Chemoselective Transfer Hydrogenation of Aldehydes with HCOONH4 Catalyzed by RuCl(CNNPh)(PP) Pincer Complexes

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Chemoselective Transfer Hydrogenation of Aldehydes with $HCOONH_4$ Catalyzed by $RuCl(CNN^{Ph})(PP)$ Pincer Complexes

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Abstract: Aldehydes are chemoselectively reduced to primary alcohols using $HCOONH_4$ as hydrogen donor, via transfer hydrogenation catalyzed by benzo[*h*]quinoline pincer complexes $RuCl(CNN^{Ph})(PP)$ at S/C = 2000-20000. This practical reaction performed with aldehydes of commercial grade purity in a water / toluene biphasic system affords alcohols without formation of condensation or amination side products.

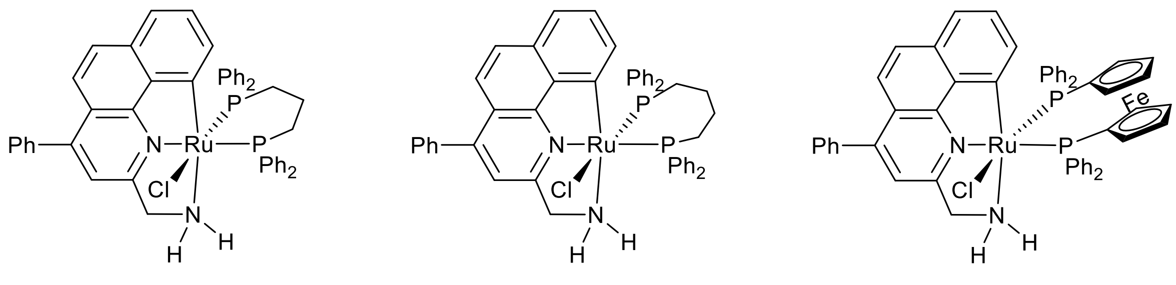
Keywords: aldehydes • ligands • formate • hydrogen transfer • ruthenium

The search of well-designed and productive catalysts for the selective hydrogenation[1] and transfer hydrogenation (TH)[2] of aldehydes to primary alcohols is a fundamental reaction of broad application in the industry.[3] As matter of fact, this catalytic route promoted by transition metals, results in a lower environmental impact and an easier work-up with respect to the classical approach entailing $NaBH_4$, $LiAlH_4$, boranes and Al alkoxides as reducing agents.[4] Among the transition metals used in catalytic homogeneous reductions, ruthenium, which is cheaper with respect to rhodium and iridium, has played a crucial role leading to a number of efficient catalysts for the aldehyde reduction using H_2 under pressure[5] or 2-propanol.[5e, 6] While the TH with 2-propanol is an equilibrium reaction that, on scale, requires the removal of acetone to drive the reaction to completion, the use of formic acid derivatives as hydrogen donors have the advantage of generating CO_2, which is released from the reaction solution, driving the reaction and minimizing the reversibility problems.[7] Alkali formates HCOOM (M = Na, K) were employed in TH of aldehydes with $RuCl_2(PPh_3)_3$,[8] $[RuCl_2(m\text{tppms})_2]_2$ (mtppms = sodium 3-diphenylphosphinobenzenesulfonate),[9] $CpRuCl(PPh_3)(PN)$ (PN = diphenyl-2-pyridylphosphine),[10] $RuCl_2(PTA)_4$ (PTA = 1,3,5-triaza-7-phosphaadamantane)[11] and $RuCl_2(PO)_2$

(PO=(2-methoxyethyl)diphenylphosphine)[12] catalysts at S/C ≤ 1000, whereas the HCOOH-NEt_3 system has been used with $[RuCl_2(benzene)]_2$, but at a low S/C = 50.[13]

