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Transfer Hydrogenation and Hydrogenation of Commercial-Grade Aldehydes to Primary Alcohols Catalyzed by 2-(Aminomethyl)pyridine and Pincer Benzo[*h*]quinoline Ruthenium Complexes

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The chemoselective reduction of commercial-grade aldehydes (97–99%) to primary alcohols is achieved with *cis*-[$RuCl_2$(ampy)(PP)] [ampy = 2-(aminomethyl)pyridine; PP = 1,4-bis(diphenylphosphino)butane, 1,1′-ferrocenediyl-bis(diphenylphosphine)] and pincer [RuCl(CNN^R)(PP)] [PP = 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,1′-ferrocenediyl-bis(diphenylphosphine); $HCNN^R$ = 4-substituted-2-aminomethyl-benzo[*h*]quinoline; R = Me, Ph] complexes by transfer hydrogenation and hydrogenation reactions. Aromatic, conjugated, and aliphatic aldehydes are converted quantitatively to the corresponding alcohols using 2-propanol with potassium carbonate at substrate/catalyst ratios up to 100 000 by transfer hydrogenation, whereas aldehyde hydrogenation (5–20 atm of H_2) is achieved efficiently in MeOH in the presence of KO*t*Bu at substrate/catalyst ratios up to 40 000.

Introduction

The metal-catalyzed hydrogenation (HY)[1] and transfer hydrogenation (TH)[2] of carbonyl compounds, with particular regard to ketones, are widely accepted as cost-efficient routes for the synthesis of alcohols in industry.[3] The HY and TH procedures, which involve H_2 and 2-propanol or formic acid as hydrogen sources, have a lower environmental impact and an easier work up with respect to the classical reduction that involves $NaBH_4$ or boranes still employed in industry.[4] In recent decades great attention has been devoted to the development of chiral Ru catalysts based on well-designed ligands for the synthesis of optically active alcohols by the asymmetric reduction of ketones.[1] In addition to the Noyori-type TH and HY Ru catalysts,[5] which have an arene or a diphosphane in combination with a bidentate N ligand with a NH function, a new generation of highly active pincer Ru catalysts that contain neutral or anionic tridentate ligands has been reported.[6] These systems are active in several organic reactions, which include alcohol dehydrogenation,[7] ester and amide hydrogenation,[8] and borrowing hydrogen transformations.[9] In the last decade, we developed highly active and productive Ru and Os catalysts, which have substituted 2-(aminomethyl)pyridine ligands, for the TH and HY of carbonyl compounds, and progress in this area has been reviewed recently.[10] The commercially available *cis*-[$RuCl_2$(ampy)(PP)] [ampy = 2-(aminomethyl)pyridine; **1**: PP = 1,4-bis(diphenylphosphino)butane (dppb),[11] **2**: PP = 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf)][12] and pincer [RuCl(CNN)(dppb)] (HCNN = 6-(*p*-tolyl)-2-aminomethylpyridine; **3**)[13] are practical catalysts for ketone reduction and other organic transformations, which include the dehydrogenation, deuteration, and isomerization of alcohols (Figure 1).[12,14]

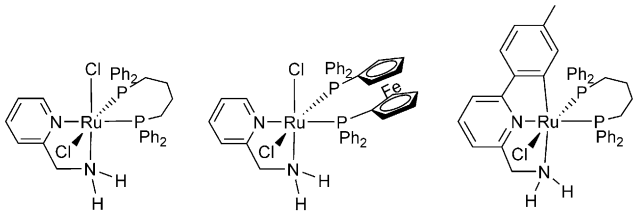

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Figure 1. Ampy and CNN pincer Ru catalysts.

Conversely, for the reduction of simple aldehydes to primary alcohols, $NaBH_4$ remains the preferred reagent in industry.[3,15] Several heterogeneous catalysts, such as those based on Pd/C, are used in the HY of aromatic aldehydes to benzyl alcohols, and particular attention has been devoted to avoid over-reduction to methylarenes.[16] Furthermore, heterogeneous catalysts display a low tolerance to several aromatic substituents, such as nitro and halide groups, which are hydrogenated easily.

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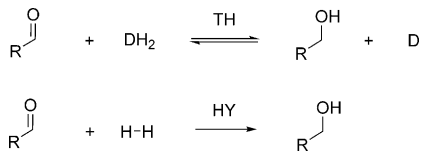
With regard to the reduction of conjugated aldehydes, the chemoselective HY of cinnamaldehyde at C=O without the reduction of the C=C bond has been a challenging target for heterogeneous catalysts for decades.[17] By contrast to ketone reduction, the number of catalysts for the TH and HY of aldehydes is much lower and the catalysis is usually performed with a substrate to catalyst ratio (S/C) $\leq 10^3$ to achieve the complete conversion of the substrate (Scheme 1).[1,2,18]

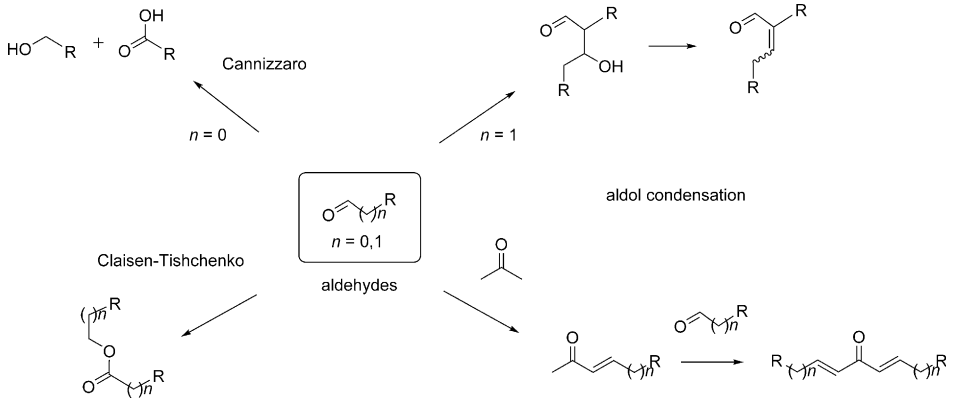


Scheme 1. Transfer hydrogenation and hydrogenation of aldehydes.

