.5 mol % in the presence of 1 mol % of $KOBu^t$) catalyzes the reduction of *p*-fluorobenzaldehyde (**3**) with no competing decarbonylation at 30 °C. When a 1:1:1 mixture of *p*-fluorobenzaldehyde, α-methylstyrene, and *N*-benzylbenzylidineimine was treated with hydrogen at room temperature in the presence of 0.5 mol % of catalyst **2**, only the aldehyde was reduced after 20 h reaction time. The hydrogenation of cinnamaldehyde (**4**) was then investigated as an example of a particularly challenging α,*β*-unsaturated aldehyde (Scheme 2). Initial experiments revealed that, while the C═O bond is preferentially reduced, the reaction was sluggish and was sometimes accompanied by minor amounts of C═C hydrogenation products. Pure cinnamyl alcohol was obtained in 48% yield.

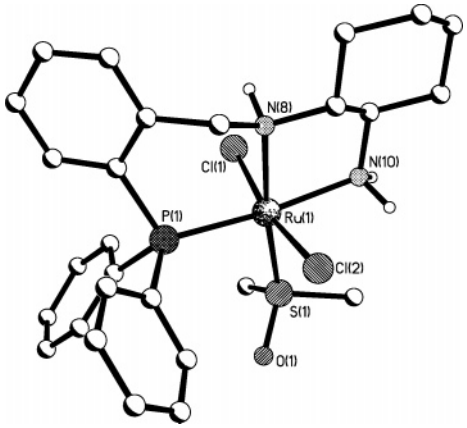
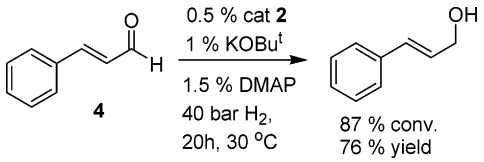


Figure 2. X-ray structure of **2**. Two MeCN molecules and all hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru−P(1) = 2.2912(13), Ru−N(8) = 2.160(4), Ru−N(10) = 2.155(4); N(10)−Ru(1)−P(1) = 171.14(10), N(8)−Ru(1)−P(1) = 91.67(10).

Scheme 2. Chemoselective Hydrogenation of Cinnamaldehyde



Scheme 3. Hydrogenation of Bulky Ketones

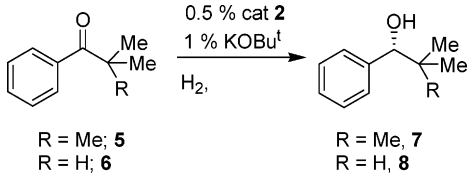


Table 1. Hydrogenation and Transfer Hydrogenation of α,α′,α″-Trimethylacetophenone (5)

entry	solvent	*T* (°C)	*P* (bar)	conversn (yield) %[a]	ee[b]
1	IPA (3 mL)	50	50	>99 (99)	74
2	IPA (3 mL)	50	no H_2	>99 (99)	73
3	EtOH (3 mL)	50	50	>99	51
4	EtOH (3 mL)	50	no H_2	9	n.d.
5	IPA (1 mL)/acetone (1 mL)[c]	50	50	>99	75
6	IPA (1 mL)/acetone (1 mL)[c]	50	no H_2	>99	76
7	IPA (1 mL)/THF (3 mL)	50	50	>99	53
8	IPA (1 mL)/THF (3 mL)	50	no H_2	30	70
9	IPA (6 mL)[d]	70	50	>99	77
10	IPA (6 mL)[d]	70	no H_2	19	66

[a] Reactions were carried out overnight (20 h), using 1 mmol of substrate, 0.5 mol % of catalyst, and 1 mol of $KOBu^t$ unless otherwise stated. Conversions were determined by NMR and HPLC; isolated yields are for the pure products after chromatography. [b] Determined using HPLC (Chiral OD-H column), The absolute configuration was determined to be *S* by comparison of optical rotation values with the literature values.[41] [c] 0.5 mmol of substrate. [d] 4 mmol substrate, reaction time 40 min.