Ammonium formate is a cheap and readily accessible reducing agent widely employed in organic transformations. In addition to the Leuckart-Wallach reductive amination of carbonyl compounds,[14] the metal catalyzed version reaction has been reported by Kitamura[15] and Talwar[16] with Cp* Rh(III) and Ir(III) complexes, respectively, whereas Kadyrov described the asymmetric version with $RuCl_2$[(*R*)-tol-BINAP].[17] $HCOONH_4$ has also been widely used in Pd/C-catalyzed conversion of carbonyl compounds into alkanes,[18] nitro derivatives to amines[19] and in the hydrodehalogenation of aromatic chlorides.[20]

For the employment of $HCOONH_4$ in the TH of carbonyl compounds, recently Grainger[21] described the use of Wills' tethered Ru complexes in the reduction of ketones, while Nie[22] observed the concomitant TH and reductive amination of acetophenone with $RuCl_2(PPh_3)_3$. Curiously, the TH of aldehydes with $HCOONH_4$ has only been described by Iyer in the reduction of 4-methoxybenzaldehyde and *trans*-cinnamaldehyde catalyzed by $Ni[P(OPh)_3]_4$ at 110 °C, but at a very low S/C = 30.[23] Since the catalytically active metal-hydride species[24] are generated in basic conditions, where aldehydes, more than ketones, may undergo several side reactions (Claisen-Tishchenko,[25] Cannizzaro[26] and aldol condensation reactions[27]), the selective aldehyde reduction remains a delicate point. Recently, we described the preparation of the benzo[*h*]quinoline pincer complexes RuCl(CNN^{Ph})(PP) **1-3** which are active catalysts in the hydrogenation and TH with 2-propanol of ketones[28] and aldehydes[29] (Figure 1).



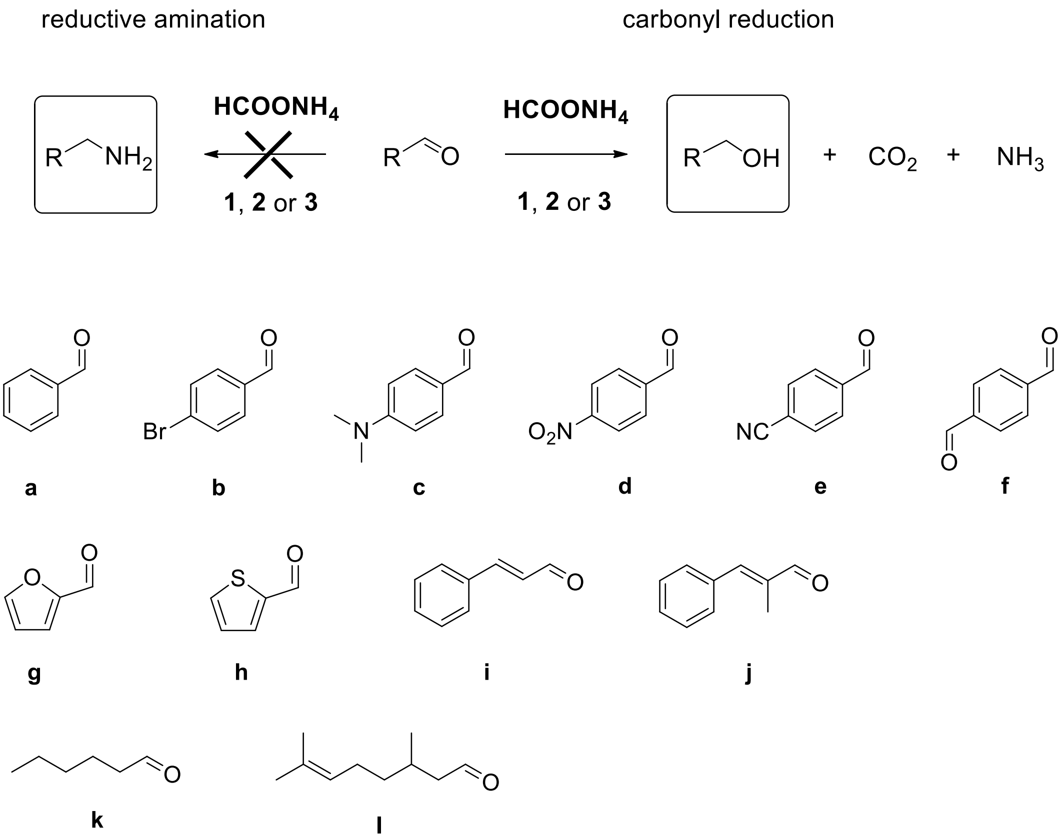
1 **2** **3**

Figure 1. Benzo[*h*]quinoline pincer ruthenium complexes **1**-**3**.

