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Ruthenium-Catalyzed Highly Chemoselective Hydrogenation of Aldehydes

Lucia Bonomo, Laurent Kermorvan, and Philippe Dupau*[a]

The use of a [(ethylenediamine)(dppe)Ru(OCO*t*Bu)$_2$] [dppe = 1,2-bis(diphenylphosphino)ethane] complex under base-free conditions allowed highly efficient and selective hydrogenation of aldehydes in the presence of ketones in addition to olefins. Even in the case of highly sensitive 1,6-ketoaldehydes, the desired ketoalcohols were obtained in high yields with 94–99% overall selectivity at complete aldehyde conversion with a TON up to 30000. The lack of requirement for strong basic co-catalysts and polar protic solvents also allowed efficient and highly chemoselective reduction of aldehydes bearing other functional groups, such as epoxides, carboxylic acids, esters, amides, and nitriles emphasizing the potential synthetic utility of the catalyst.

The search for highly enantioselective chemical processes has been the main driving force towards the development of new synthetic catalytic methodologies for many years, probably related to the ever-growing number of optically pure drugs produced in the pharmaceutical industry.[1] Nevertheless, if astonishingly high enantiocontrol was achieved for a large number of chemical transformations, it was quite often done at the expense of process efficiency in terms of catalyst loadings and reaction scope. Initially introduced and further developed as a concept by Trost,[2] chemoselectivity was more recently claimed by Baran and co-workers[3] to be the key for further synthetic efficiency, especially to access highly complex molecules. Discovery of new chemoselective transformations should indeed allow some traditional retrosynthetic approaches to be reconsidered and avoid some tedious protection/deprotection sequences. New transformations should also be able to efficiently meet some increasing industrial requirements related to the environment with the potential to decrease the E-factor.

Research towards highly efficient chemoselective processes has been nicely illustrated by recent developments in the reduction of carbonyl groups into alcohols. Noyori-type catalysts are widely used for the hydrogenation of ketones in the presence of olefins, even in the case of achiral transformations, thanks to their amazingly high catalytic activity.[4] Nevertheless, such catalysts were never reported for selective reduction of aldehydes in the presence of ketones, such a transformation represents a step further in chemoselectivity. This could be related to the general requirement for a strongly basic co-catalyst to achieve high catalytic efficiency, such conditions favoring the aldol side reaction. In addition to this, if aldehydes are known to be more reactive than ketones, some with only a slight difference in bond energy (about 5 kcal mol^{-1}), it is a true obstacle to achieve high chemoselectivity results at complete aldehyde conversion. Also, several homogeneous catalysts, such as [Ir(H$_3$)(PPh$_3$)$_3$], [RuCl$_2$(PPh$_3$)$_3$], [Rh(cod)Cl]$_2$/TPPTS (cod = 1,5-cyclooctadiene; TPPTS = tris(3-sulfophenyl)-phosphine trisodium salt), developed earlier were reported to exhibit some decent activity for the hydrogenation of aldehydes rather than ketones.[5] However, the hydrogenation reaction in general had been scarcely reported for the selective reduction of aldehydes in the presence of ketones. Indeed, Masson and co-workers[6] described some competitive experiments using a heterogeneous Raney-nickel-type catalyst also known for efficient C=C bond hydrogenation. Later, Casey and co-workers[7] reported the use of Shvo-type ruthenium catalysts for selective hydrogenation of benzaldehyde in the presence of acetophenone. Benzyl alcohol was obtained with high chemoselectivity (up to >99%), which was achieved by using relatively high ruthenium loadings (3–4 mol%) and performing the hydrogenation reaction at incomplete aldehyde conversion. More recently, Breit and co-workers[8] also described a few examples of such chemoselective transformation by using an in situ generated rhodium catalyst. Along with the use of additional carbon monoxide to reach the desired catalytic results (0.2 mol% Rh loadings) starting from a metal carbonyl precursor, this system also required some excess non-commercially available supramolecular ligand (10 equiv. Rh).