Addition of 4-(dimethylamino)pyridine (DMAP) cocatalyst suppressed C═C reduction completely and increased the catalytic activity (>87% conversion to alcohol; 76% isolated yield for pure alcohol). A stoichiometric reaction between complex **2** and DMAP in $CDCl_3$ did not give a new (DMAP-coordinated) complex. The origin of the DMAP effect remains unclear and does not extend to providing any beneficial effects in the hydrogenation of the ketones described below.

One of our main goals when we initiated this research was to hydrogenate unreactive ketones using the new catalysts, ideally with some asymmetric induction. The enantiopure variant (*R*,*R*)-**2** was used for the experiments below (Scheme 3 and Table 1). Noyori and co-workers have reported that 1,1′,1″-trimethylacetophenone gave only a 6% yield when hydrogenated using [Ru(BINAP)(DPEN)Cl_2]. When this work was carried out, there were no effective ruthenium catalysts for asymmetric hydrogenation of this substrate;[27] therefore, it was selected as a challenging example of a bulky ketone. We were delighted

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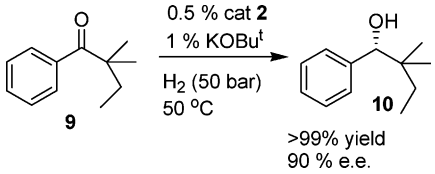
Scheme 4. Highly Enantioselective Hydrogenation of a Very Bulky Ketone

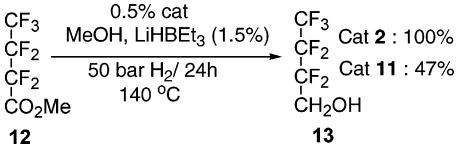


to find that the hydrogenation proceeds smoothly at 50 °C to give the (*S*)-alcohol in quantitative yield and 74% ee. To our surprise, if the reaction was carried out under exactly the same conditions, but without hydrogen, the (*S*)-alcohol was also produced in the same yield and ee. It has been reported by Morris that some hydrogenation catalysts can also promote transfer hydrogenation, but in these examples, good hydrogenation catalysts were poorly selective transfer hydrogenation catalysts and vice versa.[22,28] In order to shed light on the mechanism of this process, the hydrogenation and transfer hydrogenation reactions were run side by side in vessels preheated to 70 °C and left for 40 min. The hydrogenation reaction was carried out in an apparatus that measured hydrogen uptake: this showed hydrogen uptake for 40 min with no further gas used after this time. NMR and HPLC analysis showed 100% conversion to (*S*)-alcohol of 77% ee. In the transfer hydrogenation reaction, run at the same temperature and concentration, a 19% conversion to alcohol of 66% ee was recorded after 40 min. In a further experiment, a hydrogenation was carried out in 2-propanol-d_8 to >99% conversion; 23% of the alcohol product had incorporated the deuterium in the C−H(D) position, in agreement with the observations made above. This catalyst system therefore catalyzes both hydrogenation and transfer hydrogenation with similar enantioselectivity. This is a potentially useful feature, since hydrogenation is preferred at larger scale, and transfer hydrogenation is more convenient in a research laboratory. Catalyst **2** is the first member of what could be a diverse series of catalysts: the level of enantioselectivity observed for a difficult substrate is very promising.

A similar series of experiments were conducted on isobutyrophenone, **6** and 4-fluoroacetophenone. These experiments show that in complete contrast to [Ru(Diphos)(DPEN)Cl_2] catalysts, pronounced steric bulk within the ketone substrates is a prerequisite for enantioselective catalysis (Isobutyrophenone, **6**: 93% conversion, 48% e.e. 4-fluoroacetophenone >99% conversion, 5% e.e.; both reactions with 0.5% catalyst, 1% KOBu^t, 20 h., IPA solvent, 50 °C.).[29] The hydrogenation of the even bulkier, unexplored ketone **9** was then investigated and was also found to be smoothly hydrogenated at 50 °C with even higher selectivity (Scheme 4).

