Catalytic Hydrogenation

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Unexpected Role of Anionic Ligands in the Ruthenium-Catalyzed Base-Free Selective Hydrogenation of Aldehydes

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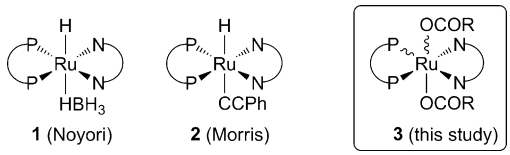
Among alumino- and borohydrides commonly used in organic synthesis,[1] $NaBH_4$ has been the reagent of choice for the selective reduction of ketones and aldehydes in the presence of alkenes.[2] Nevertheless, the discovery in 1995 by Noyori and co-workers[3] of selective hydrogenation with very low amounts of [(diphosphine)(diamine)$RuCl_2$] catalysts afforded a highly sustainable alternative to the use of stoichiometric amounts of this highly waste generating reducing agent. Although this methodology is nowadays employed extensively for the reduction of ketones[4] owing to its widely recognized exceptional efficiency,[5] only few examples have been described in the case of aldehydes,[3,6] possibly because reported systems generally require the use of a strong base as a cocatalyst. As aldehydes are far more sensitive to such conditions than ketones, self-aldol side reactions could readily occur.

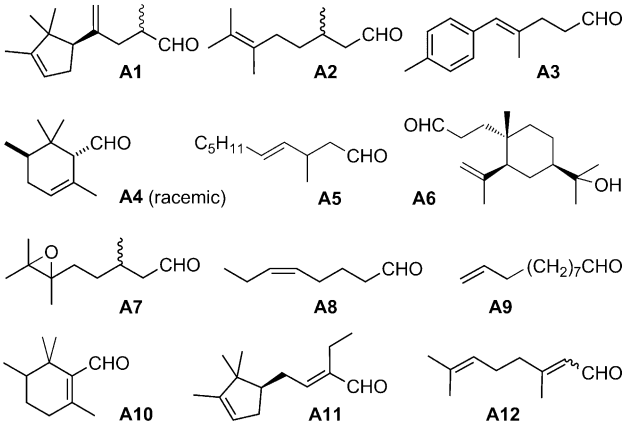
For a hydrogenation reaction under base-free conditions, some nonhalogenated hydride ruthenium catalysts of type **1** and **2** (Scheme 1) were later developed by Noyori and co-workers[7] and Morris and co-workers.[8] These systems proved to be intrinsically less active,[9] but they also unfortunately appeared to be much more sensitive to various reaction parameters, including substrate quality: an issue that is generally much more important in the case of aldehydes than for ketones. Recently, the use of other metals, such as rhodium and iron, enabled Breit and co-workers[10] and Beller and co-workers[11] to circumvent this problem and access unsaturated primary alcohols in high yields through the hydrogenation of aldehydes.

The influence of the nature of neutral ligands in systems of the type reported by Noyori and co-workers have been widely examined in the case of ketone reduction, and these studies led to some different combinations of the P_2N_2 ligand system[12] and to the further replacement of a phosphorus atom with a sulfur atom.[13] As a logical next step, we therefore investigated the modification of the nature of anionic ligands in these systems. We also replaced chloride ligands in the original Noyori system with carboxylates, which had previously been reported to play an important role in hydrogen activation.[14] Some ruthenium complexes of type **3** (Scheme 1) have previously been mentioned in the context of the hydrogenation of ketones in the presence of a base;[15] however, we now report[16] the use of non-hydride complexes of this type as highly efficient catalysts for the challenging base-free selective hydrogenation of aldehydes in the presence of alkenes.



Scheme 1. Different types of ruthenium catalysts for base-free hydrogenation.

Starting from readily available [(cod)$Ru(OCOR)_2$]-type precursors (cod = 1,5-cyclooctadiene),[17] we synthesized [(diamine)(diphosphine)$Ru(OCOR)_2$] complexes **3**, generally as a *cis*/*trans* mixture of biscarboxylate isomers, through sequential ligand-coordination steps, as described in the Supporting Information. We tested a very large variety of complexes of type **3** without isomer separation in the selective hydrogenation of aldehydes[16] and report herein the use of a limited number of these catalysts with the substrates shown in Scheme 2.



Scheme 2. Substrates tested in this study.