In addition to Ir complexes,[19] the Ru Noyori system [(arene)-RuCl(TsDpen)] (Tsdpen = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine),[20] [CpRu(PPh_3)(PN)] (PN = diphenyl-2-pyridylphosphine),[21] [$RuH_2(PPh_3)_4$],[22] [$RuCl_2(PTA)_4$] (PTA = 1,3,5-triaza-7-phosphaadamantane),[23] [$RuCl_2$(*m*tppms)$_2$]$_2$ (mtppms = sodium 3-diphenylphosphinobenzenesulfonate),[24] [$RuCl_2(PO)_2$] (PO = (2-methoxyethyl)diphenylphosphine),[25] [$RuCl_2$(POP)-(dmso)] (POP = xantphos),[26] [$RuCl_2(PPh_3)$(NNN)] (NNN = 2-(benzoimidazol-2-yl)-6-(3,5-dimethylpyrazol-1-yl)pyridine),[27] [$RuCl(PPh_3)_2(MeCN)_3$][BPh_4],[28] [$RuCl_2(CO)_2$(PS)] (PS = bis(2-diphenylphosphanylphenyl)ether monosulfide and 9,9-dimethyl-4,5-bis(diphenylphosphanyl)xanthene monosulfide), and Ru cluster carbonyl derivatives[29] catalyze the aldehyde TH using 2-propanol or formates as hydrogen donors that work at relatively low S/C (100–1000). Complexes **2**[12] and **3**[30] were active in the TH of aldehydes with NaO*i*Pr and K_2CO_3 as the base. To achieve complete reduction, the aldehydes were distilled under an inert atmosphere and used rapidly in TH as commercial-grade substrates led to poor or no conversion.[26] Notably, aldehydes are reduced slowly by alcohols in the presence of Group 1 alkoxides, hydroxides, or carbonates and aluminum alkoxides through the Meerwein–Verley–Pondorf (MPV) reaction.[31] With regard to HY, the Shvo-type catalysts,[32] arene-[33] and phosphane-based Ru complexes[34] were active in the aldehyde reduction. Commercial-grade aromatic aldehydes can be hydrogenated using Will's tethered catalyst [(C3-teth-TsDpen)-RuCl] in MeOH/H_2O[35] as water shifts the acetal–aldehyde equilibrium to aldehyde. Recently, Dupau et al. reported that [$Ru(O_2CR)_2$(diamine)(PP)] (PP = 1,2-bis(diphenylphosphino)-ethane, xantphos), which bears bulky carboxylates, are highly efficient catalysts for the reduction of redistilled commercially available aldehydes in alcoholic and nonprotic apolar solvents in neutral or slightly acidic conditions with S/C = 10^4–10^5, whereas ketones lead to a very poor conversion.[36]

A comparison of the properties of the aldehydes versus ketones may suggest that aldehydes can be reduced more easily to alcohols than ketones because of their higher redox potentials.[37] In addition, aldehydes have lower steric requirements, which facilitates their approach to the metal center. However, in practice aldehydes are substrates that are difficult to reduce selectively, and the catalysis is affected by the substrate quality and nature and the concentration of the base. As the TH and HY of carbonyl compounds are usually performed under basic conditions to allow the formation of the catalytically active metal hydrides,[38] the control of chemoselectivity is a delicate point. Aldehydes, which have a formyl group, show a broader reactivity than ketones. Under basic conditions, aldehydes may undergo the Claisen–Tishchenko (dimerization)[39] and Cannizzaro[40] reactions (Scheme 2).

In addition to alkoxides and hydrides of the main group elements,[39b,41] [$RuH_2(PPh_3)_4$],[42] [$RuHCl(CO)(PPh_3)_3$],[43] [$RuCl(SiMe_3)(CO)(PPh_3)_2$],[44] [$(\eta^5$-$C_5Ph_4O)_2HRu_2H(CO)_4$],[45] [$RuCl_2$(*p*-cymene)]$_2$/$PR_3$,[46] and Os, Ir, and Ni complexes catalyze the Claisen–Tishchenko reaction.[47] Aldehydes that display reactive α-hydrogen atoms can easily undergo aldol condensation in basic media.[48] Notably, during the TH of aldehydes in 2-propanol, conjugated mono- and dienones can also be produced by cross-coupling reactions between the aldehyde and the formed acetone (vide infra; Scheme 2). Furthermore, aldehydes can also undergo decarbonylation with Ru[49] and Os[43a] complexes to afford metal carbonyl derivatives, and this reaction is considered as a deactivation pathway for Ir and Ru catalysts to result in a low S/C ratio.[19h,i,50] A strategy to achieve both high productivity and chemoselectivity in aldehyde reduction entails



Scheme 2. Base-mediated aldehyde reactions.

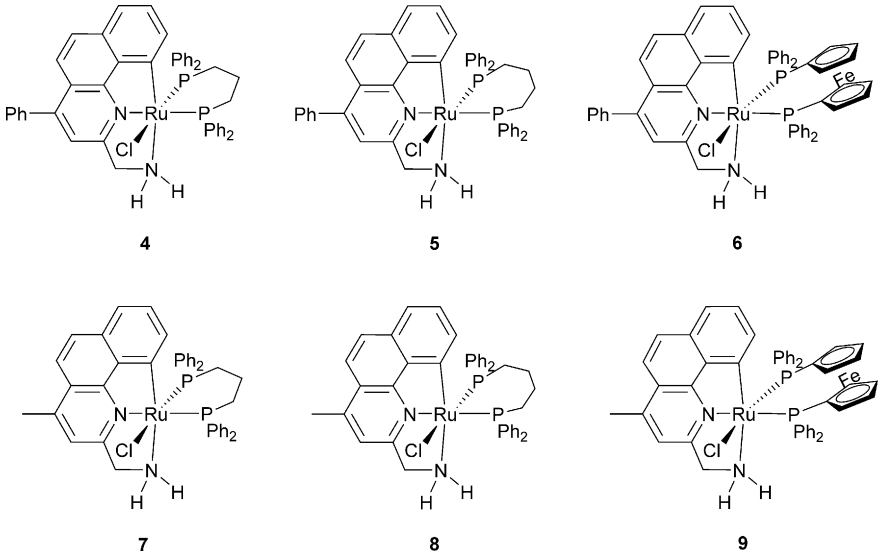


Figure 2. 4-Functionalized 2-aminomethyl-benzo[*h*]quinoline ruthenium complexes [RuCl(CNN^R)(PP)] **4**–**9**.

