Preferential Hydrogenation of Aldehydes and Ketones

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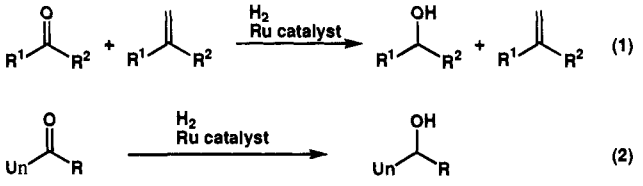
Complex metal hydrides are among the most widely used reagents in organic synthesis.[1] $NaBH_4$ is particularly appreciated because of its high chemoselectivity for conversion of aldehydes and ketones to alcohols, leaving olefinic or acetylenic bonds intact. Development of reliable hydrogenation catalysts with excellent carbonyl selectivity is highly desirable, especially for large-scale reactions for practical reasons. Most existing homogeneous and heterogeneous catalyses using molecular hydrogen, however, saturate carbon−carbon multiple bonds preferentially over a carbonyl moiety.[1b,d,2] Although some catalyst systems have been claimed to effect carbonyl-selective hydrogenation,[2d,3] their scopes remain unclear, except for the reaction of conjugated enals.[4] We demonstrate here that the recently discovered $RuCl_2[P(C_6H_5)_3]_3$−$NH_2(CH_2)_2NH_2$−KOH ternary catalyst system[5] meets this requirement (eqs 1 and 2). This hydrogenation is very general and practical. A wide variety of conjugated and unconjugated enal or enone substrates are selectively convertible to the corresponding unsaturated alcohols.



$RuCl_2[P(C_6H_5)_3]_3$ is an excellent catalyst for olefin hydrogenation[6] but very poor for carbonyl hydrogenation. In fact, a competition experiment using a mixture of heptanal and 1-octene with the Ru complex (aldehyde:olefin:Ru molar ratio = 500:500:1, 0.7 M solution in 6:1 2-propanol−toluene, 28 °C, 4 atm of H_2) revealed that the terminal olefin is saturated 250 times faster than the aldehyde. However, when $NH_2(CH_2)_2NH_2$ and KOH (1 and 2 equiv with respect to Ru, respectively) were present under otherwise identical conditions, heptanal was hydrogenated 1500 times faster than 1-octene (eq 1, R^1 = n-C_6H_{13}; R^2 = H). Thus, *the combined effects of $NH_2(CH_2)_2NH_2$ and KOH decelerate olefin hydrogenation catalyzed by $RuCl_2[P(C_6H_5)_3]_3$ and in turn accelerate carbonyl hydrogenation.* The amine additive, in an amount of only 1 equiv with respect to the catalyst (0.0014 M) or 0.002 equiv with respect to the substrate,[7] together with KOH changes the selectivity profile by a factor of 375 000! In a similar manner, the hydrogenation of an equimolar mixture of acetophenone and α-methylstyrene under standard conditions proceeded with 1500:1 selectivity to give, after 30 min, 1-phenylethyl alcohol and cumene in >99.9% and 0.5% yields, respectively (eq 1, R^1 = C_6H_5; R^2 = CH_3).

This selective hydrogenation is applicable to a range of carbonyl compounds possessing an olefinic or acetylenic bond (eq 2). Both unconjugated and conjugated enals or enones can be used. Table 1 lists some representative results. The excellent C=O *vs* C=C selectivity is reminiscent of that attained by the stoichiometric $NaBH_4$ reduction. In most cases, unsaturated alcohols are obtainable with 98−100% purity and in a near-quantitative yield. The hydrogenation took place smoothly at room temperature under 1−8 atm, and very rapidly at 50 atm, with a substrate/catalyst molar ratio (S/C) ranging from 500 to 10 000. In order to obtain high catalytic activity, particularly in a reaction with a high S/C value, contamination by acidic impurities should carefully be avoided. Thus, the hydrogenation of conjugated enals **1** and citral gave selectively the allylic alcohols. The aliphatic or aromatic ketone, **2** or **3**, with an unconjugated terminal olefinic bond was hydrogenated prefer-