We compared various biscarboxylate complexes with hydride and borohydride complexes as catalysts in the hydrogenation of aldehyde **A1** in *i*PrOH under H_2 (50 bar) at a ruthenium loading of 0.01 mol% under base-free neutral conditions (Table 1). Whereas the acetate and trifluoroacetate complexes **3a** and **3b** afforded only moderate results comparable to those observed with Noyori-type systems **1a**

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Table 1: Influence of the ruthenium catalyst on the hydrogenation of aldehyde **A1**.[a]

Entry	Ruthenium complex[b]	*T* [°C]	*t* [h][c]	Conv. [%][d]	Yield [%][e]
1	*trans*-[Ru(H)(BH_4)(*S*-binap)(*S*,*S*-dpen)] (**1a**)	30	24	12	12
2	*trans*-[Ru(H)(BH_4)(*S*-binap)(*S*,*S*-dpen)] (**1a**)	100	24	15	14
3	*trans*-[Ru(H)(BH_4)(dppe)(en)] (**1b**)[f]	100	24	14	13
4	[(en)(dppe)Ru($OCOMe)_2$] (**3a**)	100	24	10	10
5	[(en)(dppe)Ru($OCOCF_3)_2$] (**3b**)	100	24	8	7
6	*cis*-[(en)(dppe)Ru($OCOtBu)_2$] (**3c**)	100	8.5	100	>99
7	*trans*-[(en)(dppe)Ru($OCOtBu)_2$] (**3d**)	100	8	100	>99
8	[(en)(dppe)Ru($OCOPh)_2$] (**3e**)	100	6	100	>99
9	[(en)(dppe)Ru($OCOPh)_2$] (**3e**)	30	24	0	

[a] Reaction conditions: aldehyde **A1** (0.05 mol), catalyst (0.01 mol%), *i*PrOH (13 mL), H_2 (50 bar: maintained throughout the reaction). [b] binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dpen = 1,2-diphenyl-1,2-diaminoethane, en = ethylenediamine, dppe = 1,2-bis(diphenylphosphanyl)ethane. [c] The time required for the reaction to reach completion was determined by H_2 consumption. [d] Conversion was measured by GC. [e] After solvent removal and bulb-to-bulb distillation, the reaction yield was determined on the basis of product purity by GC. [f] Complex **1b** was synthesized according to the procedure described by Noyori and co-workers.[7]

and **1b**, the pivalate and benzoate derivatives **3c**–**e** (isomers **3c** and **3d** were separated by crystallization) displayed much higher catalytic activity, with complete conversion in 6–8.5 h. The desired unsaturated primary alcohol was then isolated in nearly quantitative yield: we did not detect the formation of heavy by-products or the hydrogenation of either of the two alkene groups in the substrate. Although previously reported ruthenium base-free systems had been reported to be active at room temperature,[7,8] a higher reaction temperature was generally required when the biscarboxylate complexes were used as catalysts.

In attempts to further improve these results, we found that the reaction is usually most efficient in apolar aprotic solvents, such as heptane. We then discovered that the catalytic efficiency could be further increased significantly by carrying out the hydrogenation in the presence of catalytic amounts of carboxylic acids. Turnover numbers (TONs) up to 40000 and turnover frequencies (TOFs) up to 6153 h^{-1} were then observed at complete conversion in the hydrogenation of the same aldehyde **A1** even with the poorly active bisacetate complex **3a** (Table 2).

Whereas the catalytic activity generally increased with the steric hindrance of the aliphatic carboxylic acid cocatalyst, in analogy with the trend observed for the carboxylate ligand, we observed the reverse tendency between 1-adamantanecarboxylic acid and pivalic acid (Table 2, entries 6 and 7). In the case of aromatic cocatalysts, highly bulky 2,4,6-trimethylbenzoic acid also proved to be inferior to both benzoic acid and 2-naphthoic acid, which were the most effective cocatalysts tested at a 2.5 mol% loading (< Table 2). Under these mildly acidic conditions, the unsaturated primary alcohol was obtained with complete conversion and chemoselectivity and isolated in high yield (≥98%).

