



Room-temperature Ru(II)-catalyzed transfer hydrogenation of ketones and aldehydes in air

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ABSTRACT

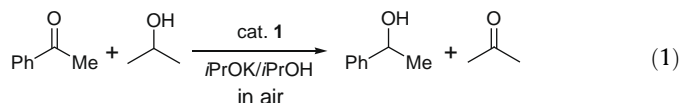
Transfer hydrogenation (TH) of ketones and aldehydes was efficiently carried out in 2-propanol at room temperature by means of a ruthenium(II) complex catalyst bearing a 2-(benzimidazol-2-yl)-6-(pyrazol-1-yl)pyridine ligand. TH of the ketone substrates proceeded in air, reaching final TOFs of up to 59,400 h⁻¹, and the reduction of aldehydes proceeded under a nitrogen atmosphere to achieve final TOFs of up to 5940 h⁻¹.

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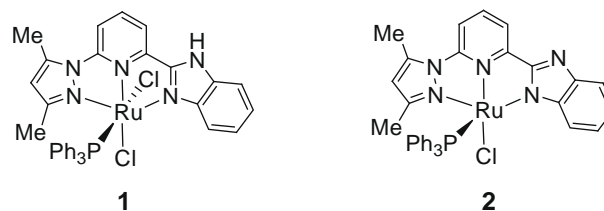
Transfer hydrogenation (TH) is a potentially useful protocol for the reduction of ketones and aldehydes to their corresponding alcohols and TH of ketones has been extensively studied.¹ Ruthenium(II) complexes are usually applied as the most useful catalysts for transfer hydrogenation of ketones. Ruthenium(II) complexes containing monotosylated 1,2-diamines or aminoalcohols can offer high catalytic activity and selectivity due to the presence of a N–H functionality (bifunctional catalysis).² A great variety of related ligands and transition metal complex catalysts have been developed for this purpose.³ Although aldehydes seem to be more easily reduced to their corresponding alcohols by transfer hydrogenation with 2-propanol, reduction of aldehydes to primary alcohols with controlled chemoselectivity of the products is considered rather difficult because catalytic TH of aldehydes usually leads to side reactions which occur under basic conditions.⁴ Thus, catalytic TH of aldehydes has been occasionally studied.⁵ Transition metal complex-catalyzed TH of ketones is usually carried out in refluxing 2-propanol under an inert atmosphere (N₂ or Ar) in order to keep the catalysts active during the reaction and to reach a high conversion for the ketone substrates.¹ For asymmetric TH of ketones, the reactions may be carried out in 2-propanol,⁶ HCO₂H–Et₃N,⁷ or water (usually an aqueous solution of HCO₂Na)⁸ at room temperature to obtain relatively satisfactory enantioselectivity for the chiral alcohol products with very low reaction rates. In the view of the practical application, room-temperature catalytic TH of carbonyl compounds in air is strongly desired for the production of alcohols in organic syntheses and industries. Unfortunately, only a few examples of TH of ketones in air at elevated temperatures have been documented.⁹

In order to realize TH of carbonyl compounds under mild conditions such as at room temperature and/or in air, highly active tran-

sition metal complex catalysts should be employed for the catalytic reactions. Recently, we reported a new class of highly active robust ruthenium(II) NNN complexes bearing a hemilabile unsymmetrical pyridyl-based pyrazolyl–imidazolyl ligand which can potentially provide a dynamic ‘on and off’ chelating effect for the metal center during catalysis,¹⁰ and found that both complexes **1**^{10d} and **2**^{10f} can exhibit the same exceptionally high catalytic activity in TH of ketones in refluxing 2-propanol under nitrogen atmosphere, reaching 100% conversion for the ketone substrates and final TOFs of up to 7.2 × 10⁵ h⁻¹ with 0.05 mol % catalyst, and **2** showed a final TOF value of 55,800 h⁻¹ in room-temperature TH of ketones in nitrogen with 0.1 mol % loading. Herein, we report the exploration of the catalytic behaviors of complex **1** in TH of ketones and aldehydes in air at room temperature (Scheme 1).



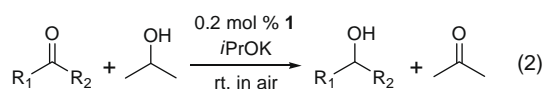
In our initial studies, TH of acetophenone was chosen as the model reaction to screen the reaction conditions (Eq. 1). With 0.05 mol % **1** as the catalyst in a 0.1 M solution of acetophenone in 2-propanol,



Scheme 1. Complexes **1** and **2**.