Table 1. Chemoselective Hydrogenation of Unsaturated Aldehydes and Ketones Catalyzed by a $RuCl_2[P(C_6H_5)_3]_3$−$NH_2(CH_2)_2NH_2$−KOH System[a]

substrate	solvent	H_2, atm	time, h	% yield[b]	product distribution, %[b] unsatd alcohol	satd alcohol	satd ketone
1a	P/T	4	0.3	(88)	100	0	0
1b	P/T	4	0.5	99.7 (95)	99.8	0	0.2
citral[c]	P/T	4	0.3	(92)	100[c]	0	0
2	P/T	4	2	97.4 (95)	98.6	1.4	0
3	P/T	4	0.7	100 (97)	98.2	1.8	0
4	P	4	1.5	99.5 (98)	100	0	0
5	P	1	3	99.6 (96)	99.4	0	0.6
5[d]	P	4	18	100 (97)	>99.9	0	<0.1
6b	P	4	1.5	98.2 (90)	99.6	0.4	0
7a	P/T	4	1	100	70	30	0
7b	P/T	8	1.5	99.8 (98)	>99.9	<0.1	0
carvone	P	4	7	100 (95)	92.8[e]	7.2[f]	0
β-ionone	P	4	1	>99 (96)	100	0	0

[a] Reaction was conducted at 28 °C using a 0.4−1.0 M solution of substrate (5.0 mmol) in a 6:1 2-propanol−toluene mixture (P/T) or 2-propanol (P). Substrate:$RuCl_2[P(C_6H_5)_3]_3$:$NH_2(CH_2)_2NH_2$:KOH = 500:1:1:2. [b] Determined by GC and/or 200-MHz ^1H NMR analysis. Isolated yield after short-path chromatography on silica gel is given in parentheses. [c] *E*:*Z* = 67:33. [d] A 30 g scale reaction in a 1.5 M solution of substrate. Substrate:$RuCl_2[P(C_6H_5)_3]_3$:$NH_2(CH_2)_2NH_2$:KOH = 10 000:1:1:2. [e] Cis:trans = 81:19. [f] 2-Methyl-5-(2-propenyl)cyclohexanol.

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(1) Reviews: (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567−607. (b) Hudlický, M. *Reduction in Organic Chemistry*; Ellis Horwood Limited: Chichester, 1984. (c) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 1−24. (d) Keinan, E.; Greenspoon, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 523−578. (e) Seyden-Penne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, 1991.

(2) Reviews: (a) James, B. R. *Homogeneous Hydrogenation*; John Wiley & Sons: New York, 1973. (b) Birch, A. J.; Williamson, D. H. *Org. React. (N.Y.)* **1976**, *24*, 1−186. (c) Augustine, R. L. *Adv. Catal.* **1976**, *25*, 56−80. (d) Rylander, P. *Catalytic Hydrogenation in Organic Syntheses*; Academic: New York, 1979. (e) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 417−442. (f) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 443−469.

(3) For unconjugated systems, see: (a) Mestroni, G.; Spogliarich, R.; Camus, A.; Martinelli, F.; Zassinovich, G. *J. Organomet. Chem.* **1978**, *157*, 345−352. (b) Ishiyama, J.; Maeda, S.; Takahashi, K.; Senda, Y.; Imaizumi, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1721−1726. For conjugated enones, see: (c) Gilman, G.; Cohn, G. *Adv. Catal.* **1957**, *9*, 733−742. (d) Gradeff, P. S.; Formica, G. *Tetrahedron Lett.* **1976**, 4681−4684. (e) Farnetti, E.; Kašpar, J.; Spogliarich, R.; Graziani, M. *J. Chem. Soc., Dalton Trans.* **1988**, 947−952. (f) Mashima, K.; Akutagawa, T.; Zhang, X.; Takaya, H.; Taketomi, T.; Kumobayashi, H.; Akutagawa, S. *J. Organomet. Chem.* **1992**, *428*, 213−222.

(4) For example, see: (a) Giroir-Fendler, A.; Richard, D.; Gallezot, P. *Catal. Lett.* **1990**, *5*, 175−181. (b) Nitta, Y.; Hiramatsu, Y.; Imanaka, T. *J. Catal.* **1990**, *126*, 235−245. (c) Grosselin, J. M.; Mercier, C.; Allmang, G.; Grass, F. *Organometallics* **1991**, *10*, 2126−2133 and references therein.

(5) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675−2676.

(6) (a) Evans, D.; Osborn, J. A.; Jardine, F. H.; Wilkinson, G. *Nature* **1965**, *208*, 1203−1204. (b) Bennett, M. A.; Matheson, T. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 4, pp 931−965.

