

# Highly Stereoselective Hydrocarbation of Terminal Alkynes via Pt-Catalyzed Hydrosilylation/Pd-Catalyzed Cross-Coupling Reactions

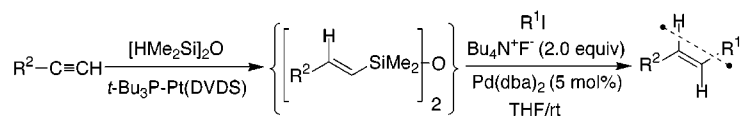
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Received February 7, 2001

## ABSTRACT



The formal addition of an aryl-H or alkenyl-H bond across a terminal alkyne has been accomplished by the combination of platinum-catalyzed hydrosilylation followed by palladium-catalyzed cross-coupling. The use of the *t*-Bu<sub>3</sub>P–Pt(DVDS) catalyst in combination with tetramethylsiloxane gave excellent regio- and stereoselectivity with a number of alkyne substrates. Subsequent, fluoride-promoted cross-coupling proceeded in high yield and stereospecificity for a variety of aryl halides.

The formation of carbon–carbon bonds by Pd-catalyzed cross-coupling reactions of aryl and alkenyl halides with organometallic reagents represents an important transformation in organic synthesis.<sup>1</sup> Formerly the province of organotin, organoboron, and organozinc reagents, in recent years the coupling reactions of organosilicon compounds have emerged as a viable alternative.<sup>2</sup> The benefits of silicon-based cross-couplings are the ease of introduction of silicon into organic substrates, compatibility with a range of chemical transformations, and low toxicity of the byproducts. The principal disadvantage of these coupling reactions is the

low reactivity of the silicon donor groups compared to the other more traditional partners. This lack of reactivity has been addressed by modulation of the silicon substituents and the use of new additives and catalysts.<sup>3</sup>

Recent disclosures from this laboratory have introduced a new class of silicon-based coupling reagents, alkenyl- and arylsilylcyclobutanes, which undergo facile cross-coupling reactions in high yield with good functional group compatibility and high stereoselectivity.<sup>4</sup> Further, our discovery of the central role played by the silyloxy-type functions have given rise to synthetically valuable alternatives.<sup>5a</sup> For example, we have now demonstrated that alkenylsilanols and disiloxanes,<sup>5b</sup> silyl hydrides,<sup>5c</sup> cyclic silyl ethers,<sup>5d</sup> and even oligosiloxanes<sup>5e</sup> are effective coupling components under similar conditions.

The efficiency and stereoselectivity of intramolecular

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**Table 1.** Optimization of Platinum-Catalyzed Hydrosilylation<sup>a</sup>

	1	2	3	4	5	6
<b>H<sub>2</sub>PtCl<sub>6</sub><sup>b</sup></b>	80 (100/0)	100 (84/16)	100 (88/12)	100 (88/12)	no reaction	58 (66/34)
<b>Pt(0)<sup>c</sup></b>	many products	100 (85/15)	100 (88/12)	100 (88/12)	no reaction	54 (72/28)
<b><i>t</i>-Bu<sub>3</sub>P-Pt(0)</b>	many products	100 (98/2)	100 (87/13)	100 (87/13)	70 (98/2)	55 (92/8)

<sup>a</sup> Stoichiometry for the hydrosilylation: silane:7:8a, 1.3/*n*:1.3:1.0 (*n* = available hydrides); results in the table represent conversion based on 8a, data in parentheses are the ratio 9a/10a. <sup>b</sup> Reaction conditions: 50 °C/30 min. <sup>c</sup> Pt(DVDS) in xylene.

hydrosilylation/cross-coupling as demonstrated for homopropargylic alcohols<sup>5d</sup> suggested the extension of this protocol to terminal alkynes. It is well-known that silanols and disiloxanes can be prepared in high yield by the hydrosilylation of terminal alkynes with dialkylchlorosilanes in the presence of a Pt catalyst (H<sub>2</sub>PtCl<sub>6</sub>, Speier's catalyst), followed by in situ hydrolysis or by direct hydrosilylation with hydridodisiloxanes.<sup>6,7</sup> In this Letter, we report our preliminary results on the combination of Pt-catalyzed hydrosilylation of alkynes with the Pd-catalyzed cross-coupling of the resulting alkenyldisiloxanes with aryl or alkenyl halides. The net result of this efficient and selective one-pot process is to effect the hydrocarbation of a terminal alkyne.

