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Sequential Silylcarbocyclization/Silicon-Based Cross-Coupling Reactions

Scott E. Denmark* and Jack Hung-Chang Liu

Contribution from the Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

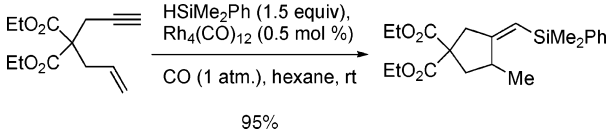
Received November 2, 2006; E-mail: denmark@scs.uiuc.edu

Abstract: A sequential rhodium-catalyzed silylcarbocyclization of enynes parlayed with a palladium-catalyzed, silicon-based cross-coupling reaction has been developed for the synthesis of highly substituted cyclopentanes. 1,6-Enynes reacted with benzyldimethylsilane in the presence of rhodium catalysts to afford five-membered rings bearing a (*Z*)-alkylidenylbenzylsilyl group. A variety of substitution patterns and heteroatom substituents were compatible. The silylcarbocyclization in which an unsaturated ester participated was also achieved. The resulting alkylidenylsilanes underwent palladium-catalyzed cross-coupling using tetra-*n*-butylammonium fluoride. This cross-coupling reaction displayed a broad substrate scope. A wide variety of substitution patterns, electronic properties, and heteroatoms were compatible. All of the cross-coupling reactions proceeded in high yields under very mild conditions and with complete retention of double bond configuration, resulting in densely functionalized 3-(*Z*)-benzylidenecyclopentanes and heterocycles.

Introduction

Silylcarbocyclization[1] is a ring-forming reaction of a polyunsaturated acyclic substrate initiated by silylmetalation of a double bond or a triple bond. As first described by Tamao and Ito in 1989, 1,7-diynes and hydrosilanes react in the presence of a low-valent nickel catalyst to afford exocyclic 1-(*Z*)-silylmethylene-2-methylenecyclohexanes.[2a] Substrates suitable for silylcarbocyclization are not limited to diynes[2] but also include enynes,[3] dienes,[4] allenynes,[5] alkynals,[6] allenals,[7] tetraenes,[8] and endiynes,[9] of which enynes have been most extensively studied. Ojima and co-workers have developed a highly efficient silylcarbocyclization of 1,6-enynes with hydrosilanes, catalyzed by $Rh_4(CO)_{12}$ under very mild conditions, with a very broad range of substrates (Scheme 1).[3a,c] Closely related to silylcarbocyclization is carbonylative silylcarbocyclization,[1] which affords a formylated homologue of the silylcarbocyclization product. Notably, asymmetric variants of both silylcarbocyclization[3d,g] and carbonylative silylcarbocyclization[10] have been reported recently. The products obtained from the silylcarbocyclization reaction of enynes feature a silylalkylidenyl functionality with a defined double bond geometry, which we envisioned as an opportunity for further synthetic elaboration.

Scheme 1



95%

Palladium-catalyzed, silicon-based cross-coupling has emerged as a useful alternative to the classical Stille and Suzuki cross-coupling reactions.[11] One of the main advantages of the silicon-based cross-coupling process is that the silicon-containing functionality can be easily introduced into substrates by a wide variety of methods with a high degree of functional group tolerance. To better harness of the power of silicon-based cross-coupling, we have developed a number of sequential processes

(1) For reviews on silylcarbocyclization, see: (a) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1991**, 539−546. (b) Ojima, I.; Moralee, A. C.; Vassar, V. C. *Top. Catal.* **2002**, *19*, 89−99. (c) Widenhoefer, R. A. *Acc. Chem. Res.* **2003**, *35*, 905. (d) Varchi, G.; Ojima, I. *Curr. Org. Chem.* **2006**, *10*, 1341−1362. (e) Fujiwara, M.; Ojima, I. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, 2005; Chapter 7.

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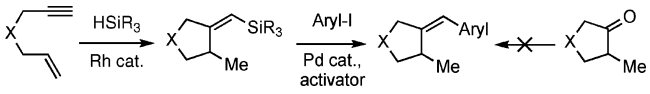
that begin with introduction of the silyl moiety by intramolecular hydrosilylation,[12] intermolecular hydrosilylation,[13] ring-closing metathesis,[14] or silylformylation[15] and are followed by silicon-based cross-coupling. These methods allow for the expedient introduction of silicon-containing functionality in a regioselective and stereocontrolled fashion, which is a prerequisite for the construction of alkenes with a defined geometry. To this end, we have also developed the cross-coupling of highly substituted vinylsilanols to afford highly substituted olefins with defined geometry.[16]

As a part of an ongoing effort to expand the scope of methods for introducing silicon-containing functionalities for cross-coupling, we envisioned that the silylcarbocyclization of 1,6-enynes would allow access to tri- or tetrasubstituted vinylsilanes with exclusively *Z*-geometry. When subjected to the conditions of the cross-coupling reaction with aryl iodides, this intermediate will be transformed into a highly substituted alkene, which would be difficult to synthesize using conventional carbonyl olefination methods[17] in a stereocontrolled manner (Scheme 2).

Scheme 2



Similar sequential carbocyclization/cross-coupling reactions have been reported in the literature. For example, in their original work, Tamao and Ito combined the nickel-catalyzed silylcarbocyclization of 1,7-diynes with a cross-coupling reaction.[2a,18] More recently, Zhou and co-workers described an enantioselective, rhodium-catalyzed silylcarbocyclization with a cross-coupling.[3g] In addition, Widenhoefer and co-workers described a sequential rhodium-catalyzed asymmetric borylcarbocyclization of 1,6-enynes followed by a Suzuki coupling.[19] Herein we describe the sequential rhodium-catalyzed silylcarbocyclization followed by palladium-catalyzed cross-coupling reactions, to provide access to functionalized cyclopentanes with a highly substituted exocyclic double bond with a defined geometry.[20]

Results

1. Silylcarbocyclization of Enynes with Benzyldimethylsilane. The optimized protocol[3c] developed by Ojima for silylcarbocyclization was employed because of its efficiency and generality. Benzyldimethylsilane was chosen as the source of the silyl group because the benzyl−silicon linkage can be readily cleaved in the presence of fluoride to afford silanols.[21] In addition, benzylsilanes are stable under acidic and basic conditions. As such, vinylbenzylsilanes can serve as silanol surrogates for cross-coupling.