As a consequence, the use of stoichiometric amounts of hazardous and waste-generating modified metal hydrides[9] still remains the method of choice to perform selective reduction of aldehyde in the presence of ketones as exemplified in the synthesis of (+)-trienomycins A and F[10] and diterpenoid (−)-cyathin B$_2$ antibiotics.[11] In some instances, such levels of chemoselectivity were also achieved by using non alumino or borohydride-type waste-generating stoichiometric reducing reagents[12] or by slightly more environmentally friendly reducing methods.[13]

In previous studies, we developed some highly efficient base-free chemoselective hydrogenation of aldehydes in the presence of olefins by using [(diamine)(diphosphine)Ru(OCOR)$_2$] complexes.[14] After screening for further functional groups tolerance, we are now reporting the use of such ruthenium complexes as efficient catalysts for the highly challenging

[a] *Dr. L. Bonomo, L. Kermorvan, Dr. P. Dupau*
R&D Division
Firmenich SA
125 route de la Plaine
1283 La Plaine (GE) (Switzerland)
E-mail: philippe.dupau@firmenich.com

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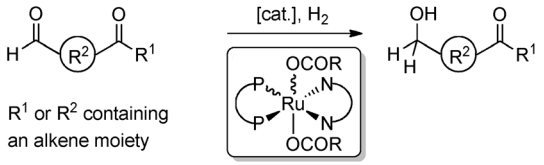
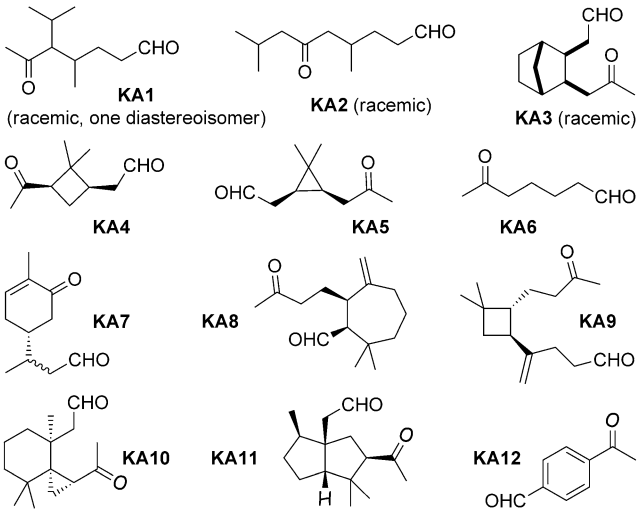


Scheme 1. Chemoselective hydrogenation of aldehydes in the presence of ketones and olefins.

chemoselective hydrogenation of aldehydes in the presence of ketones in addition to olefins (Scheme 1).[15]

Except for the commercially available **KA12** substrate, ketoaldehydes (see Scheme 2) were easily synthesized by using



Scheme 2. Ketoaldehydes tested in chemoselective hydrogenation.

classical synthetic methods. Substrates **KA1**, **KA2**, and **KA7** were obtained by the hydroformylation reaction of terminal or gem-disubstituted olefins of unsaturated ketones. In the case of substrates **KA3**–**KA6** and **KA8**–**KA11**, carbonyl groups were introduced concomitantly by oxidative cleavage of trisubstituted olefins by using ozonolysis or by osmium-catalyzed dihydroxylation (see the Supporting Information).

The hydrogenation of ketoaldehydes **KA1**–**KA12** was efficiently performed in toluene by using [(en)(dppe)Ru(OCO*t*Bu)$_2$] [en = ethylenediamine; dppe = 1,2-bis(diphenylphosphino)-ethane] complex (**1**) as a catalyst as reported in Table 1. Despite some negative influence on catalytic activity,[14] the reaction generally had to be performed in the absence of an acidic co-catalyst to avoid the formation of side products. As a matter of fact, in addition to basic conditions generally unadapted for aldehydes, 1,6-ketoaldehydes **KA2**, **KA3**, and **KA5**–**KA8** were found to be quite sensitive to even slightly acidic conditions owing to intramolecular cross-aldol condensation. For **KA8**, **KA9**, and **K10**, the desired alcohols also underwent an acid-catalyzed intramolecular cyclization side reaction onto olefins or activated cyclopropane rings. Finally, depending on steric hindrance at the ketone moiety, reactions were performed between 80–100 °C under 1–5 MPa hydrogen to afford

Table 1. Selective aldehyde reduction in the hydrogenation reaction of ketoaldehydes **KA1**–**KA12** shown in Scheme 1.[a]