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Table 1Transfer hydrogenation of ketones catalyzed by complex **1** at room temperature in air^{a,14}

Entry	Ketone	Time (min)	Yield ^b (%)	Final TOF (h ⁻¹)
1		1 (0.5) ^c	95 (98)	28,500 (235,200)
2		0.5 ^d	98	39,200
3		0.5 (0.5) ^c	>99 (97)	59,400 (232,800)
4		0.5	>99	59,400
5		1	93	27,900
6		1 (0.5) ^c	91 (97)	27,300 (232,800)
7		1	89 ^e	26,700
8		0.5	98	58,800
9		0.5	98	58,800
10		0.5 (0.5) ^c	93 (96)	55,800 (230,400)
11		1	83	24,900
12		0.5	98	58,800
13		0.5	98	58,800
14		0.5	92	55,200
15		1	97 ^e	29,100

Table 1 (continued)

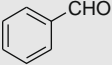
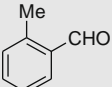
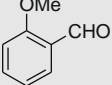
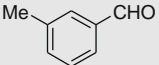
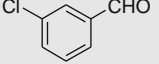
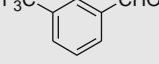
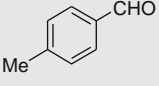
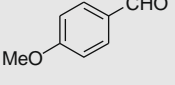
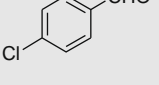
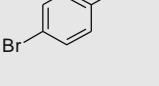
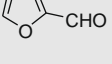
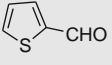
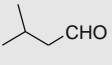
Entry	Ketone	Time (min)	Yield ^b (%)	Final TOF (h ⁻¹)
16		0.5	>99	59,400
17		0.5	98	58,800
18		1 (0.5) ^d	73 (91)	21,900 (36,400)

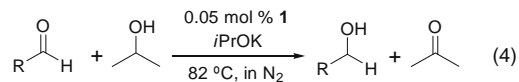
^a Reaction conditions: ketone, 2.0 mmol (0.1 M in 20 mL *i*PrOH); 0.2 mol % **1**, ketone/*i*PrOK/cat. **1** = 500:20:1; 28 °C, in air.^b By GC analysis.^c 0.05 mol % **1**, 82 °C.^d 0.3 mol % **1**.^e By ¹H NMR determination.

the TH reaction in air reached 35% and 49% conversions for the ketone substrate within 10 min at room temperature (28 °C) and 40 °C, respectively, and then the reaction halted. On increasing the catalyst loading to 0.1 mol %, the reaction proceeded faster to form 1-phenylethanol in 73% and 91% yields at room temperature within 10 min and at 40 °C over a period of 2 min, respectively, and then the reaction became very slow. However, in refluxing 2-propanol and with a lower catalyst loading (0.05 mol % **1**) the same reaction approached completion in air within 0.5 min, and under nitrogen atmosphere acetophenone can be reduced to 1-phenylethanol within 10 s.^{10d} These results have demonstrated the possible deactivation¹¹ of complex **1** in air and the unpreferable generation of the catalytically active species at room temperature under the TH conditions, suggesting that higher catalyst loading should be used to promote the TH of ketones at room temperature in air. When 0.2 mol % **1** was applied in the reaction at room temperature in air, 95% conversion was obtained for acetophenone within 1 min, revealing that considerable amount of the complex catalyst should be present during the catalysis. It should be noted that 1-phenylethanol is the only product obtained from TH of acetophenone at room temperature in air, and the most suitable molar ratio of *i*PrOK base to Ru is 20:1.

Thus, 0.2 mol % **1** was used as the catalyst for TH of a variety of ketones at room temperature in air (Eq. 2 and Table 1). Acetophenone was converted to 1-phenylethanol in 95% yield within 1 min (entry 1). The TH of propiophenone was much slower under the same conditions, affording the alcohol product in 80% yield within 1 min and in 88% yield over a period of 10 min, while 98% conversion was achieved for the ketone substrate by using 0.3 mol % catalyst within 30 s (entry 2). In most cases, TH of ketones reached 95–99% conversion for the ketone substrates (Table 1) with final TOFs of up to 59,400 h⁻¹ (entries 3, 4, and 16). To date, the known transition metal catalysts for TH and/or hydrogenation of ketones near room temperature have only shown the highest TOFs in the range of 100–4000 h⁻¹.¹² Cyclic ketones cyclohexanone and cyclopentanone were also efficiently reduced to the corresponding alcohols within 30 s (entries 16 and 17). However, aliphatic ketone 2-heptanone could not be efficiently reduced under the same conditions or even with a higher catalyst loading such as 0.3 mol % **1** (entry 17). It is noteworthy that the ketones could be more efficiently reduced to alcohols in air with a lower catalyst loading such as 0.05 mol % **1** in refluxing 2-propanol, achieving final TOFs of up to 235,200 h⁻¹ (entries 1, 3, 6, and 10).

