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Catalytic Leuckart−Wallach-Type Reductive Amination of Ketones

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Abstract: A Cp*Rh(III) complex catalyzes reductive amination of ketones using $HCOONH_4$ at 50−70 °C to give the corresponding primary amines in high yields. The reaction is clean and operationally simple and proceeds at a lower temperature and with higher chemoselectivity than the original Leuckart−Wallach reaction. The new method has been applied to the synthesis of α-amino acids directly from α-keto acids.

Reductive amination of carbonyl compounds is attractive in organic synthesis because ketones or aldehydes can be transformed, in one reaction vessel, directly to the corresponding secondary or primary alkylamines without isolation of the intermediary imines or hydroxy amines.[1] The reaction with formic acid as a reducing agent is called the Leuckart−Wallach (LW) reaction.[2] The LW reaction is very simple and clean, but it suffers from several drawbacks such as the requirement of high temperature (mostly above 180 °C), the formation of *N*-formyl derivative, and the difficulty of the selective synthesis of primary amine from ammonia.[3] Such a reaction is in general most useful and efficient when performed catalytically, rather than stoichiometrically, but during the past 100 years, only a few reports on the catalytic version of LW reaction have been made.[4] This is apparently because the reported methods using Raney Ni or Co could not overcome the above deficiencies. In this paper, we describe a new and efficient catalytic LW-type reductive amination of ketones.

The 8, 9, and 10 group metal complexes having Cp*, Cp, COD, or $P(C_6H_5)_3$ ligand were selected because most of these complexes are able to hydrogenate the unsaturated organic molecules.[5] The catalytic activity for the LW reaction was screened by use of 3−5 mmol of acetophenone (**1a**) and ammonium formate by fixing the concentrations of the complex, **1a**, and ammonium formate, temperature, reaction time, and solvent to 5 mM, 1 M, 5 M, 70 °C, 2 h, and methanol, respectively. The yields of the possible products, 1-phenylethylamine (**2a**), di(1-phenylethyl)amine (**3a**), *N*-formyl-1-phenylethylamine (**4a**), and 1-phenylethanol (**5a**), were determined by ^{1}H NMR analysis (δ 2.62 (s, CH_3 of **1a**), δ 4.18 (q, J = 6.6 Hz, CH of **2a**), δ 3.59 (q, J = 6.6 Hz, CH of *meso*-**3a**), δ 3.86 (q, J = 7.4 Hz, CH of *dl*-**3a**), δ 4.69 (dq, J = 7.4, 7.4 Hz, CH of the minor rotamer of **4a**), δ 5.22 (dq, J = 7.3, 7.3 Hz, CH of the major rotamer of **4a**), δ 4.90 (q, J = 6.6 Hz, CH of **5a**)).

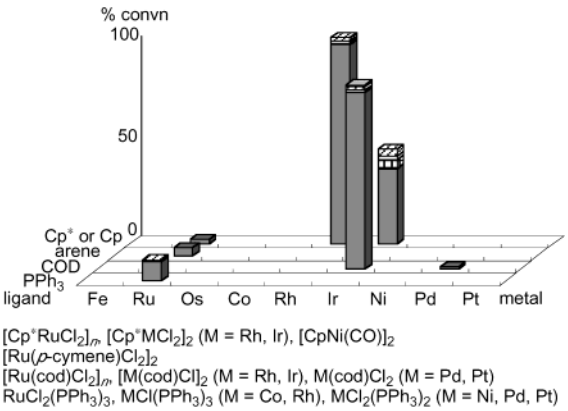

FIGURE 1. The reactivity and selectivity profiles of the 8, 9, and 10 group metal complexes in the catalytic LW reaction using acetophenone and ammonium formate: dark shading, 1-phenylethylamine (**2a**); lighter shading, di(1-phenylethyl)-amine (**3a**); white, *N*-formyl-1-phenylethylamine (**4a**); striped, 1-phenylethanol (**5a**); light shading, others.

