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Hydrogenation of Amides by the Use of Bimetallic Catalysts Consisting of Group 8 to 10, and Group 6 or 7 Metals

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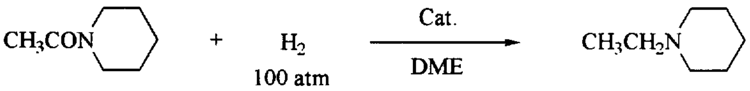
Abstract: Hydrogenation of amides can be catalyzed by bimetallic systems, which consist of Group 8 to 10 late transition-metals and Group 6 or 7 early transition-metals, under the mild conditions to afford the corresponding amines selectively in good to excellent yields.

Transition-metal catalyzed hydrogenation is one of the most useful and versatile tools provided to the synthetic organic chemists.[1] However, the catalytic hydrogenation of amides has remained to be solved, where McAlees and McCrindle established the following increasing order of difficulty for carbonyls: anhydrides > esters > carboxylic acids > amides.[2] Therefore, the stoichiometric reduction using metal hydride complexes such as lithium aluminum hydride has been used in organic syntheses. Although there have been reported some catalytic systems such as copper chromite,[3] rhenium oxide,[4] and Group 8 to 10 transition metals,[5-7] they usually required vigorous conditions (high pressures and elevated temperature) and it is difficult to obtain the desired amines selectively. Recently, we have reported that bimetallic catalysts, which consist of Group 8 to 10 late transition metals and Group 6 or 7 early transition metals, show extremely potent reducing abilities in the hydrogenation of carboxylic acids to afford alcohols selectively, whereas having no or little catalytic activity for the reduction of ester functions.[8] We wish to report herein the application of these bimetallic catalysts to the hydrogenation of a variety of amides.

Initially, the effectiveness of Group 6 to 10 transition metals by themselves was examined using N-acetylpiperidine as a substrate. Although $Rh_6(CO)_{16}$ afforded 19 % yield of N-ethylpiperidine at 160 °C, none of them showed a significant catalytic activity under the conditions of below 170 °C and 100 atm of hydrogen pressure. On the other hand, bimetallic catalysts consisting of Group 8 to 10 late transition metal complexes such as $Rh_6(CO)_{16}$ or $Ru_3(CO)_{12}$ and Group 6 or 7 early transition metal complexes such as $Re_2(CO)_{10}$, $W(CO)_6$, or $Mo(CO)_6$ were found to exhibit powerful reducing abilities in the hydrogenation of N-acetylpiperidine to afford N-ethylpiperidine in good to excellent yields. The representative results are shown in Table 1. Synergistic effects of rhenium, molybdenum, or tungsten with rhodium or ruthenium were observed not only in homogeneous but also in heterogeneous catalyst systems. The combinations of rhodium-rhenium, rhodium-molybdenum, and ruthenium-rhenium were especially effective for the reduction of N-acetylpiperidine. It is noteworthy that by-products such as hydrocarbons or alcohols were not detected by GLC analyses in the present conditions.

Table 1. Hydrogenation of N-Acetylpiperidine [a]



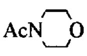
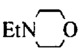
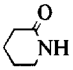
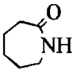
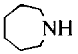
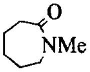
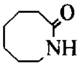
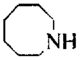
Entry	Cat. 1	Cat.2	Temp. (°C)	Conv. (%)	Yield (%)
1	$Rh_6(CO)_{16}$		160	24	19
2	$Ru_3(CO)_{12}$		160	1	1
3	$Re_2(CO)_{10}$		160	14	7
4	$Mo(CO)_6$		160	2	2
5	$W(CO)_6$		160	1	1
6	$Rh_6(CO)_{16}$	$Re_2(CO)_{10}$ [b]	160	100	96
7	$Rh_6(CO)_{16}$	$W(CO)_6$	160	51	50
8	$Rh_6(CO)_{16}$	$Mo(CO)_6$	160	100	98
9	$Ru_3(CO)_{12}$	$Re_2(CO)_{10}$	160	100	96
10	$Ru_3(CO)_{12}$	$Mo(CO)_6$	170	55	54
11	$Rh_6(CO)_{16}$	Re / C	170	83	82
12	Rh / C	Re / C	170	100	98
13	$Ru_3(CO)_{12}$	Re / Al_2O_3	170	100	94
14	Ru / Al_2O_3	Re / Al_2O_3	170	100	92

[a] All reactions were carried out with substrate (1.0 mmol) and catalyst (1 mol%) in DME (1.0 ml) at given temperature for 16 h. [b] 0.5 mol% of Re was used.