(7) Addition of $NH_2(CH_2)_2NH_2$ also retards transfer hydrogenation of acetophenone with 2-propanol that contains KOH.[5]

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entially at the carbonyl site to give the unsaturated alcohol of >98% purity. The olefinic bond did not migrate to internal positions. In a similar manner, the acetylenic ketone **4** was hydrogenated to the benzylic alcohols without saturation of the C≡C bond.[8] Benzalacetone (**5**), an open-chain α,β-unsaturated ketone, afforded the corresponding allylic alcohol in a nearly quantitative yield and with >99.9% chemoselectivity.[9,10] 1-Acetylcycloalkenes (**6**), another class of enones, also show very high keto selectivity. The 1,2 *vs* 1,4 selectivity of the reaction of cyclic enones is, as in the $NaBH_4$ reduction,[11] highly dependent on the substitution mode. Hydrogenation of 2-cyclohexenone (**7a**) gave a 70:30 mixture of 2-cyclohexenol and cyclohexanol. However, 3-methyl derivative **7b** was hydrogenated with perfect chemoselectivity to give only allylic alcohol. Carvone, possessing a conjugated and an isolated olefinic bond, is hydrogenated predominantly at the keto group. β-Ionone exhibited perfect selectivity, giving only β-ionol, a dienol.

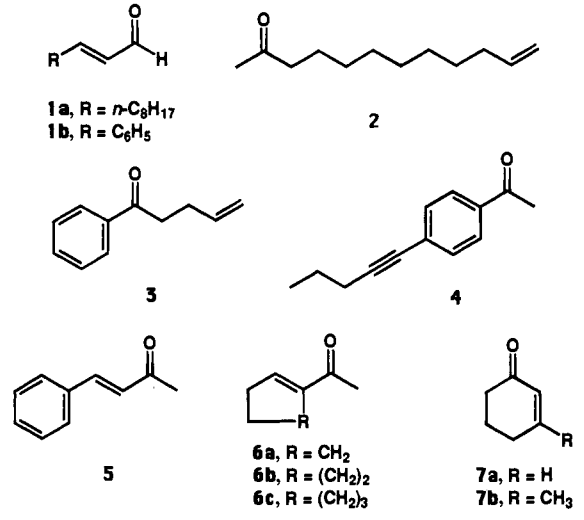


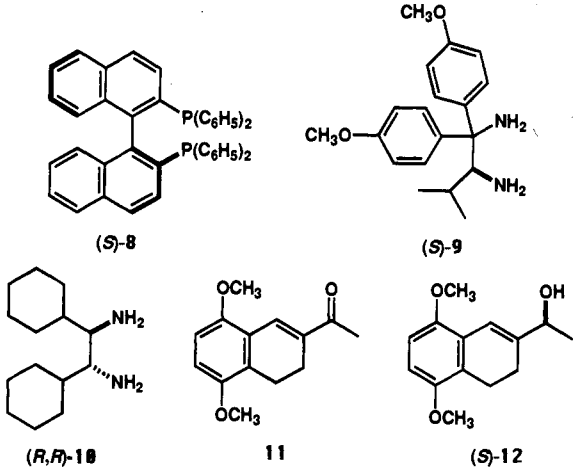
Table 2 lists some examples of the asymmetric hydrogenation attained with a catalyst system[5] consisting of $RuCl_2$(binap)$(dmf)_n$,[12] a chiral diamine,[13] and KOH. The extent of the enantioselection is dependent on the structures of the ketonic substrates and chiral elements, while the chemoselectivity and chemical yield are consistently high. The hydrogenation of the enone **11** catalyzed by a $RuCl_2$[(*R*)-binap](dmf)$_n$−(*R*)-**9**−KOH system gave the unsaturated alcohol (*S*)-**12** in 94% ee, a key intermediate for the synthesis of anthracyclin antibiotics.[14]

The carbonyl-selective hydrogenation of unsaturated aldehydes and ketones has been a long-sought synthetic operation. Now, the $RuCl_2$(phosphine)$_n$−1,2-diamine−KOH combined system provides a simple, general solution to this problem. This catalytic hydrogenation is accomplished smoothly at room temperature under 1−8 atm of H_2 with high substrate and low catalyst concentration.[15] This procedure is particularly useful for a large-scale reaction because of the low cost of the catalyst,

Table 2. Enantioselective Hydrogenation of Unsaturated Ketones by a $RuCl_2$(binap)$(dmf)_n$−Diamine−KOH System[a]

					alcohol product		
enone	chiral elements	H_2, atm	time, h	% yield[b]	% selectivity[b,c]	% ee[d]	config[e]
3	(*S*)-**8**/(*S*)-**9**	8	3	99.6 (97)	98.9	90	*R*
5	(*S*)-**8**/(*S*)-**9**	8	1	99.8 (98)	99.8	70	*R*
6a	(*S*)-**8**/(*S*)-**9**	4	5[f]	100	98.7	91	*R*[g]
6b	(*S*)-**8**/(*S*)-**9**	8	5	99.6 (91)	>99.9	98	*R*
6c	(*S*)-**8**/(*S*)-**9**	4	2[f]	100 (95)	99.5	81	*h*
11	(*R*)-**8**/(*R*)-**9**	8	1.5[f]	>99 (100)	>99	94	*S*
β-ionone	(*R*)-**8**/(*R,R*)-**10**	8	20[i]	>99 (95)	>99	92	*S*

