

Highly Stereospecific, Cross-Coupling Reactions of Alkenylsilacyclobutanes

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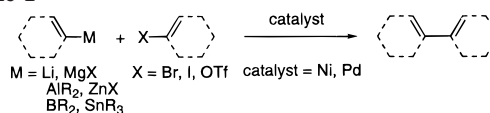
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The advent of metal-catalyzed, cross-coupling reactions between organometallic nucleophiles and organic halide (and related) electrophiles has revolutionized the strategies for construction of carbon–carbon bonds (Scheme 1).¹ In the intervening years since the landmark disclosures by the Kumada^{2a} and Corriu^{2b} groups, many significant advances have been recorded that have expanded the scope and utility of this process. Among the most notable are the Suzuki coupling of organoboranes³ and Stille (Migita–Kosugi) coupling⁴ of organostannanes. These methods have the common advantage of employing stable, isolable entities that are also extremely weak nucleophiles with good functional group compatibility. However, they are not without disadvantages such as attenuated and substrate-dependent reactivity, oxygen sensitivity (B), high molecular weight, and toxicity (Sn).

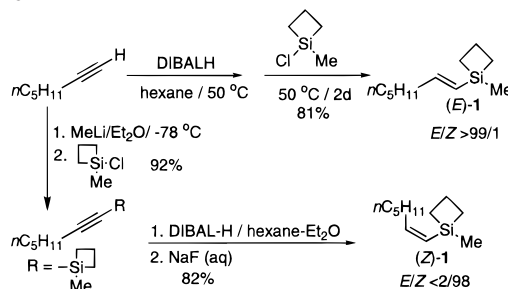
Organosilicon compounds can, in principle, provide a practical solution to these problems. Despite their much lower reactivity, functionalized (fluoro, alkoxy) organosilanes have been shown, through extensive studies by the Hiyama group, to engage in palladium-catalyzed, cross-coupling reactions.⁵ These reagents, however, still do not fulfill the objectives of ease of synthesis in geometrically defined form, ease of purification, and mildness of conditions for coupling. Ideally, the organosilicon moiety would be: (1) low molecular weight, (2) easy to synthesize, (3) stable under chromatographic purification, (4) easily activated toward organic halides, and (5) converted to harmless byproducts. On the basis of our previous studies⁶ (along with ample literature precedent⁷) on the enhanced ability of silacyclobutanes to access a hypercoordinate state in the presence of Lewis bases, we surmised that such aliphatic silicon derivatives might be capable of fulfilling these criteria and effectively participating in cross-coupling reactions. We describe herein the successful employment of alkenylsilacyclobutanes toward this end.⁸

For these preliminary studies we chose to examine the coupling of (*E*)- and (*Z*)-1-(1-heptenyl)-1-methylsilacyclobutane (*E*-**1** and (*Z*)-**1**) with a variety of electrophiles. These substrates can be readily prepared in high yield and geometrical purity⁹ as shown in Scheme 2. In view of the enhanced electrophilicity of 1-chloro-1-methylsilacyclobutane, we found that the intermediate vinyla-

Scheme 1



Scheme 2



lane obtained by hydroalumination of 1-heptyne reacted in good yield to afford (*E*)-**1** in >99/1 isomeric purity. This procedure is also notable as it does not require the formation of the more nucleophilic ate complex. The corresponding (*Z*)-**1** isomer was prepared by adaptation of related literature procedures.¹⁰ Although 1-chloro-1-methylsilacyclobutane¹¹ is commercially available, it can be prepared in large quantities by Wurtz coupling of dichloro-(3-chloropropyl)methylsilane.^{6a,12}

Orienting coupling studies with iodobenzene (or iodonaphthalene) under the conditions employed by Hiyama (2.5 mol % [allyl]PdCl₂, 1.5 equiv of tetrabutylammonium fluoride (TBAF, 1.0 M in THF)) were extremely encouraging as reaction took place at ambient temperature to afford (*E*)-1-heptylbenzene, (*E*)-**3**. A secondary reaction pathway provided benzene (or naphthalene) by reduction of the halide. Extensive optimization of reaction conditions revealed three variables that were critical for successful coupling: (1) the palladium source, (2) the fluoride source, and (3) the order of mixing of reagents.