Thus, in the presence of 1.5 equiv of benzyldimethylsilane and 0.5 mol % of $Rh_4(CO)_{12}$ in hexane at room temperature under a CO atmosphere (1 atm), the silylcarbocyclizations of 4,4-bis(carbethoxy)-6-hepten-1-yne (**1**) and *N*-benzylallylpropargylamine (**2**) proceeded rapidly to afford cyclization products **6** and **7** in 84% and 91% yields, respectively (Table 1, entries 1 and 2). The tertiary amine moiety in **2** did not attenuate the activity of the rhodium catalyst. Pyrrolidine **7** was found to be very sensitive, as a trace amount of adventitious acid, such as in deuterated chloroform, can cause the exocyclic double bond to isomerize to an endocyclic double bond. Accordingly, neutral alumina (Activity I) and reverse-phase silica gel chromatography were used for the purification of **7**. In addition, either chloroform-*d* that was passed through a plug of basic alumina (Activity I) or deuterated benzene-d_6 was used for the ^{1}H NMR analysis. In contrast to the high reactivity of **2**, *N*-*tert*-butoxycarbonylallylpropargylamine did not undergo silylcarbocyclization reaction under identical conditions. Only the decomposition of the starting material was observed, and this is presumably due to the very rapid C−N bond cleavage caused by rhodium-containing species, as judged by ^{1}H NMR analysis. For the silylcarbocyclization of allyl propargyl ether (**3**) with benzyldimethylsilane, elevated temperature (70 °C) was required, and a more thermally stable rhodium catalyst, $Rh(acac)(CO)_2$, was employed.[3c] Disappointingly, only 53% of **8** was isolated (entry 3). The modest yield is most likely due to competing unconstructive pathways that produced silylated, uncyclized products (observed by ^{1}H NMR spectroscopy) under the reaction conditions.[22]

The effects of substitution were examined by studying the silylcarbocyclization of substituted enynes with benzyldimethylsilane. The procedure described by Ojima and co-workers for the silylcarbocyclization of **4** with dimethylphenylsilane[3c] was followed. Thus, a solution of **4** and benzyldimethylsilane in hexane was stirred in the presence of 0.5 mol % of $Rh_4(CO)_{12}$ at room temperature under 1 atm of CO for 3 h. Surprisingly, the results diverged significantly from those in the literature (Ojima reported that the phenyl analogue of **9** was obtained in 89% yield).[3c] In addition to approximately 25% of **9**, silylformylation product **12** and both constitutional isomers of

(11) For reviews on silicon-based cross-coupling, see: (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845−853. (b) Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471−1478. (c) Hiyama, T. In *Metal Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 10. (d) Hiyama, T.; Shirakawa, E. *Top. Curr. Chem.* **2002**, *219*, 62−85. (e) Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531−1541. (f) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846. (g) Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 57−85. (h) Denmark, S. E.; Sweis, R. F. In *Metal Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 4. (i) Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954−4963.

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(20) Similar structures have recently been accessed via an alternative method: the rhodium-catalyzed sequential carborhodation/cyclization of enynes. See: (a) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54−55. (b) Shintani, R.; Tsurusaki, A.; Okamoto, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3909−3912.

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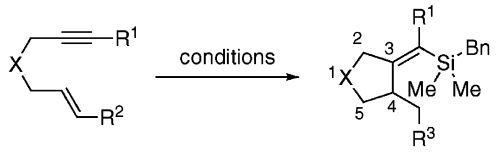
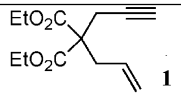
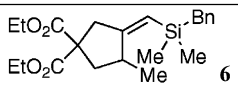
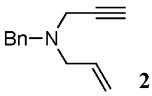
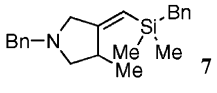
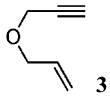
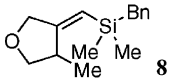
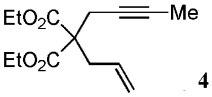
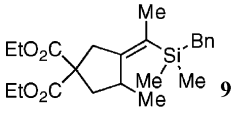
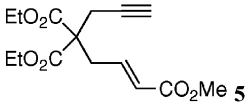
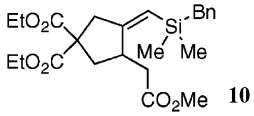
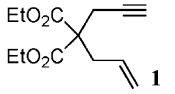
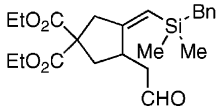
(22) In response to a comment from one of the reviewers, we investigated the silylcarbocyclization of 1-heptyn-6-ene, a substrate similar in structure to **3**, but without the geminal diester moiety. The silylcarbocyclization of this substrate had not been reported previously.[1] We studied the reaction of this enyne with benzyldimethylsilane in the presence of $Rh_4(CO)_{12}$ (1.0−2.5 mol %) under a variety of conditions (0.05−0.2 M in hexane or pentane with temperature control to modulate the exotherm). Unfortunately, the desired product could not be isolated in a synthetically useful yield (39−43% at best), and the reaction was plagued by the appearance of many of byproducts.

