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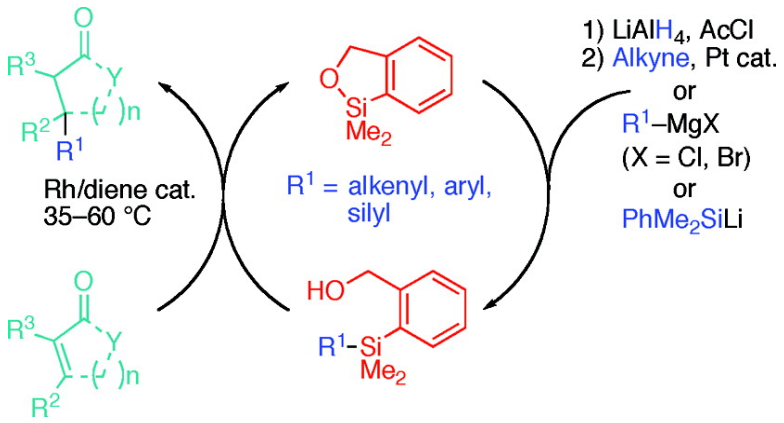
J. Am. Chem. Soc., **2007**, 129 (29), 9137-9143• DOI: 10.1021/ja071969r • Publication Date (Web): 30 June 2007



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Organo[2-(hydroxymethyl)phenyl]dimethylsilanes as Mild and Reproducible Agents for Rhodium-Catalyzed 1,4-Addition Reactions

Yoshiaki Nakao,*,† Jinshui Chen,† Hidekazu Imanaka,† Tamejiro Hiyama,*,†
Yoshitaka Ichikawa,‡ Wei-Liang Duan,‡ Ryo Shintani,‡ and Tamio Hayashi*,‡

Contribution from the Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan, and Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan

Received March 20, 2007; E-mail: nakao@npc05.kuic.kyoto-u.ac.jp; thiyama@npc05.kuic.kyoto-u.ac.jp; thayashi@kuchem.kyoto-u.ac.jp

Abstract: Stable and reusable tetraorganosilicon reagents, alkenyl-, aryl-, and silyl[2-(hydroxymethyl)phenyl]-dimethylsilanes, undergo 1,4-addition reactions to α,β-unsaturated carbonyl acceptors under mild rhodium-catalysis. The reaction tolerates a diverse range of functional groups and is applicable to gram-scale synthesis. Use of a chiral diene ligand allows the achievement of the corresponding enantioselective transformations using the tetraorganosilicon reagents, providing the silicon-based approach to optically active ketones and substituted piperidones that serve as synthetic intermediates of pharmaceuticals. A rhodium alkoxide species is suggested to be responsible for a transmetalation step on the basis of the observed kinetic resolution of a racemic chiral phenylsilane in the enantioselective 1,4-addition reaction under the rhodium−chiral diene catalysis.

Introduction

Transition metal-catalyzed addition reactions of organometallic reagents to electron-deficient olefins have attracted much attention and have been developed extensively in the past decade. Especially, since the landmark report by Miyaura and co-workers in 1997,[1] use of organoboron reagents has found many synthetic applications including asymmetric synthesis because of their tolerance toward many functional groups as well as easy handling and ready availability.[2−4] Alternative organometallic reagents have also been developed including silicon,[3d,f,5] titanium,[6] zinc,[7] zirconium,[8] indium,[9] tin,[10] lead,[11] and bismuth.[12] Among these, organosilicon reagents should have significant importance in view of stability and nontoxicity as well as natural abundance of silicon element. Nevertheless, reported examples of such silicon-based reactions rely on the use of acid-, base-, and/or moisture-sensitive organotri(alkoxy)-silanes, organosilanediols, and chlorosilanes in excess under relatively harsh conditions. Furthermore, use of highly nucleophilic activators including metal fluorides in a stoichiometric amount is essential in some cases[3f,5f,h,l,m] to activate the silicon reagents to be reactive enough and undergo transmetalation to rhodium(I) or palladium(II) species. Thus, the development of new silicon reagents that are highly stable but reactive enough at the same time have remained elusive.

