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# Stereo- and Chemoselective Transfer Hydrogenation of Carbonyl Groups with $RuCl_2(PPh_3)_3$ and BINAP-Ru as catalysts and $Et_3NH^+H_2PO_2^-\cdot 1,5H_2O$ as a hydrogen donor.

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**Abstract.** Using $Et_3NH^+H_2PO_2^-.1.5\ H_2O$ as a hydrogen donor, the $RuCl_2(Ph_3P)_3$, $RuCl_2(PPh_3)_3$ / C and BINAP-Ru proved highly active catalysts for transfer hydrogenation of ketones under milder conditions than other hydrogen donors. 2-Methyl-, 2-chloro-, 2-(ethoxy-carbonyl)cyclohexanones and -cyclopentanones were reduced to the less stable axial alcohols in excellent diastereoisomeric excess (de: 90-100%), and the carbonyl group of α,β-unsaturated ketones was selectively reduced, in contrast with other hydrogen donors the C=C bond was reduced.


The complex $RuCl_2(Ph_3P)_3$ (**I**) has been reported as good catalyst for olefin reduction but poor for carbonyl reduction with molecular hydrogen[1a] or hydrogen donors[1b-f]. Recently we have reported using $Et_3NH^+H_2PO_2^-,1.5H_2O$ (**A**) as a hydrogen donor, however (**I**) is a highly active catalyst for ketone reduction but its lifetime is short[1b], we now find that this disadvantage can be overcome by using $RuCl_2(Ph_3P)_3$ / C (**II**) [2], while maintaining the same chemo-and stereoselectivity as using (**I**) (Table 2). In this study we have investigated chemoselective and diastereoselective reduction with **A** as a hydrogen donor and **I**, **II** and BINAP-Ru (**III**) as catalysts in the reaction condition in the presence or absence of a solvent, and compared the results with other hydrogen donors such as $HCO_2Na$[1c], $HCO_2H$[1d,e], 2-propanol[1f], $Et_3N/HCO_2H$ (**B**) and molecular hydrogen[1a,3a]

The catalyst **III** is more reactive than **I** (Table 2), and this explains why we have found with **B**, **I** was unable to catalyze olefin reduction[1g] but Brown and Brunner have reported with **B**, **III** could catalyze to reduce olefin[1h]; Both **I, II** and **III** gave the same result for chemoselective reduction of α,β-unsaturated ketones (Table 1) and diastereoselective reduction of α-substituted cyclohexanones (Table 2). The chemoselectivity is affected by steric and electronic factors: Cyclohexanone was selectively reduced in the presence of 2-methylcyclohexanone, but 2-Chlorocyclohexanone was selectively reduced in the presence of cyclohexanone and methylcyclohexanone. Similar to Bianchini's reports with $[(PP_3)RuH(H_2)]BPh_4$(**IV**)[1i] and iridium complexes (**VI**)[1j], benzylideneacetone gave unsaturated alcohol (98.5-100% selectivity by **III** and **I**), chalcon gave a mixture of saturated and unsaturated alcohols. But overreduction of unsaturated. alcohol or saturated. ketone to saturated alcohol have not been found (Table 1). This fact can be explained by assuming that there is competition between transfer hydrogenation and decomposition of $H_3PO_2$ to $H_2$ and $H_3PO_3$[1k]:

$$\text{Sat. substrate} + H_3PO_3 \xleftarrow[\text{unsat. substrate}]{RuCl_2(Ph_3P)_3 \text{ or BINAP-Ru}} H_3PO_2,\ H_2O \xrightarrow{RuCl_2(Ph_3P)_3 \text{ or BINAP-Ru}} H_2 + H_3PO_3 \quad (1)$$

After about 2 hours the catalysts **I** and **III** become less active, the decomposition of $H_3PO_2$ to $H_2$ and

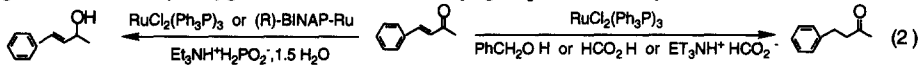
**Table 1**: Chemoselective reduction catalyzed by $RuCl_2(Ph_3P)_3$ and (R)-BINAP-Ru (II) and $Et_3N$ / $HCO_2H$,n $H_2O$ and $Et_3NH^+H_2PO_2^-$,1.5 $H_2O$ as the hydrogen donors with or without a solvent [(a)].