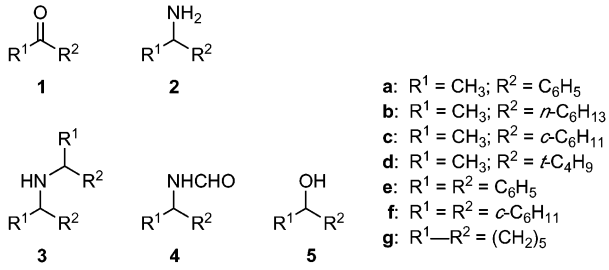

Figure 1 illustrates the reactivity and selectivity of the complexes investigated. $[RhCp^*Cl_2]_2$ (**6**)[6] shows the highest efficiency among others. Under the standard conditions, 98% of acetophenone is converted to **2a**, **3a**, **4a**, and **5a** in a 96.5:0.5:1.0:2.0 ratio. The desired product **2a** can be isolated in pure form in 90% yield by a simple partition between organic and aqueous layers. $[Ir(cod)Cl]_2$[7] also catalyzes the LW reaction to give a 96:0:1:2 mixture of **2a**, **3a**, **4a**, and **5a**, although the reactivity is lowered. Table 1 lists the results of the optimization of the conditions using $[RhCp^*Cl_2]_2$. The complete consump-

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TABLE 1. [RhCp*Cl$_2$]$_2$-Catalyzed Reductive Amination of Simple Ketones[a]

	concentrations (M)						product ratio[b,c]				
entry	substrate	hydride and amine source	catalyst	solvent	time, h	% convn	**2**	**3**	**4**	**5**	others
1	**1a** (1)	$HCOONH_4$ (5)	[Cp*RhCl$_2$]$_2$ (**6**) (0.005)	CH_3OH	2	98	96.5 [d]	0.5	1.0	2.0	0
2	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	6	>99	90	1.0	7.0	2.0	0
3[e]	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	5	98	95.5	0.8	1.3	2.4	0
4	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	31	>99	55.7	0	34	1.4	8.9
5[f]	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	6	85	89.8	2.2	0	3.6	4.4
6	**1a** (1)	$HCOONH_4$ (2)	**6** (0.005)	CH_3OH	6	95	85	4.5	1.0	9.5	0
7	**1a** (1)	$HCOONH_4$ (1)	**6** (0.005)	CH_3OH	6	54	43	2.0	0	30.6	24.4
8	**1a** (0.5)	$HCOONH_4$ (5)	**6** (0.0025)	CH_3OH	1	>99	95.2	2.2	0	2.3	0.3
9	**1a** (0.33)	$HCOONH_4$ (1.65)	**6** (0.00165)	CH_3OH	6	89	94.5	0.5	1.0	4.0	0
10	**1a** (5)	$HCOONH_4$ (25)	**6** (0.025)	CH_3OH	2	78	85.8	4.1	0	7.6	2.5
11[f]	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	30:1 CH_3OH-H_2O	6	64	93.7	1.1	1.0	4.2	0
12[f]	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	1:1 $CH_3OH-CF_3CH_2OH$	6	80	88.4	5.3	0	6.3	0
13[f]	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	1:1 *i*-$C_3H_7OH-CF_3CH_2OH$	6	71	78.7	6.6	1.3	13.4	0
14	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	*i*-C_3H_7OH	2	41	85	4.5	0	10.5	0
15	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3CN	2	3	0	0	0	>99	<1
16	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	DMF	2	13	96.3	0	0	3.7	0
17	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_2Cl_2	2	14	0	0	0	>99	<1
18	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	THF	2	13	65.8	0	0	34.2	0
19	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	C_6H_6	2	8	0	0	0	>99	<1
20	**1a** (1)	$HCOONH_4$ (5)	**6** (0.005)	*c*-C_6H_{12}	2	3	0	0	0	>99	<1
21	**1a** (1)	HCOOH (5)NH_3 (ca. 7)	**6** (0.005)	CH_3OH	2	50	83.3	4.0	2.6	5.5	4.6
22	**1a** (1)	HCOOH (7)NH_3 (ca. 5)	**6** (0.005)	CH_3OH	2	93	91	0.8	3.3	4.9	0
23	**1a** (1)	$HCOONH_4$ (5)	[Cp*RhI$_2$]$_2$ (0.005)	CH_3OH	1	63	97.6	0	0	1.2	1.2
24	**1a** (1)	$HCOONH_4$ (5)	[Rh$_2$Cp*$_2$Cl$_3$]BARF (0.005)	CH_3OH	1	65	94.6	0	0	2.2	3.2
25	**1b** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	3	>99	98.9	0	0.5	0.6	0
26	**1c** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	5	>99	95.0	0	1.0	4.0	0
27	**1d** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	30	43	71.9	0	27.4	0.7	0
28	**1e** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	9	47	61.9	0	2.8	35.3	0
29	**1f** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	11	11	-	-	-	-	-
30	**1g** (1)	$HCOONH_4$ (5)	**6** (0.005)	CH_3OH	2	>99	80.8	14.1	0	5.1	0

