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Palladium-Catalyzed Hiyama Couplings of α-Silylenoates and α-Silylenamides

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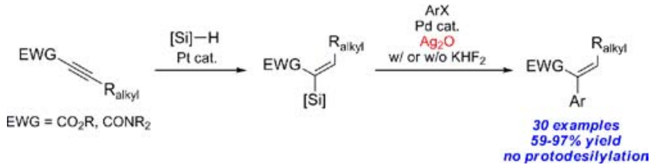
ABSTRACT



The Hiyama couplings of both α-silylenoates and α-silylenamides are described. These sensitive substrate classes require particularly specific conditions, employing both appropriate silicon-based species and a silver additive to realize high yields of the coupling products. Regioselective platinum-catalyzed hydrosilylations provide a direct and convenient entry into these stereodefined trisubstituted alkenes.

Palladium-catalyzed cross-couplings have become an essential tool in the synthetic chemist's arsenal. In particular, the Hiyama coupling is an attractive option because of the relative stability and low toxicity of the vinylsilane nucleophiles.[1] In this transformation, activated silicon species are generally necessary for transmetalation to proceed. This requirement has been achieved most commonly through either the formation of a pentavalent siliconate intermediate or the use of a silanol species. These individual species, however, are often too labile to be maintained through synthetic steps, and therefore chemists frequently employ surrogates that can readily generate the reactive intermediates via triggering reagents (e.g., fluoride ion).

We recently described the platinum-catalyzed hydrosilylations of internal alkynes, where the electronic effects of the two substituents primarily governed the addition of the silicon hydride.[2] In particular, high levels of regioselection were observed using electron-deficient alkynes such as ynoates and ynamides (Figure 1). As part of assessing the synthetic utility of the hydrosilylation products, one immediate application we envisioned was the direct cross-coupling of these electron-deficient vinylsilanes. Recently, Hosoya reported an effective Hiyama coupling of electron-deficient triethoxyvinylsilanes.[3] Herein, we present our studies on related cross-couplings, demonstrating that the appropriate choices of both silane species and reaction conditions are essential for a successful hydrosilylation/C–C bond-formation process.

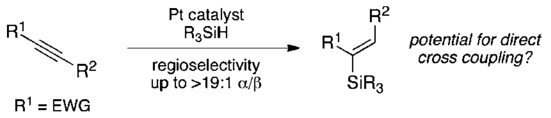


Figure 1. Pt-catalyzed hydrosilylations of internal alkynes.

The cross-couplings of α-silylenoates and α-silylenamides, representative products of our hydrosilylations, present particularly unique challenges (Figure 2). The electron-poor vinylsilane should be inherently slower in transmetalation. With α,*β*-unsaturated carbonyl substrates, competitive conjugate addition processes could possibly thwart the target transformation.[4] Additionally, the formation of the anionic siliconate intermediate has the potential of desilylation, leading to stabilized enolate

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[1] For an excellent comprehensive review, see: Chang, W. T.; Smith, R. C.; Regens, C. S.; Bailey, A. D.; Werner, N. S.; Denmark, S. E. *Org. React.* **2011**, *75*, 213–745.

[2] (a) Rooke, D. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3225–3230. (b) Rooke, D. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2010**, *132*, 11926–11928.

[3] Sumida, Y.; Kato, T.; Yoshida, S.; Hosoya, T. *Org. Lett.* **2012**, *14*, 1552–1555.

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intermediates that could protonate or participate in other nucleophilic side reactions.

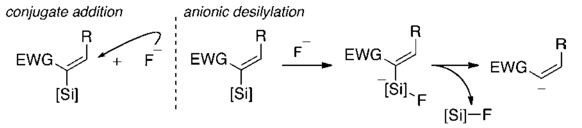


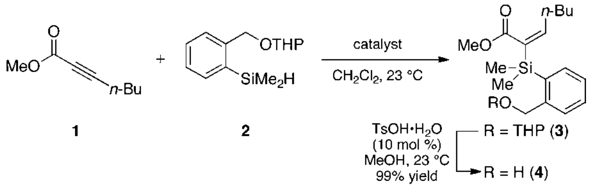
Figure 2. Potential complications with α-silicon, α,β-unsaturated nucleophiles.

Indeed, initial experiments based on several of the established silicon species were ineffective in this context.[5] 2-Pyridyldimethylsilane was unreactive in our platinum-catalyzed hydrosilylations of alkynes, even at elevated temperatures. Both allyl- and benzyldimethylsilane were competent hydrosilylation agents, affording the α-silylenoates in >90% yield. Unfortunately, however, fluoride-activated protocols for enabling transmetalation also caused protodesilylation and other complicating background reactions.

