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Notes

An Unusual Type of Ruthenium-Catalyzed Transfer Hydrogenation of Ketones with Alcohols Accompanied by C−C Coupling

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Transition metal-catalyzed transfer hydrogenation of hydrogen acceptors by hydrogen donors has been recognized to be of importance in reduction chemistry.[1] In contrast to conventional reduction routes, which frequently require a high hydrogen pressure and hazardous reducing reagents,[2] the transfer hydrogenation has some unique advantages in its simplicity and avoidance of cumbersome reducing agents. Of various hydrogen donors so far employed, a primary or secondary alcohol is the choice of preference for various reasons.[3] In conventional transfer hydrogenation, the alcohol is oxidized to the corresponding ketone (or aldehyde) depending on the nature of the alcohol (Scheme 1, route a).

Scheme 1

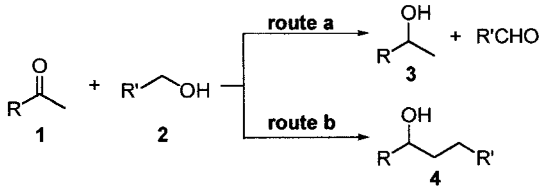


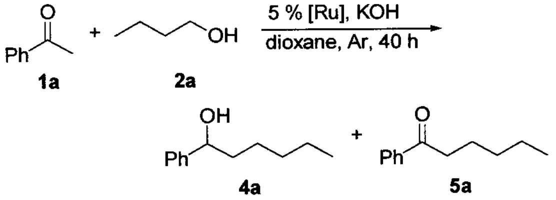
Table 1. Optimization of Conditions for the Reaction of 1a with 2a[a]

entry	ruthenium catalyst	temp (°C)	yield[b] (%)	**4a**/**5a**
1	$RuCl_2(PPh_3)_3$	80	92	97/3
2	$RuCl_2(PPh_3)_3$	50	76	86/14
3	$RuCl_2(PPh_3)_3$	25	52	81/19
4[c]	$RuCl_2(PPh_3)_3$	80	76	63/37
5	$RuCl_3{\cdot}nH_2O/3PPh_3$	80	32	97/3
6	$RuH_2(PPh_3)_4$	80	81	97/3
7	$RuCl_2({=}CHPh)(PCy_3)_2$	80	70	98/2
8	$Cp^*RuCl_2(CO)$[d]	80	78	90/10
9	$Ru_3(CO)_{12}$	80	0	

[a] Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), ruthenium catalyst (5 mol %), KOH (3 mmol), dioxane (3 mL), under argon, for 40 h. [b] Determined by GLC based on **1a**. [c] [**2a**]/[**1a**] = 1. [d] Cp* = η^5-C_5Me_5.

We have recently been engaged in ruthenium-catalyzed reactions and developed some novel reactions.[4−6] Prompted by these findings and intrigued by diverse reactivities of ruthenium catalysts, we have directed our attention to the transfer hydrogenation of ketones by alcohols only to discover the formation of unconventional transfer hydrogenation products (Scheme 1, route b). Here we are pleased to report our new findings.

Table 1 shows optimization of the conditions for the transfer hydrogenation of acetophenone (**1a**) with butanol (**2a**) (eq 1).[7] Under all circumstances, the reaction gives rise to unconventional alkylated products, 1-phenylhexan-1-ol (**4a**) and 1-phenylhexan-1-one (**5a**), rather than the expected direct transfer hydrogenation product, 1-phenylethanol, the yield of which remains less than 5%.[8] The best result in terms of both overall yield and the relative amount of **4a** to **5a** is best accomplished by $RuCl_2(PPh_3)_3$ under the standard set of reaction conditions (entry 1). The ratio **4a**/**5a** increases with an increase in the reaction temperature (entries 1−3). To account for



(1)

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[1] For reviews, see: (a) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567. (b) Matteoli, U.; Frediani, P.; Bianchi, M.; Botteghi, C.; Gladiali, S. *J. Mol. Catal.* **1981**, *12*, 265. (c) Bennet, M. A.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 945−953. (d) Johnstone, R. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129. (e) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (f) Bäckvall, J.-E.; Chowdhury, R. L.; Karlsson, U.; Wang G. In *Perspectives in Coordination Chemistry*; Williams, A. F., Floriani, C., Merbach, A. E., Eds.; VCH: New York, 1992; pp 463−486. (g) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (h) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (i) Palmer, M.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.

[2] (a) In *Comprehensive Organometallic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8. (b) Hudlicky, M. *Reductions in Organic Chemistry*; American Chemical Society: Washington, DC, 1996.