In the TH of aldehydes in 2-propanol the reaction was carried out at low substrate concentration (0.1 M) and under weak basic conditions to inhibit the condensation reaction with the formed acetone, a side reaction which strongly depends on the type of the aldehyde.[29]

We report here the straightforward and chemoselective TH of aldehydes of commercial-grade purity to alcohols using ammonium formate as hydrogen donor in a water / toluene biphasic system, catalyzed by the pincer complexes **1-3** at S/C 2000-20000. Employment of $HCOONH_4$ with **1-3** allowed the clean reduction of aliphatic, conjugated and functionalized aromatic and heteroaromatic aldehydes, without formation of condensation and amination side products.

Reaction of benzaldehyde **a** of commercial grade purity (assay 99%) in toluene (0.5 M) with 2 eq. of $HCOONH_4$ in water (1 M) and in the presence of complex **1** (S/C = 5000) affords selectively benzyl alcohol (76%) in 22 h at 90 °C (Table 1, entry 1), without formation of products of the Leuckart-Wallach reductive amination (Scheme 1).



Scheme 1. TH of aldehydes with $HCOONH_4$ catalyzed by **1-3**.

Complex **2** shows higher activity than **1** with 98 and 97% of alcohol in 9 and 15 h with S/C = 2000 and 5000, respectively (entries 2, 3). Complete conversion was also achieved at higher substrate concentration (1 M) with 2 and 4 eq. of formate (entries 4, 5). In addition, chemoselective TH of **a** to alcohol (96%) was attained with $HCOONH_4$ using a 2 M of substrate and at high S/C = 20000 in 48 h (entry 6). It is worth noting that performing the reaction at high aldehyde concentration is of particular advantage for industrial applications and that the TH with 2-propanol requires lower aldehyde concentration (0.1 M) to avoid coupling reactions.[29]

Table 1. TH of benzaldehyde **a** to benzyl alcohol catalyzed by **1-3** using $HCOONH_4$, HCOONa, and HCOOH / NEt_3 as hydrogen donors (DH_2) in water / toluene at 90 °C.

Entry	Cat.	S/C	[S][a]	[DH_2][b]	DH_2 (eq.)	Time (h)	Conv. (%)[c]
1	**1**	5000	0.5	1[d]	2	16	60
						22	76
2	**2**	2000	0.5	1[d]	2	9	98
3	**2**	5000	0.5	1[d]	2	15	97
4	**2**	5000	1	1[d]	2	15	85
						24	96
5	**2**	5000	1	1[d]	4	15	97
6	**2**	20000	2	2[d]	4	15	58
						22	89
						48	96
7	**3**	5000	0.5	1[d]	2	16	96
8	**3**	10000	0.5	1[d]	2	20	86
						40	96
9	none	--	2	2[d]	4	24	11
10	**2**	2000	0.5	2[e]	4[e]	24	50
11	**2**	5000	4.5	6.5[f]	1.5[f]	24	48
12	**2**	2000	0.5	2[g]	4[g]	14	2

[a] Substrate concentration in toluene. [b] DH_2 concentration in water. [c] The conversion and the purity were determined by GC and NMR analyses. [d] $HCOONH_4$. [e] HCOOH / NEt_3 = 1 / 1. [f] Benzaldehyde was reacted in neat HCOOH / NEt_3 = 5 / 2. [g] HCOONa.