Table 1. Results of Silylcarbocyclization of Enynes with Benzyldimethylsilane[a]



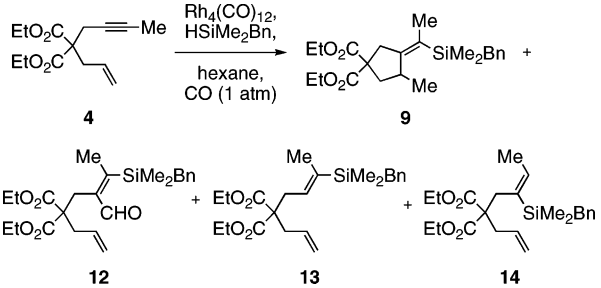
1-5 **6-11**

entry	substrate	silane loading, equiv	catalyst loading,[b] mol %	temperature, °C	atmosphere	time	product	yield,[c] %
1	 **1**	1.5	0.5	rt	CO (1 atm)	10 min	 **6**	84
2	 **2**	1.5	0.5	rt	CO (1 atm)	15 min	 **7**	95
3[d]	 **3**	1.5	5	70	CO (1 atm)	20 min	 **8**	53
4	 **4**	2.0	2	50	CO (1 atm)	15 min	 **9**	81
5	 **5**	1.5	2	rt	CO (8 mol %)/Ar	3.5 h	 **10**	87
6[e]	 **1**	1.05	1	105	CO (20 atm)	48 h	 **11**	83

[a] All reactions run in hexane unless otherwise specified. [b] $Rh_4(CO)_{12}$ used unless otherwise specified. [c] Yields of analytically pure products. [d] Reaction run in toluene; catalyst, $Rh(acac)(CO)_2$. [e] Reaction run in dioxane; 20 mol % of $P(OEt)_3$ was used in addition to $Rh_4(CO)_{12}$.

hydrosilylation products **13** and **14** were obtained in 17%, 25%, and 15% yields, respectively (Table 2, entry 1). To determine the source of this disparity, the silylcarbocyclization of **4** with dimethylphenylsilane was repeated using the same batch of $Rh_4(CO)_{12}$ as in entry 1; however, the literature findings were not successfully reproduced. Approximately 55% of silylcarbocyclization product, 11% of silylformylation product, and 10% of carbonylative silylcarbocyclization product along with approximately 18% of unreacted **4** were obtained. Therefore, at this time we can only conclude that the difference rests in the difference in purity of the commercially available $Rh_4(CO)_{12}$.[23] Fortunately, the silylcarbocyclization of **4** with benzyldimethylsilane could be optimized using the available batch of rhodium catalyst. The hydrosilylation of **4** could be completely suppressed if the solvent used was presaturated with CO. With this modification, the rate of formation of the desired product **9** was significantly lower (Table 2, entry 2). However, rate of formation of **9** could be accelerated by heating **4** with 2 equiv of benzyldimethylsilane and 2 mol % of $Rh_4(CO)_{12}$ dissolved in CO-saturated hexane under a CO atmosphere (1 atm) at 50 °C. The complete conversion of **4** was observed in 20 min, and an 85% yield of **9** was obtained (Table 2, entry 3). Gratifyingly, the silylformylation pathway was suppressed, as **12** was not observed by ^{1}H NMR analysis. After distillation, analytically pure **9** was obtained in 81% yield (Table 1, entry 4). This silylation was completely regioselective, as C(3)-silylated product was not observed.

Table 2. Optimization of Silylcarbocyclization of **4**[a]

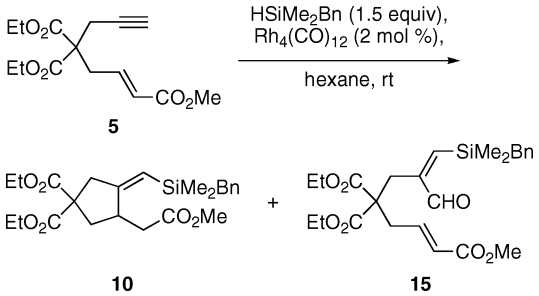


4 **9** **12** **13** **14**

entry	$Rh_4(CO)_{12}$ loading, mol %	$HSiMe_2Bn$ loading, equiv	temp, °C	time	yield,[b] % **9**	**12**	**13**	**14**
1	1	1.5	rt	3 h	25[c]	17	25[c]	15
2[d]	1	1.5	rt	24 h	20[e]	23	0	0
3[d]	2	2.0	50	20 min	85	0	0	0

[a] All reactions performed in hexane at 1.0 mmol scale under a CO atmosphere. [b] Yield of chromatographically homogeneous product unless otherwise noted. [c] Yield estimated from NMR integration of a mixture of **9** and **13**. [d] Hexane used was saturated with CO by bubbling for 30 min. [e] Yield estimated from NMR integration of a mixture of **4** and **9**. Approximately 61% of unreacted **4** remained.

Table 3. Optimization of Silylcarbocyclization of **5**[a]



5 **10** **15**

entry	scale, mmol	atmosphere	time, h	yield,[b] %	remark[c]
1	0.50	dynamic CO	2	nd	**10**/**15** ≈ 3/1
2	1.75	static Ar	12	76	
3	2.00	24 mol % CO/Ar	2.5	72	**10**/**15** ≈ 17/1
4	2.00	8 mol % CO/Ar	3.5	90	**10**/**15** ≈ 33/1
5	5.00	8 mol % CO/Ar	3.0	91	**10**/**15** ≈ 14/1

[a] All reactions performed with 1.0 equiv of **5**, 1.5 equiv of benzyldimethylsilane, and 2 mol % of $Rh_4(CO)_{12}$ in hexane at 1.0 mmol scale under the specified atmosphere. [b] Yield of chromatographically homogeneous product unless otherwise noted. [c] The amount of **15** was estimated by NMR integration.

