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Fast and Chemoselective Transfer Hydrogenation of Aldehydes Catalyzed by a Terdentate CNN Ruthenium Complex [RuCl(CNN)(dppb)]

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Abstract: Aromatic, aliphatic and α,β-unsaturated aldehydes are quickly, quantitatively and chemoselectively reduced to primary alcohols with 2-propanol using 0.05–0.01 mol% of the terdentate CNN ruthenium complex RuCl(CNN)(dppb) (**1**) [HCNN = 6-(4′-methylphenyl)-2-pyridylmethylamine; dppb = $Ph_2P(CH_2)_4PPh_2$] in the presence of potassium carbonate (K_2CO_3; 1–10 mol%) as a weak base, affording TOF values up to 5.0×10^5 h^{-1}.

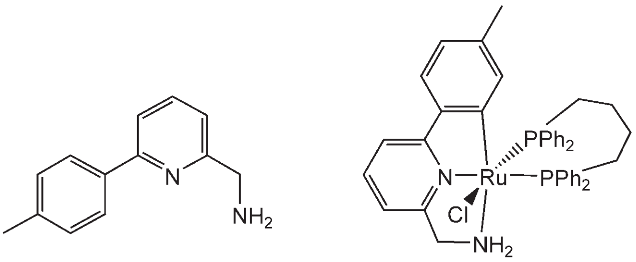
Keywords: M-NH bifunctional effect; phosphanes; pyridine; ruthenium; transfer hydrogenation

Catalytic transfer hydrogenation of carbonyl compounds mediated by transition metal complexes has received increasing attention as a possible synthetic route for the production of a wide range of alcohols. Excellent results have been obtained in the asymmetric transfer hydrogenation of ketones to optical active secondary alcohols, which are an important class of intermediates in the fine chemical industry, using 2-propanol or formic acid derivatives as hydrogen sources.[1] It is worth noting that, because of the higher redox potentials of aldehydes compared to ketones, the equilibrium of the transfer hydrogenation reaction of aldehydes with 2-propanol is more shifted toward the products, compared to the corresponding transfer hydrogenation of ketones.[2] By contrast, reduction of aldehydes to primary alcohols *via* transfer hydrogenation as well as the control of the chemoselectivity of this reaction are considered rather difficult processes.[3] The difficulty for the catalytic reduction of aldehydes resides in the side reactions that may occur during the catalytic reaction, usually performed in basic media. As a matter of fact, the hydrogens of the α-CH group are susceptible to deprotonation and can lead to aldol condensation. Furthermore, during catalysis aldehydes may also undergo decarbonylation reactions,[4] which may result in deactivation of the catalysts through coordination of carbon monoxide. Therefore, in order to suppress these side reactions, weak basic conditions and very short reaction time are prerequisites to achieve efficient aldehyde reduction. One of the most active catalyst has been described by Crabtree and co-workers using an iridium NHC complex that catalyzes the reduction of aldehydes in 2-propanol with TOF values up to 3000 h^{-1}.[4b] More recently, Xiao and co-workers reported the most efficient system prepared by reacting $[Cp^*IrCl(\mu\text{-}Cl)]_2$ with diamines and leading to TOF values up to 130,000 h^{-1} (calculated on the conversion after 5 min) for the reduction of benzaldehyde with sodium formate in the aqueous phase.[5] Despite the catalysts of choice for transfer hydrogenation of ketones being ruthenium-based derivatives, only few catalytic systems with this metal have been described for the transfer hydrogenation of aldehydes, namely some ruthenium phosphane complexes,[3a,c,6] and chiral arene-amino derivatives.[3g,7]