[3] Besides primary and secondary alcohols, various hydrogen donors have been explored for transition metal-catalyzed transfer hydrogenation. Formic acid/trialkylamines and alkyl formates: (a) Vol'pin, M. E.; Kukolev, V. P.; Chernyshev, V. O.; Kolomnikov, I. S. *Tetrahedron Lett.* **1971**, 4435. (b) Khai, B. T.; Arcelli, A. *Tetrahedron Lett.* **1985**, *26*, 3365. (c) Brunner, H.; Kunz, M. *Chem. Ber.* **1986**, *119*, 2868. (d) Leitner, W.; Brown, J. M.; Brunner, H. *J. Am. Chem. Soc.* **1993**, *115*, 152. (e) Yamada, I.; Noyori, R. *Org. Lett.* **2000**, *2*, 3425. Aldehydes: Blum, J.; Sasson, Y.; Iflah, S. *Tetrahedron Lett.* **1972**, 1015. Amines, ethers, and hydroaromatic compounds: Nishiguchi, T.; Tachi, K.; Fukuzumi, K. *J. Org. Chem.* **1975**, *40*, 237 and references therein.

[4] Formation of indoles by ruthenium-catalyzed amine exchange reaction between anilines and alkanolamines: (a) Cho, C. S.; Lim, H. K.; Shim, S. C.; Kim, T. J.; Choi, H.-J. *Chem. Commun.* **1998**, 995. (b) Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811. (c) Cho, C. S.; Kim, J. H.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2001**, *57*, 3321.

[5] Formation of quinolines by ruthenium-catalyzed amine exchange reaction between anilines and alkylamines: (a) Cho, C. S.; Oh, B. H.; Shim, S. C. *Tetrahedron Lett.* **1999**, *40*, 1499. (b) Cho, C. S.; Kim, J. S.; Oh, B. H.; Kim, T.-J.; Shim, S. C.; Yoon, N. S. *Tetrahedron* **2000**, *56*, 7747. (c) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885.

[6] Ruthenium-catalyzed regioselective α-alkylation of ketones with trialkylamines: Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 958.

[7] Strong bases are frequently used as cocatalysts to promote transition metal-catalyzed transfer hydrogenation: see ref 1.

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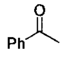
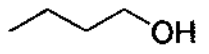
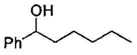
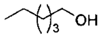
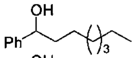
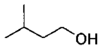
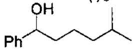
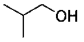
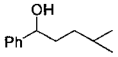
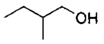
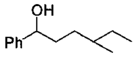
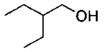
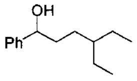
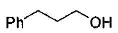
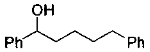
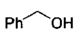
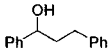
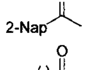
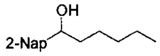
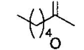
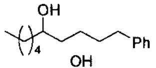
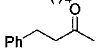
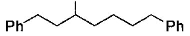
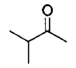
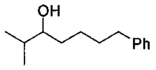
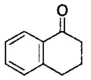
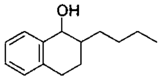
Table 2. Ruthenium-Catalyzed Reaction of Ketones with Various Primary Alcohols

ketone **1**	primary alcohol **2**	product **4**	yield^a (%)
 **1a**	 **2a**	 **4a**	80
	 **2b**	 **4b**	80
	 **2c**	 **4c**	77
	 **2d**	 **4d**	76
	 **2e**	 **4e**	81^b
	 **2f**	 **4f**	80
	 **2g**	 **4g**	81
	 **2h**	 **4h**	77^c
 **1b**	**2a**	 **4i**	85
 **1c**	**2g**	 **4j**	49
 **1d**	**2g**	 **4k**	47
 **1e**	**2g**	 **4l**	43
 **1f**	**2a**	 **4m**	47^{d,e}

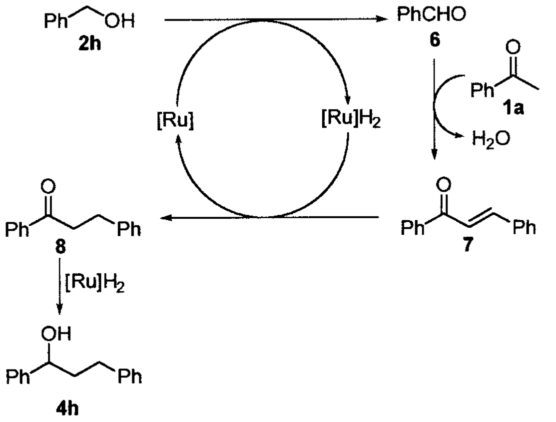
[a] Isolated yield based on **1**. [b] Mixture of diastereomers (1:1). [c] For 20 h. [d] Mixture of diastereomers (69:31). [e] 2-Butyl-1-tetralone was also isolated in 45%.

the odd result in entry 4, solvent dioxane may be considered as an additional source of hydrogen.[3]