Silylcarbocyclization products **6**−**9** bear a methyl group at C(4) resulting from the terminal alkene in the starting materials. To increase the degree of functionalization at this position, the silylcarbocyclization of an enyne bearing an α,β-unsaturated ester group **5** was examined. The presence of an electron-deficient double bond in **5** led to different behavior compared to that of other enynes under these conditions. If the reaction was carried out under a CO atmosphere, a significant amount of acyclic silylformylation product was observed (**10**/**15** ≈ 3/1) (Table 3, entry 1). The formation of the undesired byproduct could be completely suppressed by carrying out the reaction in a sealed Schlenk flask under an atmosphere of argon. The desired product **10** was obtained in 76% yield (entry 2). However, the consumption of **5** was significantly slower than that in an atmosphere of CO. The solution to this problem was to blend a substoichiometric amount of CO with the argon. Thus, enyne **5**, 1.5 equiv of benzyldimethylsilane, and 2 mol % of $Rh_4(CO)_{12}$ were combined in a Schlenk flask purged with argon. Subsequently, 24 mol % of CO (11.6 mL, equimolar to the CO ligand of $Rh_4(CO)_{12}$ employed) was added via gastight syringe, and the Schlenk flask remained sealed throughout the reaction period. The conversion to **10** was complete within 2.5 h. A similar amount (72% yield) of **10** was isolated, and the ratio **10**/**15** was 17/1 (due to the small amount of **15** produced, the ratio of **10**/**15** cannot be estimated accurately). When the loading of CO was reduced to 8 mol % (3.9 mL, equimolar to the rhodium in $Rh_4(CO)_{12}$ employed), under otherwise identical conditions, the yield of **10** improved to 90%, and the ratio **10**/**15** also increased to 33/1 (entry 3). When the reaction was carried out at 5.00 mmol scale, after 3 h of stirring under conditions identical to those of entry 3, the desired product **10** was isolated in 91% yield (entry 4), and after distillation, analytically pure **10** was obtained in an 87% yield (Table 1, entry 5).

An alternative method to prepare a C(4)-functionalized cyclopentane is the carbonylative silylcarbocyclization of enynes. Following the procedure of carbonylative silylcarbocyclization described by Ojima and co-workers,[3c] a solution of enyne **1**, 1.05 equiv of benzyldimethylsilane, 1 mol % of $Rh_4(CO)_{12}$, and 20 mol % of $P(OEt)_3$ in dioxane was stirred under 20 atm of CO at 105 °C for 48 h in an autoclave. The resulting aldehyde **11** was obtained in 72% yield (Table 1, entry 6). The silylcarbocyclization of **1**−**5** was found to be completely *Z*-selective, as verified by nuclear Overhauser effect (NOE) experiments. In no case was the *E*-isomer ever observed.

2. Cross-Coupling. 2.1. Identification of Catalyst. With the objective of identifying the most active catalyst for the cross-coupling, a number of palladium complexes were surveyed. Thus, **6** was subjected to the conditions previously developed in these laboratories for alkenyl−aryl cross-coupling with tetra-*n*-butylammonium fluoride (TBAF) and ethyl 4-iodobenzoate as the coupling partner.[24] Thus, 1.1 equiv of **6** was treated with 2.0 equiv of TBAF (1.0 M in tetrahydrofuran (THF)), and the resulting light-yellow solution was stirred at room temperature for 3 min before the palladium catalyst (5 mol % of Pd) and 1.0 equiv of aryl iodide were added sequentially. This reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by HPLC analysis.

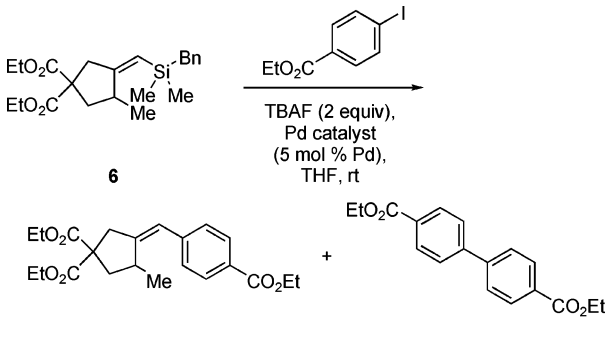
Gratifyingly, the conversion of **6** to **16a** was essentially complete within 2 h at room temperature using 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ (Table 4, entry 3). By comparison, $Pd(dba)_2$, $Pd_2(dba)_3$, and $[allylPdCl]_2$ displayed somewhat attenuated catalytic activity (entries 1, 2, and 4). Thus, the optimal palladium catalyst was identified to be $Pd_2(dba)_3{\cdot}CHCl_3$, and the optimal conditions were 2 equiv of TBAF, 1.1 equiv of **6**, and 1.0 equiv of aryl iodide in THF at room temperature. In general, the production of homo-coupling product **17** was insignificant.

2.2. Coupling Partner Studies. To explore the scope of the coupling partner with silane **6**, a variety of aryl iodides were examined using the optimized conditions described above. The reaction proceeded smoothly with a broad range of aryl iodides. For example, electron-deficient arenes such as ethyl 4-iodobenzoate, 4-iodoacetophenone, and 4-iodobenzonitrile were viable coupling partners, as the yields of **16a**−**c** ranged from 76% to 90% (Table 5, entries 1−3). Notably, 4-iodoacetophenone, bearing an enolizable ketone, was well tolerated (entry 2). Likewise, 4-iodoanisole, an aryl iodide with an electron-donating substituent, smoothly cross-coupled with **6** under identical conditions to afford an 82% yield of **16d** (entry 4). Both 2-iodotoluene (entry 5) and methoxymethyl 3-iodobenzyl ether (**18**) (entry 6) cross-coupled with **6** to give **16e** and **16f** in

