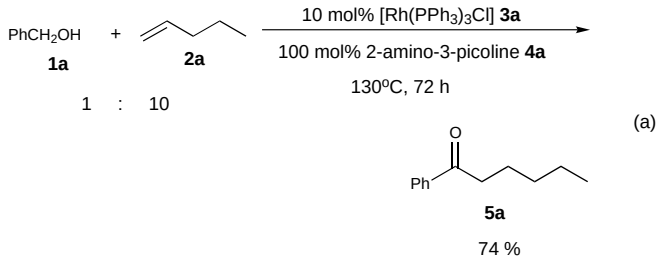
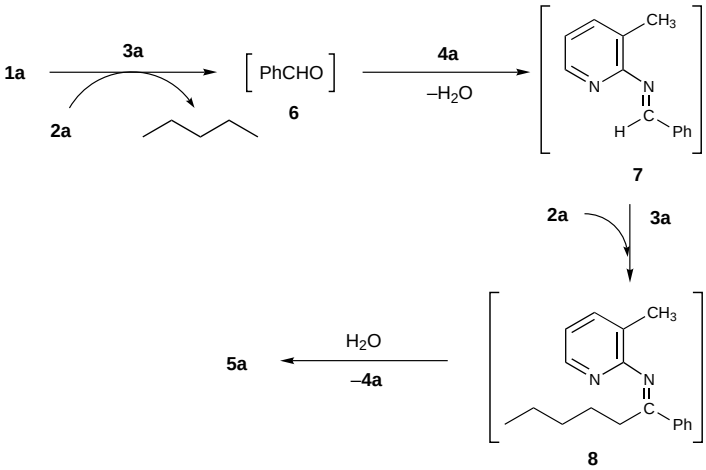
Direct Synthesis of Ketones from Primary Alcohols and 1-Alkenes**

Chul-Ho Jun,* Chan-Woo Huh, and Sang-Jin Na

Activation of the aldehydic carbon–hydrogen bond by transition metal complexes has received much attention in organic synthesis because of its potential to convert aldehydes into ketones by hydroacylation.[1] Although intramolecular hydroacylation has been studied in detail,[2] only a few methods have been reported for transition metal catalyzed intermolecular hydroacylation.[3] Recently, we developed a direct chelation-assisted intermolecular hydroacylation.[4] Primary and secondary alcohols can be oxidized to aldehydes and ketones through hydrogen transfer by a transition metal catalyst. In the course of this oxidation, hydrogen atoms are transferred to hydrogen acceptors such as ketones or alkenes to produce alcohols and alkanes, respectively.[5,6] If oxidation by transition metal mediated hydrogen transfer and hydroacylation occur consecutively with the aid of identical catalysts and olefins, it should be possible to prepare ketones directly from primary alcohols and alkenes. We describe here a one-pot synthesis of a ketone from a primary alcohol and a 1-alkene using a transition metal catalyst together with 2-aminopyridine derivatives. To the best of our knowledge, this is the first example of a direct ketone synthesis from a primary alcohol and a 1-alkene.