We were then attracted to a report by Nakao, Hiyama, and co-workers[6] that showed that the (2-hydroxymethyl)phenyl group, when attached to silicon, could induce cross-couplings.[7] In these systems, added base enabled intramolecular attack of the alkoxide to silicon, which activated the species for subsequent transmetalation. We anticipated that the mild conditions (K_2CO_3) would facilitate the desired process without the aforementioned complications.

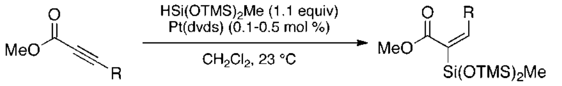
Hydrosilylations of methyl 2-heptynoate with the THP-protected benzyl alcohol derivative (**2**) based on our previously described conditions for internal alkynes (cat. $PtCl_2$, silane, CH_2Cl_2, 23 °C) resulted only in decomposition of the silane (Scheme 1).[8] Zeise's dimer ($[(C_2H_4)PtCl_2]_2$) was more suitable for this transformation, although the yields and regioselectivities were still suboptimal. In both cases, the potential generation of HCl was likely degrading the silane due to the lability of the acetal functional group.[9] Indeed, Pt(dvds), absent the chloride counterion, provided substantial improvement, and the α-silylenoate could be obtained in 92% yield and in 11:1 regioselectivity. The benzyl alcohol could then be revealed under standard methanolysis conditions.[10]

Scheme 1. Hydrosilylation/Deprotection with Silane **2**



entry	catalyst (mol % Pt)	time (h)	yield **3** (%)[a]	regioselectivity (α:β)[b]
1	$PtCl_2$ (5)	96	--	--
2	$[(C_2H_4)PtCl_2]_2$ (2)	23	56	7.5:1
3	Pt(dvds) (1)	26	94	9:1
4	Pt(dvds) (0.5)	30	92	11:1

Scheme 2. Hydrosilylations with 1,1,1,3,5,5,5-Heptamethyltrisiloxane



1 (R = n-Bu)
7 (R = i-Pr)
8 (R = CH_2CH_2OTHP)

9 (R = n-Bu, 98% yield, 16:1 α:β)
10 (R = i-Pr, 75% yield, 19:1 α:β)
11 (R = CH_2CH_2OTHP, 94% yield, 11:1 α:β)

With the desired α-silylenoate in hand, we proceeded to evaluate its cross-coupling potential (Table 1). Early optimization trials, originating from Hiyama's reported conditions, provided erratic results, with yields in the range of 0–55%. Unfortunately, in even the best cases, protodesilylation and other decomposition pathways plagued the reaction. A breakthrough was achieved when Ag_2O was employed as the base. Further evaluation of the reaction parameters revealed that anhydrous dioxane was the optimal medium, and coupled product **6** could be obtained in excellent overall yield. Notably, a more difficult coupling partner, electron-rich 4-iodoanisole, was similarly effective in this Hiyama reaction.

An array of aryl iodides and bromides could be coupled to the α-silylenoate under these optimized conditions (Table 2). Elevated temperatures (100 °C) were required for the formation of sterically hindered alkenes (e.g., **6f**) or alkenes arising from electron rich aryl bromides (e.g., **6i**). In all cases, the Hiyama cross-couplings proceeded in good to excellent yields.[11]

Although the use of silane **2** was generally effective, we still desired to use a more convenient silicon precursor. 1,1,1,3,5,5,5-Heptamethyltrisiloxane, commercially available

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(4) β-Silyl-α,β-unsaturated carbonyl compounds have been employed in a few isolated cases. See: (a) Denmark, S. E.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 5153–5159. (b) Shindo, M.; Matsumoto, K.; Shishido, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 104–106. (c) Shindo, M.; Matsumoto, K.; Shishido, K. *Synlett* **2005**, 176–178.

(5) See the Supporting Information for experimental details.

(6) Nakao, Y.; Imanaka, H.; Sahoo, A. K.; Yada, A.; Hiyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 6952–6953.

(7) For select applications of this silicon species in cross-coupling, see: (a) Chen, J.; Tanaka, M.; Sahoo, A. K.; Takeda, M.; Yada, A.; Nakao, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 554–569. (b) Shirbin, S. J.; Boughton, B. A.; Zammit, S. C.; Zanatta, S. D.; Marcuccio, S. M.; Hutton, C. A.; Williams, S. J. *Tetrahedron Lett.* **2010**, *51*, 2971–2974. (c) Nakao, Y.; Chen, J.; Tanaka, M.; Hiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 11694–11695. (d) Nakao, Y.; Imanaka, H.; Chen, J.; Yada, A.; Hiyama, T. *J. Organomet. Chem.* **2007**, *692*, 585–603. (e) Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett.* **2007**, *36*, 606–607.