† Graduate School of Engineering.
‡ Graduate School of Science.

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Of many types of organosilicon compounds, tetraorganosilanes should be ideal in view of their high stability. As is the case with ubiquitous triorganosilyl protecting groups, alkenyl- and aryltriorganosilanes survive many synthetic transformations, allowing their installation at an early stage of complex natural product syntheses.[13] A wide range of (*E*)-, (*Z*)-, and α-substituted triorgano(vinyl)silanes are readily available by virtue of recent progress in transition metal-catalyzed hydrosilylation of alkynes.[14] Whereas a classical strategy involving transmetalation between aryl-Grignard or -lithium reagents with triorganosilyl halides still serves as a convenient access to simple aryltriorganosilanes, the metal-catalyzed cross-coupling reactions of aryl halides with disilanes[15] or hydrosilanes[16] and direct silylation of Ar−H bonds[17] have gained significant synthetic value as highly chemoselective and atom economical alternatives to classical syntheses of arylsilanes. In light of the growing importance of silicon-based transformations, we have recently disclosed that organo[2-(hydroxymethyl)phenyl]dimethylsilanes (**1**) behave as a new class of silicon reagents for the palladium-catalyzed cross-coupling reaction.[18] The reagents allow chemically stable tetraorganosilicon compounds[19] to participate in the cross-coupling chemistry under fluoride-free conditions for the first time with excellent chemoselectivities. The proximal hydroxyl group is supposed to coordinate to the nearby silicon atom upon treatment with a mild base, such as K_2CO_3, to produce a requisite five-membered pentacoordinated silicate species.[18] With the given success of the silicon reagents **1** in the cross-coupling chemistry, we envisioned the use of **1** as a new entry to silicon-based rhodium-catalyzed 1,4-addition reactions. We report herein full details of the rhodium-catalyzed transformations using **1** under mild conditions without any activators to produce a wide range of adducts in good yields with excellent chemoselectivities. Enantioselective 1,4-addition reactions are also demonstrated by the aid of rhodium/chiral diene catalysis.

