Chelation-Assisted Intermolecular Hydroacylation: Direct Synthesis of Ketone from Aldehyde and 1-Alkene

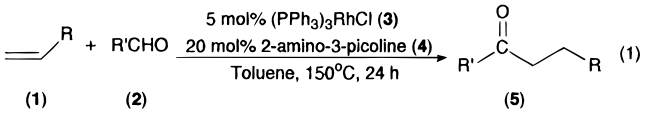
Chul-Ho Jun,* Hyuk Lee, and Jun-Bae Hong

Department of Chemistry, Yonsei University, Seoul 120-749, Korea

Received October 8, 1996

Activation of the aldehydic carbon−hydrogen bond by transition-metal complexes has especially received interest because of its relevance to organic synthesis through conversion of aldehyde into ketone (i.e., hydroacylation).[1] A negative consequence in the synthesis of ketone from aldehyde is decarbonylation in the acylmetal intermediate, formed by cleavage of the aldehydic carbon−hydrogen bond.[2] There are limitations to attempts to solve decarbonylation for direct intermolecular hydroacylation by cyclometalation with a specially designed model compound[3] or by stabilization of the complex by pressurization with carbon monoxide gas.[4] An indirect method consisting of a few steps to make ketone from aldehyde has also been developed with carboxaldimine, which can be converted by catalytic reaction with 1-alkene into carboxketimines.[5] This reaction is followed by hydrolysis under acid conditions to produce ketone. Until now, no practical direct intermolecular hydroacylation has been reported. Herein, we describe a one-step synthesis of ketone from aldehyde with the cocatalyst system of the transition-metal complex and 2-amino-3-picoline.

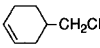
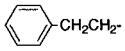
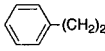
In our experiment, 1-alkene **1** reacted with aldehyde **2** in toluene at 150 °C for 24 h under a mixture of 5 mol % of chlorotris(triphenylphosphine)rhodium (I) (**3**) and 20 mol % of 2-amino-3-picoline (**4**) as a cocatalyst based upon **2** (eq 1).[6]



Following the reaction, the corresponding hydroacylated product, ketone, was isolated by column chromatography. The reactions between various aldehydes and 1-alkenes were examined, and the results are shown in Table 1.[7]

The resulting hydroacylated ketones were linear in shape, not branched alkyl ketones. The reaction of a chiral olefin such as 4-vinylcyclohexene (**1g**) with benzaldehyde (run 7) affords the corresponding ketone **5g**, which retains an asymmetric center in a 3-cyclohexenyl group. Aliphatic aldehyde still showed comparable reactivity with the aromatic aldehyde (runs 10−12). The reaction of a sterically hindered aliphatic aldehyde such as *tert*-butyl aldehyde **2f** afforded a lower yield of ketone compared with those of primary and secondary aliphatic

Table 1. Ligand-Assisted Intermolecular Hydroacylation of 1-Alkene with Aldehyde[a]

Entry	1-Alkene R (1)		Aldehyde R' (2)		Hydroacylated Product (5)		Yield (%)[b]
1	n-C_4H_9-	(1a)		(2a)	n-C_6H_{13}-CO-Ph	(5a)	72
2	n-C_3H_7-	(1b)			n-C_5H_{11}-CO-Ph	(5b)	75
3	H	(1c)			C_2H_5-CO-Ph	(5c)	92[c]
4	t-C_4H_9-	(1d)			t-$C_4H_9CH_2CH_2$CO-Ph	(5d)	68
5	n-C_8H_{17}-	(1e)			n-$C_{10}H_{21}$-CO-Ph	(5e)	74
6	$PhCH_2$-	(1f)			$PhCH_2CH_2CH_2$CO-Ph	(5f)	83
7		(1g)				(5g)	67[d]
8	C_6F_5-	(1h)			C_6F_5-CH_2CH_2CO-Ph	(5h)	90
9	n-C_3H_7-	(1b)	CH_3O-	(2b)	CH_3O-	CO-n-C_5H_{11} (5l)	66
10			n-C_6H_{13}-	(2c)	n-C_6H_{13}-CO-n-C_5H_{11}	(5j)	49
11				(2d)		CO-n-C_5H_{11} (5k)	67
12				CH_2CH_2- (2e)		$(CH_2)_2$-CO-n-C_5H_{11} (5l)	67
13			t-C_4H_9-	(2f)	t-C_4H_9-CO-n-C_5H_{11}	(5m)	6

