DOI: 10.1002/adsc.201200555

Conjugate Reduction of α,β-Unsaturated Carbonyl and Carboxyl Compounds with Poly(methylhydrosiloxane) Catalyzed by a Silica-Supported Compact Phosphane–Copper Complex

Soichiro Kawamorita,[a] Kenji Yamazaki,[a] Hirohisa Ohmiya,[a] Tomohiro Iwai,[a] and Masaya Sawamura[a,]*

[a] Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan
Fax: +(81)-11-706-3449; phone: +(81)-11-706-3434; e-mail: sawamura@sci.hokudai.ac.jp

Received: June 25, 2012; Revised: August 29, 2012; Published online: November 28, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200555.

Abstract: A silica-supported, cage-type, compact phosphane (Silica-SMAP) was used for the copper-catalyzed conjugate reduction of α,β-unsaturated carbonyl and carboxyl compounds with poly(methylhydrosiloxane) (PMHS). The heterogeneous catalyst system showed high activity and chemoselectivity, and was easily separable from the reaction mixture after the reaction. Furthermore, the catalyst was reusable without loss of its high catalytic activity or selectivity.

Keywords: conjugate reduction; copper catalysts; heterogeneous catalysis; immobilized ligands

The copper-catalyzed conjugate reduction of α,β-unsaturated carbonyl and carboxyl compounds with hydrosilanes is a useful transformation in organic synthesis, because of its mild reaction conditions and excellent chemoselectivity.[1,2] Generally, phosphane-coordinated hexameric copper hydride $[CuH(PPh_3)]_6$, so-called "Stryker's reagent", and *in-situ* generated Cu−H species with phosphane or N-heterocyclic carbene ligands are used as a catalyst.[3] Lipshutz and coworkers introduced 1,2-bis(diphenylphosphino)benzene (*o*-BDPPB, shortened herein to BDP) as an achiral ligand that shows exceptionally high performance in the reactions with poly(methyhydrosiloxane) (PMHS) as a stoichiometric hydride source. Prior to this work, Lipshutz's group had shown DTBM-SEGPHOS[3g,h,i,k] to be an excellent chiral ligand for an enantioselective version. In these studies, the formation of 16-electron monomeric species with a bidentate phosphane, (bisphosphane)CuH, was proposed. On the other hand, we developed Silica-SMAP, a silica-supported, monodentate trialkylphosphane,[4,5] and showed this ligand to be useful for forming coordinatively unsaturated mono(phosphane)–metal (P/M 1:1) species in Rh, Ir, and Pd catalysis. Based on this knowledge, we then expected that an active copper(I) hydride species coordinated with a single monodentate phosphane ligand could be formed using Silica-SMAP.

Herein, we report that a Silica-SMAP-Cu system showed high activities for the conjugate reduction of α,β-unsaturated carbonyl and carboxyl (ester, amide, and nitrile) compounds with PMHS. Applicability toward sterically demanding and challenging substrates is a notable feature of the catalysis with Silica-SMAP. Additionally, the heterogeneous nature allowed the relatively easy recovery and reuse of the catalyst.

The reduction of isophorone (**1a**, 5.0 mmol) with PMHS (**2**, 3.0 equiv.) in *t*-BuOH[6] in the presence of $Cu(OAc)_2 \cdot H_2O$ (0.02 mol%) and Silica-SMAP (0.02 mol%) proceeded at room temperature to give the corresponding saturated ketone (**3a**) in 86% yield without forming a carbonyl reduction product [Eq. (1)].[7] It is noteworthy that a basic work-up was not necessary after the reaction in the present system; crude material was obtained only by filtration.[8]