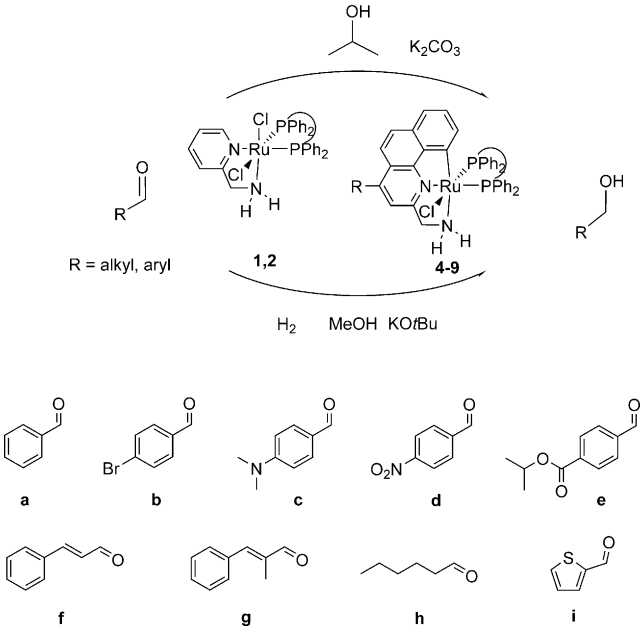
the use of both fast and robust catalysts that work in weakly basic media. In addition, the development of catalysts that can work with a S/C ratio higher than 1000 to meet industrial requirements and can be employed with commercial-grade substrates and solvents is highly desirable for applications. Recently, we described that the easily accessible pincer complexes [RuCl(CNN^R)(PP)] (**4**–**9**) based on 4-functionalized 2-aminomethyl-benzo[*h*]quinoline ligands (HCNN^R) prepared by a scalable synthesis are highly productive catalysts for both the TH and HY of ketones (Figure 2).[51a]

We report here the use of the ampy and CNN^R pincer Ru complexes in the TH and HY of aldehydes of commercial-grade purity at S/C = 2000–100 000. A comparison of the activity of the ampy and pincer complexes and the effect of the reaction parameters are also provided.

Results and Discussion

Catalytic TH of aldehydes catalyzed by 1 and 2

The commercially available ampy complexes **1** and **2** were used in the TH of several aldehydes of commercial-grade purity (Scheme 3).



Scheme 3. Transfer hydrogenation of aldehydes catalyzed by **1** and **2** and **4**–**9**.

If benzaldehyde **a** (assay 99%) was heated to reflux in 2-propanol with **1** (S/C = 2000) and the weak base K_2CO_3 (5 mol%), 98% conversion was achieved in 1.75 h, which afforded 92% of benzyl alcohol (Table 1, entry 1). Complex **2** (S/C = 2000), which bears dppf in place of dppb, afforded 85% conversion of **a** with 74% of benzyl alcohol in 4 h, whereas with S/C = 5000, only 49% of the alcohol is obtained (entries 3 and 4). Notably, with the use of freshly distilled **a**, complex **1** (S/C = 2000) with K_2CO_3 (5 mol%) gives 94% of benzyl alcohol in 1 h (entry 5), whereas complex **2** (S/C = 20 000) in the presence of NaO*i*Pr (2 mol%) gives 95% conversion in 2 h.[12] Complex **1** (S/C = 2000) catalyzes the selective reduction of 4-bromobenzaldehyde **b** (assay 99%) to 4-bromobenzyl alcohol (> 97%) in 30 min (entry 6).

If the reaction was performed at S/**1** = 5000, almost full conversion was achieved in 1.5 h (92%) but with the formation of 70% of alcohol (entry 7), which indicates that at longer reaction time generally results in a decrease of selectivity. NMR spectroscopy of the product distribution revealed the formation of (*E*)-4-(4-bromophenyl)but-3-en-2-one and (1*E*,4*E*)-1,5-bis(4-bromophenyl)penta-1,4-dien-3-one in an approximately 1:2 molar ratio as the outcome of the condensation between **b** and acetone formed during the TH (Scheme 4, see Supporting Information).

Table 1. TH of aldehydes (0.1 M) catalyzed by **1** and **2** with K_2CO_3 (5 mol%) in 2-propanol at 82 °C.

Entry	Substrate	Complex	Loading (S/C)	*t* [h]	Conv[a] [%]	Alcohol[a] [%]	Byproducts[a] [%]
1	**a**	**1**	2000	1.75	98	92	6
2	**a**	**1**	5000	5	43	39	4
3	**a**	**2**	2000	4	85	74	11
4	**a**	**2**	5000	5	59	49	10
5[b]	**a**	**1**	2000	1	95	>94	<1
6	**b**	**1**	2000	0.5	98	>97	<1
7	**b**	**1**	5000	1.5	92	70	22
8	**b**	**2**	2000	2.5	92	62	30
9	**c**	**1**	2000	0.5	98	>97	<1
10	**c**	**1**	5000	1	99	>98	<1
11	**c**	**1**	10000	4.5	95	89	6
12	**c**	**2**	2000	0.5	99	98	1
13	**c**	**2**	5000	4	52	49	3
14	**e**	**1**	2000	2	36	21	15
15	**e**	**2**	2000	2	42	28	14
16	**f**	**1**	2000	3	78	>77	<1
17	**f**	**1**	5000	3	11	>10	<1
18	**f**	**2**	2000	0.5	98	>97	<1
19	**f**	**2**	5000	4	52	50	2
20[c]	**f**	**2**	2000	0.5	95	>94	<1
21	**g**	**1**	2000	3.5	60	42	18
22	**g**	**2**	2000	3	98	93	5
23	**h**	**1**	2000	4	89	66	23
24	**h**	**2**	2000	4	95	29	66
25	**i**	**1**	2000	3	>99	70	30
26	**i**	**2**	2000	3	94	70	24

[a] The conversion and the amount of byproducts were determined by using GC analysis or ^{1}H NMR spectroscopy. [b] Substrate was distilled. [c] Substrate and 2-propanol were distilled and NaO*i*Pr (2 mol%) was used as base (see Ref. [12]).