[a] Aldehyde (0.44 mmol), 1-alkene (1.30 mmol), $(PPh_3)_3RhCl$ (0.022 mmol), and 2-amino-3-picoline (0.086 mmol) in toluene (0.1 g) at 150 °C for 24 h. [b] Isolated yield after chromatographic isolation (hexane:ethylacetate = 5:2). [c] Benzene was used as a solvent. [d] $[\alpha]_D$ + 3.62 from 4-vinylcyclohexene of $[\alpha]_D$ + 1.08.

Table 2. Effect of 2-Amino-3-picoline (4) on Hydroacylation of 1b with 2b[a]

entry	mol % of **4**	product ratio **5i**:anisole	isolated yield (%) of **5i**
1	0	0[b]:100	0
2	10	58:42	14
3	20	85:15	57
4	50	85:15	70
5	70	90:10	80
6	100	93:7	83

[a] Anisaldehyde (0.22 mmol), 1-pentene (1.08 mmol), $(Ph_3P)_3RhCl$ (0.022 mmol) in THF (2 mL) at 100 °C for 60 h under different mol % of 2-amino-3-picoline based upon anisaldehyde. [b] 46% yield of anisole was obtained, determined by GC.

(1) (a) Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, *96*, 4721. (b) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281. (c) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257. (d) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1982**, *240*, 285. (e) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451.

(2) (a) McQuillin, F. J.; Parker, D. G.; Stephenson, G. R. *Transition metal organometallics for organic synthesis*; Cambridge University Press: Cambridge, 1991; p 306. (b) Kondo, T.; Tantayanon, S.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1989**, *30*, 4137. (c) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 99. (d) Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* **1968**, *90*, 94. (e) Doughty, D. H.; Pignolet, L. H. *J. Am. Chem. Soc.* **1978**, *100*, 7083. (f) Walborsky, H. M.; Allen, L. E. *J. Am. Chem. Soc.* **1971**, *93*, 5465. (g) O'connor, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075.

(3) (a) Jun, C.-H. *Organometallics* **1996**, *15*, 895. (b) Jun, C.-H.; Lim, Y.-G. *Tetrahedron Lett.* **1995**, *36*, 3357. (c) Lee, H.; Jun, C.-H. *Bull. Korean Chem. Soc.* **1995**, *16*, 66. (d) Jun, C.-H. *J. Organomet. Chem.* **1990**, *390*, 361. (e) Suggs, J. W.; Wovkulich, M. J.; Cox, S. D. *Organometallics* **1985**, *4*, 1101. (f) Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640.

(4) (a) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (b) Tsuji, Y.; Yoshii, S.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *331*, 379.

(5) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 489. (b) Jun, C.-H.; Han, J.-S.; Kang, J.-B.; Kim, S.-I. *J. Organomet. Chem.* **1994**, *474*, 183. (c) Jun, C.-H.; Kang, J.-B.; Kim, J.-Y. *J. Organomet. Chem.* **1993**, *458*, 193. (d) Jun, C.-H.; Kang, J.-B.; Kim, J.-Y. *Tetrahedron Lett.* **1993**, *34*, 6431.

(6) A mixture of 46.6 mg (0.44 mmol) of **2a**, 9.3 mg (0.086 mmol) of **4**, and 20 mg (0.022 mmol) of **3** was dissolved in toluene (0.1 g) in a 1 mL screw-capped vial. After the mixture was stirred for several minutes, 109.0 mg (1.30 mmol) of **1a** was added. The mixture was magnetically stirred for 24 h at 150 °C. The solution was concentrated to give a residue that was purified by column chromatography (hexane: EtOAc = 5:2, SiO_2) to give 60.1 mg of **5a** (72% isolated yield), which was characterized by spectroscopic analysis.