The catalytic results reported in Table 3 support the general efficiency of the biscarboxylate complexes of type **3** in the selective base-free hydrogenation of aldehydes; nearly no heavy by-products were formed under these conditions. The catalyst [(en)(dppe)Ru($OCOtBu)_2$] (**3f**) proved to be highly selective (≥98%) in the presence of tetra- and trisubstituted, *E*, and *gem*-disubstituted alkenes as well as epoxides, which remained intact, and aldehydes **A1**–**7** were reduced with high efficiency to the desired alcohols at 100°C under hydrogen (10–50 bar) with TONs of 40000–100000. Even the sterically hindered aldehyde **A4** could be hydrogenated at a ruthenium loading of just 0.002 mol% to afford the desired alcohol with nearly no alkene hydrogenation or isomerization nor epimerization at the α position (99.5% selectivity). In the case of substrates containing terminal or *Z*-disubstituted alkenes, such as **A8** and **A9**, we applied slightly different conditions to maintain high chemoselectivity (90 and 95%, respectively). Because of the absence of an acidic cocatalyst (to minimize alkene isomerization) and the lower reaction temperature, a higher catalyst loading was required (0.01 mol%). The reactions also needed to be stopped right upon completion to avoid a noticeable decrease in selectivity. The complex [(en)(dppe)Ru(OCO(1-adamantyl))$_2$] (**3g**), which displayed higher catalytic activity under such conditions, was used in these two cases. With α,β-unsaturated aldehyde substrates, such as **A10**–**12**, the catalyst [(en)(Xantphos)Ru($OCOtBu)_2$] (**3h**) was generally used to promote high chemoselectivity (≥96%) and thus avoid further reduction of the allylic alcohol formed. Although substrates of this type are often less sensitive to basic conditions, the desired products were obtained with complete conversion at catalyst loadings of 0.0025–0.005 mol% and isolated in higher yields than those observed for reactions carried out under classical basic conditions.[6,18]

Table 2: Influence of the carboxylic acid additive on the hydrogenation of aldehyde **A1**.[a]

Entry	Carboxylic acid	*t* [h][b]	Conv. [%][c]	Yield [%][d]	Remarks[e]
1	none	48	2	n.d.	
2	3-methylbutanoic acid	48	100	98	25% at 6.5 h
3	2,4,6-trimethylbenzoic acid	24	100	>99	65% at 6.5 h
4	isobutyric acid	24	100	>99	70% at 6.5 h
5	3,3-dimethylbutanoic acid	20	100	>99	75% at 6.5 h
6	1-adamantanecarboxylic acid	20	100	>99	75% at 6.5 h
7	pivalic acid	12	100	>99	87% at 6.5 h
8	benzoic acid	8	100	>99	95% at 6.5 h
9	2-naphthoic acid	6.5	100	>99	

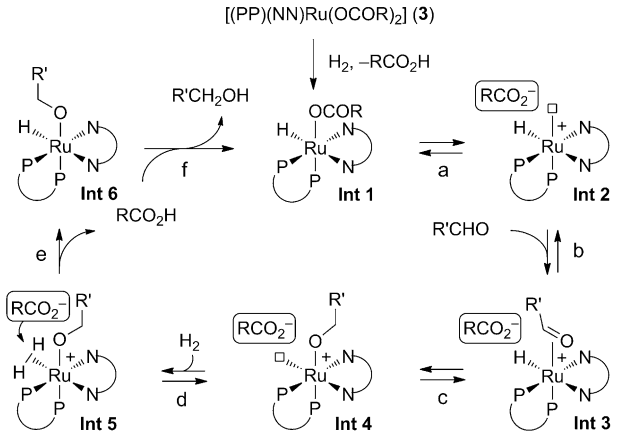
[a] Reaction conditions: aldehyde **A1** (0.1 mol), catalyst **3a** (0.0025 mol%), carboxylic acid (2.5 mol%), heptane (30 mL), 100°C, H_2 (50 bar: maintained throughout the reaction). [b] The time required for the reaction to reach completion was determined by H_2 consumption. [c] Conversion was measured by GC. [d] After solvent removal and bulb-to-bulb distillation, the reaction yield was determined on the basis of product purity by GC; n.d. = not determined. [e] Partial conversion was determined on the basis of H_2 consumption.

Table 3: Hydrogenation of aldehydes **A1–12** (see Scheme 2).[a]

Entry	Aldehyde	Catalyst	S/Ru[b]	Acid	S/acid[c]	Solvent	*P* [bar][d]	*T* [°C]	*t* [h][e]	Sel. [%][f]
1	**A1**	**3 f**	50000	2-naphthoic acid	80	–	50	100	8	100
2	**A2**	**3 f**	100000	2-naphthoic acid	40	–	50	100	24	100
3	**A3**	**3 f**	40000	benzoic acid	45	toluene	10	100	12	100
4	**A4**	**3 f**	50000	2-naphthoic acid	80	–	50	100	10	99.5
5	**A5**	**3 f**	50000	benzoic acid	30	pentane	30	100	8	98
6	**A6**	**3 f**	40000	pivalic acid	60	CH_2Cl_2	50	100	20	98.5
7	**A7**	**3 f**	40000	benzoic acid	100	–	50	100	8	100
8	**A8**	**3 g**	10000	–		pentane	10	70	20	90
9	**A9**	**3 g**	10000	–		heptane	20	80	16	95
10	**A10**	**3 h**	20000	2-naphthoic acid	120	CH_2Cl_2	50	100	8	99.5
11	**A11**	**3 h**	40000	benzoic acid	100	–	50	100	7	98.5
12	**A12**	**3 h**	30000	benzoic acid	133	–	30	100	5	96