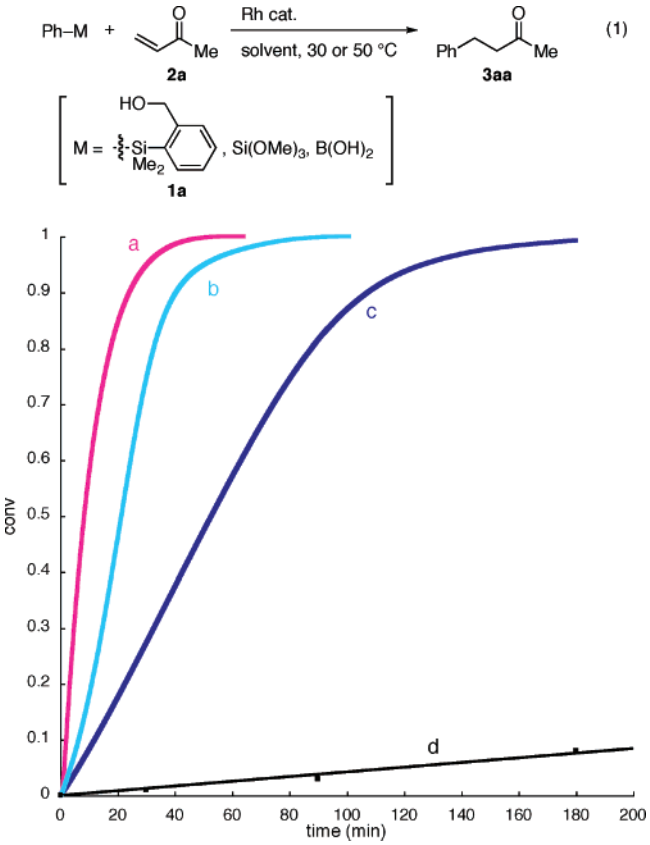

Figure 1. Conversion vs time for the reactions of a phenylmetal reagent ($[Ph\text{-}M]_0$ = 67 mM) with methyl vinyl ketone ($[\mathbf{2a}]_0$ = 201 mM) in the presence of a rhodium catalyst ($[Rh]_{total}$ = 2.7 mM) at 30 or 50 °C: (a) $PhB(OH)_2$ as the nucleophile and $[Rh(OH)(cod)]_2$ as the catalyst in 1,4-dioxane/H_2O (10/1) at 30 °C in the presence of $[B(OH)_3]_0$ = 536 mM (for the reaction conditions, see ref 21); (b) **1a** as the nucleophile and $[Rh(OH)(cod)]_2$ as the catalyst in 1,4-dioxane at 50 °C; (c) **1a** as the nucleophile and $[Rh(OH)(cod)]_2$ as the catalyst in THF at 30 °C; (d) $PhSi(OMe)_3$ as the nucleophile and $[Rh(cod)(MeCN)_2]BF_4$ as the catalyst in 1,4-dioxane/H_2O (10/1) at 50 °C.

Results and Discussion

Rhodium-Catalyzed 1,4-Addition Reactions of Organo[2-(hydroxymethyl)phenyl]dimethylsilanes. At the onset, we assessed the reactivity of **1** by the reaction of phenyl[2-(hydroxymethyl)phenyl]dimethylsilane (**1a**) with an excess amount of methyl vinyl ketone (**2a**) in the presence of $[Rh(OH)(cod)]_2$ as a catalyst (eq 1). The reaction was carried out in 1,4-dioxane at 30 °C and monitored in a reaction calorimetry (Omnical SuperCRC).[20] Almost quantitative conversion of **1a** was observed after 3 h (curve c, Figure 1), whereas the reaction trimethoxy(phenyl)silane, a representative silicon reagent frequently used for rhodium-catalyzed transformations,[5a−g] in the presence of cationic $Rh(cod)(MeCN)_2BF_4$ as a catalyst in 1,4-dioxane/H_2O (10/1)[5a] showed less than 10% yield of 1,4-adduct

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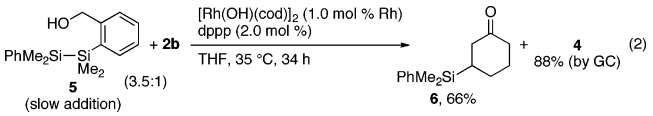
3aa by ^{1}H NMR analysis even at 50 °C (curve d), and no reaction was observed by the use of $[Rh(OH)(cod)]_2$ as a catalyst. We further found that the rate of the reaction using **1a** at 50 °C was comparable with that using phenylboronic acid[21] at 30 °C (curve a vs curve b). Apparently, these results indicated an enhanced reactivity of organo[2-(hydroxymethyl)phenyl]-dimethylsilanes as alternatives of organoboronic acids, compared with conventional silicon reagents such as trialkoxy(organo)-silanes.

Indeed, the equimolar reaction of **1a** with **2a** with a 1.0 mmol scale in the presence of $[Rh(OH)(cod)]_2$ (1.0 mol % Rh) in THF at 35 °C gave **3aa** in 94% yield after 4 h (entry 1 of Table 1 using). The observed excellent reactivity of the silicon reagent under mild conditions prompted us to further investigate the scope of both silicon reagents and electrophiles. The addition of **1a** across 2-cyclohexen-1-one (**2b**) also took place smoothly under the identical conditions to give 3-phenylcyclohexanone (**3ab**) in 90% yield (entry 2). The same reaction on a gram-scale (10 mmol scale) allowed us to isolate cyclic silyl ether **4**, a silicon residue of the reaction, in 92% yield by distillation of the crude product and **3ab** in 92% yield by flash chromatography on silica gel of the residue (entry 3). As we have already demonstrated that **4** serves as a silylating agent of various aryl-Grignard reagents to give the arylsilane reagents employed in this study,[18a,b] the metal residue of the 1,4-addition reaction is demonstrated to be reproducible for the first time. Reactions of **1a** met success not only with cyclic or acyclic enones (entries 4−6) but also with various α,β-unsaturated esters, amides, and nitrile in good yields (entries 7−14). Phenylsilanes having methoxy (**1b**), fluoro (**1c**), bromo (**1d**), cyano (**1e**), and pinacolatoboryl (**1f**) at the para position all reacted with **2b**, these functional groups being intact during the reactions (entries 15−19). Sterically highly demanding 2,4,6-trimethylphenylsi-lane (**1g**) gave the corresponding adduct **3gb** in 85% yield although extra loading of the arylsilane reagent (total 1.5 equiv) was necessary (entry 20). In sharp contrast to the transmetalation of arylsilanes **1** to a palladium(II) complex which requires the use of a copper(I) cocatalyst for the success of cross-coupling,[18a,b] it should be noted that transmetalation to rhodium-(I) proceeds very efficiently without the aid of other metal cocatalyst.