Complex **2** was less active and selective than **1** for **b** and led to 62% of alcohol (entry 8). The substrate 4-(dimethylamino)-benzaldehyde **c** (assay 99%) is reduced efficiently with **1** at S/C = 5000 and 10000 to afford 99 and 89% of 4-(dimethylamino)benzyl alcohol in 1 and 4.5 h, respectively (entries 10 and 11). With **2** (S/C = 2000) 98% of alcohol was attained in 0.5 h, whereas at S/C = 5000 incomplete conversion was achieved (entries 12 and 13). The TH of *iso*-propyl 4-formylbenzoate **e** with **1** and **2** (S/C = 2000) attained a moderate conversion (36 and 42%, entries 14 and 15) with the formation of the aldol condensation dienone product with acetone (Scheme 4, see Supporting Information), which indicates that the presence of the carboxylate function inhibits the catalytic activity of **1**. Complexes **1** and **2** catalyze the chemoselective reduction of conjugated aldehydes. With **1** (S/C = 2000), *trans*-cinnamaldehyde **f** (assay 98%) was converted to the corresponding allylic alcohol (77%) in 3 h, whereas **2** gave 97% in 0.5 h without reduction at the C=C bond (entries 16 and 18). This result is similar to that obtained if we used freshly distilled **f** with **2** in the presence of NaO*i*Pr (entry 20).[12] At a lower loading of **1** and **2** (S/C = 5000), incomplete conversion was observed (entries 17 and 19). The TH of α-methylcinnamaldehyde **g** (assay 97%, predominantly the *E* isomer) with **1** gave 60% conversion with 42% of α-methylcinnamol, whereas the chemoselective formation of alcohol (93%) was attained with **2** (entries 21 and 22). Hexanal **h** (assay 98%) with **1** and **2** led to 1-hexanol (66 and 29%) with the formation of aldol condensation byproducts (entries 23 and 24). The TH of the heteroaromatic thiophene-2-carbaldehyde **i** (assay 98%) with **1** and **2** gave quantitative conversions in 3 h to afford 70% of 2-thienylmethanol with the formation of enone and dienone side products in an approximately 2:1 molar ratio (entries 25 and 26, see Supporting Information).

These results indicate that the commercially available ampy complexes **1** and **2** can be employed in the TH of commercial-grade aromatic and conjugated aldehydes at S/C = 2000–10000. For aromatic aldehydes, chemoselective TH was achieved using the dppb-containing complex **1**. Conversely, conjugated aldehydes can be converted selectively to allylic alcohols with the less basic dppf derivative **2**.

Catalytic TH of aldehydes catalyzed by 4–9

The easily accessible pincer complexes **4**–**9** obtained from 4-functionalized 2-aminomethyl-benzo[*h*]quinoline ligands[47a] have been studied in the TH of aldehydes of commercial-grade purity in basic 2-propanol. Benzaldehyde **a** (assay 99%) was reduced quantitatively and selectively to benzyl alcohol (98-99%) with complexes **4**–**9** (S/C = 2000) in the presence of K_2CO_3 (5 mol%) within 1.25–6.5 h, the dppf-containing catalysts **6** and **9** being more active than the dppp and dppb derivatives (Table 2, entries 1–6).

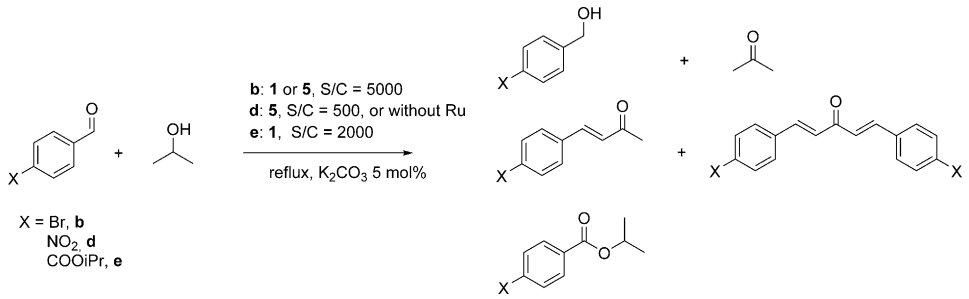
Notably, under the same conditions but using distilled **a**, the pincer **5** (S/C = 2000) affords 97% of alcohol in 35 min, whereas quantitative conversion is achieved in 30 s with **3**.[26] The bromo aldehyde **b** was converted quantitatively with **4**–**6**, **8**,

Table 2. TH of aromatic aldehydes (0.1 M) catalyzed by **4**–**9** with K_2CO_3 (5 mol%) in 2-propanol at 82 °C.