In our recent study on catalytic transfer hydrogenation reactions, we have found that ruthenium phosphane complexes containing 2-(aminomethyl)pyridine (ampy) are highly efficient catalysts for the reduction of ketones,[8] with the derivatives of general formula $RuCl_2(PP)(ampy)$ (PP = chiral diphosphane)[8d] affording *ee* values up to 94%. An extremely active system has subsequently been prepared using 6-(4′-methylphenyl)-2-pyridylmethylamine (HCNN), leading to the terdentate complex RuCl(CNN)(dppb) (**1**) [dppb = $Ph_2P(CH_2)_4PPh_2$] which catalyzes the reduction of ketones with 2-propanol at low ruthenium loadings (0.05–0.001 mol%), in a very short reaction time and with high TOF values (10^6 h^{-1}) (Figure 1).[9]

In this paper we describe the use of complex **1** as a highly efficient catalyst for the chemoselective reduction of aldehydes with 2-propanol as hydrogen donor.

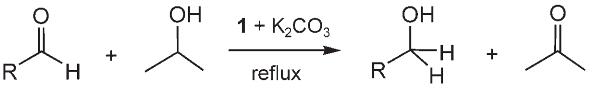
When a 0.1 M solution of benzaldehyde is refluxed in 2-propanol with **1** (0.05 mol%) and K_2CO_3 (1 mol%), quantitative formation of benzyl alcohol has been observed within 1 min, leading to a high turn-



HCNN 1

Figure 1.

over frequency value of $1.3\times10^5\,h^{-1}$ calculated at 50% conversion [Eq. (1) and Table 1].



(1)

By increasing the base concentration to 5 and 10 mol%, the reaction is complete in 30 and 20 s, respectively, affording TOF values of 3.0×10^5 and of $5.0\times10^5\,h^{-1}$, which are the highest values reported to date.[5] The effectiveness of using **1** in synthesis has been tested by carrying out the reaction at a lower loading of **1**. Thus, benzaldehyde is quantitatively reduced using 0.01 mol% of **1** with a rate that progressively increases at higher base concentrations with TOF values of of 3.2×10^4, 3.6×10^4, 1.6×10^5 and $2.2\times10^5\,h^{-1}$ with 1, 2, 5 and 10 mol% of K_2CO_3, respectively, without deactivation of the catalyst. Because of the high performance of **1** we extended this reduction procedure to a wider range of aldehyde substrates. Methyl-substituted benzaldehydes are rapidly and completely reduced to the corresponding alcohols in a few minutes using 0.05 mol% of **1** in refluxing 2-propanol. Thus, for 4-methylbenzaldehyde the TOF value is $3.0\times10^4\,h^{-1}$ when the base is 1 mol% and increases to $8.0\times10^4\,h^{-1}$ when the base is 5 mol%. A similar trend has been observed for 2,4-dimethylbenzaldehyde which is reduced in 5 min, displaying a TOF value of $3.6\times10^4\,h^{-1}$ with 1 mol% of K_2CO_3, whereas at 5 mol% of base quantitative conversion is achieved in 20 s, affording a TOF of $4.5\times10^5\,h^{-1}$ (Table 1).