We then examined the 1,4-addition reaction using alkenyl-silanes (Table 2). The stoichiometric reaction (1.0 mmol scale) of (*E*)-[2-(hydroxymethyl)phenyl]dimethyl(1-octenyl)silane (**1h**) with **2a** in the presence of $[Rh(OH)(cod)]_2$ (1.0 mol % Rh) in THF at 35 °C gave the corresponding adduct **3ha** in 67% yield after 4 h (entry 1 of Table 2). The reaction of **1h** with **2b** proceeded successfully irrespective of its reaction scale (entries 2 and 3), and cyclic silyl ether **4** was again recovered in 80% yield (entry 3). Reusability of **4** for preparation of the alkenyl-silane reagents has been demonstrated previously.[18a,c] Cyclic enones, **2c** and **2d**, also underwent the 1,4-addition reaction of **1h** to give the corresponding adducts in good yields (entries 4 and 5). We then surveyed the scope of alkenylsilanes, which were obtained readily by platinum-catalyzed hydrosilylation of the corresponding alkynes.[18a,c] Excellent chemoselectivity was observed with (*E*)-alkenylsilanes having a functional group, such as cyano, ester, chloro, siloxy, malonate, phthalimide, or free hydroxyl, giving various 3-alkenylcyclohexanones in good yields (entries 6−12). Conjugated 1,3-dienylsilane **1p**, (*E*)-styrylsilane **1q**, and (*Z*)-propenylsilane **1r** added to **2b** with retention of the olefinic configuration (entries 13−15). (*Z*)-Styrylsilane (**1s**) also gave **3sb** as a major product (∼95%) albeit being contaminated by a small amount (∼5%) of its stereoisomer **3qb** (entry 16).[22] Ethenylsilanes having substituent(s) like 1-methyl, 1-phenyl, 2,2-dimethyl, and (*E*)-1,2-dipropyl participated in the reaction with **2b** with perfect regio- and stereospecificities in good yields (entries 17−20). Especially, successful addition of α-substituted vinylsilanes, **1t** and **1u**, is worth noting, because the corre-sponding vinylboronic acids are relatively unstable thermally[23] and, thus, have rarely been employed in the rhodium-catalyzed transformations.

We also applied the present protocol to 1,4-addition of a silyl group to enones.[24] Disilane reagent **5** was prepared by the reaction of cyclic silyl ether **4** with dimethylphenylsilyllithium and was subjected to the reaction with **2b** using 1,3-bis-(diphenylphosphino)propane (dppp) as a ligand (eq 2).[24a] Desired adduct **6** was obtained in 66% yield, although extra loading of **5** (3.5 molar equiv to **2b**) was necessary because of competitive protonolysis of the dimethylphenylsilyl group of **5** leading to dimethylphenylsilane as a byproduct. The formation (88% yield) of silicon residue **4** was confirmed by GC analysis of the crude mixture.