[a] Reactions were carried out at 70 °C under an argon atmosphere unless otherwise specified. [b] The product ratio was determined by 500 MHz ^{1}H NMR analysis. For details, see the Supporting Information. [c] The value 0 denotes that the signals are not detected by the ^{1}H NMR analysis of the crude reaction mixture. [d] 90% isolated yield. [e] Reaction was carried out without any special care about moisture and air. [f] 50 °C.

tion of **1a** takes 6 h, while the *N*-formyl compound **4a** is formed in 7% yield (entry 2). Without any special care about moisture and air, 98% of acetophenone is converted to **2a**, **3a**, **4a**, and **5a** in a 95.5:0.8:1.3:2.4 ratio (entry 3). The amount of **4a** is increased to 34% after 31 h (entry 4). At 50 °C, both the reactivity and selectivity is dramatically decreased due to the low solubility of $HCOONH_4$ in methanol (entry 5). A 5 mol amount of $HCOONH_4$ is essential. Lowering the concentration to 2 M, the **2a**/**5a** ratio is decreased to 9 (entry 6). With 1 M $HCOONH_4$, the reactivity is halved and the alcohol product **5a** is produced in >50% yield (entry 7). A 10 mol amount of $HCOONH_4$ results in completed reaction with high chemoselectivity after 1 h (entry 8). The total concentration can be reduced to 0.33 M without loss of the amine/alcohol selectivity (entry 9), but an increase to 5 M results in the insolubility of $HCOONH_4$ (entry 10). Methanol is the solvent of choice. The reactivity is decreased in aqueous methanol, 1:1 alcohol$-CF_3CH_2OH$, and 2-propanol (entries 11−14). In aprotic solvents, the yields of the reduction products never exceed 15% (entries 15−20). In CH_3CN, CH_2Cl_2, benzene, and cyclohexane, the alcohol **5a** was obtained selectively (entries 15, 17, 19, and 20). On the other hand, the LW product **2a** was predominantly produced in DMF and THF (entries 16 and 18). Use of an excess either of ammonia or formic acid decreases the reactivity (entries 21 and 22). [RhCp*I$_2$]$_2$[6] and [Rh$_2$Cp*$_2$Cl$_3$]BARF[8] also showed the same reactivity and selectivity as those of [RhCp*Cl$_2$]$_2$ (entries 23 and 24).

The reproducibility was confirmed on a 10 g scale reaction using **1a**. Thus, a 1:5 mixture of **1a** and $HCOONH_4$ was reacted in methanol (83 mL) containing 257 mg of [RhCp*Cl$_2$]$_2$ at 70 °C for 7 h, giving **2a** in 92% yield as determined by NMR analysis of the crude mixture obtained by a usual workup under basic condition.[9] The pure **2a** was isolated in 85% yield (see the Experimental Section). The generality is high. All of primary, secondary alkyl methyl ketones (**1b** and **1c**) studied can be converted to the corresponding primary amines in greater than 90% yield (entries 25 and 26). The cyclic ketone (**1g**) remains a high reactivity, but the **2g**/**3g** ratio is decreased to 6 (entry 30). The reactivities of pinacolone (**1d**) and diphenyl ketone (**1e**) are low, and with dicyclohexyl ketone (**1f**) no reaction at all occurred.

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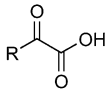
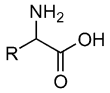
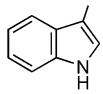
(9) For details of the workup, see the Supporting Information.

TABLE 2. [RhCp*Cl$_2$]$_2$-Catalyzed Reductive Amination of α-Keto Acids[a]

substrate	product	% yield [b]
		
7: R = C_6H_5		91 [c] (81)
8: R = 		72 [d] (72)
9: R = 		54 (53)
10: R = *t*-C_4H_9		70 [c]

[a] Conditions: [substrate] = 1 M, [**6**] = 5 mM, [$HCOONH_4$] = 5 M, CH_3OH, 50 °C, 2 h. [b] The yields were determined by ^{1}H NMR analysis using mesitylene as an internal standard. The values in parentheses correspond to the isolated yields. [c] 1.5 h. [d] 75 h.