Complex **3** gave nearly quantitative reduction of **a** in 16 and 40 h with S/C = 5000 and 10000 (entries 7, 8). In absence of ruthenium catalyst, the reaction of **a** with 4 eq. of $HCOONH_4$ afforded 11% of alcohol after 24 h (entry 9), indicating that under these conditions **a** is reduced by $HCOONH_4$, although at much lower rate with respect to the catalytic pathway. The use of HCOOH / NEt_3 = 5 / 2 and 1 / 1 mixtures (1.5 and 4 eq. of formic acid, respectively) in the presence of **2** at S/C = 5000 and 2000, gave 48-50% of alcohol after 24 h (entries 10, 11), whereas with HCOONa the conversion was 2% in 14 h (entry 12). These results indicate that the inexpensive $HCOONH_4$ can be employed as practical hydrogen donor for the selective reduction of **a** catalyzed by the robust pincer complexes **1-3**. Preliminary experiments with other media different than toluene / water system, such as methanol / water mixtures or pure methanol led to poor conversion and poor selectivity, due to the formation of aminative condensation / reduction side-products.

To broaden the scope of the aldehyde TH with $HCOONH_4$, aromatic, aliphatic, conjugated and heteroaromatic aldehydes were studied with complex **2**. Reduction of 4-bromobenzaldehyde **b** (2 M in toluene) with 4 eq. of $HCOONH_4$ afforded 97 and 98% of the corresponding alcohol in 10 and 24 h using **2** at S/C of 2000 and 10000, respectively (entries 1, 2, Table 2), whereas 75% al alcohol was obtained at S/C = 20000 (entry 3).

Table 2. TH of aldehydes (2 M in toluene) with $HCOONH_4$ (4 eq., 2 M in water) catalyzed by complex **2** in toluene / water 90 °C.

Entry	Aldehyde	S/C	Time (h)	Conv. (%)[a]
1	**b**	2000	10	97
2	**b**	10000	24	98
3	**b**	20000	48	75
4	**c**	5000	15	96
5	**d**	2000	6	99, 87[b]
6	**e**	2000	3.5	99, 70[b]
7	**f**	2000	10	98[c]
8	**f**	2000	4	99[d]
9	**g**	10000	20	98
10	**h**	10000	24	97[e]
11	**i**	2000	10	97[f]
12	**i**	5000	48	97[g]
13	**j**	5000	20	98[e], 88[b]
14	**k**	5000	8	95
15	**l**	5000	18	99[e]

[a] The conversion and the purity were determined by GC and ^{1}H-NMR analyses. [b] Isolated yield. [c] Only the double-reduction product was detected. [d] With 1.5 eq. of $HCOONH_4$ a mixture of 4-(hydroxymethyl)benzaldehyde / 1,4-phenylenedimethanol in a 9 / 1 ratio was observed. [e] [$HCOONH_4$] = 4 M in water. [f] 91% of *trans*-cinnamol and 6% of the saturated alcohol 3-phenylpropan-1-ol. [g] 85% of *trans*-cinnamol and 12% of 3-phenylpropan-1-ol.