The hydrogenation of imines is not readily achieved by ruthenium catalysts.[30] In preliminary experiments, catalyst **2** has been found to be an active imine hydrogenation catalyst (and inactive for imine transfer hydrogenation; see the Supporting Information). Our final catalyst screen was aimed at hydrogenating esters. These substrates are more normally reduced using $LiAlH_4$ in a research laboratory, but the greener alternative of using molecular hydrogen has attracted considerable industrial attention, since it it does not generate any solid waste. Some heterogeneous catalysts have been successfully used,[31] but homogeneous ruthenium-catalyzed hydrogenations have been under development in several companies.[32−37] Progress has been very difficult: prior to the report of Elsevier in 1998, only a highly activated substrate, dimethyl oxalate, could be partially hydrogenated after 144 h at 180 °C under a high pressure of hydrogen.[17,38,39] The use of [Ru(acac)$_3$], an acidic or basic additive, and a triphosphine ligand enabled much lower temperatures and pressures to be used (120 °C, 80 atm of H_2) and even allowed hydrogenation of unactivated esters.[17] Catalyst **2** was compared with [Ru(PPh$_3$)$_3$Cl$_2$] (**11**), which was one of the first effective ester hydrogenation catalysts,[40] in the reduction of methyl heptafluorobutanoate (**12**). Either $LiHBEt_3$ (1.5%) or KOBu^t (1%) was used as a catalytic additive to generate Ru−H species. Scheme 5 shows how complex **2** catalyzes reduction of this ester to 1*H*,1*H*-heptafluorobutan-1-ol (**13**), with no other products detectable after 24 h. In contrast, [Ru(PPh$_3$)$_3$Cl$_2$] was not effective. In contrast to most previous catalysts, which only partially hydrogenate ester **14**, the hydrogenation catalyzed by **2** gave a mixture containing diol **15** as the major product under the same conditions (Scheme 6). The results suggest that this catalyst is less active than the Elsevier or Milstein systems but is an improvement on all prior ester hydrogenation catalysts.

Scheme 5. Hydrogenation of an Activated Ester



In conclusion, the new ruthenium complex reported here shows good activity for hydrogenation of a very broad range of substrates. These include the enantioselective hydrogenation of ketones that are not hydrogenated with [Ru(BINAP)-

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(29) All of the hydrogenation experiments described here have been set up under non-inert conditions in simple steel bombs with simple magnetic stirring. For these reasons, we have not optimized turnover frequencies, since direct drive stirring and inert conditions are known to maximize TOF's for this reaction. However, 4-fluoroacetophenone could also be cleanly hydrogenated to alcohol with an *S*/*C* value of 10 000 (30 °C, 40 bar, IPA, 1% KOBu^t, <20 h). The corresponding transfer hydrogenation was not effective at this catalyst loading.

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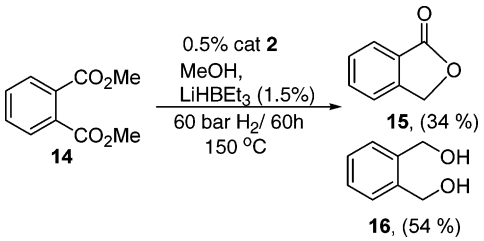
(42) Crystal data for **2**·2MeCN: $C_{31}H_{41}Cl_2N_4OPRuS$, M_r = 720.68, orthorhombic, space group $P2_12_12_1$, a = 9.6872(13) Å, b = 14.333(2) Å, c = 24.351(4) Å, Z = 4, μ(Mo Kα) = 0.761 mm^{-1}, 20 813 reflections collected, 5997 unique reflections (R(int) = 0.0472), and 5262 observed reflections, which were used in all calculations. Final R indices ($I > 2\sigma(I)$): R1 = 0.0420, wR2 = 0.0683. See the Supporting Information for details.

Scheme 6. Double Hydrogenation of Ester and Lactone



(DPEN)Cl_2] catalyst. The enantioselectivity of these reactions is promising, given that these reactions are catalyzed by the first member of a new class of modular hydrogenation catalysts. A new project involving the synthesis and evaluation of a large collection of tridentate ruthenium complexes of general form [Ru(P^N^N)$(Cl)_2$(solv)] will shortly be underway. It is hoped that significant improvements in catalytic activity (in ester hydrogenations) and enantioselectivity in the hydrogenation of unreactive ketones will be possible.

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Supporting Information Available: Text, tables, figures, and a CIF file giving full details of the X-ray structure of complex **2**, details on the characterization of reaction products, and additional experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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