Entry	Substrate	Complex	Loading (S/C)	*t* [h]	Conv.[a] [%]	Alcohol[a] [%]	Byproducts[a] [%]
1	**a**	**4**	2000	2	100	99	1
2	**a**[b]	**5**	2000	1.5	100	>99	<1
3	**a**	**6**	2000	1.25	99	98	1
4	**a**	**7**	2000	5	99	98	1
5	**a**	**8**	2000	5	99	98	1
6	**a**	**9**	2000	1.25	99	98	1
7	**b**	**4**	2000	0.5	98	78	20
8	**b**	**5**	2000	2	100	82	18
9	**b**	**5**	5000	3	66	36	19
10	**b**	**6**	2000	0.5	98	>97	<1
11	**b**	**7**	2000	3	67	44	23
12	**b**	**8**	2000	1	100	81	19
13	**b**	**9**	2000	0.5	>99	>98	<1
14	**c**	**4**	5000	1.5	95	>94	<1
15	**c**	**4**	10000	3	98	>97	<1
16	**c**	**5**	2000	0.5	98	>97	<1
17	**c**	**5**	5000	0.5	98	>97	<1
18	**c**	**5**	10000	1.5	97	>96	<1
19	**c**	**5**	20000	3	98	>97	<1
20	**c**	**5**	40000	7	>99	>99	<1
21	**c**	**5**	100000	20	>99	>99	<1
22	**c**	**6**	5000	1.5	92	>91	<1
23	**c**	**6**	10000	3	98	>97	<1
24	**c**	**7**	2000	2	98	>97	<1
25	**c**	**8**	2000	2	99	>98	<1
26	**c**	**9**	2000	2	98	>97	<1
27	**c**	–	–	10	–	–	–
28	**d**	**5**	2000	2	41	36	5
29	**d**	**5**	500	2	80	65	15[c]
30	**d**	–	–	2	31	17	14
31	**e**	**4**	2000	5	52	>51	<1
32	**e**	**5**	2000	5	75	>74	<1
33	**e**	**6**	2000	0.75	95	>94	<1
34	**e**	**7**	2000	6	33	>32	<1
35	**e**	**8**	2000	5	53	>52	<1
36	**e**	**9**	2000	1	96	>95	<1

[a] The conversion and the amount of byproducts were determined by using GC analysis or ^{1}H NMR spectroscopy. [b] By using distilled **a**, 97% of benzyl alcohol is formed in 35 min. [c] (1*E*,4*E*)-1,5-Bis(4-nitrophenyl)penta-1,4-dien-3-one and *iso*-propyl 4-nitrobenzoate in 2:3 ratio.

and **9** (S/C = 2000) in a shorter time than that required for **a**. A high selectivity was achieved with the dppf-containing complexes **6** and **9** to lead to 98–99% of 4-bromobenzyl alcohol (entries 10 and 13), whereas the dppp-bearing complexes **4** and **7** and dppb-containing **5** and **8** gave 44–82% of alcohol. The NMR spectra of the isolated products of the TH of **b** with **5** (S/C = 5000, entry 9) after 3 h showed the formation of 4-bromobenzyl alcohol (36%) and (1*E*,4*E*)-1,5-bis(4-bromophenyl)-penta-1,4-dien-3-one (18%) in a 2:1 molar ratio with a small amount of *iso*-propyl 4-bromobenzoate (1%; Scheme 4, see Supporting Information). The *iso*-propyl benzoate is likely produced from **b** by a cross-Claisen–Tischenko or Claisen–Tischenko reaction followed by transesterification. These results indicate that with a high S/C (≥5000) and longer reaction time, C–C coupling reactions compete significantly with TH to result in a low selectivity. Initial attempts to inhibit the aldol condensation by the fractional distillation of acetone (b.p. = 56 °C) failed.[52] The effect of substrate concentration has also been investigated. As aldehydes show a higher reduction potential than ketones,[33] a higher substrate concentration could be employed in TH, which is a significant advantage for industrial applications. However, by increasing the concentration of **b** from 0.1 to 1 M (**b**/**5** = 10000, 5 mol% K_2CO_3) the conversion decreased from 69 to 33% (16 h) with the formation of 37, 27, and 22% of alcohol at 0.1, 0.2, and 1 M, respectively. Complexes **4**–**9** efficiently catalyzed the chemoselective TH of 4-(dimethylamino)benzaldehyde **c** (0.1 M) to alcohol. With **4** at S/C = 5000 and 10000, 4-(dimethylamino)benzyl alcohol was attained in 94 and 97% (1.5 and 3 h, respectively; entries 14 and 15), whereas 99% conversion was achieved at a remarkably high S/C = 100000 in 20 h with **5** with no erosion of the selectivity (entries 16–21). Without a Ru catalyst and in the presence of K_2CO_3, no reduction occurred (entry 27). The strong electron-donating properties of the dimethylamino group of **c** lead to a low electrophilic formyl functionality, which hinders the C–C coupling reactions. However, the TH of *p*-nitrobenzaldehyde **d** with **5** (S/C = 2000) affords a poor conversion (41% in 2 h) with 36% of alcohol (entry 28). The analysis of the prod-



Scheme 4. Transfer hydrogenation of **b**, **d**, and **e** in 2-propanol.

ucts at S/**5** = 500 revealed the formation of 4-nitrobenzyl alcohol **A** (65%), (1*E*,4*E*)-1,5-bis(4-nitrophenyl)penta-1,4-dien-3-one **B** (2%), and *iso*-propyl 4-nitrobenzoate **C** (13%; Scheme 4, entry 29). Without **5** and in the presence of K_2CO_3 (5 mol%), **d** undergoes 31% conversion in 2 h to form **A**/**B**/**C** in an approximately 6:2:3 molar ratio (entry 30, see Supporting Information). Thus, the Ru-catalyzed TH of **d**, which has a highly electrophilic formyl group, leads to the alcohol through both ruthenium hydride and potassium alkoxide species[53] and the products of the aldol condensation and Claisen–Tischenko reactions. By contrast to the ampy complexes **1** and **2**, the pincer complexes **4**–**9** (S/C = 2000) promote the selective reduction of *iso*-propyl 4-formylbenzoate **e** to alcohol (up to 95%). With the dppf derivatives **6** and **9**, the corresponding hydroxymethyl benzoate is obtained in 94 and 95% (entries 33 and 36), whereas the dppp and dppb catalysts gave a lower conversion. *trans*-Cinnamaldehyde **f** has been reduced to *trans*-3-phenyl-2-propen-1-ol with **4**–**9** (S/C = 5000–10000) with conversions in the range of 52–98% in 0.5–6.5 h (Table 3, entries 1–12). Complex **5** at S/C = 10000 gave 84% of the allylic alcohol in the presence of a small amount of 3-phenylpropan-1-ol (4%, entry 4). As the pincer catalysts **4**–**9** show a high activity for C=O but not C=C bond reduction, it is likely that the saturated alcohol is formed through an isomerization of the allylic alcohol to the saturated aldehyde.[12] Notably, with **1** and **2** the TH of **f** gave allylic alcohol with nearly no byproducts (Table 1, entries 16–19).