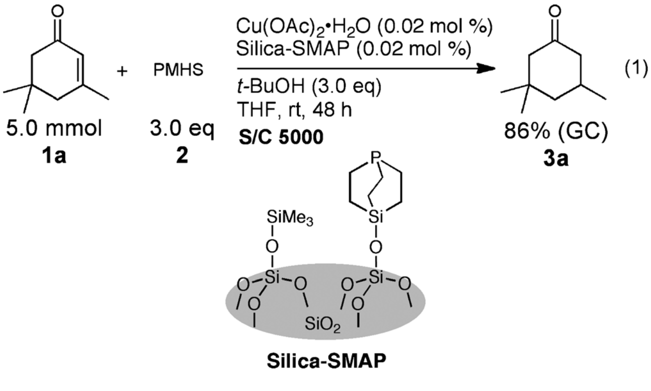
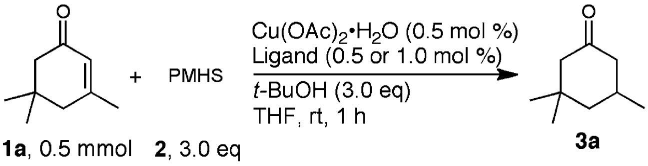


Table 1. Ligand effect in the Cu-catalyzed conjugate reduction of isophorone **1a**.[a]



Entry	Ligand	Cu/P	GC Yield[b] [%]
1	Silica-SMAP	1:1	96
2	Ph-SMAP	1:1	0
3	Ph-SMAP	1:2	1
4	Ph_3P	1:1	8
5	Ph_3P	1:2	7
6	Me_3P	1:1	1
7	Me_3P	1:2	1
8	$(n\text{-Bu})_3P$	1:1	5
9	$(n\text{-Bu})_3P$	1:2	5
10	$(t\text{-Bu})_3P$	1:1	1
11	$(t\text{-Bu})_3P$	1:2	1
12	Cy_3P	1:1	22
13	Cy_3P	1:2	22
14	dppe	1:2	6
15	dppp	1:2	11
16	Xantphos	1:2	1
17	BDP	1:2	14
18	none	–	0

[a] The reaction was carried out with isophorone **1a** (0.5 mmol), PMHS **2** (3 equiv., 1.5 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.5 mol%), phosphane ligand (0.5 or 1.0 mol%), *t*-BuOH (3 equiv., 1.5 mmol) in THF (0.5 mL) at room temperature for 1 h.

[b] GC yield based on **1a**. Dibenzyl was used as internal standard.

To investigate the rate accelerating effect, various ligands were examined in the reduction of isophorone **1a** with PMHS at room temperature for 1 h with 0.5 mol% of $Cu(OAc)_2{\cdot}H_2O$ (Table 1). The Silica-SMAP-Cu system afforded **3a** in 96% GC yield (entry 1).[9] Interestingly, the corresponding homogeneous catalysts that were prepared *in-situ* from $Cu(OAc)_2{\cdot}H_2O$ and Ph-SMAP (0.5 mol% Cu, 1:1 or 1:2 Cu/P) afforded only a trace amount of the product (entries 2 and 3), indicating that immobilization of the phosphane is crucial. Other commonly used monophosphane and bisphosphane ligands also gave only low conversions (entries 4–16). Notably, BDP was not effective under these conditions using THF as solvent (entry 17).[10] No reaction occurred without a phosphane ligand (entry 18). These experiments demonstrated excellent ligand performance of immobilized compact monophosphane Silica-SMAP and indicate that the steric bulkiness and rigid backbone are not essential factors for the ligand to promote the Cu-catalyzed conjugate reduction efficiently.

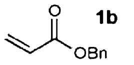
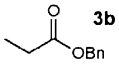
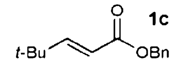
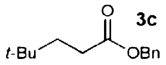
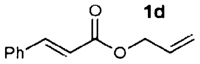
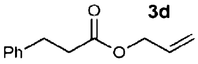
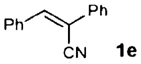
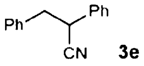
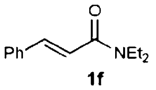
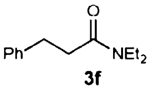
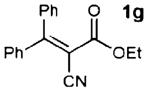
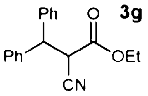
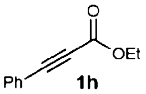
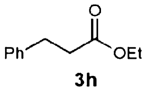
Next, Silica-SMAP-Cu was used for the conjugate reduction of various α,β-unsaturated carboxylic acid derivatives (**1b–d**), and the same series of reactions were conducted with the BDP ligand for comparison. Results are summarized in Table 2.[11] Note that the basic work-up was not necessary for all of the entries listed in this table irrespective of the ligands used. The reductions of benzyl acrylate (**1b**) and β-*t*-Bu-substituted benzyl acrylate **1c** proceeded in good yields with both ligands (entries 1–4). Allyl cinnamate **1d** was a suitable substrate despite having a potentially reactive allyl ester moiety (entries 5 and 6). Substituted acrylonitrile derivative **1e** underwent a clean conjugate reduction to give saturated nitrile **3e** (entries 7 and 8).