Enantioselective 1,4-Addition Reactions of Organo[2-(hydroxymethyl)phenyl]dimethylsilanes. The success with the 1,4-addition reactions of the silicon reagents under mild reaction conditions encouraged us to turn our attention to the application of **1** to asymmetric synthesis. The recent innovation in the highly reactive and enantioselective rhodium-catalysis with chiral diene ligands[25−27] prompted us to utilize this chemistry for the asymmetric transformations using **1**. Thus, the equimolar reaction of phenylsilane **1a** with **2b** in the presence of $[RhCl(C_2H_4)]_2$ (3.0 mol % Rh), (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]-

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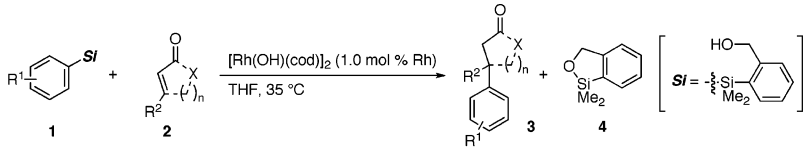
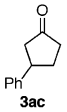
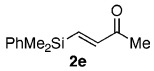
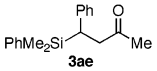
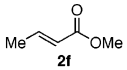
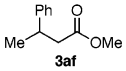
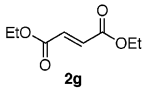
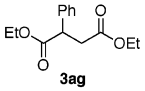
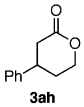
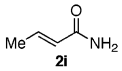
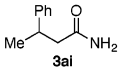
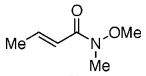
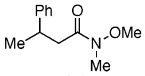
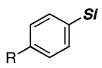
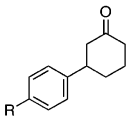
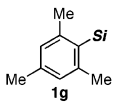
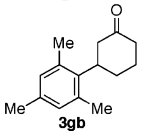
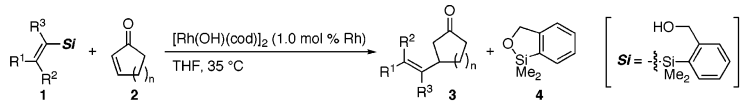
Table 1. Rhodium-Catalyzed 1,4-Addition Reactions of Aryl[2-(hydroxymethyl)phenyl]dimethylsilanes to Electron-Deficient Olefins[a]



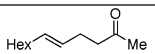
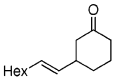
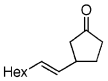
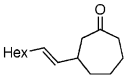
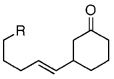
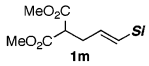
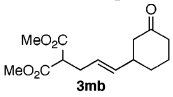
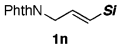
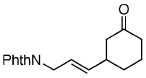
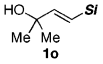
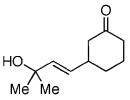
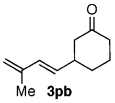
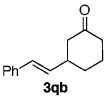
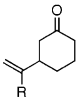
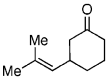
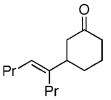
entry	arylsilane	electrophile	time (h)	product	yield (%)[b]
1	**1a**	**2a**	4	**3aa**	94
2	**1a**	 **2b**	5	 **3ab**	90
3[c]	**1a**		6		92[d]
4	**1a**	 **2c**	4	 **3ac**	95
5	**1a**	 **2d**	5	 **3ad**	86
6	**1a**	 **2e**	4	 **3ae**	90
7	**1a**	 **2f**	4	 **3af**	86
8	**1a**	 **2g**	8	 **3ag**	98
9[e]	**1a**	 **2h**	4	 **3ah**	91
10	**1a**	 **2i**	4	 **3ai**	80
11[f]	**1a**	 **2j**	4	 **3aj**	100
			4		78
12	**1a**	R = Me (**2k**)	4	R = Me (**3ak**)	78
13	**1a**	Cy (**2l**)	4	Cy (**3al**)	74
14[g]	**1a**	 **2m**	7	 **3am**	94
					
15	R = MeO (**1b**)	**2b**	4	R = MeO (**3bb**)	96
16	F (**1c**)	**2b**	6	F (**3cb**)	89
17	Br (**1d**)	**2b**	4	Br (**3db**)	90
18	NC (**1e**)	**2b**	6	NC (**3eb**)	93
19	(pin)B (**1f**)	**2b**	18	(pin)B (**3fb**)	69
20[h]	 **1g**	**2b**	4	 **3gb**	85