Entry	Keto-aldehyde	S/Ru[b]	*P* [MPa][c]	*T* [°C]	*t* [h][d]	Conversion [%][e]	Selectivity [%][e]
1[f]	**KA1**	30000	5	100	5	100	99
2	**KA2**	15000	5	100	6	100	99
3	**KA3**	10000	2	90	8	100	97
4[f]	**KA4**	30000	5	100	6	100	99
5	**KA5**	10000	3	90	8	100	95
6	**KA6**	8000	1	80	12	100	95
7	**KA7**	15000	5	100	7	100	99
8	**KA8**	8000	2	80	10	100	97
9	**KA9**	8000	3	80	10	100	96
10	**KA10**	15000	5	100	5	100	98
11[f]	**KA11**	30000	5	100	7	100	98
12[f]	**KA12**	10000	2	80	3	100	94

[a] Conditions unless otherwise noted: ketoaldehyde (0.1 mol), [(en)-(dppe)Ru(OCO*t*Bu)$_2$] catalyst (**1**), toluene (300 wt.%), heating, H_2 pressure. Upon complete aldehyde conversion and after solvent removal, crude product was flash distilled under high vacuum in the presence of a ballast and the desired ketoalcohol was obtained with less than 1 wt% residue. [b] Substrate to ruthenium catalyst ratio. [c] H_2 pressure value was maintained throughout the reaction. [d] Time for complete aldehyde conversion, checked by GC, was determined by H_2-gas consumption. [e] Conversion and selectivity were determined by GC analysis. [f] Reaction was run in the presence of 1.5 mol% 2-naphtoic acid.

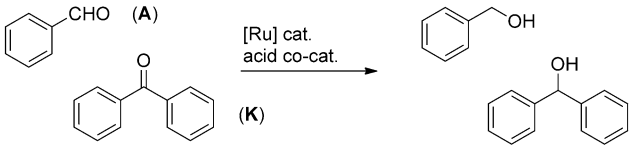
ketoalcohols with more than 94% selectivity at complete aldehyde conversion and a TON of up to 30000.

Reduction of substrates bearing sterically hindered (**KA1**, **KA2**, **KA4**, **KA10**, and **KA11**) or α,β-unsaturated (**KA7**) ketone moieties at 100 °C under 5 MPa H_2 afforded the corresponding ketoalcohols with 98–99% selectivity, both C=C bond (**KA7**) and cyclopropane ring (**KA10**) remaining intact. The best activity results (0.0033 mol% Ru loadings) were achieved in the case of ketoaldehydes **KA1**, **KA4**, and **KA11**, tolerating the use of 2-naphtoic acid co-catalyst without the formation of side products. In the case of compounds **KA3** and **KA5**, the reaction was conducted under milder conditions (90 °C, 2–3 MPa H_2) owing to the presence of a slightly less crowded ketone functional group.

The desired products were then obtained in 97 and 95% selectivity, respectively, with TON's of 10000. Substrates **KA6**, **KA8**, and **KA9**, containing some highly linear ketone functions, were hydrogenated at 80 °C under 1–3 MPa H_2 by using 0.0125 mol% of catalyst **1**. The corresponding ketoalcohols were formed with 95–97% overall selectivity, additional gem-disubstituted olefins remained intact in the case of both **KA8** and **KA9**. The high chemoselectivity level was maintained in the case of substrate **KA8**, which displays relatively high steric hindrance at the aldehyde moiety; it is worth mentioning that no epimerization at the α-position was detected and the initial *cis* stereochemistry of the seven-membered ring was maintained. Finally, 4-hydroxymethylacetophenone was obtained in 94% selectivity by using 0.01 mol% catalyst **1** in the presence of a naphtoic acid co-catalyst. The reaction was performed under mild conditions (2 MPa H_2, 80 °C) to minimize ketone moiety hydrogenation, which mainly occurred on substrate 4-acetylbenzaldehyde **KA12**, probably because of ketone-group

activation by the electron-withdrawing nature of the aldehyde moiety. In all cases, ketoalcohols were obtained with almost no byproduct formation ($\leq$1 wt%).