The palladium-catalyzed, one-pot formation and coupling reactions of organoboron reagents with aryl or alkenyl halides

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and its application in organic synthesis is well documented.<sup>8</sup> Moreover, the systematic study of a similar process with organotin<sup>9</sup> and zinc reagents<sup>10</sup> was also reported recently. A thorough search of the literature reveals a number of examples of hydrosilylation/cross-coupling as applied to specific synthetic targets,<sup>11</sup> but a systematic investigation is lacking.

The initial development of a one-pot protocol focused on the Pt-catalyzed hydrosilylation event. To optimize the hydrosilylation we studied the reaction of 1-heptyne (7) with diisopropylchlorosilane and evaluated the results by directly carrying out the Pd-catalyzed cross-coupling<sup>12</sup> on the product with 1-iodonaphthalene (8a), Table 1. Thus, hydrosilylation of 7 with diisopropylchlorosilane (1) in the presence of H<sub>2</sub>PtCl<sub>6</sub> (<0.1 mol %) at 50 °C for 30 min, followed by treatment with TBAF, Pd(dba)<sub>2</sub>, and 8a resulted in an incomplete coupling (70–80% conversion). Gratifyingly, no other isomeric, cross-coupling products ((*Z*)-9a or 10a) were observed by GC analysis. However, all attempts to improve the conversion failed. Consequently, we then undertook a survey to screen other silane sources and Pt catalysts for their activity and stereoselectivity in this transformation; the results are collected in Table 1.

Orienting experiments revealed that the regio- and stereoselectivity is strongly affected by the structure of silane. In the presence of Speier's catalyst, tetramethyldisiloxane (2), tetramethylcyclotetrasiloxane (3), and methyldiethoxysilane (4) can participate in the hydrosilylation/cross-coupling reaction smoothly as evidenced by the complete consumption

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(12) The coupling conditions from our previous studies<sup>5b</sup> were employed (THF, 1.0 M TBAF (2.0 equiv), Pd(dba)<sub>2</sub> (5 mol %), room temperature, 10 min).

**Table 2.** One-Pot Hydrosilylation/Cross-Coupling of 1-Heptyne with Aryl and Alkenyl Iodides<sup>a</sup>

entry	halide, R <sup>1</sup> ( <b>8</b> )	time, min	product	yield, <sup>b</sup> %	ratio ( <i>E</i> )- <b>9</b> / <i>(Z)</i> - <b>9</b> / <b>10</b> <sup>c</sup>
1	1-naphthyl ( <b>8a</b> )	10	<b>9a</b>	82	98.4/0.1/1.5
2	4-(CH <sub>3</sub> CO)C <sub>6</sub> H <sub>4</sub> ( <b>8b</b> )	10	<b>9b</b>	94	99.1/0.4/0.5
3	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> ( <b>8c</b> )	10	<b>9c</b>	84	96.5/1.4/2.1
4 <sup>d</sup>	4-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> ( <b>8c</b> )	10	<b>9c</b>	89	97.7/1.0/1.3
5	3-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>8d</b> )	10	<b>9d</b>	85	97.5/2.5 <sup>e</sup>
6 <sup>f</sup>	3-(NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>8d</b> )	60	<b>9d</b>	89	98.5/1.5 <sup>e</sup>
7	3-(CH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub> ( <b>8e</b> )	10	<b>9e</b>	78	97.4/2.6 <sup>e</sup>
8 <sup>g</sup>	2-(CH <sub>3</sub> OCO)C <sub>6</sub> H <sub>4</sub> ( <b>8f</b> )	20 h	<b>9f</b>	88	96.7/2.3 <sup>e</sup>
9	2-(CH <sub>3</sub> O)C <sub>6</sub> H <sub>4</sub> ( <b>8g</b> )	10	<b>9g</b>	82	99.4/0.6 <sup>e</sup>
10	( <i>E</i> )-ICH=CHC <sub>5</sub> H <sub>11</sub> ( <b>8h</b> )	16 h	<b>9h</b>	67	91.4/8.6 <sup>h</sup>
11 <sup>i</sup>	( <i>E</i> )-BrCH=CHC <sub>6</sub> H <sub>5</sub> ( <b>8i</b> )	14 h	<b>9i</b>	70	92.0/3.2/4.8