Having established suitable reaction conditions, a series of ketones and alcohols were employed to investigate the reaction scope. The results are summarized in Table 2. The table demonstrates that this reaction can be extended to a wide range of combinations of ketones and alcohols with excellent to good yields of the corresponding coupled secondary alcohols. Here again, the production of conventional transfer hydrogenated alcohols (uncoupled) remains minimal (<3%). Of various ketones, alkyl aryl ketones (**1a** and **1b**) give the highest yields of corresponding products (**4a-4i**) ranging from 76 to 85%, while cyclic ketone **1f** gives a poor yield of alcohol with concomitant formation of alkylated ketone. In the reaction of dialkyl ketones (**1c**−**1e**), exclusive regioselectivity in favor of alkylation at the less-hindered position over α-methylene and methine was observed.[9] Similar observations have also been made by others[10] and in our recent report.[6]

A possible reaction pathway is proposed in Scheme 2 on the basis of the work of Bäckvall.[11] The key step involves the cross aldol reaction of aldehyde (**6**) with the substrate ketone (**1a**) to form α,β-unsaturated ketone (**7**) which is subsequently hydrogenated to **4h** and/or **8** by a dihydridoruthenium species generated in the initial oxidation stage of the alcohol (**2h**). With regard to the initial oxidation of alcohol to aldehyde, it is well-documented that the reaction proceeds via oxidative addition of the O−H bond to a low-valent ruthenium and subsequent β-hydrogen elimination.[1] In fact, careful GLC analysis allowed us not only to observe the formation of both intermediates **6** and **7** but also to follow the product distribution during the reaction course. The relative amount of **6** and **7** remained constant (1−2%) as the reaction proceeded, while that of **8** decreased from 23% (1 h), 12% (5 h), 3% (10 h), to 1% (20 h). During the same period of time, the amount of **4h** increased from 6% (1 h), 44% (5 h), 54% (10 h), to 86% (20 h). These observations suggest that the olefinic double bond of **7** is reduced first to form **8** which in turn undergoes further reduction to **4h**.[1,12]

Scheme 2



In conclusion, we have developed an unusual example of ruthenium-catalyzed transfer hydrogenation between an array of ketones and primary alcohols involving carbon−carbon bond formation. The present transfer hydrogenation will serve as an alternative synthetic route for secondary alcohols. Further study of synthetic applications for heterocycles and an enantioselective version of this reaction is in progress.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 (400) and 75.5 (100) MHz, respectively. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The GLC analyses were carried out on a Shimadzu GC-17A (FID) instrument equipped with a CBP10-S25-050 column (Shimadzu, fused silica capillary column, 0.33 mm × 25 m, 0.25 μm film thickness) using nitrogen as the carrier gas. All GLC yields were determined using undecane as an internal standard. Mass spectra were obtained using EI ionization at 70 eV. The isolation of pure products was carried out via column chromatography (silica gel 60, 70−230 mesh, Merck) and thin-layer chromatography (silica gel 60 GF$_{254}$, Merck). Commercially available organic and inorganic compounds were used without further purification.

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(8) It is known that primary alcohol is not adequate as a hydrogen donor for the ruthenium-catalyzed transfer hydrogenation of ketone since the aldehyde formed from dehydrogenation of the primary alcohol deactivates the ruthenium catalyst via decarbonylation: Chowdhury, R. L.; Bäckvall, J.-E. *J. Chem. Soc., Chem. Commun.* **1991**, 1063.

(9) In a separate experiment, we further confirmed that similar ruthenium-catalyzed treatment of propiophenone with **2a** scarcely afforded the alkylative reduction product, 2-methyl-1-phenylhexan-1-ol.

(10) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108.

(11) Mechanism of transition metal-catalyzed transfer hydrogenation of ketones by alcohols is quite well studied: Santosh Laxmi, Y. R.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611.

(12) Selective carbonyl reduction of α,β-unsaturated ketones to allylic alcohols by ruthenium-catalyzed transfer hydrogenation is also reported: Bianchini, C.; Farnetti, E.; Frediani, P.; Graziani, M.; Peruzzini, M.; Polo, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1336.

Typical Procedure for the Formation of 4. Acetophenone (**1a**) (0.120 g, 1 mmol), butanol (**2a**) (0.222 g, 3 mmol), KOH (0.168 g, 3 mmol), $RuCl_2(PPh_3)_3$ (0.048 g, 0.05 mmol), and dioxane (3 mL) were placed in a 5-mL screw-capped vial. The system was flushed with argon and allowed to react at 80 °C for 40 h. The reaction mixture was filtered through a short silica gel column (ethyl acetate), washed with brine, and dried over Na_2SO_4. Removal of the solvent left an oil, which was separated by column chromatography (silica gel, ethyl acetate:hexane 1:10) to give 1-phenylhexan-1-ol (**4a**) (0.143 g, 80%).

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Supporting Information Available: Spectroscopic and analytical data for **4a**−**4m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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