Typical procedure is as follows: In a 10 ml stainless autoclave were placed 1.8 mg (1/6 mol%) of hexarhodium hexadecacarbonyl, 2.6 mg (1 mol%) of molybdenum hexacarbonyl, 127.1 mg (1.0 mmol) of N-acetylpiperidine, and 1,2-dimethoxyethane (1.0 ml) as a solvent. The autoclave was pressurized by hydrogen to 100 atm and the mixture was stirred for 16 h at 160 °C. GLC analysis of the reaction mixture showed the formation of N-ethylpiperidine in 98 % yield.

In order to demonstrate usefulness of the present catalytic systems, $Rh_6(CO)_{16}$-$Re_2(CO)_{10}$ catalysts were applied to the hydrogenation of various amide derivatives, and the results were summarized in Table 2. At first, we examined the reaction of N,N-disubstituted amides (Entries 1-4). N,N-Diisopropylformamide was easily hydrogenated at 160 °C to afford the desired amine in 92 % yield, regardless of the bulkiness at nitrogen atom. N-Acetylmorpholine was also converted into the corresponding amine in 85 % yield without the cleavage of ether bond. The reductions of N,N-diethylpropanamide and N,N-diethyl pivalamide were reluctant to proceed on using 1 mol% of catalysts, however, satisfactory results (62 and 70 %, respectively) were obtained when 3 mol% catalysts and prolonged reaction time (36 h) were employed. Mono-substituted amides also underwent the hydrogenation in a similar way (Entries 5-7).

Table 2. Hydrogenation of Various Amides[a]

Entry	Amide	Rh (mol%)	Re (mol%)	Temp. (°C)	Time (h)	Conv. (%)	Amine	Yield (%)
1	$HCON(CHMe_2)_2$	1	1	160	16	100	$MeN(CHMe_2)_2$	92
2		1	1	170	16	100		85
3	$EtCONEt_2$	3	3	160	36	75	$EtCH_2NEt_2$	62
4	t-$BuCONEt_2$	3	3	170	36	87	t-$BuCH_2NEt_2$	70
5	AcNH(n-C_6H_{13})	3	3	170	16	97	EtNH(n-C_6H_{13})	82
6	AcNHPh	3	3	170	16	100	EtNHCy[b]	90
7	$AcNHCH_2Ph$	3	3	180	16	100	$EtNHCH_2Cy$[b]	88
8	n-$C_5H_{11}CONH_2$[c]	3	6	180	8	100	n-$C_6H_{13}NH_2$	76
9		1	1	180	16	100		91
10		1	1	160	16	100		75
11		1	1	170	32	88		70
12		3	3	170	16	82		69

[a] All reactions were carried out with substrate (1.0 mmol) and catalysts (1-3 mol%) in DME (2.0 ml) at given temperature. [b] Cy: cyclohexyl group. [c] The reaction was carried out with 2 eq. of diethylamine under the diluted conditions (0.25 mol/l).

The reaction of mono-substituted amides proceeded smoothly at 170-180 °C to afford the corresponding amines in excellent yields (82-90 %). In these cases, 3 mol% of catalysts were required for the completion of the reaction. Under these reaction conditions employed, the phenyl groups in the substrates were converted into cyclohexyl groups throughout the course of the reaction.

The reaction of N-unsubstituted amide gave a significantly different result. That is, the reduction of hexanamide under the usual conditions resulted in the predominant formation of dihexylamine, and the yield of desired hexylamine was rather low. Then, the influence of a variety of additives was investigated in order to improve the selectivity, and diethyl amine was found to be effective one to prevent the side-reaction. Consequently, hexanamide was hydrogenated in the presence of 2 equivalents of diethylamine to produce hexylamine in 76 % yield (Entry 8).

Finally, we examined the hydrogenation of lactams, which are defined as cyclic amides (Entries 9-12). It is noteworthy that the reactivities of lactams remarkably vary with their ring-sizes. The reduction of ε-caprolactam (7-membered ring) proceeded even at 160 °C, while that of δ-valerolactam (6-membered ring) required elevated temperature (180 °C). The reaction of ω-heptalactam (8-membered ring) with 1 mol% of catalysts was much slower than former two lactams, so the use of 3 mol% of catalysts was essential in order to obtain the corresponding amine in the satisfactory yield. It was also observed that the substituent on the nitrogen atom reduces the reactivity of the lactam (Entries 11 *vs* 10). Probably, the increased steric bulkiness may restrain the coordination of the carbonyl group to these catalysts.

In conclusion, various amides could be effectively hydrogenated to amines in good to excellent yields by the use of the bimetallic catalysts. It is remarkable that the reaction proceeds under the mild reaction conditions and amines are produced selectively without the formation of alcohols or hydrocarbons. These new systems can be the candidate for the practical catalysts for the preparation of amines by the hydrogenation of amides.

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