As shown in Table 2, the present catalytic LW-type reaction can be applied to the α-keto acids.[10] When benzoylformic acid (**7**) was subjected to the above established conditions ([**6**] = 5 mM, [**7**] = 1 M, [$HCOONH_4$] = 5 M, CH_3OH, 50 °C), the reductive amination product was precipitated from the reaction mixture. Filtration gives pure phenylglycine in 81% isolated yield. Other keto acids possessing indole and thiophene groups (**8** and **9**) were also converted to the corresponding amino acids in good isolated yields. These amino acids cannot be synthesized via enzymatic methods.[11] *tert*-Butylglycine was obtained in 70% yield by use of 3,3-dimethyl-2-oxobutanoic acid (**10**). 3-(2-Furanyl)-2-oxoethanoic acid and pyruvic acid possessing α proton did not work under the present conditions.

When the Rh(III) complex **6** is mixed with a 37 mol amount of $HCOONH_4$ in CD_3OD, the ^{1}H NMR signals appear at δ −8.7 (t, J = 27.5 Hz) and δ −9.4 (t, J = 26.0 Hz) after 20 min at room temperature. These converge, after 2 h at 70 °C, to the signals at δ −18.4 (dd, J = 26.0 Hz) and δ −18.5 (dd, J = 26.0 Hz). These hydride species can be assigned to hydride-bridged dinuclear Rh complexes,[12] which would be just kinetic repositories for the real catalytic species.[13] We assume that [RhCp*Cl$_2$]$_2$ is converted, by the action of NH_3 and HCOOH, into an ammonia-coordinated metal hydride RhCp*HCl(NH_3) that acts as a chain carrier in the catalytic cycle.[14] Coordination of NH_3 onto Rh enhances the acidity of the hydrogen atom of NH_3 and also the nucleophilicity of the hydride of RhH.[13,15] The synergetic effect facilitates the formation of a catalyst−imine complex and then stabilizes the transition state by realizing the charge alternation on the C═N···H−N−Rh−H six atoms.[13] The hydride transfer from RhH to the C═N carbon gives a catalyst-product complex, which releases a free amine product together with the formation of a metal amide species. The Rh−NH_2 reacts quickly with formic acid to generate CO_2 and RhCp*HCl(NH_3), completing the catalytic cycle.

In summary, a novel catalytic system facilitating the Leuckart−Wallach-type reaction at a lower temperature with high chemoselectivity and generality has been established. Other than the desired primary amine products, the reaction produces only CO_2 and H_2O. Using 0.005 mol amount of catalyst and $HCOONH_4$, a variety of substrates including simple ketones are converted to the corresponding primary amines. With α-keto acids, α-amino acids are the products. The reaction is clean and operationally simple. In most cases, only filtration is necessary to arrive at α-amino acids in high yields. Related studies on the asymmetric synthesis as well as the mechanism are being carried out. These results will be reported in due course.

Experimental Section

Ten-Gram-Scale Procedure. Acetophenone (9.71 mL, 83.2 mmol) and CH_3OH (83.2 mL) were added to a 1000 mL Schlenk tube containing [RhCp*Cl$_2$]$_2$ (**6**) (257 mg, 416 μmol) and $HCOONH_4$ (26.2 g, 416 mmol). The reddish brown mixture was frozen, and the whole system was evacuated. The system was closed and then stirred at 70 °C for 7 h. After the dark green resulting solution was cooled to room temperature, 1 M aqueous HCl solution (160 mL) was added, and the mixture was washed twice with CH_2Cl_2 (20 mL) to remove the neutral compounds. After addition of a cold 12 M aqueous NaOH solution (15 mL) to the aqueous layer, the mixture was extracted six times with CH_2Cl_2 (50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation under reduced pressure gave crude **2a** (9.3 g, 92%) in >99% purity determined by ^{1}H NMR and GC analyses (for details, see the Supporting Information). This was distilled at 83 °C/44 mmHg to give **2a** (8.6 g, 85% yield).

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Supporting Information Available: General procedures for screening and the reductive amination of α-keto acids and characterization of all substrates and products obtained by the present method. This material is available free of charge via the Internet at http://pubs.acs.org.

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