The advantage of using Silica-SMAP-Cu over BDP-Cu was clearly observed in the reduction of α,β-unsaturated amide **1f**. While the former gave a complete conjugate reduction, the latter induced only a 64% substrate conversion (Table 2, entries 9 and 10). Moreover, Silica-SMAP exhibited a superior ligand effect in the reaction of tetrasubstituted alkene substrate **1g**, which is a challenging substrate due to its steric demands (entries 11 and 12). It seems that the compact nature of the Silica-SMAP ligand was beneficial for the reaction of the sterically demanding substrate.[5a,b,c,g] In addition, the conjugate reduction of alkynoate **1h** to give the corresponding saturated ester (**3h**) was successful with Silica-SMAP-Cu, while BDP-Cu induced only a low substrate conversion (entries 13 and 14).

The Silica-SMAP-Cu heterogeneous catalyst was easily separated from the reaction mixture by decantation or Celite® filtration. Additionally, the catalyst was reusable for the reduction of (*E*)-benzyl but-2-enoate **1i**: the catalyst at 0.5 mol% loading was used three times without detection of a decrease in the activity (Table 3).

To investigate the nature of interactions between Silica-SMAP and Cu species in the reaction system, ^{31}P CP-MAS-NMR measurements of solid phases were conducted before and after the catalytic reaction with isophorone (**1a**) (Figure 1, a and b, respectively). To obtain the spectrum of the sample before the catalysis, Silica-SMAP (0.036 mmol P) was treated with $Cu(OAc)_2{\cdot}H_2O$ (1 equiv.), PMHS (50 equiv.), and *t*-BuOH (50 equiv.) in THF (1.0 mL) at room temperature for 20 min, and the resulting dry solid was used for the measurement. On the other hand, in order to obtain the spectrum of the sample after the catalysis, procedures similar to the ones mentioned above were followed: **1a** (10 equiv.) was added and the resulting mixture was allowed to react for 1 h. Even though the loading ratio of P and Cu was 1:1, a signal corresponding to free Silica-SMAP (−58.8 ppm) was observed together with a minor signal assignable to the phosphane-coordinated copper species in the lower

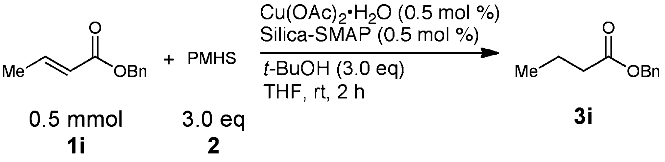
Table 2. Conjugate reduction of various α,β-unsaturated carboxylic acid derivatives with Silica-SMAP-Cu and BDP-Cu systems.[a]

Entry	Substrate **1**	Product **3**	Ligand	Conv. [%]	Yield[b] [%]
1			Silica-SMAP	100	83
2			BDP	100	(99)
3			Silica-SMAP	100	84
4			BDP	100	(99)
5			Silica-SMAP	100	92
6			BDP	93	(93)
7			Silica-SMAP	100	85
8			BDP	100	(99)
9			Silica-SMAP	100	88
10			BDP	64	(64)
11			Silica-SMAP	100	94
12			BDP	9	(9)
13			Silica-SMAP	100	79
14			BDP	19	(6)

[a] The reaction was carried out with **1** (0.5 mmol), PMHS **2** (3 equiv., 1.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mol%), ligand (0.5 mol%), *t*-BuOH (3 equiv., 1.5 mmol) at room temperature. THF (0.5 mL) was used as solvent in Silica-SMAP system, and toluene (0.5 mL) was used in BDP system.