<sup>a</sup> All reactions used 1.3/2 equiv of **2** and 1.3 equiv of **7** (except entry 3 which used 1.56/2 equiv of **2**, 1.3 equiv of **7**); hydrosilylation required 30 min at rt. <sup>b</sup> Yield of analytically pure materials. <sup>c</sup> Determined by GC or GC-MS analysis. <sup>d</sup> Iodide added last. <sup>e</sup> Ratio (*E*)-**9**/*(Z)*-**9** + **10**. <sup>f</sup> 1.0 mol % of Pd(dba)<sub>2</sub>. <sup>g</sup> 10 mol % of Ph<sub>3</sub>As was used. <sup>h</sup> Ratio (*E,E*)-**9h**/*(E,Z)*-**9h** + **10**. <sup>i</sup> 2.5 mol % of [allylPdCl]<sub>2</sub> was used.

**8a** after 10 min. However, a small amount of the isomer **10a** (12–16%) resulting from regio-reversed hydrosilylation was observed. To improve the hydrosilylation regioselectivity, tetraisopropylidisiloxane (**5**) was used, but only a trace of cross-coupling product was observed even after extended reaction time or at elevated reaction temperatures. Diethyl-ethoxysilane (**6**) was then examined as a compromise of reactivity and selectivity. Surprisingly, this silane gave the poorest results; the regioselectivity was worse than with the methylsilanes, and the conversion of **8a** was below 60%.

The next stage of optimization involved the examination of these silanes with other platinum catalysts to improve the rate and/or regioselectivity. The organic soluble complex Pt(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane (Pt(DVDS)) gave results comparable to those obtained with Speier's catalyst. However, the *t*-Bu<sub>3</sub>P-modified Pt(DVDS) complex gave significantly improved results.<sup>13</sup> The hydrosilylation with both **2** and **3** was completed *within 30 min at room temperature* in the presence of *t*-Bu<sub>3</sub>P–Pt(DVDS), and the subsequent coupling reaction with **8a** was complete in 10 min at room temperature. Moreover, we were pleased to find that with **2** the coupling product contained only 2% of the regioisomer **10a**.

With an optimized procedure for the hydrosilylation/cross-coupling reaction in hand, a variety of iodides bearing various functional groups and substitution patterns were selected to define the scope of the one-pot process. The results presented in Table 2 reveal that the rate, yield, and selectivity of this protocol correspond well to those features of the previous cross-coupling reactions of isolated silanols. For example, both electron-rich (entries 3, 4, 7, and 9) and electron-poor (entries 2, 5, 6, and 8) iodides underwent the coupling smoothly to give the desired product in high yield and

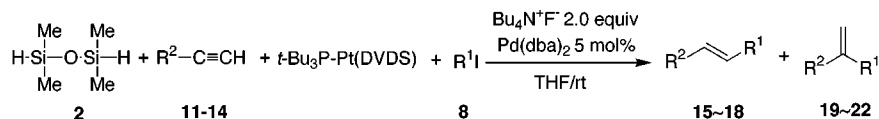
excellent stereoselectivity. The position and nature of substituents had little effect for most iodides (cf. entries 3 and 9). However, the rate of coupling of **8f** was very slow and stalled as has been noted previously.<sup>4c,5d,e</sup> This problem was resolved by adding 10 mol % of AsPh<sub>3</sub>.<sup>4c</sup> The coupling of **8h** also proceeded smoothly to give desired product in reasonable yield, although some loss of specificity was observed. Further, **8i** also showed good results when [allylPdCl]<sub>2</sub> was used, but the specificity again was lower than with aryl halides. The origin of the erosion in stereospecificity is not understood at this time.

As found in our previous studies,<sup>4c</sup> it was possible to reduce the loading of the Pd catalyst for the coupling of electron-poor iodides, e.g., **8d**. In the presence of 1 mol % of Pd(dba)<sub>2</sub> the coupling product **9d** was produced in 89% yield by extending the reaction time to 60 min with comparable selectivities (cf. entries 5 and 6).

The standard reaction protocol developed in earlier studies for the cross-coupling calls for the addition of the palladium catalyst last (procedure I). For reactive electrophiles such as electron-deficient aryl iodides, the reaction becomes rather exothermic. This potential problem can be solved by simply changing the addition sequence such that TBAF and Pd(dba)<sub>2</sub> were added to the hydrosilylation mixture first. The heat of reaction is then modulated by the slow addition of the iodide such that the internal temperature does not exceed 30 °C (procedure II). The one-pot coupling of **8c** gave **9c** in 89% yield by using this modified procedure (cf. entries 3 and 4).

