Letter

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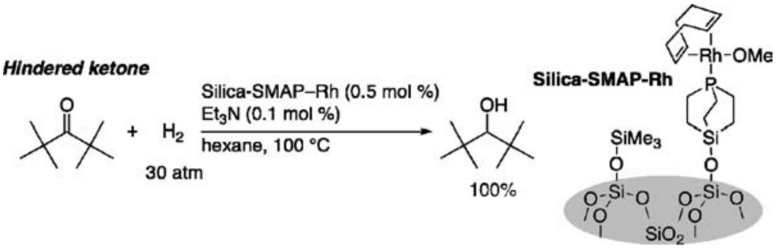

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Hydrogenation of Hindered Ketones Catalyzed by a Silica-Supported Compact Phosphine−Rh System

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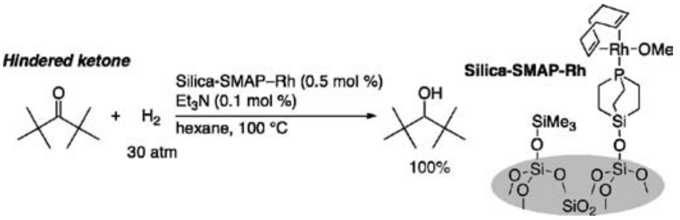
ABSTRACT



A heterogeneous mono(phosphine)−Rh catalyst system silica-SMAP−Rh(OMe)(cod), where silica-SMAP stands for a caged, compact trialkylphosphine (SMAP) supported on silica gel, showed broad applicability toward the hydrogenation of hindered ketones. Doubly α-branched ketones such as diisopropyl ketone was hydrogenated under nearly atmospheric conditions. Di-*tert*-butyl ketone could be hydrogenated under more forcing conditions.

Hydrogenation of ketones is feasible with various types of catalysts under transfer hydrogenation conditions that make use of secondary alcohols as a hydrogen source,[1] but catalysts effective for that of simple, nonchelating ketones with molecular hydrogen is not so common.[2] In particular, the hydrogenation of hindered ketones is extremely difficult.[3,4] In the course of our studies on the application of caged, compact trialkylphosphine Ph-SMAP[5] toward transition metal catalysis, we found that its rhodium complex displays exceptionally high catalytic activity for the hydrogenation of simple, noncoordinating, and sterically demanding ketones.[5c] On the other hand, in our previous study, the silica-immobilized SMAP (silica-SMAP, **1**) was used for the selective formation of a mono(phosphine)−rhodium species. The immobilized complex was identified to be a precursor that generates a highly active catalyst for the hydrosilylation of ketones with triorganosilanes especially for the reaction

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(1) Klomp, D.; Hanefeld, U.; Peters, J. A. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J., Ed.; Wiley-VCH: Winheim, Germany, 2007; Vol. 2, pp 585−630.

(2) (a) Blum, Y.; Czarkle, D.; Rahamim, Y.; Shvo, Y. *Organometallics* **1985**, *4*, 1459–1461. For review on homogeneous hydrogenation of carbonyl compounds, see: (b) Clarke, M. L.; Roff, G. J. In *Handbook of Homogeneous Hydrogenation*; de Vries, J. G.; Elsevier, C. J., Ed.; Wiley-VCH: Winheim, Germany, 2007; Vol. 1, pp 413−454.

(3) Diisopropyl ketone (**3a**) could not be reduced with Raney nickel or with nickel and some promoters, but was finally reduced with an equal weight of catalyst promoted with chloroplatinic acid and sodium hydroxide. See: (a) Blance, R. B.; Gibson, D. T. *J. Chem. Soc.* **1954**, 2487–2489. See also: (b) Freiferder, M. In *Catalytic Hydrogenation in Organic Synthesis. Procedures and Commentary*; Wiley: New York, 1978; Chapter 9, pp 78−89. Hydrogenation of **3a** with Shvo's Ru catalyst required a high hydrogenation pressure (34 atm) and a high reaction temperature (145 °C, 3 h) to gain the TON of 1760 (ref 2a).

(4) For the vapor phase transfer hydrogenation using isopropyl alcohol as a hydrogen donor over a calcinated Mg−Al hydrotalcites catalyst at 200 °C, see: Jyothi, T. M.; Raja, T.; Rao, B. S. *J. Mol. Catal., A* **2001**, *168*, 187–191.

(5) SMAP: silicon-constrained monodentate trialkylphosphine. See: (a) Ochida, A.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2003**, *5*, 2671–2674. (b) Ochida, A.; Ito, S.; Miyahara, T.; Ito, H.; Sawamura, M. *Chem. Lett.* **2006**, *35*, 294–295. (c) Ochida, A.; Hamasaka, G.; Yamauchi, Y.; Kawamorita, S.; Oshima, N.; Hara, K.; Ohmiya, H.; Sawamura, *Organometallics*, in press.