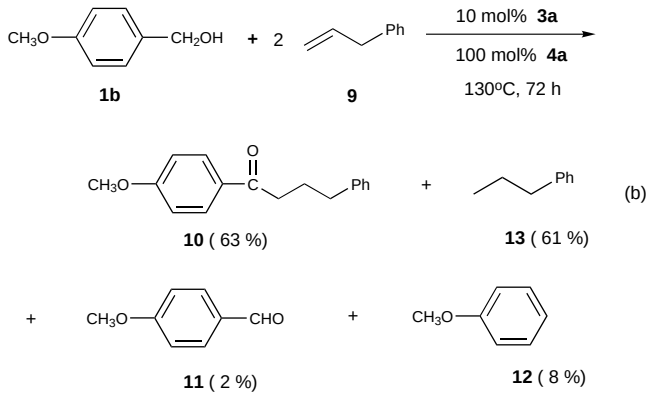
Benzyl alcohol (**1a**) was treated with 1-pentene (**2a**) at 130 °C for 72 h using as catalyst a mixture of [chlorotris(triphenylphosphane)rhodium(I)] (**3a**, 10 mol % based upon **1a**) and 2-amino-3-picoline [**4a**, 100 mol %; Eq. (a)]. Hexanophenone (**5a**) was isolated in 74 % yield after chromatography. The reaction proceeded quite well without a solvent. A possible mechanism for this one-pot synthesis of **5a** from **1a** and **2a** is illustrated in Scheme 1. The first step must be oxidation by hydrogen transfer, in which primary alcohol **1a** is converted into aldehyde **6** via complex **3a**. Hydrogen atoms generated from **1a** must be transferred to **2a** to afford pentane.[6] The aldehyde then reacts with **4a** to form aldimine **7** and H_2O. Formation of an aldimine from a primary alcohol and a primary amine in the presence of a transition metal catalyst is presumed to be the key step in N-alkylation of primary amines with primary alcohols.[7] Subsequent hydroiminoacylation of **2a** with **7** leads to ketimine **8**, as reported earlier.[8] Hydrolysis of **8** by H_2O, formed through the reaction of **4a** with **6**, affords ketone **5a** as the final product. Direct synthesis of **5a** from **2a** and **6** by chelation-assisted hydroacylation has already been reported.[4] Since **2a** must serve both as a hydrogen acceptor in the first step and as a hydroacylation substrate in the second step, the amount of **2a** should be at least twice that of **1a**.[9]





Scheme 1. Mechanism for the direct synthesis of ketones from primary alcohols and 1-alkenes by oxidation and hydroacylation.

To determine the intermediates, *p*-methoxybenzyl alcohol (**1b**) was allowed to react at 130 °C for 72 h with allylbenzene (**9**) under cocatalysis with **3a** (10 mol %) and **4a** (100 mol %). This resulted in a mixture of *p*-methoxy-γ-phenylbutanophenone (**10**), anisaldehyde (**11**), anisole (**12**), and propylbenzene (**13**) in 63, 2, 8, and 61 % yield, respectively, based upon **1b** [Eq. (b)].[10] Compound **13** is the hydrogenation product of **9**, while **11** is an oxidation product of **1b** and **12** the decarbonylation product of **11**. Establishment of the presence of **11** and **13** confirms that hydrogen transfer occurs from the primary alcohol to the 1-alkene.



[*] Prof. Dr. C.-H. Jun, C.-W. Huh, S.-J. Na
Department of Chemistry
Yonsei University
Seoul 120-749 (Korea)
Fax: Int. code + (82) 2-364-7050
e-mail: junch@alchemy.yonsei.ac.kr

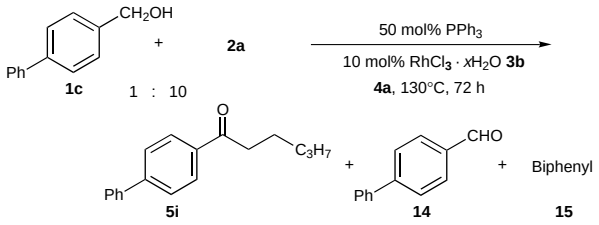
[**] This work was supported by the Korean Science and Engineering Foundation (grant-in-aid 961-0306-054-2) and the Korean Ministry of Education (project no. BSRI-96-3422). The authors wish also to thank IBRD (the International Bank for Reconstruction and Development) for the purchase of a 250-MHz NMR spectrometer.

  1433-7851/98/3701-0145 $ 17.50+.50/0

In the catalytic reaction of **1a** and **2b** with $RhCl_3 \cdot H_2O$ (**3b**) and PPh_3 under the same reaction conditions as above, heptanophenone (**5b**) was obtained in much higher yield (84%) than in the reaction with **3a**. The reason is not clear, but the active catalyst **3a** might be freshly generated in situ by the reaction of **3b** with PPh_3.[11]

To clarify the influence of **4a**, this substance was introduced in various concentrations into the hydroacylation of **2a** with 4-biphenylmethanol (**1c**). Reaction occurred at 130 °C in the course of 72 h with the catalytic system composed of **3b** (10 mol%) and PPh_3 (Table 1). No ketone was obtained in the absence of **4a**, as expected. The yield of decarbonylation product **15** decreased with increasing concentration of **4a**. This suggests that a high concentration of **4a** retards the decarbonylation of aldehyde generated from alcohol by increasing the probability of carbon–hydrogen bond cleavage of carboxaldimine, which is present in higher concentration.