The overall process displays good generality and functional compatibility with regard to the alkyne component as well, Table 3. A number of alkynes were evaluated with typical electron-poor (**8b**) and electron-rich (**8c**) substrates. The alkyne diversity is represented by aromatic (**11**), linear aliphatic (**12**), and branched aliphatic (**13**) types. In addition,

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**Table 3.** One-Pot Hydrosilylation/Cross-Coupling of 1-Alkynes with Aryl Iodides<sup>a</sup>

entry	alkyne, R <sup>2</sup>	<b>8</b> , R <sup>1</sup>	ratio ( <b>2</b> /alkyne), equiv	time, min	product	yield, <sup>b</sup> %	ratio <sup>c</sup>
1	C <sub>6</sub> H <sub>5</sub> ( <b>11</b> )	<b>8b</b>	0.72/1.5	10	<b>15b</b>	89	≥99%
2	C <sub>6</sub> H <sub>5</sub> ( <b>11</b> )	<b>8c</b>	0.72/1.5	10	<b>15c</b>	74	≥99%
3	HO(CH <sub>2</sub> ) <sub>3</sub> ( <b>12</b> )	<b>8b</b>	0.9/1.8	30	<b>16b</b>	82	≥99%
4	HO(CH <sub>2</sub> ) <sub>3</sub> ( <b>12</b> )	<b>8c</b>	0.9/1.8	60	<b>16c</b>	89	≥99%
5	C <sub>6</sub> H <sub>5</sub> C(OH)(CH <sub>3</sub> ) ( <b>13</b> )	<b>8b</b>	0.65/1.3	24 h	<b>17b</b>	72	≥98% <sup>d</sup>
6	C <sub>6</sub> H <sub>5</sub> C(OH)(CH <sub>3</sub> ) ( <b>13</b> )	<b>8c</b>	0.65/1.3	24 h	<b>17c</b>	79	≥98% <sup>d</sup>
7	CH <sub>2</sub> = CHCH <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub> ( <b>14</b> )	<b>8b</b>	0.98/1.5	10	<b>18b</b>	78	≥99%
8	CH <sub>2</sub> = CHCH <sub>2</sub> O(CH <sub>2</sub> ) <sub>3</sub> ( <b>14</b> )	<b>8c</b>	0.98/1.5	10	<b>18c</b>	76	99.6/0.4

<sup>a</sup> Procedure I was employed in entries 1–6; procedure II was employed in entries 7–8. <sup>b</sup> Yield of analytically pure materials. <sup>c</sup> Ratio of (*E*)-**15**–(*E*)-**18**/((*Z*)-**15**–(*Z*)-**18** + (**19**–**22**)) was determined by GC-MS. <sup>d</sup> Ratio was determined by <sup>1</sup>H NMR.

we included unprotected alcohol functions (**12** and **13**) and a remote double bond (**14**). The coupling reaction of **11** proceeded smoothly to give products in high yield, and no regioisomer was detected by GC analysis. Furthermore, those alkynes that contain free hydroxy groups underwent facile, highly stereoselective coupling though the latter required a longer reaction time. The coupling of **14** also gave exceptional results. The double bond did not compete with the alkyne in the hydrosilylation, and no Heck reaction products were observed. However, some Sonogashira coupling of the alkyne was observed<sup>14</sup> when the ratio of **2** to **14** was 0.65/1.5 equiv. The byproduct can be eliminated by increasing the **2**/**14** ratio to 0.98/1.5 and also extending the reaction time to 60 min.

In summary, we have found an efficient hydrosilylation

(14) This copper-free Sonogashira coupling of 1-heptyne with 1-iodonaphthalene was also observed in our previous study, 83% conversion at rt for 20 h (2.0 equiv of TBAF, 5 mol % of Pd(dba)<sub>2</sub>). For a recent review of the Sonogashira coupling, see: Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 5.

system by using inexpensive, nontoxic silicon reagents and a soluble Pt catalyst. The in situ generated disiloxanes then undergo a Pd-catalyzed, cross-coupling for the mild, one-pot hydrocarbation of 1-alkynes. This method is characterized by good generality, functional group compatibility, and stereoselectivity. Newer methods for the introduction of silicon moieties for cross-coupling reactions will be reported in due course.

**Acknowledgment.** We are grateful to the National Science Foundation (NSF CHE-9803124) for generous financial support.

**Supporting Information Available:** Full experimental details including procedures for a one-pot coupling reaction and full spectroscopic and analytical characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0156751