| Entry | Substrates | Products (yield %) | | |
|---|---|---|---|---|
| | PhCH=CHCOPh | PhCH=CHCOPh | $PhCH_2CH_2COPh$ | PhCH=CHCHOHPh |
| 1 | ($b_1$) | ( 40% ) | ( 40% ) | ( 20% ) |
| 2 | ($b_2$) | ( 43% ) | ( 47.2% ) | ( 9.8% ) |
| 3 | ($c_1$) | ( 68% ) | ( 32% ) | ( 0% ) |
| 4 | ($c_2$) | ( 64% ) | ( 30.7% ) | ( 0% ) |
| 5 | (d) | ( 10% ) | ( 13% ) | ( 7% ) (f) |
| | $PhCH=CHCOCH_3$ | $PhCH=CHCOCH_3$ | $PhCH_2CH_2COCH_3$ | $PhCH=CHCHOHCH_3$ |
| 6 | ($b_1$) | ( 27% ) | ( 0% ) | ( 71% ) (g) |
| 7 | ($b_2$) | ( 34% ) | ( 1% ) | ( 65% ) |
| 8 | ($c_1$) | ( 82% ) | ( 18% ) | ( 0% ) |
| 9 | ($c_2$) | ( 84% ) | ( 12.2% ) | ( 3.8% ) |
| 10 | (d) | ( 30% ) | ( 0% ) | ( 70% ) |

(a) Ref 4; (b) $Et_3NH^+H_2PO_2^-$, 1.5 $H_2O$ without a solvent: ($b_1$) 0.03 mmol $RuCl_2(Ph_3P)_3$ , ($b_2$) 0.018 mmol (R)-BINAP-Ru (c) $Et_3NH^+HCO_2^-$, n $H_2O$ without a solvent at 75°C: ($c_1$) 0.03 mmol $RuCl_2(Ph_3P)_3$, ($c_2$) 0.018 mmol (R)-BINAP-Ru; (d) $Et_3NH^+$ $H_2PO_2^-$,1.5 $H_2O$ in ethanol, 0.03 mmol $RuCl_2(Ph_3P)_3$; (f) PhCHOEtCH=CHPh(70%) ; (g) PhCH=CHCH=$CH_2$(2%).

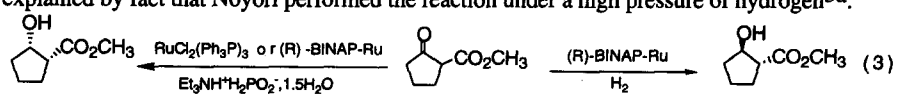
$H_3PO_3$ is a predominant reaction therefore overreduction of saturated ketone or unsaturated alcohol to saturated alcohols can not occur and the system offers a higher chemoselectivity. Unlike the catalysts **IV** or **V**, aldehydes are catalytic poisons[1i,j], we now find that a mixture of benzaldyde and acetophenone in the presence or absence of EtOH solvent gives only benzyl alcohol (100%) while acetophenone remaines unchanged (100%).

It has been reported that **I** can catalyze to reduce ketones with formic acid[1e], 2-propanol[1f], $HCO_2Na$[1k] and **B** as hydrogen donors, but for the reduction of α,β-unsaturated ketones the C=C bond was selectively reduced[1f,d,l]. In contrast, with **A** the carbonyl group was selectively reduced by **I** and **III** (Table 1). To the best of our knowledge, this is the first case in which **I** and **III** catalyze selectively the transfer hydrogenation of carbonyl group, similar to the $RuCl_2(Ph_3P)_3/NH_2(CH_2)2NH_2/KOH$ system with dihydrogen[1a]. This fact can be explained by assuming that $Et_3NH^+H_2PO_2^-$ converted to $Et_3NH^+H_2PO_3^-$ which gives the hydrogen bonding with the carbonyl oxygen, therefore the carbonyl group is selectively reduced.



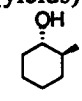
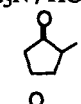
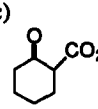
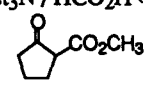
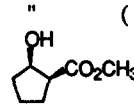
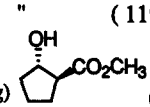
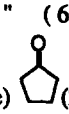
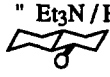
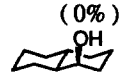
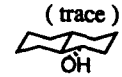
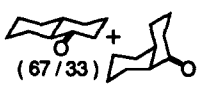
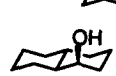
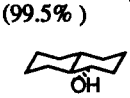
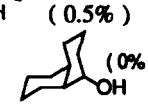
(2)