Table 2Transfer hydrogenation of aldehydes catalyzed by complex **1** at room temperature under nitrogen atmosphere^a

Entry	Aldehyde	Time (min)	Yield ^b (%)	Final TOF (h ⁻¹)
1		10	98	2940
2		5	>99	5940
3		5	>99	5940
4		10	97	2910
5		10	39	1170
6		10	45	1350
7		5	98	5880
8		5	96	5760
9		10	49	1470
10		10	32	960
11		10	98	2940
12		30	25	250
13		5 ^c	98	3920

^a Reaction conditions: aldehyde, 2.0 mmol (0.1 M in 20 mL *i*PrOH); 0.2 mol % **1**, aldehyde/*i*PrOK/cat. **1** = 500:20:1; 28 °C, in N₂.^b By GC analysis.^c 0.3 mol % **1**.**Table 3**Transfer hydrogenation of aldehydes catalyzed by complex **1** at 82 °C under nitrogen atmosphere^a

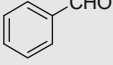
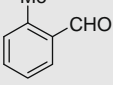
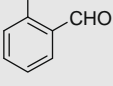
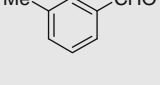
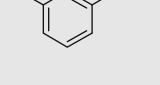
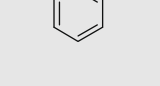
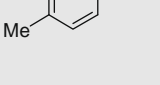
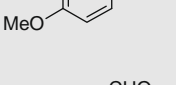
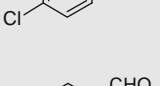

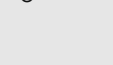
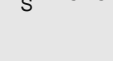
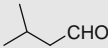
Entry	Aldehyde	Time (min)	Yield ^b (%)	Final TOF (h ⁻¹)
1		0.5 ^c 0.5 ^d 1/6	98 >99 >99	235,200 594,000 712,800
2		0.5	>99	237,600
3		0.5	>99	237,600
4		1	98	117,600
5		1	98	117,600
6		1	98	117,600
7		0.5	98	235,200
8		1	97	116,400
9		0.5	98	235,200
10		1	98	117,600
11		5 (0.5) ^e	>99 (>99)	23,760 (118,800)
12		5 ^f	95	5700

Table 3 (continued)

Entry	Aldehyde	Time (min)	Yield ^b (%)	Final TOF (h ⁻¹)
13		2 (0.5) ^e	98 (>99)	58,800 (118,800)

^a Reaction conditions: aldehyde, 2.0 mmol (0.1 M in 20 mL *i*PrOH); 0.05 mol % **1**, aldehyde/*i*PrOK/cat. **1** = 2000:20:1; 82 °C, in N₂.

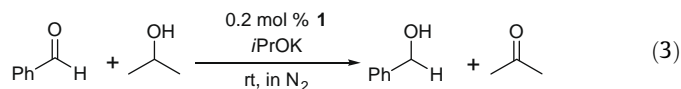
^b By GC analysis.

^c In air.

^d 0.02 mol % **1**.

^e 0.1 mol % **1**.

^f 0.2 mol % **1**.



Intrigued by the excellent catalytic activity of complex **1** in room-temperature TH of ketones in air, we then tried the TH of benzaldehyde under the same conditions as given in Table 1. The reduction of benzaldehyde by 2-propanol at room temperature in air only reached 50% conversion for the aldehyde under the stated conditions, forming a mixture of benzyl alcohol and some unknown side products within 5 min. However, with 0.2 mol % **1** as the catalyst, TH of benzaldehyde at room temperature under nitrogen atmosphere afforded benzyl alcohol as the only product in 98% yield within 10 min (Table 2, entry 1). If the reaction was carried out with 0.05 mol % **1** as the catalyst in refluxing 2-propanol in air, 98% conversion was obtained for the aldehyde to produce benzyl alcohol over a period of 30 s, and the same reaction gave >99% yield of the desired alcohol product within 10 s (final TOF = 712,800 h⁻¹) under nitrogen atmosphere. These results have demonstrated that TH of aldehydes should be carried out under an inert atmosphere or at elevated temperatures in air to reduce the possible side reactions which usually take place under basic conditions. Using 0.2 mol % **1** as the catalyst, unsubstituted and electron-donating substituent-bearing aromatic aldehydes were efficiently reduced to the corresponding alcohols by 2-propanol at room temperature under nitrogen atmosphere, reaching up to >99% conversion for the aldehyde substrates and final TOFs of up to 5940 h⁻¹ within 10 min (Table 2, entries 1–4, 7, 8, and 11). Aliphatic aldehyde 3-methylbutyraldehyde was also efficiently transformed to the corresponding alcohol with 0.3 mol % **1** as catalyst under the same conditions (entry 13). However, electron-withdrawing substituent-bearing aromatic aldehydes could not be efficiently reduced to the desired products due to their side reactions under the TH reaction conditions (entries 5, 6, 9, and 10).