[a] Reaction conditions: aldehyde (0.5–1 mol), [(en)(dppe)Ru(OCO*t*Bu)$_2$] (**3 f**), [(en)(dppe)Ru(OCO(1-adamantyl))$_2$] (**3 g**), or [(en)(Xantphos)Ru(OCO*t*Bu)$_2$] (**3 h**), carboxylic acid cocatalyst, solvent (1 wt equiv), heat, H_2 pressure. Upon reaction completion and after solvent removal (when required), the crude product was flash distilled under a high vacuum in the presence of a ballast, and the desired alcohol was obtained with residues comprising less than 1 wt%. [b] Ratio of the substrate to the ruthenium catalyst. [c] Ratio of the substrate to the carboxylic acid cocatalyst. [d] The H_2 pressure given was maintained throughout the reaction. [e] The time required for the reaction to reach completion was determined by H_2 consumption. [f] The selectivity of the reaction was determined by GC. Xantphos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene.

On the basis of the catalytic data described herein and a recent experimental–theoretical study reported by Crabtree, Eisenstein, and co-workers,[19] we propose that ruthenium catalysts of type **3** could operate through an inner-sphere mechanism (Scheme 3) even though they display high



Scheme 3. Proposed mechanism for the hydrogenation reaction.

selectivity in the presence of alkene functionalities. Biscarboxylate complexes of type **3** would first be activated by H_2 to produce a free acid along with a (hydride)(carboxylate)ruthenium intermediate **Int1**.[20] In step a, **Int1** would then undergo some thermal ionization of the carboxylate ligand with the formation of the cationic 16-electron species **Int2**. Such a reaction could be highly favored by steric congestion caused by bulky carboxylate ligands. After aldehyde coordination to give **Int3** (step b) and insertion into the Ru–H bond to give **Int4** (step c),[21] coordinated H_2 in **Int5** (formed in step d) may be deprotonated by RCO_2^- [22] to afford neutral **Int6** along with the corresponding carboxylic acid (step e). The protonation of **Int6** would finally regenerate **Int1** and provide the desired primary alcohol.

Such a reaction mechanism is consistent with the highly positive effect that we generally observed when the hydrogenation was carried out in the presence of carboxylic acids. Nevertheless, competition between a classical acid–base reaction and H_2 deprotonation may lead to some optimal value for the cocatalyst loading that could potentially correspond to the variations applied in the reactions in Table 3. As in the case of H_2 deprotonation, too much steric hindrance could be detrimental to the efficiency of the protonation of **Int6**, as observed when 1-adamantanecarboxylic acid and 2,4,6-benzoic acid were used as cocatalysts (Table 2). Finally, not only could the absence of steric hindrance potentially disfavor the ionization reaction in step a, but if an esterification reaction of acetic acid with the primary alcohol product is responsible for catalyst deactivation in the case of complex **3 a**, the pK_b value of trifluoroacetate (13.7) could explain the poor results also observed for derivative **3 b** under neutral conditions (Table 1).

In conclusion, we have developed some (diamine)(diphosphine)ruthenium-type complexes as unprecedented highly efficient catalysts for the hydrogenation of aldehydes under base-free conditions by using sterically hindered carboxylates as anionic ligands. These relatively air stable and robust catalysts showed high selectivity for aldehyde hydrogenation in the presence of alkene and epoxide functionalities and were successfully used for the hydrogenation of a large variety of aldehydes. Their better performance in apolar aprotic solvents and the impressive increase in catalytic activity in the presence of catalytic amounts of carboxylic acids strongly suggest that these catalysts operate by a different reaction mechanism to the outer-sphere mechanism generally used to describe catalysis by the Noyori-type system. We are currently further investigating the reaction mechanism along with the tolerance towards other functional groups of the base-free hydro-

genation of aldehydes in the presence of these [(diamine)(diphosphine)Ru(OCOR)$_2$] catalysts.

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