(23) For the preparation of $Rh_4(CO)_{12}$, see: (a) Chini, P.; Martinengo, S. *Chem. Commun.* **1968**, 251−252. (b) Booth, B. L.; Else, M. J.; Fields, R.; Goldwhite, H.; Haszeldine, R. N. *J. Organomet. Chem.* **1968**, *14*, 417−422. (c) Chini, P.; Martinengo, S. *Inorg. Chim. Acta* **1969**, *3*, 21−24. (d) Chini, P.; Martinengo, S. *Inorg. Chim. Acta* **1969**, *3*, 315−318. (e) Martinengo, S.; Chini, P.; Giordano, G. *J. Organomet. Chem.* **1971**, *27*, 389−391. (f) James, B. R.; Rempel, G. L. *Chem. Ind.* **1971**, 1036−1037. (g) Cattermole, P. E.; Osborne, A. G. *J. Organomet. Chem.* **1972**, *37*, C17−C18. (h) Giordano, G.; Martinengo, S.; Donatella, S.; Chini, P. *Gazz. Chim. Ital.* **1975**, *105*, 613−615. (i) Uson, R.; Oro, L. A.; Cuchi, J. A. *Quim. Nat. Zaragoza* **1975**, *20*, 173−177. (j) Cattermole, P. E.; Osborne, A. G. *Inorg. Synth.* **1977**, *17*, 115−117. (k) Hunter, D. L. U.S. Patent 4514380, 1985. (l) Martinengo, S.; Giordano, G.; Chini, P. *Inorg. Synth.* **1990**, *28*, 242−245. (m) Hoshi, H. Japanese Patent 03097628, 1991. (n) Moszner, M.; Ziolkowski, J. *J. Organomet. Chem.* **1991**, *411*, 281−283. (o) Serp, P.; Kalck, P.; Feurer, R.; Morancho, R. *Rhodium Express* **1995**, *9*, 5−7. (p) Serp, P.; Kalck, P.; Feurer, R.; Morancho, R. *Inorg. Synth.* **1998**, *32*, 284−287. (q) Cariati, E.; Dragonetti, C.; Roverto, D.; Ugo, R.; Lucenti, E. *Inorg. Chim. Acta* **1969**, *349*, 189−194.

(24) Denmark, S. E.; Wehrli, D. *Org. Lett.* **2000**, *2*, 565−568.

Table 4. Survey of Palladium Catalysts for Cross-Coupling[a]

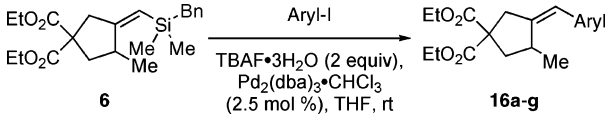


entry	Pd catalyst	time, h	HPLC yield,[b] % 16a	17[c]
1	$Pd(dba)_2$	2	92	1
		4	104	2
2	$Pd_2(dba)_3$	2	83	1
		4	90	2
3	$Pd_2(dba)_3$•$CHCl_3$	2	99	2
		4	100	2
4	$[allylPdCl]_2$	2	80	1
		4	78	3

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of **6**, 1.0 equiv of aryl iodide, and 5 mol % of Pd catalyst at 0.20 mmol scale under an Ar atmosphere at room temperature. [b] Yield determined by HPLC analysis using naphthalene as the internal standard. [c] Yield of **17** calculated on the basis of 0.10 mmol theoretical yield.

81% and 85% yields, respectively. Finally, 1-iodonaphthalene proved to be an excellent coupling partner, and the corresponding cross-coupling product was obtained in 93% yield (entry 7). In all of the cross-coupling reactions, the product was obtained with exclusively *Z*-geometry, which was unambiguously verified by NOE experiments.

Table 5. Cross-Coupling Reaction with Aryl Iodides[a]



entry	Aryl-I	product	yield,[b] %
1	4-$(EtO_2C)C_6H_4I$	**16a**	90
2	4-$(MeCO)C_6H_4I$	**16b**	86
3	4-NCC_6H_4I	**16c**	76
4	4-$MeOC_6H_4I$	**16d**	82
5	2-MeC_6H_4I	**16e**	81
6	3-$(MOMOCH_2)C_6H_4I$ (**18**)	**16f**	85
7	1-iodonaphthalene	**16g**	93

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of **6**, 1.0 equiv of aryl iodide, and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ at 1.00 mmol scale under an Ar atmosphere at room temperature. [b] Yields of analytically pure products.

The purification of cross-coupling products **16a**−**g** was complicated by the contamination with polysiloxanes shown in Figure 1 (the structure of the polysiloxanes was obtained by ^1H NMR analysis). In general, one-column chromatography was not sufficient to remove all the polysiloxanes. Depending on the polarity of the cross-coupling product different polysiloxanes co-eluted. In addition, although the H_2SO_4 stain was found to be most general for the visualization of polysiloxanes on thin-layer chromatographic plates, not all of them were readily visualized. As such, a survey of a variety of eluents was needed to identify the optimal combination of solvents for column chromatography. In the cases where normal-phase chromatography did not remove the polysiloxanes completely, reverse-phase (C-18) chromatography was performed to obtain the products free from polysiloxanes.

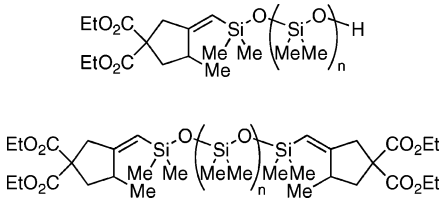
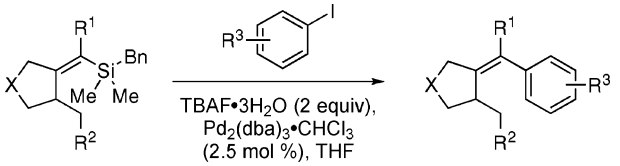


Figure 1. Possible structures of polysiloxanes.

2.3. Substrate Studies. The generality of the cross-coupling of functionalized alkylidenylsilane substrates was next examined. Each of the silanes **7**−**10** was subjected to TBAF-promoted cross-coupling reactions with an electron-poor aryl iodide (ethyl 4-iodobenzoate), an electron-rich aryl iodide (4-iodoanisole), and an *ortho*-substituted aryl iodide (2-iodotoluene) to establish the utility of each substrate.

The nitrogen-containing alkylidenylsilane **7** was an excellent substrate for cross-coupling. The tertiary amine moiety did not interfere with the catalytic activity of $Pd_2(dba)_3$•$CHCl_3$, as evidenced by the good to excellent yields of cross-coupling products **19a**−**c** (Table 6, entries 1−3).