Table 1. Influence of the concentration of 2-amino-3-picoline (**4a**) on the reaction of 4-biphenylmethanol (**1c**) with 1-pentene (**2a**).[a]

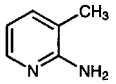
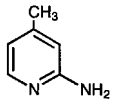
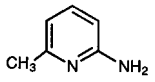
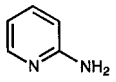
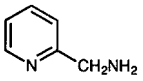
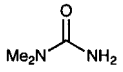


Entry	**4a** [mol%]	Yield (**5i**) [%]	**5i**[b]	**14**[b]	**15**[b]
1	20	21	55	9	36
2	50	55	86	4	10
3	100	67	92	0	8
4	200	88	100	0	0

[a] A mixture of **1c** (0.48 mmol), **2a** (4.8 mmol), **3b** (0.048 mmol), PPh_3 (0.24 mmol), and various amounts of **4a** was heated for 72 h at 130 °C. [b] Relative amounts determined by gas chromatography.

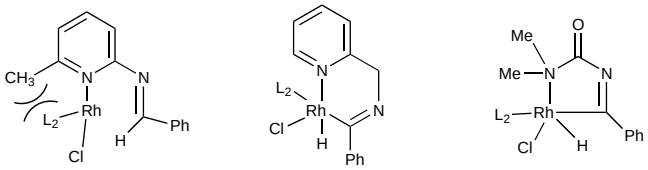
Various types of amine derivatives were examined with the catalytic system consisting of **3b** and PPh_3 (Table 2). Among 2-aminopyridine derivatives, 2-amino-4-picoline (**4b**) showed the greatest catalytic activity, and 2-amino-6-picoline (**4c**) the least. This may be because of steric hindrance by the 6-methyl group (see **16**). The nitrogen atom in the pyridinyl group would coordinate to the metallic center with difficulty in this case, so that the metal and carbon–hydrogen bonds in the aldimine would not be brought into sufficiently close proximity. 2-Aminomethylpyridine (**4e**) showed no catalytic activity, perhaps due to the formation of a less-favored six-membered ring metallacyclic complex such as **17**, or to the instability of the *N*-alkylaldimine compared with the more conjugated *N*-arylaldimine. Even *N*,*N*-dimethylurea (**4f**), which lacks the 2-aminopyridine moiety, provided a hydroacylated product in 3% yield, possibly via intermediate **18**. This clearly demonstrates that formation of the five-membered metallacyclic intermediate is a prerequisite for this reaction. No hydroacylated product was detected with triethylamine (**4g**).

Table 2. Results of the hydroacylation of 1-pentene (**2a**) with benzyl alcohol (**1a**) to give hexanophenone (**5a**) in the presence of $RhCl_3 \cdot xH_2O$ and PPh_3 as catalyst system, as well as various amines (100 mol%).[a]

Entry	Amine		Yield [%][b]
1		**4a**	54
2		**4b**	91
3		**4c**	9
4		**4d**	63
5		**4e**	0
6		**4f**	3
7	NEt_3	**4g**	0

[a] A mixture of **1a** (0.48 mmol), **2a** (4.8 mmol), **3b** (0.048 mmol), PPh_3 (0.24 mmol), and an amine (0.48 mmol) was heated for 40 h at 130 °C. [b] Isolated **5a**.