Table 3. TH of conjugated and aliphatic aldehydes (0.1 M) catalyzed by **4**–**9** with K_2CO_3 (5 mol%) in 2-propanol at 82 °C.

Entry	Substrate	Complex	Loading (S/C)	*t* [h]	Conv.[a] [%]	Alcohol[a] [%]	Byproducts[a] [%]
1	**f**	**4**	5000	1	99	89	10 (10)[b]
2	**f**	**4**	10000	6.5	68	59	9 (1)[b]
3	**f**	**5**	5000	1	99	90	9 (7)[b]
4	**f**	**5**	10000	6.5	98	84	14 (4)[b]
5	**f**	**6**	5000	0.5	96	77	19 (19)[b]
6	**f**	**6**	10000	4	98	80	18 (3)[b]
7	**f**	**7**	5000	4	93	73	20 (3)[b]
8	**f**	**7**	10000	4	96	77	19 (4)[b]
9	**f**	**8**	5000	4	93	73	20 (3)[b]
10	**f**	**8**	10000	4	96	77	19 (4)[b]
11	**f**	**9**	5000	1	98	84	14 (5)[b]
12	**f**	**9**	10000	4	57	44	13 (2)[b]
13	**g**	**4**	5000	0.25	95	>95	<1
14	**g**	**4**	10000	2.75	92	>91	<1
15	**g**	**5**	5000	0.25	92	>91	<1
16	**g**	**5**	10000	1.75	96	>95	<1
17	**g**	**6**	5000	0.25	97	>96	<1
18	**g**	**6**	10000	0.5	97	>96	<1
19	**g**	**6**	20000	2.75	96	>95	<1
20	**h**	**4**	2000	0.25	>99	>99	<1
21	**h**	**4**	5000	0.67	>99	>99	<1
22	**h**	**5**	2000	0.1	>99	>99	<1
23	**h**	**5**	5000	0.33	>99	>99	<1
24	**h**	**5**	10000	0.8	>99	>99	<1
25	**h**	**5**	20000	3	94	54	40
26	**h**	**6**	2000	0.15	>99	>99	<1
27	**h**	**6**	5000	0.33	>99	>99	<1
28	**h**	**6**	10000	1	>99	>99	<1

[a] The conversion and the amount of byproducts were determined by using GC analysis or ^{1}H NMR spectroscopy. [b] Percentage of the saturated alcohol 3-phenylpropan-1-ol in brackets.

α-Methylcinnamaldehyde **g** was reduced rapidly to α-methylcinnamol (92–97%) with **4**–**6** (S/C = 5000–20000) in a shorter time (0.25–2.75 h) than **f** without the hydrogenation of the C=C bond (Table 3, entries 13–19). The aliphatic aldehyde **h** was reduced rapidly and selectively to 1-hexanol (> 99%) by **4**–**6** (S/C = 2000–10000) in 6 min to 1 h (entries 20–24 and 26–28). At higher S/**5** = 20000, 94% conversion is achieved in 3 h, but with a lower selectivity because of the formation of condensation products (entry 25, see Supporting Information).

These results indicate that for aromatic and aliphatic aldehydes, the pincer complexes **4**–**9** are superior to the ampy complexes **1** and **2** and can afford a high selectivity at a high S/C ratio (2000–100000) and in a shorter time. The pincer complexes **6** and **9** that bear dppf gave generally better results compared to the catalysts with the more basic dppp and dppb phosphanes. The presence of the orthometallated CNN terdentate ligand makes these complexes[47] thermally more stable and catalytically more productive compared to the related ampy catalysts. With regard to α,β-unsaturated aldehydes, a high selectivity toward the formation of the allylic alcohol was achieved with **2**. Aldol condensation with acetone and Claisen–Tischenko side reactions were observed mainly for aromatic aldehydes with electron-withdrawing groups, whereas those with electron-donating groups gave chemoselective TH to alcohols.

Catalytic HY of aldehydes catalyzed by 1 and 2 and 4–6

The Ru derivatives **1** and **2** and **4**–**6** in the presence of KO*t*Bu were active in the hydrogenation (5–20 atm of H_2) of aromatic, conjugated, and aliphatic aldehydes of commercial-grade purity (98–99%) using methanol as the solvent and with S/C up to 40000 (Scheme 3). Complex **2** (S/C = 2000) catalyzed the quantitative HY of benzaldehyde **a** (2 M) into benzyl alcohol (98%) in 16 h at 50 °C in the presence of 2 mol% of KO*t*Bu (Table 4, entry 3), whereas **1** shows poor activity (entries 1 and 2). Notably, with distilled **a**, complex **2** (S/C = 5000) afforded benzyl alcohol in 10 min.[12] The pincer complexes **4**–**6** were more active than **1** and **2** and led to quantitative conversion at a higher S/C ratio. The HY of **a** with **4** (S/C = 10000 and 20000) gave the selective reduction to benzyl alcohol (97 and 99%) in 8 h (entries 4 and 5). In a gram-scale reaction, 5 g of **a** (3.3 M) was converted to alcohol (92%, 20 h) by using a Parr autoclave (20 atm of H_2) at S/**4** = 25000 (entry 6). With complex **5** (S/C = 20000), 98% of alcohol is obtained in 16 h (entry 8), whereas less basic **6** was less active than **4** and **5** and afforded 60% of alcohol (entry 9). Interestingly, with complex **4** and under 5 atm of H_2, the electron-rich aldehyde **c** is reduced quantitatively and chemoselectively to 4-(dimethylamino)benzyl alcohol (> 97%) at high S/C = 10000–40000 in 1–22 h (entries 10–12).