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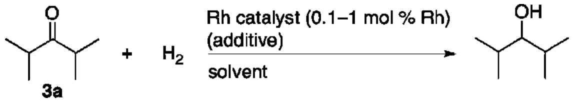
Table 1. Hydrogenation of Diisopropyl Ketone (**3a**) Catalyzed by Rh−Phosphine Systems[a]



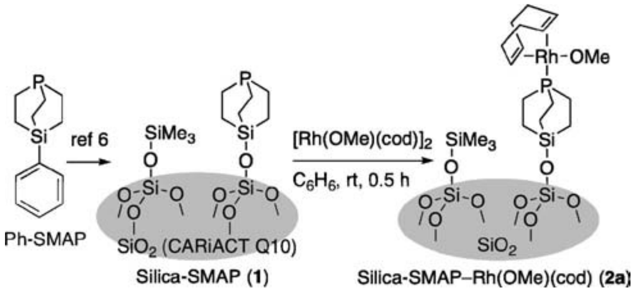
entry	catalyst precursor	Rh/**3a**	solvent	H_2[b] (atm)	temp (°C)	time (h)	yield[c] (%)
1	Silica-SMAP−Rh(OMe)(cod) (**2a**)	0.005	hexane	5	23	10	100
2	**2a**/Et_3N[d]	0.005	hexane	5	23	3	100
3[e]	**2a**/Et_3N	0.001	hexane	10	50	6	98
4	**2a**	0.005	MeOH	5	23	10	57
5	**2a**	0.005	*i*-PrOH	5	23	10	95
6	**2a**	0.005	THF	5	23	10	45
7	**2a**	0.005	CH_2Cl_2	5	23	10	6
8	silica-SMAP−RhCl(cod) (**2b**)	0.005	MeOH	5	23	10	13
9	silica-SMAP (**1**)/$[Rh(cod)_2]BF_4$	0.005	MeOH	5	23	10	32
10	**2b**/Na[B{3,5-$(CF_3)_2$-C_6H_3}$_4$] (1:1)	0.005	MeOH	5	23	10	0
11[f]	Ph-SMAP/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	5	23	20	0
12[f]	Ph-SMAP/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	30	100	20	46
13[f]	Me_3P/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	30	100	20	1
14[f]	Bu_3P/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	30	100	20	4
15[f]	(*t*-Bu_3)P/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	30	100	20	0
16[f]	Ph_3P/$\{Rh(OMe)(cod)\}_2$[g]	0.01	THF	30	100	20	0
17[f]	dppe/$\{Rh(OMe)(cod)\}_2$[h]	0.01	THF	30	100	20	0

[a] **3a**, 1.0 mmol; solvent, 1.0 mL unless otherwise noted. [b] Initial hydrogen pressure. [c] Determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [d] Et_3N; 0.1 mol %. [e] **3a**, 5.0 mmol; Et_3N, 0.02 mol %; hexane 1 mL. [f] Data taken from ref 5c. [g] Rh/P; 1:1. [h] Rh/P; 1:2.

of sterically demanding substrates.[6,7] Accordingly, we decided to examine silica-SMAP for ligand performance in the Rh-catalyzed hydrogenation of hindered ketones and found that anchoring SMAP on the silica support caused remarkable increase of catalytic activity.

Results of the hydrogenation of diisopropyl ketone (**3a**) are summarized in Table 1. The hydrogenation of **3a** catalyzed by 0.5 mol % of silica-SMAP−Rh(OMe)(cod) [**2a**, 0.06−0.07 mmol g^{-1} (for Rh)] ($S/C = 200$), which was prepared from [$\{Rh(OMe)(cod)\}_2$] and silica-SMAP (**1**) (Scheme 1)[8] proceeded smoothly at rt with 5 atm of initial hydrogen pressure in hexane, reaching quantitative conversion to the corresponding alcohol in 10 h (Table 1, entry 1). Addition of a subcatalytic amount (0.1 mol %) of Et_3N caused significant rate enhancement; the reaction time was shortened to 3 h (entry 2).[9]

Scheme 1. Synthesis of Silica-SMAP and Its Rh Complex



Alcoholic solvents such as MeOH and *i*-PrOH as well as THF can be used but the reactions were significantly slower than in hexane (entries 4−6). The reaction was almost inhibited with CH_2Cl_2 solvent (entry 7). The chloro complex silica-SMAP−RhCl(cod) (**2b**)[6b] is less reactive than methoxo complex **2a** (entries 1 vs 8). The catalyst system that was prepared in situ from **1** and cationic complex $[Rh(cod)_2]BF_4$ was slightly less active than the methoxo complex (**2a**) (entry 9). The addition of Na[B{3,5-$(CF_3)_2$-C_6H_3}$_4$] to the chlororhodium catalyst system (**2b**) caused complete loss of the activity (entry 10).