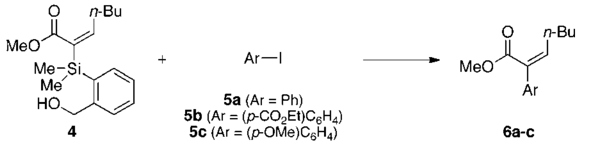
(8) To our knowledge, hydrosilylations using **2** have only been employed for terminal and symmetrical internal alkynes. See ref 5.

(9) We had observed in our previous substrate analysis that propargylic alcohols, particularly sensitive to acid-catalyzed ionization, were also problematic substrates with platinum catalysts bearing chloride counterions.

(10) This sequence can also be accomplished in a single pot in comparable yields (~90%). See the Supporting Information.

(11) Other heteroaryl iodides examined (e.g., 2-iodopyridine, 2-iodothiophene, 2-iodofuran) were unreactive under these conditions.

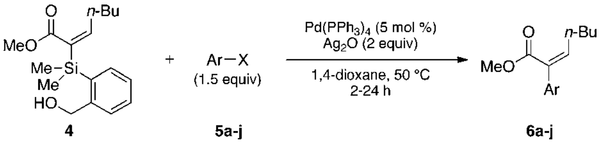
Table 1. Hiyama Coupling Conditions Optimization

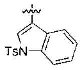


entry	Ar-I[a]	catalyst (mol %)	additive(s) (equiv)	solvent, temp (°C)	time (h)	yield (%)[b]
1	**5a**	$PdCl_2$ (5) $P(2\text{-fur})_3$ (10)	K_2CO_3 (2.0)	DMSO, 50	24	0
2	**5a**	Pd_2dba_3 (2.5)	CuI (0.1) K_2CO_3 (2.0) H_2O (5.0)	THF, 60	24	0
3	**5a**	Pd_2dba_3 (2.5)	CuI (0.1) K_2CO_3 (2.0)	THF, 60	24	55
4	**5b**	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2.0)	THF, 60	16	0
5	**5b**	$Pd(PPh_3)_4$ (5)	Ag_2O (1.1)	THF, 60	8	76
6	**5b**	$Pd(PPh_3)_4$ (5)	Ag_2O (1.5)	THF, 60	8	85
7	**5b**	$Pd(PPh_3)_4$ (5)	Ag_2O (2.0) H_2O (5.0)	1,4-dioxane, 50	8	85
8	**5b**	$Pd(PPh_3)_4$ (5)	Ag_2O (2.0)	1,4-dioxane, 50	4	92
9	**5c**	$Pd(PPh_3)_4$ (5)	Ag_2O (2.0)	1,4-dioxane, 50	4	89

[a] 1.5 equiv ArI used. [b] Isolated yield.

Table 2. Hiyama Couplings Based on α-Silylenoate **4**



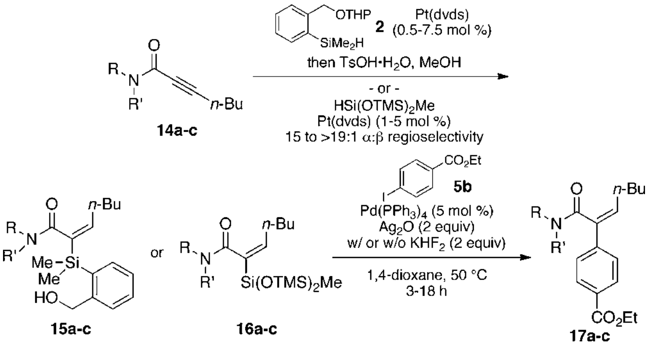
entry	Ar	X	product	time (h)	yield (%)[a]
1	Ph	I	**6a**	8	90
2	(p-CO_2Et)C_6H_4	I	**6b**	8	92
3	(p-OMe)C_6H_4	I	**6c**	2	89
4	(p-CN)C_6H_4	I	**6d**	8	96
5	(p-NO_2)C_6H_4	I	**6e**	3	79
6[b]	(o-CO_2Et)C_6H_4	I	**6f**	0.75	92
7		I	**6g**	2	95
8	(p-CN)C_6H_4	Br	**6d**	12	78
9	1-Naphthyl	Br	**6h**	24	65
10[b]	(p-CH_2OTBS)C_6H_4	Br	**6i**	20	91
11	(p-CHO)C_6H_4	Br	**6j**	3	74

[a] Isolated yield. [b] Reaction temperature: 100 °C.

and relatively inexpensive, appeared ideal for this overall goal.[12] To that end, ynoates **1**, **7**, and **8** were hydrosilylated with Pt(dvds) under our optimal conditions, and the corresponding α-silylenoates were obtained in excellent yield and regioselectivity (Scheme 2).