The diastereoselective reduction of α-substituted cyclohexanones and cyclopentanones is dependent on the hydrogen sources.: Methylcyclohexanone gave a mixture of methylcyclohexanols (cis/trans: 64/36 with 2-propanol and 62/38 with (**B**). With A, the complexes **I** and **III** catalyze transfer hydrogenation of 2-methyl-, 2-chloro-, 2-(ethoxycarbonyl)cyclohexanones and -cyclopentanones to less stable axial alcohols in excellent diastereoisomeric excess (de: 90-100%), there is no remarkable difference of diastereoselectivity when the reaction can be performed in the presence or absence of a solvent (Table 2), but in the presence of alcoholic solvent, transesterification is a dominant reaction: the reduction of 2-(methoxycarbonyl)cyclopentanone in EtOH solvent gave 2-(ethoxycarbonyl)cyclopentanone (98%) It is surprising that **I** , **II** and both (R) or (S) BINAP-Ru catalyze to reduce ethyl-or methyl-2-oxopentanecarboxylate to only cis 2-hydroxycyclopentanecarboxylate and by-product of decarboxylation (cyclopentanone), this finding is contrary to Noyori's report. This difference can be explained by fact that Noyori performed the reaction under a high pressure of hydrogen[3a].



(3)

**Table 2**: Diastereoselective reduction of a-substituted cyclohexanones and cyclopentanones catalyzed by $RuCl_2(Ph3P)_3$/C with $EtNH^+H_2PO_2^-$,1.5$H_2O$ as a hydrogen donor in the absence of a solvent [a].

| Entry | Substrate | Conversion | Products (yields) | | |
|---|---|---|---|---|---|
| 1 |  | 75 |  ( 96% ) |  | ( 4% ) |
| 2 | " in EtOH (b) | 38 | " ( 97% ) | " | ( 3% ) |
| 3 | " (c) | 52 | " ( 95% ) | " | ( 5% ) |
| 4 | " $Et_3N$ / $HCO_2H$ (d) | 32 | " ( 62% ) | " | ( 38% ) |
| 5 |  | 72 |  ( 99% ) |  | ( 1% ) |
| 6 |  (e) | 98 |  ( 92.6% ) |  | ( 4.9% )  ( 2.5% ) |
| 7 | " (c) | 95 | " ( 97% ) | " | ( 3% ) " ( trace ) |
| 8 | " $Et_3N$ / $HCO_2H$ (d) | 51 | " ( 45% ) | " | ( 16% ) " ( 39% ) |
| 9 |  (e) | 96 |  ( 99% ) |  | ( 0% )  ( 1% ) |
| 10 | " (c) | 94 | " ( 98% ) | " | ( 2% ) " ( trace ) |
| 11 |  | 48 |  ( 78% ) |  | ( 3% )  ( 19% ) |
| 12 | " in EtOH (b) | 56 | " ( 97.5% ) | " | ( 2.5% ) " ( 0% ) |
| 13 | " in EtOH (f) | 62 | " ( 81% ) | " | ( 2% ) " ( 17% ) |
| 14 | " $Et_3N$ / $HCO_2H$ (d) | 35 | " ( 26% ) | " | ( 11% ) " ( 63% ) |
| 15 |  | 41 |  (80%)(g) |  | (trace)  (20%) |
| 16 | " in MeOH(b) | 52 | " ( 97% ) | " | ( trace ) " ( 3% ) |
| 17 | " (c) | 74 | " ( 84% ) | " | ( trace ) " (16% ) |
| 18 | " in MeOH(f) | 63 | " ( 81%)(h) | " | ( trace ) " (19%) |
| 19 | " $Et_3N$ / $HCO_2H$ (d) | 31 | " ( 0% ) | " | ( trace ) " (100%) |
| 20 |  | 93 |  (99.5% ) |  | ( 0.5% ) |
| 21 |  ( 67 / 33 ) | 86 |  ( 97% ) |  | ( 3% )  ( 0% ) |

(a) Ref. 4; (b) $RuCl_2(Ph_3P)_3$ (0.03 mmol) and 4 ml of EtOH, MeOH used as solvents; (c) (R)-BINAP-Ru (0.03 mmol) without a solvent; (d) $RuCl_2(Ph_3P)_3$ (0.03 mmol) with $Et_3NH^+HCO_2^-.nH_2O$ at 75°C without a solvent; (e) $RuCl_2(Ph_3P)_3$ (0.06 mmol) without a solvent; (f) (R)-BINAP-Ru (0.03 mmol) in EtOH or MeOH as solvents; (g) By GLC (Supelcowax column) there is a peak at $t_R$:15.40 min and $^{13}C$-NMR (APT;75 MHz; $CDCl_3$): δ 49.4 ($C_1$-H), 73.61 ($C_2$-OH) attributed to cis isomer; No peak $t_R$: 18.04 min and $^{13}C$-NMR: δ 52.6 ($C_1$-H), 76.1($C_2$-OH) to trans isomer ; (h) GC analysis of (L) Lactic Acid O-acetyl ester: 60.9% of (1R,2S) and 40.1% of (1S,2R).