Catalytic reactions of various primary alcohols and 1-alkenes with **3b** (3.3 mol% based upon alcohol) and PPh_3 (16.5 mol%) as well as **4b** (100 mol%) at 130 °C for 12 h were also examined (Table 3). The resulting hydroacylated ketones

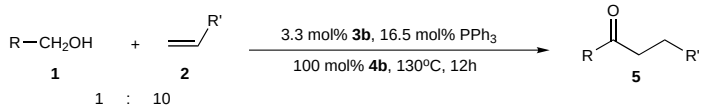


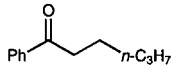
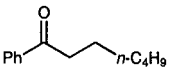
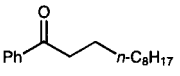
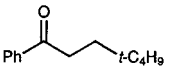
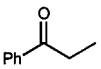
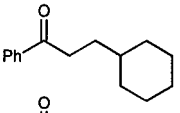
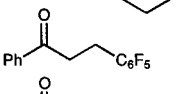
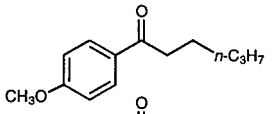
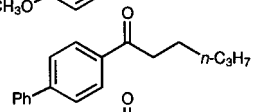
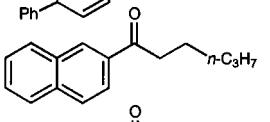
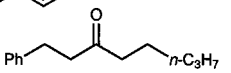
were linear, not branched systems.[12] There appear to be no limitations with respect to the 1-alkene component. Even the sterically hindered 1-alkene 3,3-dimethyl-1-butene (**2d**) provided **5d** in fairly good yield (85%). All the benzylic alcohols **1a**–**1d** provided good results, although yields with aliphatic primary alcohols like **1e** were low (22%).

We thus present a general synthesis for ketones starting from 1-alkenes and primary alcohols with the catalytic assistance of 2-aminopyridine derivatives and transition metal complexes. This newly developed synthesis achieves the generality required for a practical organic synthetic procedure.

  1433-7851/98/3701-0146 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1998**, *37*, No. 1/2

Table 3. Ligand-supported intermolecular hydroacylation of 1-alkenes **2** with primary alcohols **1**.[a]



Entry	Alcohol R (**1**)	1-Alkene R′ (**2**)	Hydroacylated product **5**		Yield [%][b]
1	Ph (**1a**)	n-C_3H_7 (**2a**)		**5a**	86
2	Ph (**1a**)	n-C_4H_9 (**2b**)		**5b**	84
3	Ph (**1a**)	n-C_8H_{17} (**2c**)		**5c**	66
4	Ph (**1a**)	t-C_4H_9 (**2d**)		**5d**	85
5[c]	Ph (**1a**)	H (**2e**)		**5e**	43
6	Ph (**1a**)	Cyclohexyl (**2f**)		**5f**	76
7[d]	Ph (**1a**)	C_6F_5 (**2g**)		**5g**	69
8	4-$MeOC_6H_4$ (**1b**)	n-C_3H_7 (**2a**)		**5h**	77
9	4-PhC_6H_4 (**1c**)	n-C_3H_7 (**2a**)		**5i**	84
10	2-Naphthyl (**1d**)	n-C_3H_7 (**2a**)		**5j**	78
11	$PhCH_2CH_2$ (**1e**)	n-C_3H_7 (**2a**)		**5k**	22[e]

[a] A mixture of **1** (1.435 mmol), **4b** (1.435 mmol), **3b** (0.048 mmol), PPh_3 (0.239 mmol), and **2** (14.300 mmol) was heated for 12 h at 130 °C. [b] Yield of hydroacylated product isolated by column chromatography (SiO_2, hexane/EtOAc, 5/2). [c] Benzene was used as solvent. [d] Toluene (200 mg) was added as a solvent. [e] With **3a** as catalyst. Use of the same molar quantity of **3b** and PPh_3 instead of **3a** led to the isolation of **5k** (10%).

Experimental Section

In a typical experiment, a mixture of **1a** (155 mg, 1.44 mmol), **4b** (155 mg, 1.44 mmol), and PPh_3 (62.6 mg, 0.239 mmol) was dissolved in **2a** (1000 mg, 14.3 mmol) in a 2.5-mL screw-capped vial. After the mixture had been stirred for several minutes, complex **3b** (10.0 mg, 0.048 mmol) was added, and the resulting mixture was stirred for 12 h at 130 °C. The solution was concentrated, and the residue obtained was purified by column chromatography (hexane/EtOAc, 5/2) to give 218 mg of **5a** (86% yield).