When the product α-silylenoates were evaluated in the Hiyama coupling based on our optimized conditions, coupling was observed, but reactivity was low (approximately 30% conversion with 4-iodoanisole). The addition

Scheme 3. Ynamide Hydrosilylation/Hiyama Couplings



ynamide	R, R'	% yield **15a-c**[a]	% yield **16a-c**	% yield **14a-c** (from **12a-c**)	% yield **17a-c** (from **16a-c**)
14a	Et, Et	76[b]	81[c]	97	81
14b	Me, OMe	73[c]	98[e]	91	88
14c	H, Ph	89[d]	94[e]	91	85

of potassium hydrogen fluoride was highly beneficial here; this very mild source of fluoride presumably assists in silyl ether cleavage, providing activated silicon species for the intended transforms. With these conditions, a number of aryl iodides and bromides could be coupled to the silyl enoates (Table 3). In general, these reactions were not quite as effective relative to the examples based on the (2-hydroxymethyl)phenylsilyl species, but they still afforded the desired alkene products in good yields overall.

α,*β*-Unsaturated amides, accessed via similar hydrosilylations of the corresponding alkynes, could also be cross-coupled efficiently (Scheme 3). Vinylsilanes bearing secondary, tertiary, and Weinreb amides were all competent nucleophilic components in these Hiyama couplings. Enones, however, remained unable to participate similarly, suggesting that the stability of the enolate has a significant role in determining the relative amounts of cross-coupling and protodesilylation products.

The crucial role of silver ion in these transformations was intriguing.[13] In the absence of silver, cross-coupling was observed in modest yields at best.[14] We primarily considered two different rationalizations to explain this necessity. The silver may be helping to ionize the Pd–X bond resulting from oxidative addition; the more cationic metal center would thus be activated for transmetalation. Alternatively, the silicon species could be transmetalating directly to silver, and the organosilver is the species that participates in transmetalation with palladium.[15]

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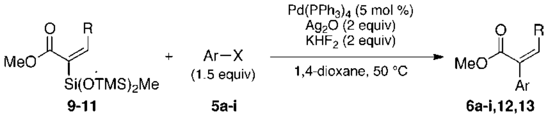
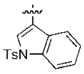
(12) For the use of 1,1,1,3,5,5,5-heptamethyltrisiloxane in hydrosilylations/Hiyama couplings, see: (a) Berthon-Gelloz, G.; Schumers, J.-M.; De Bo, G.; Markó, I. E. *J. Org. Chem.* **2008**, *73*, 4190–4197. (b) Reference 2a.

(13) For examples of the effective use of Ag_2O in Hiyama couplings, see: (a) Hirabayashi, K.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Org. Lett.* **1999**, *1*, 299–301. (b) Hirabayashi, K.; Mori, A.; Kawashima, J.; Suguro, M.; Nishihara, Y.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 5342–5349. (c) Nokami, T.; Tomida, Y.; Kamei, T.; Itami, K.; Yoshida, J.-I. *Org. Lett.* **2006**, *8*, 729–731. (d) Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2008**, *49*, 3939–3942. (e) Napier, S.; Marcuccio, S. M.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2008**, *49*, 6314–6315.

(14) (a) Similarly, Hosoya found that AgF was an essential additive to promote the cross-couplings of the vinyltriethoxysilanes. See ref 3. (b) Other silver salts (AgF, Ag_2CO_3, AgOTf) did also afford coupled products, albeit in lower yields (1–58%).

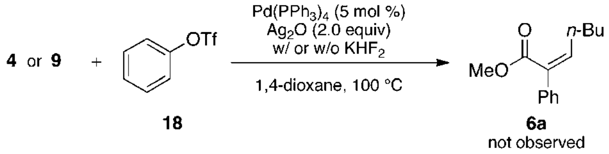
Table 3. Hiyama Couplings Based on α-Silylenoates **9**−**11**