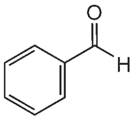
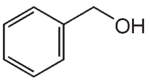
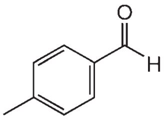
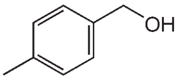
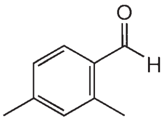
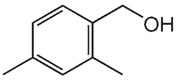
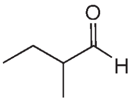
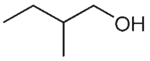
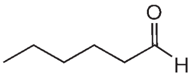
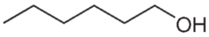
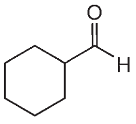
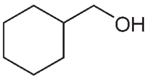
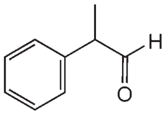
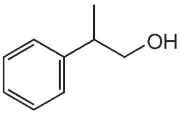
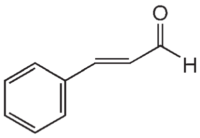
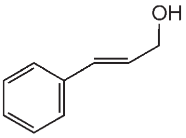
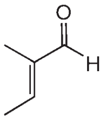
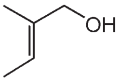
Complex **1** has been found to be extremely efficient also for the reduction of aliphatic aldehydes. Thus, under the aforementioned experimental conditions, 2-methylbutanal, hexanal and cyclohexanecarboxaldehyde are completely reduced within a few minutes using **1** (0.05–0.01 mol%), affording TOF values of 2.4×10^5, 3.0×10^5 and $2.0\times10^5\,h^{-1}$ with 5 mol% of K_2CO_3 (Table 1). The enolizable 2-phenylpropanal is also quickly converted into alcohol with 0.05 mol% of **1** and 1 and 5 mol% of base (TOF $= 1.6\times10^4$ and $9.0\times10^4\,h^{-1}$), without apparent formation of products of aldol condensation, as inferred from ^{1}H NMR analysis. Also for these aliphatic aldehydes an increase of the base concentration results in shorter reaction time, with quantitative alcohol formation even at low catalyst loading (0.01 mol%). These results can be compared with those reported for the Cp*Ir-diamine system which requires longer reaction time and dropwise aldehyde addition to prevent aldol condensation.[5]

High chemoselectivity has been observed with **1** in the transfer hydrogenation of α,β-unsaturated aldehydes leading to fast reduction at the carbonyl group. Thus, using **1** at 0.05 mol% and K_2CO_3 (1 mol%) the substrate *trans*-cinnamaldehyde is quantitatively converted into cinnamyl alcohol after 2 min (TOF $= 1.8\times10^5\,h^{-1}$). By increasing the base concentration (2, 5 and 10 mol%), the reaction occurs at a higher rate, affording TOF values up to $3.4\times10^5\,h^{-1}$ (Table 1). Under refluxing conditions in 2-propanol, the analysis of the mixture reveals slow reduction of the C=C double bond, leading to 20% of 3-phenyl-1-propanol after 1 h. Fast and chemoselective reduction has been observed for tiglic aldehyde which gives quantitative formation of *trans*-2-methyl-but-2-en-1-ol in 30 s with a TOF of $2.5\times10^5\,h^{-1}$. These results on the reduction of α,β-unsaturated aldehydes can be compared with those reported for the few systems that enable the chemoselective reduction at the C=O bond.[3f,k,5]

As regards the mechanism of the transfer hydrogenation,[10] in the presence of K_2CO_3, complex **1** in 2-propanol solution is converted into the corresponding ruthenium isopropoxide species Ru(O-*i*-Pr)(CNN)-(dppb), which subsequently undergoes a β-hydrogen elimination reaction,[11] affording the ruthenium hydride complex RuH(CNN)(dppb).[9] The subsequent insertion of aldehyde into the Ru−H bond leads to a new ruthenium alkoxide that rapidly reacts with 2-propanol, affording the primary alcohol product and the ruhenium isopropoxide that closes the catalytic cycle. Without base, compound **1** displays no catalytic activity in the reduction of both aldehydes and ketones, in agreement with the necessity to generate a ruthenium hydride species which is more active by increasing the base concentration.[9a] On the other hand, by performing the reaction with K_2CO_3 (5 mol%) in the absence of **1**, very little conversion of *trans*-cinnamaldehyde (<1%) was observed after 20 min. This result is consistent with the slow reduction of 2-naphthaldehyde (6% conversion after 6 h) using 50 mol% of K_2CO_3, reported by Crabtree and co-workers.[4b]

We have to point out that with **1** the hydrogen transfer takes place using freshly distilled aldehydes, since the presence of traces of aldehyde oxidation products inhibits the activity. For example, addition of benzoic acid at 0.5 and 1 mol% to the solution containing benzaldehyde with **1** (0.01 mol%) and K_2CO_3 (10 mol%) leads to a decrease of the rate, with TOF

Table 1. Catalytic transfer hydrogenation of aldehydes catalyzed by **1** (0.05 mol%).[a]

