Intramolecularly Activated Vinylsilanes: Fluoride-Free Cross-Coupling of (*Z*)-β-(Trialkylsilyl)acrylic Acids

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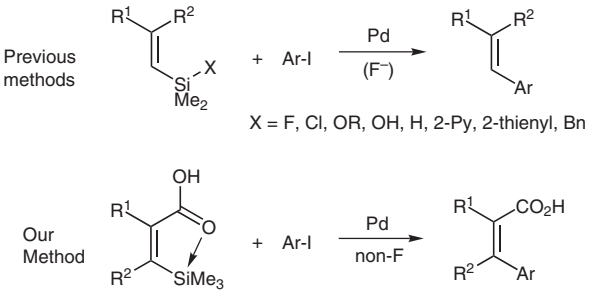
Abstract: The fluoride-free palladium-catalyzed cross-coupling reaction of trialkyl(vinyl)silanes activated by the intramolecular pentacoordination of carboxylic acid at the *Z*-β-position is described.

Key words: alkenes, carboxylic acids, cross-coupling, palladium, silicon

The palladium-catalyzed Hiyama coupling of organosilicon compounds with organic halides is an important method for producing carbon-carbon bonds. Unlike some organometallic reagents employed in cross-coupling processes, organosilicon compounds are usually easier to handle and/or possess low toxicity.[1] Since trialkyl-substituted alkenylsilanes generally are extremely stable to chemical manipulation prior to fluoride activation, they do not readily undergo productive cross-coupling.[1,2] Alkenylsilanes with heteroatom substituents are essential for efficient reactivity, but they are sensitive to acidic or basic hydrolysis.[1,3] In recent years, the alkenylsilanes with 2-pyridyl,[4a] 2-thienyl,[4b] benzyl,[4c] hydride[4d] and silacyclobutane[4e,f] have been used in palladium-catalyzed cross-coupling (Scheme 1). However, a common limitation of the aforementioned silicon based coupling reactions is the use of fluoride as the promoter, which would be incompatible in a complex molecule synthesis where one of the coupling partners contained silyl protective groups. The development of a mild and convenient, non-fluoride promoted system would therefore be highly desirable.[5] Herein, we describe a fluoride-free palladium-catalyzed cross-coupling reaction of (*Z*)-β-(trialkylsilyl)acrylic acids activated by intramolecular pentacoordination to silicon.

Recently, we found a direct electrophilic cleavage of a silicon-carbon bond activated by intramolecular pentacoordination of the carbonyl oxygen to (*Z*)-β-silylacrylic acids,[6] prepared by stereoselective olefination of acylsilanes with ynolates.[7] This result, which can be considered as an activation method for intrinsically stable C-Si bonds, led us to postulate that (*Z*)-β-(trialkylsilyl)carboxylic acids would undergo cross-coupling reactions with aryl halides to afford tetrasubstituted olefins.[8]

Initial investigation of the cross-coupling of (*Z*)-β-(trimethylsilyl)acrylic acid **1a** with iodobenzene catalyzed by $Pd_2(dba)_3{\cdot}CHCl_3$ provided the desired cross-coupling product **2a** along with fair amounts of the undesired protodesilylation product **3a**. To facilitate the cross-coupling process, various additives were surveyed with $Pd_2(dba)_3{\cdot}CHCl_3$. We found that when Cs_2CO_3 was employed as an activator, the coupling product **2a** was obtained in good yield (Table 1, entry 1).[5d] The ligands [PPh_3, 7%; P(*o*-tolyl)$_3$, 29%; P(2-furyl)$_3$, 17%; P(OEt)$_3$, 9%; $AsPh_3$, 43%] were not effective in the cross-coupling reaction with 4-chloro-iodobenzene (Table 1, entry 5).



Scheme 1 Palladium-catalyzed cross-coupling of organosilicon compounds.