[b] Isolated yield. NMR yield is in parentheses.

Table 3. Reusability of Silica-SMAP-Cu in the conjugate reduction of **1i**.[a]



Cycle	GC conv. [%]	NMR yield [%]
1	100	96
2	100	99
3	100	99

[a] The reaction was carried out with **1i** (0.5 mmol), PMHS **2** (3 equiv., 1.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.5 mol%), Silica-SMAP (0.5 mol%), *t*-BuOH (3 equiv., 1.5 mmol) in THF (0.5 mL) at room temperature for 2 h with shaking.

magnetic field region (−28.1 ppm) in both samples. These results indicate that only part of the SMAP moiety of Silica-SMAP is associated with the coordination to Cu, causing the catalytic activity observed in the present system. Although the complicated CP-MAS-NMR spectra do not provide the distinct structure of a catalytically active species, we assume that Silica-SMAP can produce a monomeric 1:1 Cu–P species regardless of its compact steric nature to achieve a high degree of coordinative unsaturation of the copper because efficient site isolation of the P-center is realized on the silica surface.[5a,b]

In summary, a silica-supported compact phosphane-Cu complex Silica-SMAP-Cu showed high activities for the conjugate reduction of various α,β-unsaturated carbonyl compounds with PMHS. This work demonstrated that the immobilization to a silica gel surface was critical for excellent ligand performance of the compact monodentate phosphane. The work also indicated that the use of bidentate phosphane ligands with sterically demanding *P*-substituents or a rigid backbone is not always necessary to prepare effective catalysts. The Silica-SMAP-Cu heterogeneous catalyst was easily separated and reusable. This is the first demonstration that Silica-SMAP is useful for copper catalysis.

Experimental Section

Typical Procedure for Conjugate Reduction of Isophorone (1a) (Table 1, Entry 1)

In a glove box, Silica-SMAP (0.063 mmol $P g^{-1}$, 40 mg, 0.0025 mmol) and an internal standard (dibenzyl) were placed in a 10-mL glass tube containing a magnetic stirring bar. Then $Cu(OAc)_2 \cdot H_2O$ (0.5 mg, 0.0025 mmol) in THF (0.5 mL) and *t*-BuOH (111.2 mg, 1.5 mmol) were added to the tube. The mixture was stirred for 1 min at room temperature. PMHS (**2**, 90.2 mg, 1.5 mmol) was added to the tube, and the mixture was stirred for 5 min. Isophorone (**1a**, 69.1 mg 0.5 mmol) was added to the tube, which was then sealed with a screw cap. The tube was removed from the