Cinnamaldehyde **f** was hydrogenated with **1** and **2** (S/C = 1000 and 2000) to cinnamol (87 and 89%, respectively) in 3 and 8 h (entries 13 and 14). Conversely, complexes **4** and **5** gave 89 and 90% of alcohol at a higher S/C (10000; entries 15 and 17). For substrate **a**, less basic **6** was less active than **4** and **5** and led to poor selectivity in the reduction of **f** (entry 18). Complex **4** catalyzes the highly chemoselective HY of α-methylcinnamaldehyde **g** (S/C = 15000) to attain the unsaturated alcohol (> 99%) in 24 h (entry 19). With **4**, hexanal **h** (S/C = 5000) is reduced rapidly to 1-hexanol with good selectivity (90%, entry 20) in 1.5 h. In addition, thiophene-2-carbaldehyde **i** (1 M)

Table 4. HY aldehydes (2 M) catalyzed by **1** and **2** and **4**–**6** with KO*t*Bu (2 mol%) in methanol at 50 °C (Biotage® Endeavor).

Entry	Substrate	Complex	Loading (S/C)	P_{H_2} [atm]	*t* [h]	Conv.[a] [%]	Alcohol[a] [%]	Byproducts[a] [%]
1	**a**	**1**	1000	10	3	35	33	2
2	**a**	**1**	2000	10	8	22	7	15
3	**a**	**2**	2000	10	16	100	98	2
4	**a**	**4**	10000	10	8	100	97	3
5	**a**	**4**	20000	10	8	100	99	1
6	**a**[b]	**4**	25000	20	20	92	92	0
7	**a**	**5**	10000	10	16	98	98	2
8	**a**	**5**	20000	10	16	99	98	1
9	**a**	**6**	10000	13	16	63	60	3
10	**c**[c,d]	**4**	10000	5	1	100	> 99	< 1
11	**c**[c,d]	**4**	20000	5	7	98	> 97	< 1
12	**c**[c,d]	**4**	40000	5	22	98	> 97	< 1
13	**f**	**1**	1000	10	3	95	87	8
14	**f**	**2**	2000	10	8	98	89	9
15	**f**	**4**	10000	10	8	99	89	10
16	**f**	**4**	20000	10	8	96	75	21
17	**f**	**5**	10000	10	8	99	90	11
18	**f**	**6**	10000	10	8	80	20	60
19	**g**[c]	**4**	15000	5	24	100	> 99	< 1
20	**h**[c,d]	**4**	5000	5	1.5	99	90	9
21	**i**[c,d]	**4**	10000	5	1	100	99	1
22	**i**[c]	**4**	5000	5	0.66	100	95	5

[a] Conversion and product distribution were determined by using GC analysis or ^{1}H NMR spectroscopy. [b] [S] = 3.3 M, 5 g scale reaction in a Parr autoclave. [c] Parr autoclave. [d] [S] = 1 M.

is transformed selectively to 2-thienylmethanol (99%) with S/**4** = 10000 (1 h), whereas at a higher substrate concentration (2 M) 95% of alcohol was formed (entries 21 and 22). The influence of the solvent in the HY of **a** was investigated for **4**–**6**. With **4** (S/C = 10000) under 13 atm of H_2 in MeOH, **a** is converted to alcohol (96%) in 16 h at 50 °C with 2 mol% of KO*t*Bu (Table 5, entry 1).

Table 5. Effect of the solvent in the HY of **a** (2 M) catalyzed by **4**–**6** (S/C = 10000) with 2 mol% of KO*t*Bu under 13 atm of H_2 in 16 h at 50 °C (Biotage® Endeavor).

Entry	Complex	Solvent	Conv.[a] [%]	Alcohol [a] [%]	Byproducts[a] [%]
1	**4**	MeOH	100	96	4
2	**4**	MeOH/EtOH = 3:1	100	93	7
3	**4**	MeOH/EtOH = 1:1	100	88	12
4	**4**	MeOH/EtOH = 1:3	100	86	11
5	**4**	EtOH	79	58	21
6	**4**	toluene[b]	11	10	1
7	**5**	MeOH	100	98	2
8	**5**	MeOH/EtOH = 3:1	100	97	3
9	**5**	MeOH/EtOH = 1:1	100	97	3
10	**5**	MeOH/EtOH = 1:3	90	80	10
11	**5**	EtOH	100	82	18
12	**5**	toluene[b]	6	6	0
13	**6**	MeOH	63	60	3
14	**6**	MeOH/EtOH = 3:1	23	19	4
15	**6**	MeOH/EtOH = 1:1	23	18	5
16	**6**	MeOH/EtOH = 1:3	19	16	3
17	**6**	EtOH	29	18	11

[a] Conversion was determined by using GC analysis or ^{1}H NMR spectroscopy. [b] The reaction was run for 32 h.

If we used MeOH/EtOH mixtures, complete conversion was observed, but with a decrease of selectivity (93–86%, entries 2–4), whereas in EtOH both lower conversion (79%) and selectivity (58% of alcohol) were attained (entry 5). In toluene, **4** displays poor activity with the formation of only 10% of alcohol after 32 h (entry 6). A similar behavior was observed with **5**, for which methanol was the solvent of choice, which led to 98% of alcohol in 16 h (entry 7), and 6% conversion was achieved in toluene (entry 12). Finally, complex **6** was less active and led to 60 and 18% of alcohol in MeOH and EtOH, respectively (entries 13 and 17). These data indicate that in the HY of aldehydes with the pincer complexes[13b] the alcohol medium plays a crucial role, and methanol is the solvent of choice. The use of KO*t*Bu in methanol results in the formation of the weaker base KOMe, which is involved in the formation of the catalytically active ruthenium hydride species from H_2 via a ruthenium-alkoxide-amide species.[13b] The comparison of the activity of the ampy and pincer complexes in HY shows that although the ampy dppf complex **2** is more active than the dppb complex **1**, for the pincer complexes the reverse behavior is observed, and the dppp and dppb complexes **4** and **5** are superior to the dppf derivative **6**.