With the silica-SMAP−Rh(OMe)(cod) (**2a**)/Et_3N/hexane system, the catalyst loading could be reduced to 0.1 mol % ($S/C = 1000$) by a slight increase of initial hydrogen pressure (10 atm), reaction temperature (50 °C), and concentration (Table 1, entry 3).

The bond between the P atom of **1** and the Rh atom is fairly robust. Leaching of Rh after the reaction (Table 1, entries 1−10) was not visually observed, and the silica-SMAP−Rh catalysts could be removed by simple filtration.[10]

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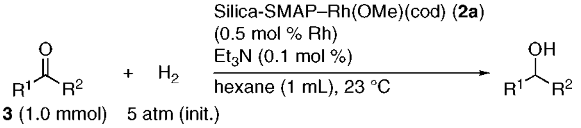
(6) (a) Hamasaka, G.; Ochida, A.; Hara, K.; Sawamura, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5381–5383. (b) Hamasaka, G.; Kawamorita, S.; Ochida, A.; Akiyama, R.; Hara, K.; Fukuoka, A.; Asakura, K.; Chun, W. J.; Ohmiya, H.; Sawamura, M. Submitted for publication.

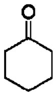
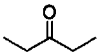
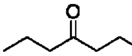
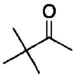
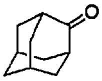
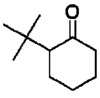
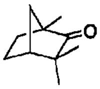
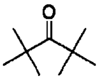
(7) For a related study with a self-assembled monolayer of SMAP on gold surface, see: Hara, K.; Akiyama, R.; Takakusagi, S.; Uosaki, K.; Yoshino, T.; Kagi, H.; Sawamura, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 5627–5630.

(8) Silica-SMAP (**1**) was prepared with CARiACT Q-10 silica gel (Fuji Silysia Chemical Ltd.). Rh complex **2a** (yellow powder) was prepared according to the reported procedure for a preparation of the corresponding chloro complex (**2b**) (see ref 6).

(9) A mechanism for the rate enhancement with Et_3N is unclear.

Table 2. Hydrogenation of Nonfunctionalized Ketones Catalyzed by the Silica-SMAP−Rh System



entry	ketone	time (h)	yield (%)[a] (cis/trans, endo/exo)
1	 **3b**	1.5	100
2	 **3c**	1	100
3	 **3d**	1.5	100
4	 **3e**	10	98
5	 **3f**	8	100
6	 **3g**	12	100 (55:45)
7	 **3h**	16	93 (68:32)
8	 **3i**	10	0

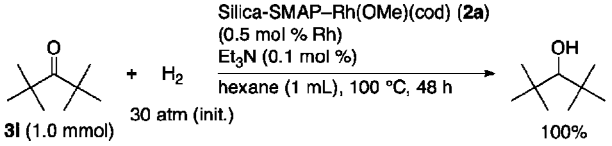
[a] Determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard.

As reported previously, Ph-SMAP is a specifically effective ligand among soluble phosphine ligands for the hydrogenation of sterically hindered ketones.[5c] Namely, the hydrogenation of diisopropyl ketone (**3a**) proceeded in the presence of a catalyst prepared in situ from [{Rh(OMe)(cod)}$_2$] and Ph-SMAP (1 mol % Rh, Rh/P 1:1) under 30 atm of hydrogen pressure at 100 °C in THF, showing 46% conversion after 20 h (Table 1, entry 12). In contrast, the hydrogenation of **3a** showed only a trace of conversion when Me$_3$P and Bu$_3$P were employed as a ligand (Rh/P 1:1) under the otherwise identical conditions (entries 13 and 14), and did not take place at all with (*t*-Bu)$_3$P, PPh$_3$ (Rh/P 1:1) and dppe (Rh/P 1:2) (entries 15−17). Nevertheless, the ligand effect of the soluble phosphine Ph-SMAP is much smaller than that of the supported phosphine silica-SMAP (**1**); the effect of the anchoring of SMAP on the solid support is critical for the hydrogenation activity at nearly ambient conditions. Indeed, no hydrogenation of **3a** occurred with the [{Rh(OMe)(cod)}$_2$]/Ph-SMAP catalyst system (1 mol % Rh, Rh/P 1:1) with 5 atm of initial hydrogenation pressure at rt (entry 11).