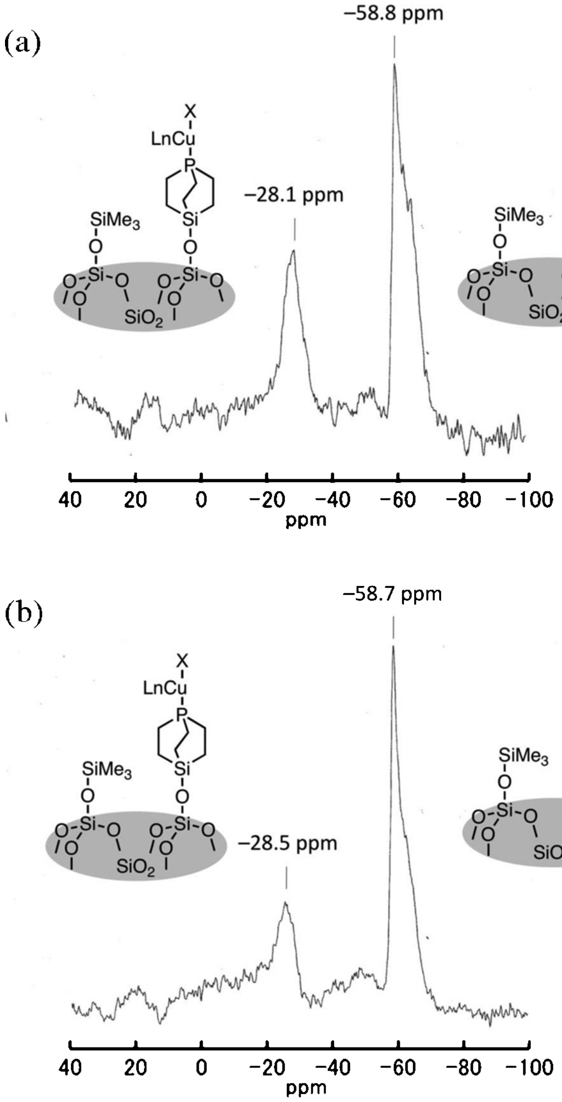


Figure 1. ^{31}P CP-MAS-NMR spectra of Silica-SMAP-Cu system (a) before and (b) after the catalytic reaction with **1a**. See text and the Supporting Information for details.

glove box. The resulting mixture was stirred at room temperature for 1 h. After the reaction, the yield of the product **3a** was determined by gas chromatography.

Acknowledgements

This work was supported by Grants-in-Aid for Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration" and a Global COE grant (YProject No. B01: Catalysis as the Basis for Innovation in Materials Science) from MEXT, and by CREST from JST. S.K. thanks JSPS for scholarship support.

References

[1] B. H. Lipshutz, in: *Modern Organocopper Chemistry*, (Ed.: N. Krause), Wiley-VCH, Weinheim, **2002**, pp. 167–187.

[2] For reviews on copper catalyzed conjugate reduction, see: a) S. Rendler, M. Oestreich, *Angew. Chem.* **2007**, *119*, 504–510; *Angew. Chem. Int. Ed.* **2007**, *46*, 498–504; b) C. Deutsch, N. Krause, B. H. Lipshutz, *Chem. Rev.* **2008**. *108*, 2916–2927; c) B. H. Lipshutz, *Synlett* **2009**, 509–524.

[3] For selected references on Cu-catalyzed 1,4-reduction of α,β-unsaturated carbonyl compounds with hydrosilane, see: a) A. Mori, A. Fujita, Y. Nishihara, T. Hiyama, *Chem. Commun.* **1997**, 2159–2160; b) H. Ito, T. Ishizuka, K. Arimoto, K. Miura, A. Hosomi, *Tetrahedron Lett.* **1997**, *38*, 8887–8890; c) B. H. Lipshutz, J. Keith, P. Papa, R. Vivian, *Tetrahedron Lett.* **1998**, *39*, 4627–4630; d) D. H. Appella, Y. Moritani, R. Shintani, E. M. Ferreira, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**. *121*, 9473–9474; e) B. H. Lipshutz, W. Chrisman, K. Noson, P. Papa, J. A. Sclafani, R. W. Vivian, J. M. Keith, *Tetrahedron* **2000**, *56*, 2779–2788; f) V. Jurkauskas, J. P. Sadighi, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 2417–2420; g) B. H. Lipshutz, J. M. Servesko, *Angew. Chem.* **2003**, *115*, 4937–4940.; *Angew. Chem. Int. Ed.* **2003**, *42*, 4789–4792; h) B. H. Lipshutz, J. M. Servesko, B. R. Taft, *J. Am. Chem. Soc.* **2004**, *126*, 8352–8353; i) B. H. Lipshutz, J. M. Servesko, T. B. Petersen, P. P. Papa, A. A. Lover, *Org. Lett.* **2004**, *6*, 1273–1275; j) M. P. Rainka, J. E. Milne, S. L. Buchwald, *Angew. Chem.* **2005**, *117*, 6333–6336; *Angew. Chem. Int. Ed.* **2005**, *44*, 6177–6180; k) B. H. Lipshutz, B. A. Frieman, *Angew. Chem.* **2005**, *117*, 6503–6506.; *Angew. Chem. Int. Ed.* **2005**, *44*, 6345–6348; l) D. Lee, D. Kim, J. Yun, *Angew. Chem.* **2006**, *118*, 2851–2853; *Angew. Chem. Int. Ed.* **2006**, *45*, 2785–2787; m) T. Llamas, R. G. Arrayás, J. C. Carretero, *Angew. Chem.* **2007**, *119*, 3393–3396; *Angew. Chem. Int. Ed.* **2007**, *46*, 3329–3332; n) B. A. Baker, Ž. V. Bošković, B. H. Lipshutz, *Org. Lett.* **2008**, *10*, 289–292; o) L. Rupnicki, A. Saxena, H. W. Lam, *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.