Conclusions

We have demonstrated that the easily accessible 2-(aminomethyl)pyridine (ampy) complexes *cis*-[$RuCl_2$(ampy)(PP)] [**1** and **2**; PP = 1,4-bis(diphenylphosphino)butane, 1,1′-ferrocenediyl-bis(diphenylphosphine)] and pincer [RuCl(CNN^R)(PP)] [**4**–**9**; PP = 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,1′-ferrocenediyl-bis(diphenylphosphine); $HCNN^R$ = 4-substituted-2-aminomethyl-benzo[*h*]quinoline; R = Me, Ph] are highly active catalysts for the reduction of commercial-grade (97–99%) aromatic, aliphatic, and conjugated aldehydes to their corresponding primary alcohols through both transfer hydrogenation (TH) with 2-propanol and hydrogenation (HY; 5–20 atm of H_2) in MeOH. The pincer catalysts **4**–**9** display a generally higher productivity than **1** and **2** for both TH (substrate to catalyst ratio (S/C) up to 100000) and HY (S/C up to 40000) of aromatic and aliphatic aldehydes. Conversely, the ampy complexes **1** and **2** were more efficient for the chemoselective reduction of unsaturated aldehydes, which thus indicates that the best performance in terms of selectivity and productivity can be achieved by the correct matching of the substrate and catalyst. For both the ampy and pincer complexes the type of diphosphine affects the aldehyde TH and HY reactions strongly. On account of the formation of acetone in the TH, cross aldol-condensation side products may form during the catalysis, which depends on the electrophilic character of the formyl group. The ability of the pincer complexes to catalyze the reduction of undistilled substrates at a high S/C ratio makes them suitable systems for applications in the reduction of industrially relevant aldehydes. Further studies are currently in progress to extend the use of ampy and pincer Ru catalysts in other organic transformations.

Experimental Section

General: All reactions were performed under an Ar atmosphere using standard Schlenk techniques. The aldehydes **a** (99%), **f** (98%), **g** (97%), and **h** (98%) were purchased from Alfa Aesar; **b** (99%) and **d** (98%) were from Aldrich; and **c** (99%) was from Merck and used without further purification, whereas **e** was prepared from 4-formylbenzoic acid.[54] Methanol (100%), ethanol (99.7%), and toluene (99%) were from VWR, whereas 2-propanol (99.7%) was from Alfa Aesar and used as received. All other chemicals were from Aldrich and Alfa Aesar. Complexes **1** and **2** were obtained from Alfa Aesar, whereas **4**–**9** were prepared according to a procedure reported previously.[51a] NMR spectra were recorded by using a Bruker AC 200, and the chemical shifts [ppm] are relative to TMS for ^{1}H and ^{13}C{^{1}H} NMR spectra. GC analyses were performed by using a Varian GP-3380 gas chromatograph with a MEGADEX-ETTBDMS-β column of 25 m of length, internal diameter 0.25 mm, column pressure 5 psi, H_2 as carrier gas, and a flame ionization detector (FID). The injector and detector temperature was 250 °C. Program used: initial T = 150 °C ramped to 190 °C at 3 °C min^{-1} and then to 220 °C at 20 °C min^{-1}. The hydrogenation experiments were performed by using a Biotage® Endeavor and a Parr autoclave.

Procedure for the TH of aldehydes: The selected aldehyde (1 mmol), K_2CO_3 (6.9 mg; 0.05 mmol), and 2-propanol (8 mL) were introduced into a Schlenk, subjected to three vacuum–Ar cycles,

and the system was put in an oil bath at 90 °C. From a 250 μM solution of the Ru complex in 2-propanol, 2 mL (0.5 μmol of Ru) was added to the mixture heated to reflux to reach a final volume of 10 mL. The reaction was sampled by the removal of an aliquot of the reaction mixture, the addition of diethyl ether (1:1 in volume), and filtration through a short silica pad before the conversion was determined by GC analysis. For solid and high-boiling compounds, the solvent was evaporated by gentle heating under vacuum, and the crude mixture was dissolved in $CDCl_3$ and analyzed by ^1H NMR spectroscopy; S/C = 2000, K_2CO_3 5 mol%.

Procedure for the HY of aldehydes: In a 10 mL glass tube, the selected Ru catalyst (0.001 mmol) and aldehyde (10 mmol) were dissolved in MeOH (4 mL) and 0.2 mL of a 1.0 M solution of KO*t*Bu (0.2 mmol) in *tert*-butanol was added. The tube was put in an Endeavour apparatus, the system was filled and vented under stirring four times with N_2, then four times with H_2 (without stirring), and finally charged to the desired H_2 pressure. The system was kept at 50 °C for the appropriate time, and the reaction was sampled by the removal of an aliquot of the reaction mixture (approximately 0.5 mL), followed by the addition of diethyl ether (2.5 mL). After filtration through a short silica pad, the conversion was determined by GC analysis; S/C = 10000, KO*t*Bu 2 mol%, aldehyde 2 M.

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Keywords: alcohols · aldehydes · hydrogen transfer · hydrogenation · ruthenium

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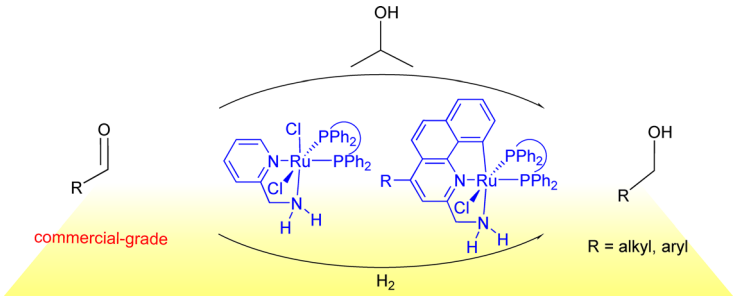

Transfer Hydrogenation and Hydrogenation: Ruthenium 2-(aminomethyl)pyridine and benzo[*h*]quinoline pincer complexes efficiently catalyze the reduction of commercial-grade aldehydes to alcohols by transfer hydrogenation with 2-propanol and hydrogenation with H_2 at substrate/catalyst ratios up to 100 000.

*S. Baldino, S. Facchetti, A. Zanotti-Gerosa, H. G. Nedden, W. Baratta**

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Transfer Hydrogenation and Hydrogenation of Commercial-Grade Aldehydes to Primary Alcohols Catalyzed by 2-(Aminomethyl)pyridine and Pincer Benzo[*h*]quinoline Ruthenium Complexes