S0022-3263(96)01887-7 CCC: $14.00

Scheme 1. Proposed Catalytic Cycle for Ligand-Assisted Hydroacylation (L = PPh_3)

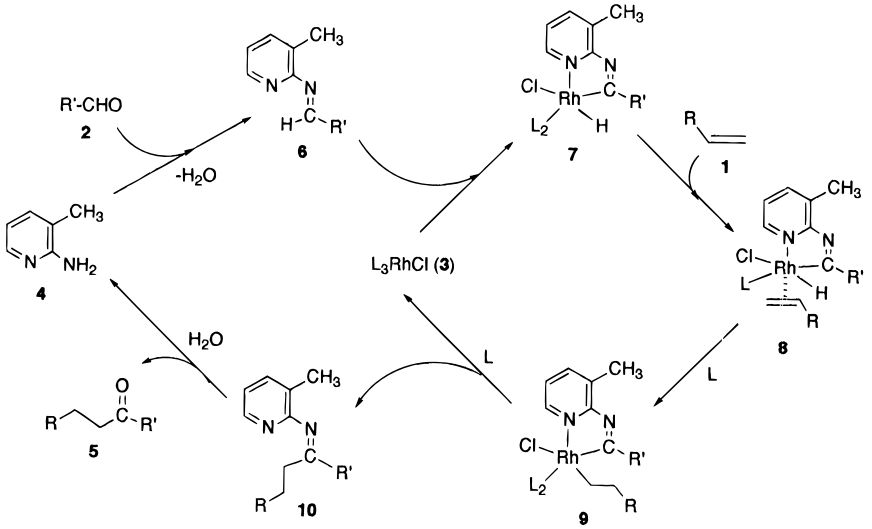


Table 3. Catalytic Activities of Some Transition Metal Complexes[a]

entry	catalyst	additive[b]	isolated yield (%) hexanophenone[c]
1	$(Ph_3P)_3RhCl$		72
2	$RhCl_3 \cdot xH_2O$	PPh_3	68
3	$Rh(CO)(PPh_3)_2Cl$		16
4	$Ru_3(CO)_{12}$	$(CH_3)_3NO$[d]	(10)
5	$Ru(PPh_3)_3Cl_2$	$NaBH_4$, PPh_3	(9)[e]
6	$Ir(CO)(PPh_3)_2Cl$		0
7	$(Ph_3P)_3IrCl$		0
8	$[(C_8H_{14})_2RhCl]_2$	PPh_3	48
9		$(p\text{-}CH_3C_6H_4)_3P$	61
10		$(p\text{-}CH_3OC_6H_4)_3P$	56
11		Cy_3P	38
12		$(CH_3)_3P$	0

[a] Benzaldehyde (0.22 mmol), 1-pentene (1.08 mmol), transition-metal complexes (0.022 mmol), and 2-amino-3-picoline (0.22 mmol) in THF (2 mL) at 100 °C for 40 h. [b] All phosphines added were 0.11 mmol. [c] Figures in parentheses were GC yield based upon benzaldehyde. [d] 0.066 mmol was added, and without additive, 3% of hexanophenone was formed. [e] Without additive, 1% of hexanophenone was formed.

aldehydes (run 13). This hydroacylation process is believed to proceed as illustrated in Scheme 1.

The first step might be condensation of aldehyde **2** and 2-amino-3-picoline (**4**) to generate aldimine **6** and H_2O. A carbon−hydrogen bond in **6** is cleaved by rhodium(I) in **3** to give an (iminoacyl)rhodium(III) hydride **7**, which was previously found from the reaction of aldimine **6** and **3**.[8] Coordination of 1-alkene **1** to **7** and subsequent hydride insertion into 1-alkene in **8** leads to an (iminoacyl)rhodium(III) alkyl **9**. Reductive elimination in **9** produces carboxketimine **10** with regeneration of catalyst **3**. Hydrolysis of **10** with H_2O, previously generated from the condensation of **2** and **4**, synthesizes products **5** and **4**. In this process, **4** and complex **3** act as catalysts. Linear alkyl ketones were obtained in this reaction through hydrometalation in **8** following anti-Markownikoff's rule, due to the steric congestion of the (iminoacyl)-rhodium(III) complex system.