Table 6. Cross-Coupling Reactions of Substrates **7**−**10**[a]



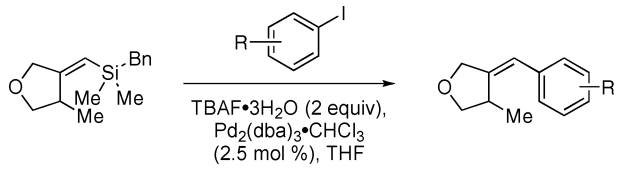
entry	substrate	X	R^1	R^2	R^3	temp, °C	product	yield,[b] %
1	**7**	N-Bn	H	H	4-CO_2Et	rt	**19a**	72[c]
2	**7**	N-Bn	H	H	4-OMe	rt	**19b**	90[c]
3	**7**	N-Bn	H	H	2-Me	rt	**19c**	85[c]
4	**8**	O	H	H	4-CO_2Et	rt	**20a**	88[c]
5	**8**	O	H	H	4-OMe	rt	**20b**	89[c]
6	**8**	O	H	H	2-Me	rt	**20c**	77
7	**9**	$C(CO_2Et)_2$	Me	H	4-CO_2Et	35	**21a**	72
8	**9**	$C(CO_2Et)_2$	Me	H	4-OMe	35	**21b**	74
9	**9**	$C(CO_2Et)_2$	Me	H	2-Me	35	**21c**	64
10	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-CO_2Et	rt	**22a**	74
11	**10**	$C(CO_2Et)_2$	H	CO_2Me	4-OMe	rt	**22b**	77
12	**10**	$C(CO_2Et)_2$	H	CO_2Me	2-Me	rt	**22c**	73

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of substrate, 1.0 equiv of aryl iodide, and 2.5 mol % of $Pd_2(dba)_3$•$CHCl_3$ at 1.0 mmol scale under an Ar atmosphere at the specified temperature. [b] Yields of analytically pure products unless otherwise specified. [c] Yields of chromatographically homogeneous materials.

In addition, the furan-containing substrate **8** underwent cross-coupling readily under the standard conditions. However, the cross-coupling of this substrate was sensitive to scale. The yield of product **20c** decreased from 75% to 61% when the reaction of **8** with 2-iodotoluene was scaled from 0.2 to 1.0 mmol (Table 7, entries 1 and 2). On a 1.0 mmol scale, an exotherm was clearly evident when 2-iodotoluene was added in one portion into the reaction mixture. However, this exotherm could be moderated by adding 2-iodotoluene (neat) to the dark purple

solution of **8**, TBAF solution, and $Pd_2(dba)_3{\cdot}CHCl_3$ such that the internal temperature was not allowed to rise more than 3 °C above the initial temperature. With this simple modification, the yield of **20c** improved to 84%. After distillation, analytically pure **20c** was obtained in 77% yield (Table 6, entry 6). The beneficial effect of slow addition of 2-iodotoluene was found to be general for the other aryl iodides as well. In the cross-coupling of **8** with 4-iodoanisole, if the iodide was added in one portion, only 78% of the product **20b** was isolated. However, the yield of **20b** was improved to 89% if a solution of 4-iodoanilsole in THF was added slowly to the reaction mixture with close monitoring of the internal temperature (Table 7, entry 3). A similar slow addition of aryl iodide was also employed for the cross-coupling of **8** with ethyl 4-iodobenzoate, which resulted in an 88% yield of **20a** (Table 6, entry 4). Products **19** and **20** were sensitive to silica gel, such that repeated purification by column chromatography led to an unacceptable loss in material.

Table 7. Optimization of Cross-Coupling Reaction of **8**[a]



8 **20b-c**

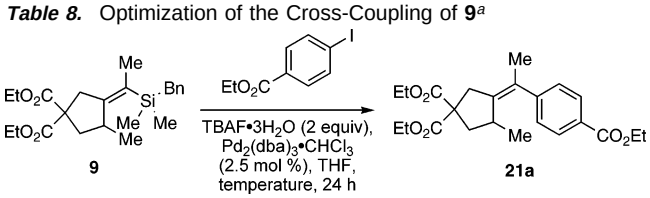
entry	R	scale, mmol	product	yield,[b] %
1	2-Me	0.2	**20c**	75
2	2-Me	1.0	**20c**	61
3[c]	2-Me	1.0	**20c**	84
4	4-OMe	1.0	**20b**	78
5[d]	4-OMe	1.0	**20b**	89

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of **8**, 1.0 equiv of aryl iodide, and 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ at under an Ar atmosphere without any external heating. [b] Yields of chromatographically homogeneous materials. [c] 2-Iodotoluene (neat) added dropwise in the course of 5 min. Internal temperature during addition, 19−21 °C. [d] A solution of 4-iodoanisole (1 mmol) in THF (0.2 mL) added dropwise in the course of 12 min. Internal temperature during addition, 25−28 °C.

To examine the effects of substitution geminal to the silicon group, **9** was subjected to the cross-coupling conditions with aryl iodides. The reaction of **9** with ethyl 4-iodobenzoate afforded only a 76% yield of **21a** when conducted at room temperature (Table 8, entry 1). However, the yield could be improved to 83% by mild heating at 35 °C (entry 2), though elevated temperature (50 °C) did not improve the yield of **21a** (entry 3). At a 1.0 mmol scale, the yield of **21a** was reproduced (entry 4). This material was further purified to afford 72% of analytically pure product (Table 6, entry 7). When conducted at 35 °C, the cross-coupling of **9** with 4-iodoanisole proceeded smoothly to afford **21b** in a comparable yield (74%) (Table 6, entry 8). However, under identical conditions, the yield of the cross-coupling of **9** with 2-iodotoluene was somewhat lower (64%), presumably due to the steric hindrance of both the substrate and the aryl iodide (entry 9).