Received: July 2, 1997 [Z10629IE]
German version: *Angew. Chem.* **1998**, *110*, 150–152

Keywords: C–H activation · homogeneous catalysis · hydroacylations · hydrogen transfer · metallacycles

[1] a) J. Schwartz, J. B. Cannon, *J. Am. Chem. Soc.* **1974**, *96*, 4721; b) C. F. Lochow, R. G. Miller, *ibid*. **1976**, *98*, 1281; c) P. Isnard, B. Denise, R. P. A. Sneeden, *J. Organomet. Chem.* **1982**, *240*, 285.

[2] a) R. W. Barnhart, B. Bosnich, *Organometallics* **1995**, *14*, 4343; b) R. W. Barnhart, X. Wang, P. Noheda, S. H. Bergens, J. Whelan, B. Bosnich, *J. Am. Chem. Soc.* **1994**, *116*, 1821; c) Y. Taura, M. Tanaka, K. Funakoshi, K. Sakai, *Tetrahedron Lett.* **1989**, *30*, 6349; d) D. P. Fairlie, B. Bosnich, *Organometallics* **1988**, *7*, 946; e) D. P. Fairlie, B. Bosnich, *ibid.* **1988**, *7*, 936; f) B. R. James, C. G. Young, *J. Chem. Soc. Chem. Commun.* **1983**, 1215; g) D. Milstein, *ibid.* **1982**, 1357; h) R. C. Larock, K. Oertle, G. F. Potter, *J. Am. Chem. Soc.* **1980**, *102*, 190; i) R. E. Campbell, Jr., C. F. Lochow, R. G. Miller, *ibid.* **1980**, *102*, 5824; j) K. Sakai, J. Ide, O. Oda, N. Nakamura, *Tetrahedron Lett.* **1972**, *13*, 1287.

[3] a) T. Kondo, M. Akazome, Y. Tsuji, Y. Watanabe, *J. Org. Chem.* **1990**, *55*, 1286; b) Y. Tsuji, S. Yoshii, T. Ohsumi, T. Kondo, Y. Watanabe, *J. Organomet. Chem.* **1987**, *331*, 379; c) T. B. Marder, D. C. Roe, D. Milstein, *Organometallics* **1988**, *7*, 1451; d) K. P. Vora, C. F. Lochow, R. G. Miller, *J. Organomet. Chem.* **1980**, *192*, 257.

[4] C.-H. Jun, H. Lee, J.-B. Hong, *J. Org. Chem.* **1997**, *62*, 1200.

[5] a) R. Noyori, S. Hashiguichi, *Acc. Chem. Res.* **1997**, *30*, 97; b) G. Zassinovich, G. Mestroni, *Chem. Rev.* **1992**, *92*, 1051; c) R. A. W. Johnstone, A. H. Wilby, *ibid.* **1985**, *85*, 129; d) G. Brieger, T. J. Nestrick, *ibid.* **1974**, *74*, 567.

[6] R. Spogliarich, A. Tencich, J. Kaspar, M. Graziani, *J. Organomet. Chem.* **1982**, 453.

[7] a) Y. Watanabe, Y. Morisaki, T. Kondo, T. Mitsudo, *J. Org. Chem.* **1996**, *61*, 4214; b) S. I. Murahashi, K. Kondo, T. Hakada, *Tetrahedron Lett.* **1982**, *23*, 229.

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

[9] By increasing the ratio of **1a** to **2a** from 1:1 to 1:2, 1:5, and 1:10, the yield of **5a** was also increased by 44, 68, and 74%, respectively. We therefore chose a ratio of 1:10 for the concentrations of **1a** to **2a**.

[10] The yield of **10** is calculated on the basis of hydrogen atoms released from **1b**.

[11] J. A. Osborn, G. Wilkinson, *Inorg. Syn.* **1967**, *10*, 67.

[12] Under these reaction conditions, no decarbonylation product was detected from **1b–e**.

  1433-7851/98/3701-0147 $ 17.50+.50/0