To identify the effect of **4**, different molar ratios of **4** were applied for hydroacylation of 1-pentene with 4-anisaldehyde (**2b**) under mild conditions (10 mol % of **3**, THF, 100 °C, 60 h) (Table 2).[9]

Without the addition of **4**, the decarbonylation product, anisole, was obtained exclusively in 46% yield (Table 2, run 1). With 10 mol % of **4**, 4′-methoxyhexanophenone (**5i**) was isolated in 14% yield along with a 10% yield of anisole. By increasing the concentration of **4** to 20 mol %, 50 mol %, 70 mol %, and 100 mol %, the ratio of **5i** to anisole was increased to 85:15, 85:15, 90:10, and 93:7. This result indicates that hydroacylation competes with the decarbonylation of aldehyde. The above results show that increasing the concentration of 2-amino-3-picoline also increases the probability of carbon−hydrogen cleavage of carboxaldimine.

A variety of organometallic compounds, with or without additives, were studied in the conversion of **1** into **5** at 100 °C for 40 h. This reaction requires the catalyst, 10 mol % of metal complex, and 100 mol % of **4** (Table 3). The complexes $(PPh_3)_3RhCl$, $RhCl_3 \cdot H_2O$ with PPh_3, $Rh(CO)(PPh_3)_2Cl$, $Ru_3(CO)_{12}$ with $(CH_3)_3NO$, $Ru(PPh_3)_3Cl_2$ with $NaBH_4$, and PPh_3 were all catalytically active. It is interesting to note that even $Rh(CO)(PPh_3)_2Cl$ showed catalytic activity since it can be generated from decarbonylation of aldehyde by **3** (Table 3, run 3).[2] This result explains that although partial decarbonylation occurred during hydroacylation, the generated $Rh(CO)(PPh_3)_2Cl$ catalyst still has catalytic hydroacylation activity. When different types of phosphines were tested under the $[(C_8H_{14})_2RhCl]_2$ catalyst, the best result was obtained using tris(*p*-methylphenyl)phosphine (Table 3, runs 8−12).

In conclusion, this report shows the general direct intermolecular hydroacylation of 1-alkene with aldehyde with the assistance of 2-amino-3-picoline.

Acknowledgment. The support of this research by the Korea Science and Engineering Foundation (Grant No. 961-0306-054-2) and the Ministry of Education (Project No. BSRI-96-3422) is gratefully acknowledged. The authors also acknowledge a Research Grant from Yonsei University.

JO961887D

(7) All ketones were the reported compounds except **5h**. Spectroscopic data for **5h**: ^1H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) δ 8.0 (dd, J = 8.3 Hz, 2H, 2,6-Hs in phenyl group), 7.4−7.2 (m, 3H, 3,4,5-Hs in phenyl group), 3.3 (t, J = 7.2 Hz, 2H, α-CH_2 to CO), 3.1 (t, J = 7.3 Hz, 2H, β-CH_2 to CO); ^{13}C NMR (72.5 MHz, $CDCl_3$, 25 °C, TMS) δ 197.7 (CO), 136.2−127.9 (Cs of C_6H_5 and C_6F_5 group), 37.3 (α-C of CO), 17.0 (β-C of CO); IR (neat) 2917, 1692 (CO), 1598, 1515, 1450, 1289, 1204, 1171, 1045, 957, 760, 695 cm^{-1}; MS (70 eV) m/z 300 (31) [M^+], 181 (5), 105 (100) [$PhCO^+$], 77 (86.2) [$C_6H_5^+$]; HRMS calcd for $C_{15}H_9OF_5$ 300.057356, found 300.057686.

(8) Intermediates, aldimine **6** (R = Ph), and complex **7** were already prepared and characterized in ref 7a.

(9) Other 2-aminopyridine derivatives have been tested for this reaction, and 2-amino-3-picoline showed the best result. Toluene and THF did not show any large difference in results, but we preferred THF to toluene under mild conditions such as 100 °C.