entry	enoate	Ar	X	product	time (h)	yield (%)[a]
1	**9**	Ph	I	**6a**	17	81
2	**9**	(p-CO_2Et)C_6H_4	I	**6b**	17	97
3	**9**	(p-OMe)C_6H_4	I	**6c**	12	86
4	**9**	(p-CN)C_6H_4	I	**6d**	8	81
5	**9**	(p-NO_2)C_6H_4	I	**6e**	12	88
6	**9**	(o-CO_2Et)C_6H_4	I	**6f**	22	59
7	**9**		I	**6g**	7.5	62
8	**9**	(p-CH_2OTBS)C_6H_4	I	**6i**	18	86
9	**10**	(p-CO_2Et)C_6H_4	I	**12**	22	90
10	**11**	(p-CO_2Et)C_6H_4	I	**13**	6	91
11[b]	**9**	(p-CN)C_6H_4	Br	**6d**	12	93
12[b]	**9**	1-Naphthyl	Br	**6h**	60	69

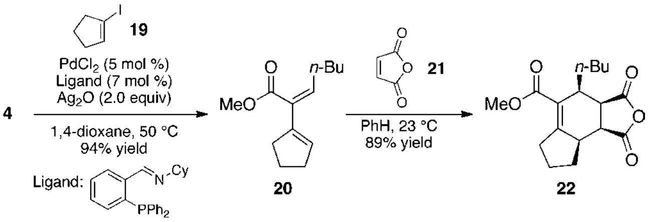
[a] Isolated yield. [b] Reaction temperature: 100 °C.

Scheme 4. Attempted Hiyama Coupling with Aryl Triflate



As a first level analysis, we decided to assess the competency of aryl triflate electrophiles in these cross-couplings. If the sole role of the silver base is to generate an organosilver intermediate prior to cross-coupling, then substitution with a triflate should be inconsequential in the overall process, presuming the Pd−OTf intermediate is competent in cross-coupling.[16−18] As illustrated in Scheme 4, Hiyama couplings with phenyl triflate were ineffective.[19] We believe this strongly suggests that the tempered ionization of the Pd−X bond is a key attribute toward reactivity in these systems.

Scheme 5. Alkenyl Iodide Coupling/Cycloaddition



Finally, these Hiyama couplings can be useful reactions in synthetic sequences toward building molecular complexity. An example is depicted in Scheme 5. The coupling of α-silylenoate **4** and vinyl iodide worked efficiently to afford diene **20**, which was immediately subjected to a Diels−Alder reaction with maleic anhydride. Despite the electron-withdrawing group on the diene moiety, the cycloaddition proceeded cleanly and effectively at room temperature to afford tricycle **22**. These types of transformations illustrate the utility these Hiyama couplings may have in complex molecule synthesis.

In summary, we have described the selective and efficient Hiyama couplings of α-silyl electron-deficient alkenes. Under carefully controlled conditions and employing the appropriate silicon species, alkene products can be obtained in good yields and with high geometrical integrity. The application of our efforts in the platinum-catalyzed hydrosilylations of internal alkynes allows for direct entry into these cross-coupling partners. We anticipate, given the facile nature of these processes, that this transformation will be of high value to the synthetic community.

Acknowledgment. Colorado State University is acknowledged for support of our program. Eli Lilly is gratefully acknowledged for a graduate research fellowship to D.A.R.

Supporting Information Available. Experimental procedures, compound characterization data, and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(15) Alternative explanations that have been previously proposed but we do not believe are applicable here are that (1) Ag_2O adds as an activator to make a silicate species to enable transmetalation (ref 13a) and (2) a tridentate mode of coordination that initiates a Si to Ag transmetalation (ref 13c).

(16) Although Hiyama couplings with triflates are less prevalent, there are a number of cases where efficient coupling has been observed. For select examples, see: (a) Hosomi, A.; Kohra, S.; Tominaga, Y. *Chem. Pharm. Bull.* **1988**, *36*, 4622–4625. (b) Hatanaka, Y.; Hiyama, T. *Tetrahedron Lett.* **1990**, *31*, 2719–2722. (c) Denmark, S. E.; Sweis, R. F. *Org. Lett.* **2002**, *4*, 3771–3774. (d) Riggleman, S.; DeShong, P. *J. Org. Chem.* **2003**, *68*, 8106–8109. (e) Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 1137–1143.

(17) Alkynylsilver species, either isolated or generated in situ, have been coupled to triflates under palladium catalysis. For examples, see: (a) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661–1664. (b) Halbes, U.; Pale, P. *Tetrahedron Lett.* **2002**, *43*, 2039–2042.

(18) Arylsilicon species based on the (2-hydroxymethyl)phenyl group have been coupled to aryl imidazol-1-ylsulfonates. See ref 7b.

(19) A number of parameter variations on these optimal conditions were also evaluated, but ester **6a** was never produced.