Enantioselectivity is similar to results of ketone reduction with 2-propanol as a hydrogen donor reported by Genet[3b]. With A as a hydrogen donor, (R)-BINAP-Ru catalyzed transfer hydrogenation of ethyl 4-chloroacetoacetate to 3-hydroxy-4-chlorobutyrate in almost quantitative yield with S/R ratio: 69/31, and methyl-2-oxopentanecarboxylate to cis-2-hydroxycyclopentanecarboxylate with (1R,2S) / (1S,2R) ratio : 60.9/40.1 .

## Reference and Notes


1 (a) Ohkuma T.; Ooka H.; Ikariya T.; Noyori R., J. Am Chem Soc. **1995**, 117, 10417. (b) Bui T. K. ; Arcelli A., J. Org. Chem. **1989**, 54, 949; (c) Bar R.; Sasson Y., Tetrahehron Lett. **1981**, 22, 1710; (d) Blum J.; Sasson Y.; Iflah Sh., Tetrahedron Lett. **1972**, 1015; (e) Watanabe Y.; Ohta T.; Tsuji Y., Bull. Chem. Soc. Jpn., **1982**, 55, 2444; (f) Chowdhury R. L.; Backvall J. E., J. Chem. Soc. **1991**, 1063; (g) Bui T. K.; Arcelli A., Tetrahedron Lett. **1985**, 26, 3365; (h) Brown J.M.; Brunner H.; Leitner W.; Rose M., Tetrahedron Asymmetry **1991**, 2, 331; (i) Bianchini C.; Farnetti E.; Graziani M.; Peruzzini M.; Polo A., Organometallics **1993**, 12, 3753; (j) Farnetti E.; Gulati N.V.; Graziani M., Gazz. Chim. Ital. **1993**, 123, 165; (k) Bui T. K. unpublished results; (l) Sasson Y.; Blum J., J. Org. Chem. 1975, 40, 1887.

2 A 50 ml flask was charged $RuCl_2(Ph_3P)_3$ (Fluka) (0.1 g; 0.104 mmol) and benzene (3ml) under argon, then 2 g of activated carbon was added, the suspension was stirred for 30 min. and then allowed to stand for 1 h. The black precipitate was filtered with suction under a nitrogen atmosphere: 2.07 g of $RuCl_2(Ph_3P)_3/C$. We found when using 0.14 mol% catalyst that 180 moles of cyclohexanone were reduced to cyclohexanol by one mole of $RuCl_2(Ph_3P)_3$ and 430 moles by one mole of $RuCl_2(Ph_3P)_3/C$ in the reaction condition without a solvent. In general, using 0.14 mol % catalyst the conversion stopped at 50%. In order to increase the conversion we used 0.5 mol % catalyst in this work (Ref 4).

3 (a) Noyori R.; Ikeda T.; Ohkuma T.; Widhalm M.; Kitamura M.; Takaya H.; Akutagawa S.; Sayo N.; Saito T.; Taketomi T.; Kumobayashi H. J. Am. Chem. Soc. **1989**, 111, 9134; (b) Genet J.P.; Vidal V.R.; Pinel C., Synlett **1993**, 478.

4 General procedure of ketone reduction : A mixture of ketone (6 mmol) and $Et_3NH^+H_2PO_2^-.1.5\ H_2O$ (4ml) was stirred under an argon atmosphere at room temperature until the ketone disappeared. Then $RuCl_2(Ph_3P)_3$ (0.029g; 0.03 mmol) (Fluka) or $RuCl_2(Ph_3P)_3/C$ (0.560g; 0.03 mmol) or (R)-BINAP-Ru (II)(0.028g; 0.03 mmol) (Fluka) were added, the flask was immersed in an oil bath at 40°C and the reaction mixture was stirred for 3 h. Water (10 ml ) was added and products were extracted with ether and dried over $MgSO_4$. The products were identified by comparison with authentic samples of alcohols ( prepared by $NaBH_4$ reduction ) by GLC , as well as by GC-MS and $^{13}C$-NMR analysis, ( cis and trans α-substituted cyclohexanols and cyclopentanols are easily identified by $^{13}C$-NMR spectrum based on the signal of a equatorial alcohol appearing at lower field than that for an axial alcohol ).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