[a] Reaction was conducted at 28 °C using a 0.4−1.3 M solution of substrate (2.0−5.0 mmol) in 2-propanol. Substrate:$RuCl_2$(binap)$(dmf)_n$:diamine:KOH = 500:1:1:2 [b] Determined by GC and/or 200-MHz ^1H NMR analysis. Isolated yield after short-path chromatography on silica gel is given in parentheses. [c] Content of an unsaturated alcohol in the whole product. [d] Determined by HPLC analysis using a chiral stationary column. [e] Determined by sign of rotation. [f] Substrate:$RuCl_2$(binap)$(dmf)_n$:**9**:KOH = 250:1:1:2. [g] Determined by conversion to 1-cyclopentylethanol. [h] Not determined. The five- to seven-membered analogues show the same sign of rotation. [i] At −20 °C.



operational simplicity, and environmental consciousness. The asymmetric version is also possible by selection of appropriate chiral phosphine and diamine ligands.

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Supporting Information Available: Full experimental procedure, GC, HPLC data, and $[\alpha]_D$ values of the hydrogenation products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(8) *p*-Ethynylacetophenone possessing a terminal acetylenic bond and 3-octyn-2-one, a conjugated ynone, were inert to the hydrogenation for some unknown reason.

(9) For catalytic methods for 1,2-reduction of conjugated enones, see: (a) Esteruelas, M. A.; Sola, E.; Oro, L. A.; Werner, H.; Meyer, U. *J. Mol. Catal.* **1988**, *45*, 1−5. (b) Nakano, T.; Umano, S.; Kino, Y.; Ishii, Y.; Ogawa, M. *J. Org. Chem.* **1988**, *53*, 3752−3757. (c) Bianchini, C.; Peruzzini, M.; Farnetti, E.; Kašpar, J.; Graziani, M. *J. Organomet. Chem.* **1995**, *488*, 91−97. (d) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614. (e) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390−1399. (f) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500−508. (g) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70−79.

(10) Hydrogenation of **5** in 6:1 CH_3OH−toluene catalyzed by $RuCl_2[P(C_6H_5)_3]_3$ without base (28 °C, 1 atm, 6 h) gave 4-phenyl-2-butanone in 7% yield.

(11) (a) Iqbal, K.; Jackson, W. R. *J. Chem. Soc. C* **1968**, 616−620. (b) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454−5459.

(12) (a) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1991**, *32*, 4163−4166. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1−13.

(13) (a) Wey, S.-J.; O'Connor, K. J.; Burrows, C. J. *Tetrahedron Lett.* **1993**, *34*, 1905−1908. (b) (*R,R*)-**10** was prepared by hydrogenation of (*R,R*)-1,2-diphenylethylenediamine, $[\alpha]^{23}_D$ +8.4° (*c* 0.95, CH_3OH). See: Schubert, H.; Krauss, U. *J. Prakt. Chem.* **1958**, *7*, 196−206.

(14) Terashima, S.; Tanno, N.; Koga, K. *Tetrahedron Lett.* **1980**, *21*, 2753−2756.

(15) Half-molar 2-propanol solutions of $NH_2(CH_2)_2NH_2$ (80 μL, 0.04 mmol) and KOH (160 μL, 0.08 mmol) were added to 10 mL of 2-propanol, and the mixture was degassed by freeze−thaw cycles. Solid $RuCl_2[P(C_6H_5)_3]_3$ (38.4 mg, 0.04 mmol) was added. The resultant mixture was sonicated for 30 min (this is important) and used as a catalyst stock solution. A solution of **5** (30.0 g, 205 mmol) in 2-propanol (100 mL) was subjected to freeze−thaw cycles. The substrate solution and an aliquot of the catalyst solution (5.1 mL, 0.0205 mmol, S/C = 10 000) were subsequently transferred to a glass autoclave. Then, hydrogen was pressurized to 4 atm. The reaction mixture was vigorously stirred at 28 °C for 18 h. The yield and chemoselectivity determined by GC were 100% and >99.9%, respectively. The solvent was removed under reduced pressure, and the residue was filtered through silica gel (100 g), eluted with a 2:8 mixture of ethyl acetate and hexane (1000 mL), and concentrated, giving (*E*)-4-phenyl-3-buten-2-ol (29.4 g, 97% yield). Due to the instability of the allylic alcohol, direct distillation without silica gel treatment should be avoided.