First, a survey of many palladium catalysts showed a dramatic influence on reaction rate in the following order: Pd(dba)₂~Pd₂(dba)₃ > Pd(OAc)₂~Pd(OTf)₂ > (COD)PdBr₂ > [allyl]PdCl₂ >> (PhCN)₂PdCl₂~(Ph₃P)₂PdCl₂~(Ph₃P)₂BnPdCl. Unfortunately, in all cases (except (COD)PdBr₂) a small amount (~10%) of a reduction product (benzene) was still detected.

Second, the nature and amount of the fluoride source proved to be crucial. TBAF is the only fluoride source found to be effective; neither (Me₂N)₃S⁺ Me₃SiF₂⁻ (TASF) nor KF gave coupling products.¹³ Also, the reactions displayed a strange rate profile. With 1.5 equiv of TBAF, initial rates were fast (nearly 80% conversion in 10 min) but the reactions required another 8–9 h to go to completion (¹H NMR analysis). We surmised that the Si byproduct was competing for the fluoride needed to activate the coupling. Thus, by simply employing 3.0 equiv of TBAF, the reactions proceeded rapidly to completion within minutes.

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(13) Interestingly, TASF, in conjunction with (COD)PdBr₂ in DMF solvent gave almost exclusively the reduction product. DMF offered no advantage over THF in successful couplings.

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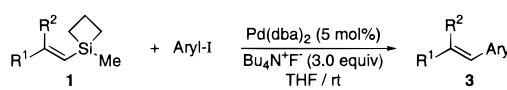
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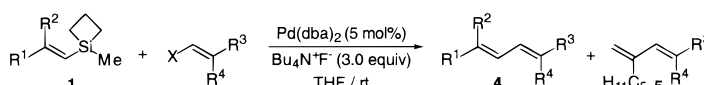
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Table 1. Pd-Catalyzed Coupling of (*E*)- and (*Z*)-**1** with Aryl Iodides^a


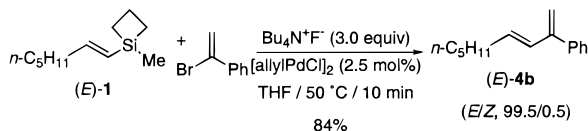
entry	silane	R ¹	R ²	aryl	time, min	product	yield, % ^b	ratio, <i>E/Z</i> ^c
1	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	C ₆ H ₅	10	(<i>E</i>)- 3a	91	99.9/0.1
2	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	C ₆ H ₅	10	(<i>Z</i>)- 3a	90	0.9/99.1
3	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	1-naphthyl	30	(<i>E</i>)- 3b	93	99.8/0.2
4	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	1-naphthyl	30	(<i>Z</i>)- 3b	91	1.5/98.5
5 ^d	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	2-thienyl	180	(<i>E</i>)- 3c	89	99.0/1.0
6 ^d	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	2-thienyl	180	(<i>Z</i>)- 3c	85	2.2/97.8
7	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	4-(CH ₃ CO)C ₆ H ₄	10	(<i>E</i>)- 3d	84	99.7/0.3
8	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	4-(CH ₃ CO)C ₆ H ₄	10	(<i>Z</i>)- 3d	88	2.0/98.0
9	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	4-(CH ₃ O)C ₆ H ₄	10	(<i>E</i>)- 3e	94	99.0/1.0
10	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	4-(CH ₃ O)C ₆ H ₄	10	(<i>Z</i>)- 3e	90	2.5/97.5

^a Reactions used 1.1 equiv of **1** unless otherwise noted. ^b Yield of analytically pure materials. ^c Determined by GC analysis. ^d 1.2 equiv of **1** used.

Table 2. Pd-Catalyzed Coupling of (*E*)- and (*Z*)-**1** with Alkenyl Halides^a


entry	silane	R ¹	R ²	R ³	R ⁴	X	time, min	product	yield, % ^b	ratios ^{c,d}	ratio, 4/5 ^d
1	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	C ₆ H ₅	H	I	10	(<i>E,E</i>)- 4a	73	98.0/2.0 ^f	96/4
2 ^e	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	C ₆ H ₅	H	Br	60	(<i>E,E</i>)- 4a	80	98.4/1.6 ^f	98/2
3	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	C ₆ H ₅	H	I	10	(<i>E,Z</i>)- 4a	75	97.2/2.8 ^g	98/2
4	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	(CH ₂) ₄ OH	H	I	90	(<i>E,E</i>)- 4c	95	98.4/1.6 ^f	90/10
5	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	(CH ₂) ₄ OH	H	I	90	(<i>E,Z</i>)- 4c	74	97.0/3.0 ^g	85/15
6	(<i>E</i>)- 1	<i>n</i> -C ₅ H ₁₁	H	H	(CH ₂) ₄ OH	I	90	(<i>Z,E</i>)- 4c	70	97.0/3.0 ^h	99/1
7 ^e	(<i>Z</i>)- 1	H	<i>n</i> -C ₅ H ₁₁	H	(CH ₂) ₄ OH	I	300	(<i>Z,Z</i>)- 4c	65	94.8/5.2 ⁱ	99/1