With the optimized reaction conditions [$Pd_2(dba)_3{\cdot}CHCl_3$/Cs_2CO_3 in DME at 60 °C] in hand, we then investigated the scope and limitations of the reaction with a variety of aryl iodides (Table 1).[9] The 4-substituted aryl iodides containing electron-withdrawing substituents exhibited similar reactivity to that of iodobenzene (entries 3 and 5). In contrast, the use of substrates with an electron-donating group resulted in relatively low yields (entries 6 and 7) while the other (*Z*)-β-(trimethylsilyl)acrylic acids (**1b–e**) gave similar products in good to moderate yields (entry 8–12). The use of Pd(P*t*-Bu$_3$)$_2$ instead of $Pd_2(dba)_3{\cdot}CHCl_3$ also gave coupling products (entries 2, 4, 11, and 12).[10] As for **1d**, Pd(P*t*-Bu$_3$)$_2$ was clearly superior to $Pd_2(dba)_3{\cdot}CHCl_3$ (entries 10 and 11). Pd(P*t*-Bu$_3$)$_2$ was also highly suitable for the reaction of **1e** (entry 12), since use of $Pd_2(dba)_3{\cdot}CHCl_3$ resulted in only the protodesilylation product. In all cases, the reaction conditions were dependent on the substrates. It is worth noting that even with these sterically hindered alkenylsilanes, cross-coupling still proceeded.[11]

The cross-coupling reaction did not occur at all using the methyl ester of **1a** and trimethyl(vinyl)silane **4**, indicating perhaps that the presence of a carboxylic acid at the *Z*-β-

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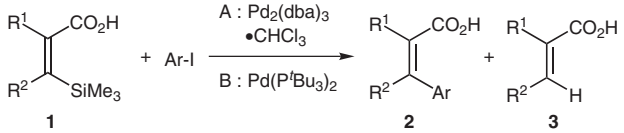
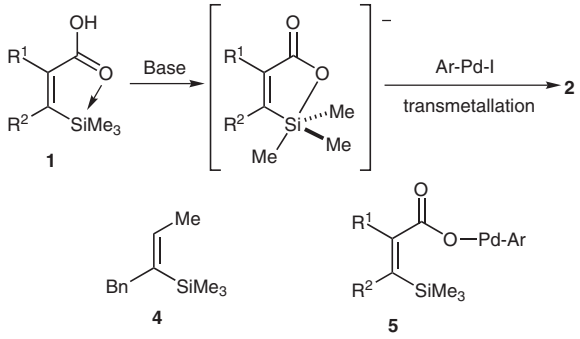
Table 1 Cross-Coupling Reaction of (*Z*)-β-(Trimethylsilyl)acrylic Acid **1** with Aryl Halide



Entry	**1**	R^1	R^2	Ar	Method[a]	**2**	Yield (%) of **2**	Yield (%) of **3**[b]
1	**1a**	Me	Bn	Ph	A	**2a**	72	6
2	**1a**	Me	Bn	Ph	B	**2a**	51	15
3	**1a**	Me	Bn	4-$CF_3C_6H_4$-	A	**2b**	65	3
4	**1a**	Me	Bn	4-$CF_3C_6H_4$-	B	**2b**	50[b]	9
5	**1a**	Me	Bn	4-ClC_6H_4-	A	**2c**	66	7
6	**1a**	Me	Bn	4-$MeOC_6H_4$-	A	**2d**	46	7
7	**1a**	Me	Bn	4-MeC_6H_4-	A	**2e**	47	3
8	**1b**	Bu	Me	Ph	A	**2f**	58	4
9	**1c**	*i*-Pr	Me	Ph	A	**2g**	46	4
10	**1d**	Ph	Me	Ph	A	**2h**	40	15
11	**1d**	Ph	Me	Ph	B	**2h**	73	15
12	**1e**	Ph	4-$MeOC_6H_4$-	Ph	B	**2i**	70	29

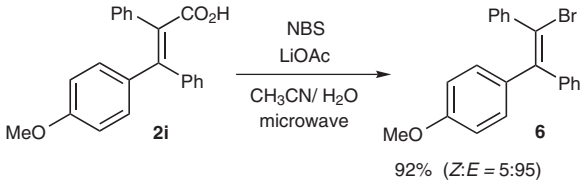
[a] Method A: The reactions were performed at 60 °C using **1** (1.0 equiv), aryl halide (1.5 equiv), Cs_2CO_3 (5.0 equiv), and $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) in DME. Method B: The reactions were performed at 60 °C using **1** (1.0 equiv), aryl halide (1.5 equiv), aq Cs_2CO_3 (5.0 M, 5.0 equiv), and Pd(P*t*-$Bu_3)_2$ (5 mol%) in THF.
[b] Determined by ^1H NMR.