[a] Unless otherwise noted, the reaction was carried out in THF (0.5 mL) using an arylsilane (1.0 mmol) and an electrophile (1.0 mmol) in the presence of $[Rh(OH)(cod)]_2$ (1.0 mol % Rh) at 35 °C. [b] Isolated yields. [c] The reaction was carried out on a 10 mmol scale. [d] Cyclic silyl ether **4** was also isolated in 92% yield. [e] The reaction was carried out using $[Rh(OH)(cod)]_2$ (3.0 mol % Rh) at 50 °C. [f] The reaction was carried out using 1.2 mmol of **1a**. [g] The reaction was carried out using 1.3 mmol of **1a** at 60 °C. [h] The reaction was carried out using 1.5 mmol of **1g**.

Table 2. Rhodium-Catalyzed 1,4-Addition Reactions of Alkenyl[2-(hydroxymethyl)phenyl]dimethylsilanes to Cyclic Enones[a]

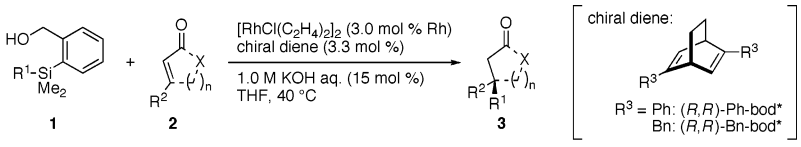


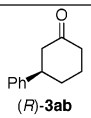
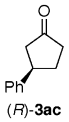
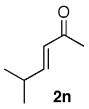
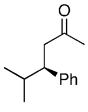
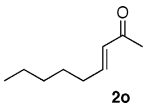
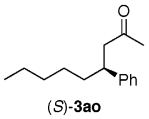
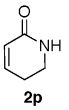
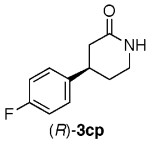
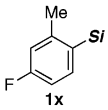
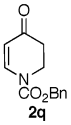
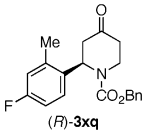
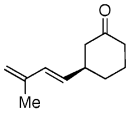
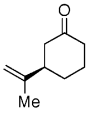
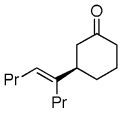
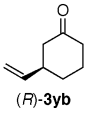
1 2 3 4

entry	alkenylsilane	enone	time (h)	product	yield (%)[b]
1	 **1h**	**2a**	4	 **3ha**	67
2	**1h**	**2b**	2	 **3hb**	89
3[c]	**1h**	**2b**	5		79[d]
4	**1h**	**2c**	3	 **3hc**	85
5	**1h**	**2d**	3	 **3hd**	78
					
6	R = CN (**1i**)	**2b**	3	R = CN (**3ib**)	87
7	CO_2Me (**1j**)	**2b**	3	CO_2Me (**3jb**)	89
8	Cl (**1k**)	**2b**	3	Cl (**3kb**)	92
9	$OSiMe_2t$-Bu (**1l**)	**2b**	3	$OSiMe_2t$-Bu (**3lb**)	94
10	 **1m**	**2b**	6	 **3mb**	91
11	 **1n**	**2b**	3	 **3nb**	84
12	 **1o**	**2b**	3	 **3ob**	81
13	 **1p**	**2b**	3	 **3pb**	81
14	 **1q**	**2b**	3	 **3qb**	87
					
15	R = Me (**1r**)	**2b**	3	R = Me (**3rb**)	77
16	Ph (**1s**)	**2b**	3	Ph (**3sb**)	94[e]
					
17	R = Me (**1t**)	**2b**	3	R = Me (**3tb**)	75
18	Ph (**1u**)	**2b**	3	Ph (**3ub**)	85
19	 **1v**	**2b**	3	 **3vb**	79
20	 **1w**	**2b**	3	 **3wb**	90

[a] Unless otherwise noted, the reaction was carried out in THF (0.5 mL) using an alkenylsilane (1.0 mmol) and an enone (1.0 mmol) in the presence of $[Rh(OH)(cod)]_2$ (1.0 mol % Rh) at 35 °C. [b] Isolated yields. [c] The reaction was carried out on a 10 mmol scale. [d] Cyclic silyl ether **4** was also isolated in 80% yield. [e] Contaminated by 5% of **3qb**.