The electron-rich 4-(dimethylamino)benzaldehyde **c** was efficiently reduced to alcohol (96%) with S/**2** = 5000 in 15 h (entry 4). Conversely, the TH of the electron poor 4-nitrobenzaldehyde **d** and 4-cyanobenzaldehyde **e** afforded quantitative formation of the corresponding alcohols, isolated in 87 and 70% yield at S/**2** = 2000, without reduction of the NO_2 and CN functionalities or deactivation of the catalyst, i.e. by coordination at the metal center (entries 5, 6). Double TH was observed for 4-formylbenzaldeyde **f** leading to quantitative formation of 1,4-phenylenedimethanol in 10 h (entry 7). Interestingly, with a lower amount of $HCOONH_4$ (1.5 eq.) the TH of **f** afforded the mono reduction product 4-(hydroxymethyl)benzaldehyde / 1,4-phenylenedimethanol in a 9 / 1 molar ratio, respectively (entry 8). Also the heteroaromatic 2-formylfuran **g** and 2-formylthiophene **h** were selectively reduced to alcohols 98 and 97% at S/**2** = 10000 in 20 and 24 h, respectively (entries 9, 10). Unsaturated *trans*-cinnamaldehyde **i** gave almost complete conversion (97%) to *trans*-cinnamol (91%) and 3-phenylpropan-1-ol (6%) at S/**2** = 2000 in 10 h, whereas at lower loading (S/**2** = 5000), formation of 85% of *trans*-cinnamol and 12% of the saturated alcohol was observed in 48 h, indicating that higher selectivity is achieved at higher catalyst loading and in shorter reaction time (entries 11, 12). On the other hand, *trans*-α-methylcinnamaldehyde **j** was chemoselectively transformed into *trans*-α-methylcinnamol, and isolated in 88% yield at S/**2** = 5000 in 20 h, with no reduction of the C=C double bond (entry 13). In addition, the aliphatic aldehydes hexanal **k** and *rac*-citronellal **l** were reduced to 1-hexanol and *rac*-citronellol 95 and 99%, with **2** at S/C = 5000 (entries 14, 15). By contrast, with **2** (S/C = 2000) the TH of vanillin and pyrrole-2-carboxaldehyde, displaying relatively acidic hydrogens, failed, leading to the unreacted starting material. It is worth noting that *cis*-$RuCl_2$(ampy)(dppf) (S/C = 2000), which is a complex related to **3** and efficiently catalyzes the TH of aldehydes with 2-propanol,[29] has been proven to be significantly less active in the TH of benzaldehyde (18 % conv., 15 h) with $HCOONH_4$ (4 eq.). All spectral data were in the agreement with the literature, as all the obtained compounds are known.

As regards the mechanism, it is likely that the pincer complex RuCl(CNN^{Ph})(PP) in the presence of $HCOONH_4$ leads to the formate complex Ru(O_2CH)(CNN^{Ph})(PP), with formation of the hydride RuH(CNN^{Ph})(PP)[30] by elimination of CO_2. The subsequent reaction with the RCHO substrate gives the alkoxide Ru(OCH_2R)(CNN^{Ph})(PP) which is protonated by $HCOONH_4$, affording the alcohol product, ammonia and the formate complex, closing the cycle, as inferred from TCD-gas analysis, showing that CO_2 and NH_3 are evolved during the reaction. Since $HCOONH_4$ displays better performances with respect to HCOONa and the HCOOH / NEt_3 system, it is reasonable that the elimination of NH_3 during the catalysis has positive effects, shifting the reaction toward the alcohol product, preventing a significant increase of the OH^- concentration, thus disfavoring the base catalyzed aldehyde side reactions. As a matter of fact, control experiments carried out during the catalytic reduction of benzaldehyde and *rac*-citronellal showed that the pH values of the aqueous phase were in the range 7.5-8.5.

In conclusion, simple and functionalized aldehydes have been chemoselectively reduced to primary alcohols using $HCOONH_4$ as hydrogen donor with the benzo[*h*]quinoline pincer complexes RuCl(CNN^{Ph})(PP) at S/C up to 20000. This straightforward reaction carried out with aldehydes of commercial grade purity at high substrate concentration (2 M) in a water / toluene biphasic system gives alcohols without formation of condensation or amination side products. These reaction conditions are experimentally simple and provide significant options for industrial applications with respect to the use of 2-propanol as reducing agent. Further studies on ruthenium catalyzed transfer hydrogenation reactions are underway.

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Graphical abstract

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Salvatore Baldino,*[a] Sarah Facchetti,[b] Hans G. Nedden,[b] Antonio Zanotti-Gerosa,[b] and Walter Baratta*[a]

Ammonium formate efficiently reduces commercial-grade aldehydes to alcohols, via transfer hydrogenation, catalyzed by benzo[*h*]quinoline pincer ruthenium complexes without formation of condensation or amination side products.