Very interestingly, the ^1H NMR spectrum of **21c** exhibited two sets of similar signals with identical splitting patterns and with equal intensities. The $^1H/^1H$ COSY spectrum showed that these two sets of signals did not have cross-peaks with each other. In addition, NOE experiments indicated that both components bore a *Z*-double bond. Thus, it was hypothesized

Table 8. Optimization of the Cross-Coupling of **9**[a]



entry	scale, mmol	temp, °C	yield,[b] %
1	0.2	rt	76
2	0.2	35	83
3	0.2	50	82
4	1.0	35	83

[a] All reactions performed in 1.0 M TBAF solution in THF with 1.1 equiv of **9**, 1.0 equiv of ethyl 4-iodobenzoate, and 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$ at under an Ar atmosphere at the specified temperature for 24 h. [b] Yields of chromatographically homogeneous materials.

that **21c** existed as a 1:1 mixture of two atropisomers, which was confirmed by variable-temperature NMR experiments. Coalescence of the NMR signals attributed to the C(6) methyl group and the C(8) methyl group was observed when **21c** was heated to approximately 60 °C in toluene-d_8. However, coalescence of the C(4) methyl and C(4) proton signals did not occur even at 100 °C, but instead, peak broadening was observed above 80 °C. On the basis of these experiments, the interconversion barrier was estimated to be 17 kcal/mol, and the rate of conversion was approximately 32 s^{-1} (Figure 2).

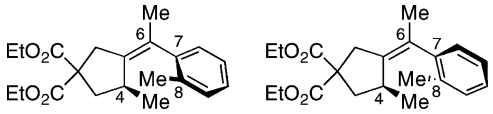


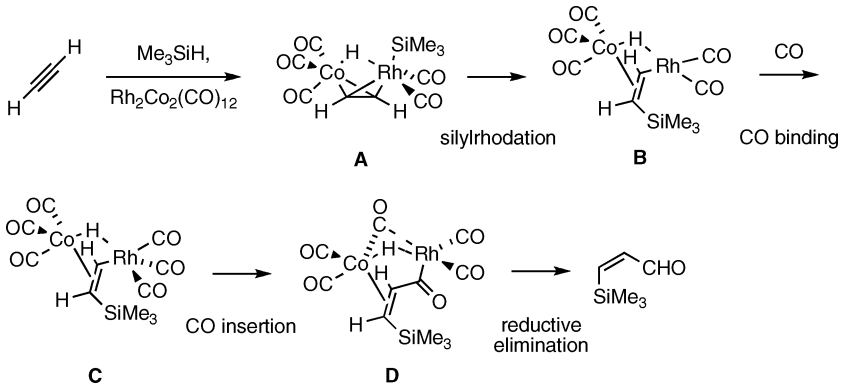
Figure 2. Atropisomers of **21c**.

Not surprisingly, cross-coupling of substrate **10** proceeded cleanly and with rates comparable to those obtained with **6**. Little interference from the additional carbomethoxy group was expected. At room temperature, in the presence of 2.5 mol % of $Pd_2(dba)_3{\cdot}CHCl_3$, **10** underwent cross-coupling with ethyl 4-iodobenzoate, 4-iodoanisole, and 2-iodotoluene smoothly to afford **22a−c** with good yields, ranging from 73% to 77% (Table 6, entries 10−12). The double bond geometry of all the cross-coupling products (**19−22**) has been verified unambiguously by NOE experiments, and the *Z*-geometry was observed exclusively. The same difficulty as noted in the purification of **16** was encountered during the purification of compounds **20** and **21**. Therefore, the survey of eluents and reverse-phase chromatography were utilized to completely remove polysiloxanes derived from starting materials **9** and **10** and to obtain analytically pure materials.

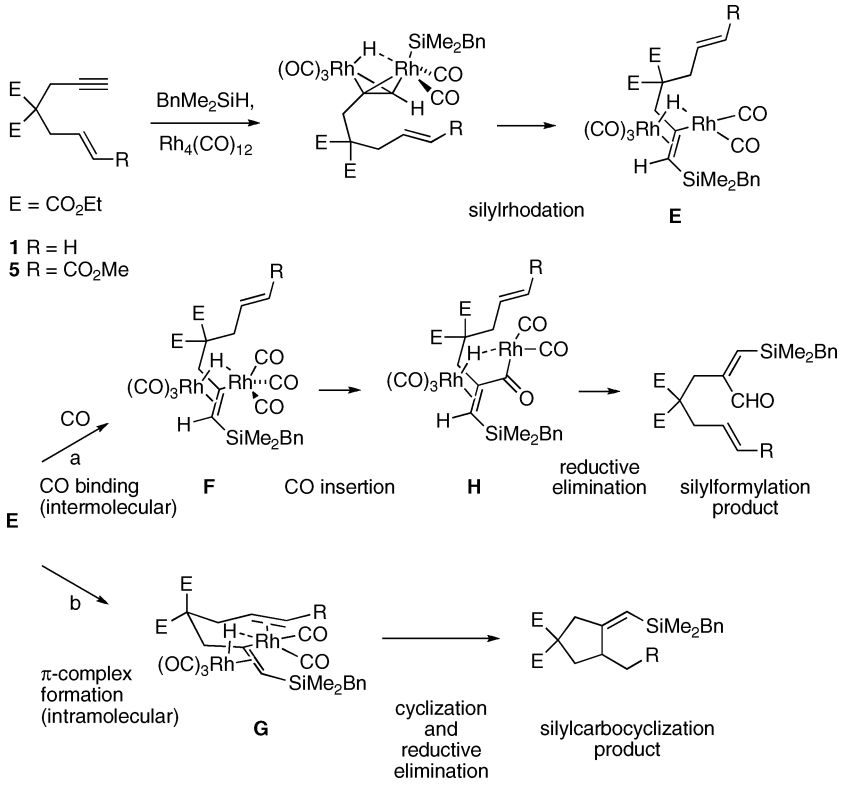
Discussion

1. Silylcarbocyclization. Although the silylcarbocyclization of 1,6-enynes has been well studied, the cyclization of a substrate bearing an electron-deficient double bond such as **5** was unprecedented. Substrates **1** and **2** cyclized without difficulty following the literature procedure, in which an atmosphere of CO was used to prevent catalyst decomposition. However, when **5** was subjected to identical conditions, the result was unsatisfactory due to the formation of a significant amount of silylformylation product. This suggests that the ability of the double bond to bind to the rhodium center to facilitate cyclization is important. Accordingly, an electron-rich double