position is important for efficient reactivity. We propose that coordination of the carboxylate anion to the silicon center may increase the pentacoordinate siliconate concentration, which accelerates transmetallation (Scheme 2). Although it is possible that an intramolecular transmetallation through the alkoxypalladium complex **5** is involved,[12] we have not yet clarified the detailed mechanism.



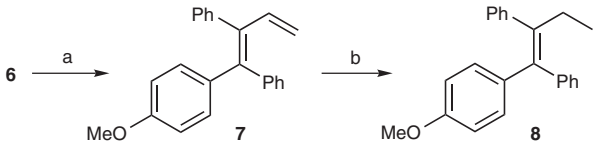
Scheme 2 Proposed mechanism.

To show the synthetic utility of our methodology, we next examined the transformation of the coupling products. Carboxylic acid **2i** underwent a modified Hunsdiecker reaction with NBS[13] to afford the bromoalkene **6**, which is a useful intermediate since alkenyl halides can be subjected to carbon-carbon bond formation to produce tetrasubstituted alkenes (Scheme 3).



Scheme 3 Transformation of carboxylic acid to alkenyl halide.

We also investigated the synthesis of tamoxifen, which is one of the most important drugs in clinical use today for the treatment of breast cancer (Scheme 4).[14] Using the Stille coupling of **6**, followed by selective hydrogenation of **7** with Wilkinson's catalyst, we were able to produce the alkene **8**, which is the intermediate in the synthesis of (*Z*)-tamoxifen reported by Miller.[15]



Scheme 4 *Reagents and conditions*: (a) Tributylvinyltin, $Pd_2(dba)_3{\cdot}CHCl_3$, P(2-furyl)$_3$, DMF, 80 °C, 68% (*Z*:*E* = 94:6); (b) $RhCl(PPh_3)_3$, H_2, benzene, r.t., 64% (*Z*:*E* = 97:3).

In conclusion, we have developed a fluoride-free cross-coupling reaction of (*Z*)-β-(trialkylsilyl)acrylic acids with aryl iodides. These results demonstrate the synthetic utility of the C-Si bond activation by intramolecular pentacoordination to silicon. We have also demonstrated that the coupling products can be transformed into alkenyl halides, which are useful for the preparation of multisubstituted alkenes. Since (*Z*)-β-(trimethylsilyl)acrylic acids are extremely stable and easily prepared by olefination of acylsilanes with ynolates, this process should have great synthetic potential.

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(9) **General Procedure for the Cross-Coupling Reaction of a (*Z*)-β-(Trimethylsilyl)acrylic Acid 1a with Iodobenzene.** To a solution of **1a** (35 mg, 0.141 mmol) and Cs_2CO_3 (230 mg, 0.705 mmol) in DME (10 mL) were added sequentially iodobenzene (43 mg, 0.211 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (7 mg, 0.00705 mmol) at room temperature. After the mixture was stirred at 60 °C for 22 h, the solvents were evaporated to give a residue, which was diluted with CH_2Cl_2 and acidified with 6 M HCl (aq). The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The organic phase was concentrated in vacuo to give a crude product, which was purified by silica gel column chromatography (hexane–EtOAc, 10–25%) to afford 27 mg of a mixture of **2a** (72%) and **3a** (6%). After recrystallization from CCl_4–hexane, compound **2a** was isolated as colorless needles. (*Z*)-2-Methyl-3,4-diphenyl-2-butenoic acid (**2a**):[6] mp 107.6–108.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.14 (s, 3 H), 3.83 (s, 2 H), 7.01–7.08 (m, 4 H), 7.13–7.24 (m, 6 H). IR ($CHCl_3$): 3062, 1691 cm^{-1}.

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