Table 3. Rhodium-Catalyzed Enantioselective 1,4-Addition Reactions of Organo[2-(hydroxymethyl)phenyl]dimethylsilanes[a]

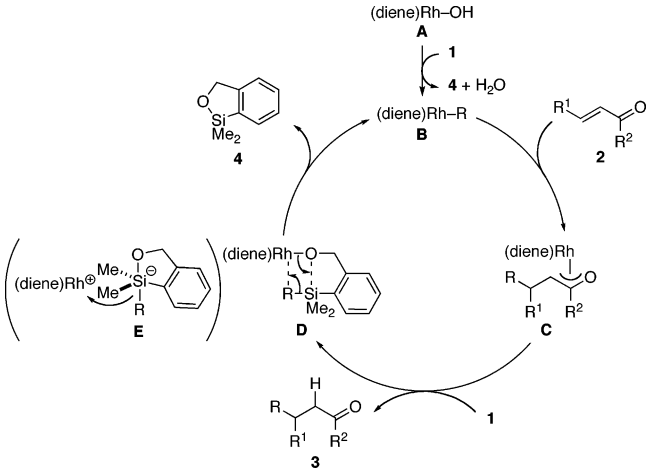


entry	1	electrophile	ligand	time (h)	product	yield (%)[b]	ee (%)[c]
1	**1a**	**2b**	(*R*,*R*)-Ph-bod*	10	 (*R*)-**3ab**	93	97
2	**1a**	**2c**	(*R*,*R*)-Ph-bod*	10	 (*R*)-**3ac**	91	99
3	**1a**	 **2n**	(*R*,*R*)-Bn-bod*	5	 (*R*)-**3an**	94	97
4	**1a**	 **2o**	(*R*,*R*)-Bn-bod*	5	 (*S*)-**3ao**	94	97
5[d]	**1c**	 **2p**	(*R*,*R*)-Ph-bod*	12	 (*R*)-**3cp**	92	96
6[e]	 **1x**	 **2q**	(*R*,*R*)-Bn-bod*	15	 (*R*)-**3xq**	94	86
7	**1p**	**2b**	(*R*,*R*)-Bn-bod*	10	 (*R*)-**3pb**	81	91
8[f]	**1t**	**2b**	(*R*,*R*)-Ph-bod*	10	 (*R*)-**3tb**	85	96
9	**1w**	**2b**	(*R*,*R*)-Ph-bod*	10	 (*R*)-**3wb**	90	90
10[g]	 **1y**	**2b**	(*R*,*R*)-Bn-bod*	10	 (*R*)-**3yb**	70	94[h]

[a] Unless otherwise noted, the reaction was carried out in THF (0.30 mL) using an organosilane (0.30 mmol) and an electrophile (0.30 mmol) in the presence of $[RhCl(C_2H_4)]_2$ (3.0 mol % Rh), a diene ligand (3.3 mol %), and 1.0 M KOH aq (15 mol %) at 40 °C. [b] Isolated yields. [c] Determined by chiral HPLC with hexane/2-propanol. [d] The reaction was carried out at 50 °C using $[RhCl(C_2H_4)]_2$ (5.0 mol % Rh) and 1.5 equiv of **1c**. [e] The reaction was carried out at 50 °C using 1.5 equiv of **1x**. [f] The reaction was carried out using 1.5 equiv of **1t**. [g] The reaction was carried out using 5.0 mol % Rh. [h] Determined by converting it to an acetal of (*R*,*R*)-1,2-diphenylethanediol.