[4] SMAP (silicon-constrained monodentate trialkylphosphane): a) A. Ochida, K. Hara, H. Ito, M. Sawamura, *Org. Lett.* **2003**, *5*, 2671–2674; b) A. Ochida, S. Ito, T. Miyahara, H. Ito, M. Sawamura, *Chem. Lett.* **2006**, *35*, 294–295; c) A. Ochida, G. Hamasaka, Y. Yamauchi, S. Kawamorita, N. Oshima, K. Hara, H. Ohmiya, M. Sawamura, *Organometallics* **2008**, *27*, 5494–5503; d) K. Hara, R. Akiyama, S. Takakusagi, K. Uosaki, T. Yoshino, H. Kagi, M. Sawamura, *Angew. Chem.* **2008**, *120*, 5709–5712; *Angew. Chem. Int. Ed.* **2008**, *47*, 5627–5630.

[5] For the synthesis and applications of Silica-SMAP, see: a) G. Hamasaka, A. Ochida, K. Hara, M. Sawamura, *Angew. Chem.* **2007**, *119*, 5477–5479; *Angew. Chem. Int. Ed.* **2007**, *46*, 5381–5383; b) G. Hamasaka, S. Kawamorita, A. Ochida, R. Akiyama, K. Hara, A. Fukuoka, K. Asakura, W. J. Chun, H. Ohmiya, M. Sawamura, *Organometallics* **2008**, *27*, 6495–6506; c) S. Kawamorita, G. Hamasaka, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura, *Org. Lett.* **2008**, *10*, 4697–4700; d) S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawa-

mura, *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059; e) S. Kawamorita, H. Ohmiya, M. Sawamura, *J. Org. Chem.* **2010**, *75*, 3855–3858; f) K. Yamazaki, S. Kawamorita, H. Ohmiya, M. Sawamura, *Org. Lett.* **2010**, *12*, 3978–3981; g) S. Kawamorita, H. Ohmiya, T. Iwai, M. Sawamura, *Angew. Chem.* **2011**, *123*, 8513–8516; *Angew. Chem. Int. Ed.* **2011**, *50*, 8363–8366; h) S. Kawamorita, M. Tatsuya, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.* **2011**, *133*, 19310–19313.

[6] *t*-BuOH was added to enhance the generation of Cu−H. The Cu-enolate intermediate could be protonated by *t*-BuOH to generate *t*-BuO−Cu, which is more active to transmetalate with hydrosilane.

[7] Lipshutz reported that CuCl and DTBM-SEGPHOS system is highly active, and the asymmetric reduction of isophorone **1a** proceeded with 1 mol% of CuCl and 0.00036 mol% of ligand (see ref.[3i]).

[8] In other reported bisphosphane systems, work-up under the strongly basic conditions is needed to obtain the products, especially when the substrate is a ketone and the reductant is PMHS (see refs.[3g,3i,3k,3n]).

[9] Conjugate reduction of **1a** with Ph_2SiH_2 (1.2 equiv.) in the presence of Silica-SMAP (1 mol%), $(CuOTf)_2$·toluene (0.5 mol%), and *t*-BuOK (6 mol%) in THF at room temperature for 4 h afforded **3a** in 98% yield (GC, work-up with 2 M aqueous NaOH).

[10] Lipshutz reported that the BDP-Cu system was effective for reduction of isophorone **1a** in toluene, and that THF was not a suitable solvent (see ref.[3n]). We confirmed that the reduction of **1a** with the BDP-Cu system proceeded in toluene with a full conversion of **1a**; however, **3a** was obtained in only a low yield (29%) after the neutral work-up.

[11] THF was used as solvent in Silica-SMAP system, and toluene was used as solvent in BDP-Cu system according to the original report (see ref.[3n]).