Data from additional competitive experiments between benzaldehyde and benzophenone in equimolar amounts at 100 °C under 5 MPa H_2 with [(en)(dppe)Ru(OCO*t*Bu)$_2$] catalyst (**1**) in the presence of 2-naphtoic acid as co-catalyst clearly shows no noticeable increase in the ketone hydrogenation reaction rate at high aldehyde conversion and even upon complete disappearance, with only 5.4% conversion (Scheme 3).



t [h]	0.5	1	1.5	2	4	5	8	10
A [% conv.]	9.5	57.0	80.0	93.0	99.0	100.0	100.0	100.0
K [% conv.]	0.2	0.5	2.0	4.0	5.0	5.4	6.5	6.8

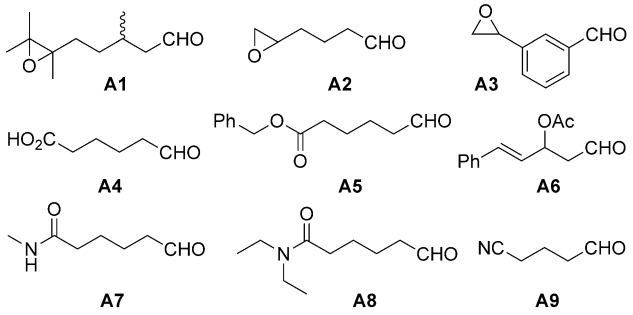
conditions: 1:1 **A**/**K** mixture, 0.0066 mol % [(en)(ddpe)Ru(OCO*t*Bu)$_2$]/**A**, 2.5 mol % naphtoic acid/**A**, 5 MPa H_2, 100°C, 600 wt % solvent/**A**.

Scheme 3. Hydrogenation reaction competitive experiment.

Such results seems to show that ketones are presumably not hydrogenated according to the same pathway as the one previously proposed in the case of aldehydes,[14] allowing access to ketoalcohols with high chemoselectivity at complete aldehyde conversion. As reported by Burk and co-workers[16] in the case of some trifluoroacetate derivatives, complex **1** allowed the efficient hydrogenation of ketones under the basic conditions classically used for Noyori-type catalysts, the competitive experiment then afforded much lower chemoselectivity with approximately 40% diphenylmethanol produced at complete benzaldehyde conversion along with some noticeable increase in the benzophenone hydrogenation rate (see the Supporting Information).

The results from Table 1 show that high chemoselectivity could be achieved for the hydrogenation of aldehydes in the presence of ketones, olefins, and also cyclopropanes. We wanted to further examine the synthetic utility of such a catalytic system. Using complex **1** in the presence of 2-naphtoic acid, the hydrogenation reaction was performed on aldehydes bearing other functional groups that could also be reduced and/or undergo consecutive reaction with alcohols (Scheme 4).

As reported in Table 2, the catalyst appeared to be highly tolerant of tetrasubstituted (**A1**), but also terminal (**A2**) and activated (**A3**), epoxides. The corresponding alcohols were indeed obtained in almost quantitative yields with no trace of epoxide opening through rearrangement, reduction, or nucleophilic-substitution reactions. Performing the reaction under slightly acidic conditions prevents nucleophilic attack of the epoxide by the formed primary alcohol. This nucleophilic attack would occur in the presence of strong acid and also



Scheme 4. Functional-group tolerance in the hydrogenation of aldehydes.

Table 2. Selective aldehyde reduction in the hydrogenation reaction of substrates **A1**–**A9** shown in Scheme 4.[a]

Entry	Aldehyde	Solvent	S/Ru[b]	*P* [MPa][c]	*T* [°C]	*t* [h][d]	Conversion [%][e]	Selectivity [%][e]
1	**A1**	–	40000	5	100	6	100	>99
2	**A2**	MTBE	20000	5	100	8	100	>99
3	**A3**	toluene	20000	5	100	7	100	>99
4	**A4**	MTBE	3000	5	80	10	100	95[f]
5	**A5**	toluene	30000	5	100	8	100	99
6	**A6**	toluene	10000	1	80	16	100	96
7	**A7**	*i*PrOH	1500	5	100	10	100	98
8	**A8**	MTBE	20000	5	100	10	100	99
9	**A9**	MTBE	30000	5	130	6	100	99

[a] Conditions unless otherwise noted: aldehyde (0.1 mol), [(en)(dppe)Ru(OCO*t*Bu)$_2$] catalyst (**1**), 1.5 mol% 2-naphtoic acid, solvent (300 wt%; MTBE = methyl *tert*-butylether), heating, H_2 pressure. Upon complete aldehyde conversion and after solvent removal, the crude product was flash distilled under high vacuum in the presence of a ballast and the desired functionalized alcohol was generally obtained with less than 1 wt% residue. [b] Substrate to ruthenium catalyst ratio. [c] H_2 pressure value was maintained throughout the reaction. [d] Time for complete aldehyde conversion, checked by GC, was determined by H_2-gas consumption. [e] Conversion and selectivity were determined by GC analysis. [f] 5 wt% dimers formed as residues.