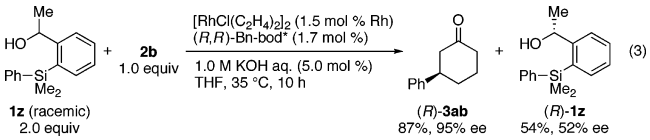
octa-2,5-diene [(*R*,*R*)-Ph-bod*] (3.3 mol %),[26] and a 1.0 M aqueous solution of KOH (15 mol %) in THF at 40 °C for 10 h gave (*R*)-**3ab** of 97% ee in 93% yield (entry 1 of Table 3). The enantioselective addition of **1a** to **2c** was also achieved under the identical conditions, affording (*R*)-**3ac** with 99% ee (entry 2). Employing (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene [(*R*,*R*)-Bn-bod*] as a ligand instead of (*R*,*R*)-Ph-bod*, acyclic enones **2n** and **2o** underwent the 1,4-addition of **1a** to give the corresponding adducts (*R*)-**3an** and (*S*)-**3ao** with excellent enantioselectivities (entries 3 and 4). Furthermore, the

Scheme 1. Plausible Mechanism



reactions of arylsilane **1c** or **1x** with nitrogen-containing substrates **2p** or **2q** provided a silicon-based approach to optically-active substituted piperidones, (*R*)-**3cp**[28] or (*R*)-**3xq**,[7] respectively (entries 5 and 6). (*R*)-**3cp** is the synthetic intermediate of (−)-paroxetine, whereas (*R*)-**3xq** serves as that of a tachykinin antagonist developed by Glaxo Group Ltd., U.K. Alkenylsilanes, **1p**, **1t**, and **1w**, also underwent the enantioselective addition across **2b** under the Rh/chiral diene catalysis to afford the corresponding 3-alkenylcyclohexanones of high % ee (entries 7−9). In addition, even an unsubstituted vinyl group was successfully installed by the use of vinylsilane **1y** to give 1,4-adduct **3yb** in 94% ee (entry 10).[5c,29] The success is remarkable in view that conjugate addition of vinyl groups with the corresponding vinylboronic acids often encounter the problem of the reagent instability.[23]

Reaction Mechanism. The catalytic cycle of the present reaction should be initiated by the reaction of rhodium hydroxide **A** with silane reagent **1** to give organorhodium intermediate **B** (Scheme 1). Michael addition of R in **B** to an enone gives rhodium enolate **C**,[30] which acts as a base to react with **1** to give Michael adduct **3** and rhodium alkoxide **D**. Transmetalation of R from silicon to rhodium would take place by the aid of the proximal hydroxyl group to regenerate **B** to complete the cycle. To gain a mechanistic insight into the transmetalation step, we examined the enantioselective addition of 2.0 molar equiv of racemic chiral phenylsilane reagent **1z** to **2b** using Rh/(*R*,*R*)-Bn-bod* to give the corresponding adduct (*R*)-**3ab** of 95% ee in 87% yield, and unreacted (*R*)-**1z** of 52% ee was recovered in 54% yield based on the amount of loaded **1z** (eq 3).[31] The observed kinetic resolution of **1z** clearly supports that rhodium alkoxide species **D** would be responsible for the transmetalation step, recognizing the chirality of **1z** effectively by the optically pure diene ligand. Intermolecular transfer of the R group via pentacoordinated silicate intermediate **E** appears to be less plausible in this particular transformation.[32]



Conclusion

In summary, we have demonstrated that organo[2-(hydroxymethyl)phenyl]dimethylsilanes serve as efficient reagents for the rhodium-catalyzed 1,4-addition reactions. All the reactions proceed with high chemoselectivity under mild conditions in good yields using equimolar amounts of the silane reagents in most cases. The ready accessibility and high stability toward acid, base, and moisture of the present tetraorganosilicon compounds as compared to conventional ones definitely present the characteristic features of the silane reagents as an attractive alternative to organoboron reagents. Other catalytic and noncatalytic transformations of the silane reagents are currently under investigations in our laboratory.

Acknowledgment. We highly acknowledge Prof. Michinori Suginome and Dr. Toshimichi Ohmura (Kyoto University) for kind assistance in chiral HPLC analysis. This work has been supported financially by Grant-in-Aids for Creative Scientific Research, No. 16GS0209, Scientific Research on Priority Areas "Reaction Control of Dynamic Complex" and "Synergy of Elements", and COE Research on "United Approach to New Material Science" from MEXT. This paper is dedicated to the memory of the late Professor Emeritus Yoshihiko Ito.

Supporting Information Available: Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

JA071969R

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