In order to get an efficient TH system for aldehydes, the applied catalyst should be active enough to result in the fast reduction of aldehydes at elevated temperatures to avoid base-promoted side reactions of aldehydes.⁴ Surprisingly, 0.05 mol % **1** promoted nearly complete reduction of benzaldehyde to benzyl alcohol in refluxing 2-propanol in air over a period of 30 s, and the same reaction could be finished within 10 s under nitrogen atmosphere, reaching a final TOF value of 712,800 h⁻¹ (Table 3, entry 1). With a lower catalyst loading such as 0.02 mol % **1**, the reaction of benzaldehyde was also finished under nitrogen atmosphere within 30 s. The TH reactions of other aldehydes in refluxing 2-propanol in air usually gave the alcohol products as well as some unknown side products, but they were efficiently reduced to the corresponding alcohols under nitrogen atmosphere (Table 3). The reduction of aromatic aldehydes was complete within 1 min (entries 1–10), achieving 97–99% conversion for the aldehydes and exclusively forming the alcohol products. By increasing the catalyst loading to 0.1–0.2 mol % or by extending the reaction time to 2–5 min,

2-furaldehyde, 2-thiophenecarboxaldehyde, and 2-methylbutyraldehyde were also efficiently reduced to their corresponding alcohols (entries 11–13).

Complexes **1** and **2** exhibited the same catalytic activity in TH of ketones and aldehydes because **1** can be instantly transformed to **2** under the reaction conditions.^{10d,f} The present transfer hydrogenation may follow an inner-sphere mechanism¹³ as we proposed previously.^{10d,f} Thus, TH of a ketone or aldehyde is presumably initiated from 16-electron complex **2** in situ instantly generated by extrusion of 1 equiv of hydrogen chloride from **1** with *i*PrOK base. Complex **2** interacts with the base to form Ru(II)-alkoxide which undergoes β-H elimination to result in a Ru–H intermediate and the release of acetone. Coordination of a ketone or aldehyde substrate to the Ru–H species followed by insertion of the coordinated substrate carbonyl into the Ru–H bond gives another Ru(II)-alkoxide which is then reacted with 2-propanol to afford the alcohol product. The Ru(II) hydride is presumably considered as the catalytically active species although it is not successfully isolated by reacting **1** or **2** with EtONa or *i*PrOK in refluxing ethanol (or 2-propanol).

In summary, we have developed an unusually active and efficient Ru(II) complex catalyst for room-temperature TH of ketones and aldehydes in air. The present TH methodology has demonstrated potential application in reduction of ketones and aldehydes to alcohols under mild conditions.

Acknowledgments

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14. A general procedure for the catalytic transfer hydrogenation of ketones and aldehydes: The catalyst solution was prepared by dissolving complex **1** (20.0 μmol) in 2-propanol (40.0 mL). Under nitrogen atmosphere or in air, the mixture of a ketone (or aldehyde) substrate (2.0 mmol), 8.0 mL of the catalyst solution (0.2 mol% catalyst **1**), and 2-propanol (11.2 mL) was stirred at room temperature (ca. 28 °C) or 82 °C for 5 min. Then, 0.8 mL

of 0.1 M *i*PrOK (0.08 mmol) solution in 2-propanol was introduced to initiate the transfer hydrogenation. At the stated time, 0.1 mL of the reaction mixture was sampled and immediately diluted with 0.5 mL of 2-propanol precooled at 0 °C for immediate GC analysis. After the reaction was complete, the reaction mixture was condensed under reduced pressure and was subjected to purification by flash silica gel column chromatography to afford the alcohol product. The alcohol products were identified by comparison of their GC traces with the authentic samples and/or by proton NMR measurements.