strong base as in the case of the Noyori-type catalysts. The absence of requirement of a co-catalyst for the hydrogenation of aldehydes by using [(en)(dppe)Ru(OCO*t*Bu)$_2$] also allowed the reaction to be performed in the presence of a carboxylic acid functional group, as demonstrated by substrate **A4**. The carboxylic acid moiety was not reduced, and running the reaction at 80 °C also minimized esterification with only 5 wt% dimers formed as byproducts. Both the reaction temperature and the nature of the functional group could potentially lead to lower efficiency in hydrogen activation according to a previously proposed reaction mechanism,[14] and are probably responsible for the lower catalytic activity observed for this substrate with a TON of only 3000. The presence of esters was also well tolerated as exemplified with substrates **A5** and **A6**, which were selectively hydrogenated to afford the corresponding hydroxyesters in 99 and 96% selectivity, respectively. Almost no ester reduction or transesterification occurred even at 100 °C under 5 MPa H_2 in the case of **A5**. Substrate **A6** was reduced under milder conditions to efficiently minimize allylic intramolecular substitution, elimination, and also reduction reactions. Alde-

hydes could also be selectively hydrogenated in the presence of amides in substrates such as **A7** and **A8**. If both secondary and tertiary amides groups remained unreduced, the presence of a remaining hydrogen atom was responsible for a huge decrease in catalytic activity. Also, the desired hydroxyamides were obtained in 98 and 99% selectivity by using 0.066 and 0.005 mol% catalyst, respectively. Finally, the strong ability of nitrile to coordinate ruthenium was presumably responsible for the absence of aldehyde reduction in substrate **A9** under general conditions; however, the hydrogenation reaction could efficiently be performed by increasing the reaction temperature. As a result, the desired hydroxynitrile was obtained in 99% selectivity after running the reaction at 130 °C under 5 MPa H_2 in the presence of 0.0033 mol% catalyst.

In summary, we have described a highly efficient and chemoselective ruthenium-catalyzed hydrogenation of aldehydes in the presence of ketones. This reaction was achieved by using [(en)(dppe)Ru(OCO*t*Bu)$_2$] complex (**1**) as a catalyst for a large variety of highly sensitive ketoaldehydes, all reactions were performed under both neutral and slightly acidic conditions and without requirement for polar protic solvents. Tolerance of other functional groups, such as olefins, epoxides, carboxylic acids, amides, esters, and nitriles emphasizes the potential interest of such methodology for the replacement of stoichiometric metal hydride reduction by hydrogenation technology in organic synthesis. We are currently investigating the reaction mechanism to understand the difference in reactivity between ketones and aldehydes, which could be due to steric factors.

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Keywords: aldehydes · chemoselectivity · hydrogenation · ketones · ruthenium

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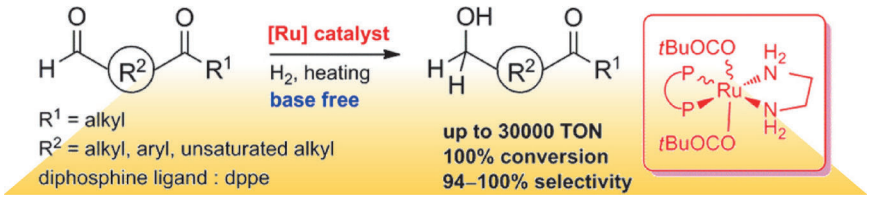

*L. Bonomo, L. Kermorvan, P. Dupau**

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Ruthenium-Catalyzed Highly Chemoselective Hydrogenation of Aldehydes

It's all about the aldehyde: The use of [(ethylenediamine)(dppe)Ru(OCO*t*Bu)$_2$] [dppe = 1,2-bis(diphenylphosphino)-ethane] under base-free conditions allows highly efficient and selective hydrogenation of aldehydes in the presence of ketones. Highly selective hydrogenation of additional aldehydes in the presence of other functional groups, such as epoxides, carboxylic acids, esters, amides, and nitriles emphasizes the potential synthetic utility of the catalyst.