Aldehyde	Alcohol	K_2CO_3 [mol%]	Time [min]	Conversion [%][b]	TOF [h^{-1}][c]
		1 5 10	1 30 s 20 s	99 99 99	1.3×10^5 3.0×10^5 5.0×10^5
		1 5	5 2	99 99	3.0×10^4 8.0×10^4
		1 5	5 20 s	99 98	3.6×10^4 4.5×10^5
		5	30 s	99	2.4×10^5
		5 10	30 s 2	99 99	3.0×10^5 $3.0\times10^{5[d]}$
		5	5	99	$2.0\times10^{5[d]}$
		1 5	5 2	99 99	1.6×10^4 9.0×10^4
		1 2 5 10	2 1 30 s 30 s	99 99 99 99	1.8×10^5 2.0×10^5 3.3×10^5 3.4×10^5
		5	30 s	99	2.5×10^5

[a] The reactions were carried out at 82°C with the aldehyde 0.1 M in 2-propanol.
[b] The conversion was determined by GC and for entry 3 also by NMR analyses.
[c] TOF: turnover frequency (moles of aldehyde converted to alcohol per mole of catalyst per hour) at 50% conversion.
[d] **1** 0.01 mol%.

values of 1.2×10^5 and 9.3×10^4 h^{-1}, respectively, compared to 2.2×10^5 h^{-1} obtained in absence of benzoic acid. Under the typical catalytic conditions (**1** 0.05 mol%, K_2CO_3 5 mol%), addition of a small amount of acetic acid (1 mol%) to 2-phenylpropanal significantly retards the reduction, the conversion being completed in 45 min at a considerably lower rate (TOF$=4.0\times10^3$ h^{-1}), with respect to 9.0×10^4 h^{-1} (Table 1). These data suggest that the carboxylates, which form by reaction of the acids with K_2CO_3, compete with the *i*-PrO$^-$ ligand, thus preventing the β-hydrogen elimination from the ruthenium isopropoxide.

As observed for the η^6-arene amino ruthenium-based catalysts,[12] the presence of the NH_2 group in **1** is fundamental for obtaining high performance in transfer hydrogenation, and for **1** this can be ascribed to the ability of the amino group to facilitate, *via* hydrogen bond interactions, the formation of ruthenium alkoxides which are in rapid equilibrium with the ruthenium hydride.[9] Furthermore, the presence in **1** of a robust framework built up by the association of a terdentate ligand with the diphosphane may hinder the aldehyde decarbonylation side reaction.

In conclusion, the terdentate ruthenium complex **1** represents one of the most active catalysts for the reduction of aldehydes reported to date, leading to rapid and quantitative conversion of aldehydes with low loading of catalyst (0.05 to 0.01 mol%), a small amount of a weak base (K_2CO_3), and affording TOF values up to 5.0×10^5 h^{-1}. The very short reaction time (minutes) required for the complete reduction, limits the side reactions, making this route a highly chemoselective transfer hydrogenation process for aldehydes.

Experimental Section

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. Aldehydes and 2-propanol were purchased from Aldrich and distilled under argon before use, whereas the complex **1** was prepared according to literature procedure.[9a]

Typical Procedure for the Catalytic Transfer Hydrogenation of Aldehydes

The ruthenium complex **1** (2.3 mg, 3.0 μmol) was dissolved in 3 mL of 2-propanol. The aldehyde (2 mmol) was dissolved in 19 mL of 2-propanol and K_2CO_3 (2.8 mg, 0.02 mmol) was added, obtaining a suspension which was rapidly heated to reflux under argon. By addition of the solution containing the ruthenium complex (1 mL) the reduction of the aldehyde starts immediately (**1** 0.05 mol% and K_2CO_3 1 mol%). The reaction was sampled by removing an aliquot of the reaction mixture, adding ether (1:1 in volume) and, after filtration over a short silica pad, the conversion was determined by GC analysis.

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