^a Reactions employed 1.1 equiv of **1** and 5 mol % Pd(dba)₂ unless otherwise noted. ^b Yield of analytically pure materials. ^c Isomeric purity of major component. ^d Determined by GC analysis. ^e 1.2 to 1.5 equiv of **1** and 2.5 mol % of [allylPdCl]₂ were used. ^f Ratio (*E,E*)/(*E,Z*). ^g Ratio (*Z,E*)/(*Z,Z*)+(*E,E*). ^h Ratio (*Z,Z*)/all other isomers.

Scheme 3

Finally, we have made the important discovery that the order of mixing of the reagents is crucial for high yields and reproducible reactions. Specifically, premixing of the silacyclobutane and TBAF is crucial to eliminate the formation of reduction byproducts with many of the Pd catalysts.¹⁴ Thus, the general reaction protocol involves 1.1–1.2 equiv of **1**, 3.0 equiv of TBAF (1.0 M in THF as solvent), and 5 mol % Pd(dba)₂.

To establish the importance of the silacyclobutane moiety for successful coupling reactions, we carried out a control experiment. Under the conditions described above, (*E*)-1-heptenyltrimethylsilane failed to give more than traces of (*E*)-**3a** after 3 days. This clearly indicated a key role for the strained ring, not just the unique combination of reaction components.¹⁵

With optimized conditions in hand, the stereoselectivity and synthetic generality of the process were investigated in coupling reactions of (*E*)- and (*Z*)-**1** with aryl iodides (Table 1). For all substrates examined, the reactions were highly stereospecific. Moreover, both electron-deficient (entries 7 and 8) and -rich (entries 9 and 10) arenes reacted rapidly and in high yield. To achieve such high yields of analytically pure materials we needed to develop a purification protocol to remove the siloxane byproducts from the rather nonpolar coupling products. Thus, the

(14) This is presumably due to a competitive insertion of the arylpalladium iodide into the silacyclobutane bond if the putative "ate" complex is not formed. Reductive elimination from this intermediate would lead to the reduced arene. A significant exotherm is observed upon mixing **1** with TBAF.

(15) The attenuated reactivity of alkenyltrimethylsilanes in cross-coupling reactions catalyzed by [allylPdCl]₂ has been documented. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

styrenes **3a–3e** were all purified by silica gel plug filtration, C–18 reversed-phase chromatography (MeOH/H₂O), and distillation.

We next demonstrated that alkenyl halides are excellent partners in sp²/sp² couplings with **1**. The results of Pd-catalyzed coupling with alkenyl iodides and bromides under identical reaction conditions are collected in Table 2. As in the alkenyl/aryl couplings these reactions were also highly stereospecific even for the production of (*Z,Z*)-**4c** (entry 7). The reactions proceeded smoothly at room temperature, though for β-bromostyrene, [allylPdCl]₂ gave the best results. Moreover, the free OH[−] group in (*E*)- or (*Z*)-6-iodo-5-hexenol¹⁶ did not interfere with the coupling. In all cases a minor byproduct of cine substitution (**5**) was detected which presumably arose from a Heck type process previously documented in organoborane³/organostannane couplings.¹⁷ However, with α-bromostyrene, (*E*)-**1** coupled in high yield and without a trace of the regioisomer (Scheme 3).

In summary, we have developed a new, stereospecific coupling reaction of readily available alkenylsilanes. Expansion of the scope of this process to include a myriad of permutations of aryl, alkenyl, allyl, acyl, and carbonylative processes is underway as are detailed investigations into the reaction mechanism.

Acknowledgment. This paper is dedicated to the memory of J. C. Martin, a pioneer in main group chemistry. We are grateful to the National Science Foundation for generous financial support (CHE 9500397 and 9803124). J.Y.C. thanks the Korea Research Foundation (KRF) for a postdoctoral fellowship.

Supporting Information Available: Procedures for the preparation and full characterization of (*E*)- and (*Z*)-**1**, **3a–3e**, and **4a–4c** and representative procedures for coupling reactions are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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