Scheme 3[25]



Scheme 4



bond favors cyclization more than an electron-poor double bond. This can be rationalized in light of the mechanistic insights from a very recent computational study on the $Rh_2Co_2(CO)_{12}$-catalyzed alkyne silylformylation reported by Nakamura, Ojima, and co-workers.[25] These authors found that when an alkyne, a hydrosilane, and $Rh_2Co_2(CO)_{12}$ are mixed, intermediate **A**, a silylrhodium η^2-alkyne π-complex, is produced. The silylrhodation reaction, the process in which the silylrhodium intermediate adds across the triple bond, then proceeds on to produce a 16-electron vinylrhodium intermediate **B**. This intermediate accepts a CO ligand, resulting in an 18-electron intermediate **C**, before undergoing carbonyl insertion to produce **D**. Direct carbonyl insertion is disfavored because this would lead to an unstable, coordinatively unsaturated 14-electron complex (Scheme 3).

This mechanistic sequence can also explain the appearance of a silylformylation product derived from **5** (Scheme 4). By analogy, if the vinylrhodium species **E** accepts a CO molecule, the carbonyl insertion will follow via the intermediacy of **F** (pathway a, Scheme 4). However, the binding of an electron-rich double bond (R = H, **1**) is favored compared to CO binding, since the formation the π-complex **G** is an intramolecular process. Thus, the cyclization takes place (pathway b, Scheme 4). In contrast, with an electron-poor double bond (R = CO_2Me, **5**), CO binding may become competitive (pathway a, Scheme 4). This implies that silylformylation can be suppressed by decreasing the amount of CO available. Indeed, this hypothesis is supported by the observation that the amount of silylformylation product was reduced as the amount of CO in the reaction mixture was decreased.

2. Cross-Coupling. Substrates **6**−**10**, obtained by silylcarbocyclization reactions, were all competent substrates for the TBAF-promoted cross-coupling, thus displaying a good functional group compatibility. In addition, aryl iodides with broad

(25) Yoshikai, N.; Yamanaka, M.; Ojima, I.; Morokuma, K.; Nakamura, E. *Organometallics* **2006**, *25*, 3867−3875.

(26) Denmark, S. E.; Sweis, R. F.; Wehrli, D. *J. Am. Chem. Soc.* **2004**, *126*, 4865−4875.

ranges of electronic properties and steric demands were all good coupling partners. No clear trend of reactivity has been observed. This is not surprising, considering that an earlier mechanistic study indicates that, under the TBAF-promoted conditions, the oxidative addition of the C−I bond of the aryl iodide is a fast process, and the Si-to-Pd transmetalation of the alkenyl group is rate limiting.[26] Therefore, the substituent on the aryl iodide will only moderately affect the rate of the cross-coupling reaction. Given that the same alkylidenylsilane is used, the reactivity should be consistent among various aryl iodides.

Unlike the cross-coupling of all other substrates, the reaction of **8** was noticeably exothermic, indicating a high rate. This outcome presumably arises because **8** lacks functional groups that can reversibly bind to the palladium catalyst, such as the *gem*-diester (**6**, **9**, and **10**) or the tertiary amine (**7**). Thus, at a given time, the concentration of the catalytically active palladium-containing species is higher when using **8** than in the presence of other substrates. The sensitivity of the cross-coupling of **8** to scale is likely found in the inefficiency of heat dissipation at a larger scale, which causes a higher internal temperature. This outcome is detrimental to the yield of the cross-coupling reaction because the undesired homo-coupling reaction is accelerated at a higher reaction temperature. Thus, the slow addition of the aryl iodide ensures that the reaction temperature does not rise significantly.

The slowest cross-coupling reaction was observed with **9**. This outcome is expected because **9** bears a substituent on the double bond, which very likely slows down the rate-determining silicon-to-palladium transmetalation.[26] Therefore, the rate of cross-coupling can be accelerated simply by mild heating. The ability to prepare **21c**, a tetrasubstituted double bond with an *ortho*-substituted aromatic moiety, under mild reaction conditions is noteworthy. The steric congestion near C(6) is evident from the fact that **21c** was isolated as a pair of slowly interconverting atropisomers, and this is due to the restricted rotation along the C(6)−C(7) bond caused by the three methyl groups that are in close proximity.

Conclusion

The sequential rhodium-catalyzed silylcarbocyclization/palladium-catalyzed, silicon-based cross-coupling has been successfully developed. 1,6-Enynes underwent silylcarbocyclization with benzyldimethylsilane to afford densely functionalized cyclopentanes and heterocycles bearing a (*Z*)-benzyldimethylsilylmethylidene group with complete stereoselectivity. The substitutions on C(1) and C(7) of the enyne as well as the presence of heteroatoms were well tolerated. It was found that if the enyne bears an electron-deficient double bond (**5**), then the major side reaction, silylformylation, can be suppressed by carrying out the reaction under a substoichiometric amount of CO. In addition to the silylcarbocyclization of **5**, the carbonylative silylcarbocyclization was also feasible, thus gaining access to C(4)-functionalized cyclopentanes. The cross-coupling of the silylcarbocyclization products with aryl iodides also proceeded smoothly under very mild conditions in good to excellent yields with a variety of coupling partners and substrates. Aryl iodides with a broad range of electronic properties as well as with *para*, *meta*, and *ortho* substituents all led to cross-coupling products in good to excellent yields. In general, heating was not required, except for the most sterically demanding substrate **9**. The application of this sequential process in the total synthesis of biologically active natural products will be reported in due course.

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Supporting Information Available: Detailed experimental procedures and full characterization of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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