Next, we applied the Rh−silica SMAP catalytic system (silica-SMAP−Rh(OMe)(cod) (**2a**)/Et$_3$N in hexane) to the hydrogenation of various ketones with simple hydrocarbon substituents. Results obtained with 0.5 mol % of catalyst loading and 5 atm of initial hydrogen pressure at rt are summarized in Table 2. The reaction of less-hindered ketones such as cyclohexanone (**3b**), diethyl ketone (**3c**), and dipropyl ketone (**3d**) required shorter reaction times (1−1.5 hs) for completion as compared with the reaction of diisopropyl ketone (**3a**) (Table 2, entries 1−3). Acyclic, *tert*-butyl methyl ketone (**3e**) and caged ketone 2-adamantanone (**3f**) were quantitatively converted to the corresponding alcohols in 10 and 8 h, respectively (entries 4 and 5). Hindered substituted cyclohexanone 2-(*tert*-butyl)cyclohexanone (**3g**) and bicyclic ketone fenchone (**3h**) were also hydrogenated smoothly (12 h, 100% and 16 h, 93%, respectively) albeit with low stereoselectivities (cis/trans, 55:45 and endo/exo, 68:32, respectively) (entries 6 and 7).

Extremely congested di-*tert*-butyl ketone (**3i**) did not undergo hydrogenation under the nearly ambient conditions (Table 2, entry 8), but complete conversion to di-*tert*-butylmethanol was accomplished under more forcing conditions (0.5 mol % Rh, 30 atm of initial hydrogen pressure, 100 °C, 48 h) (Scheme 2).

Scheme 2. Hydrogenation of Di-*tert*-butyl Ketone (**3i**) Catalyzed by the Silica-SMAP−Rh System



Results of the hydrogenation of functionalized ketones catalyzed by **2a**/Et$_3$N system are summarized in Figure 1. While functional groups such as ester, methoxy group, and the tertiary amino group in **3j−m** caused a slight retarding effect for hydrogenation, bulky steroidal ketone **3n** with a secondary hydroxy group was hydrogenated smoothly with good diastereoselectivity (α/β; 92:8). Unfortunately, however, no reaction was observed with pyridyl ketones **3o−q** and sulfide-functionalized ketone **3r** at least under the nearly ambient conditions. Overall, it seems that strongly coordinating substrates inhibit the hydrogenation catalyzed by the silica-SMAP−Rh system, contrasting with a general trend in metal-catalyzed hydrogenations that substrate chelation is favored for faster reaction.

The high activity of the silica-SMAP−Rh systems toward the hindered ketones would be attributable to the sparse

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(10) Reusability of the silica-SMAP−Rh system has not been examined in the present study because of the expected difficulty in handling highly active catalytic species under the hydrogenation conditions in the laboratory experiments. Instead, the silica-SMAP−Rh catalyst system that was generated from chloro complex **2b** displayed excellent reusability in the hydrosilylation of ketones (see, ref 6).

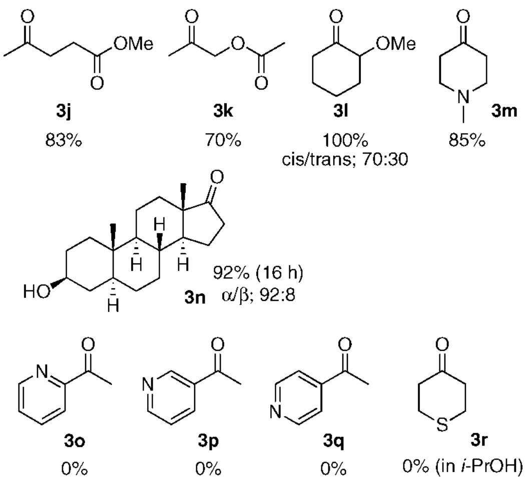

Figure 1. Results (yields and selectivities) of the hydrogenation of functionalized ketones catalyzed by **2a**. Conditions: **3**, 1.0 mmol; **2a**, 0.5 mol % Rh; Et_3N, 0.1 mol %; hexane, 1.0 mL; initial hydrogen pressure, 5 atm; 23 °C; 10 h unless otherwise noted in the parentheses.

nature of the Rh catalytic center coordinated with only a single phosphine ligand with extreme compactness, which is favorable for the access of the bulky substrates; the catalytic center should lose the 1,5-cyclooctadiene ligand upon hydrogenation prior to entering a catalytic cycle. Strong coordination of ketonic substrates through chelation and coordination of multiple substrates may prevent the formation of catalytically active species.

In summary, our studies identified the heterogeneous catalyst system composed of silica-supported, caged, compact phosphine silica-SMAP and rhodium(I)−alkoxo complex silica-SMAP−Rh(OMe)(cod) to be a useful catalyst precursor that initiates the hydrogenation of sterically hindered ketones with unprecedented high efficiency. Studies to expand applicability of the present method are underway.

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Supporting Information Available: Experimental procedures and NMR spectra for the hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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