Palladium-Catalyzed Cross-Coupling Reactions of Arylsiloxanes with Aryl Halides: Application to Solid-Supported Organic Synthesis

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S *Supporting Information*

ABSTRACT: The solid-phase version of the Pd-catalyzed Hiyama reaction between a variety of aryltriethoxysilanes and immobilized aryl halides was developed. Smooth cross-coupling was achieved to afford the corresponding biaryl products in moderate to excellent yields. The described protocol would be particularly useful for the construction of 4′-substituted 1,1′-biphenyl derivatives.

KEYWORDS: cross-coupling reactions, solid-phase organic synthesis, Hiyama coupling
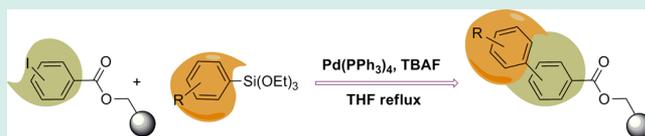
Metal-catalyzed cross-coupling reactions are indispensable synthetic tools for the formation of carbon−carbon bonds which are, in turn, the key element for the generation of libraries of useful industrial and pharmaceutical compounds. From the different combinations of organometallic nucleophiles and organic electrophiles that we can find in literature, an interesting option is the palladium-catalyzed Hiyama cross-coupling reaction.[1]

Hiyama reaction, which is potentially one of the most attractive methods for obtaining biaryl and stilbene moieties, involves the coupling of aryl or alkenyl halides or triflates with organosilicon compounds under activation by a fluoride ion or a base. Because of their ease of preparation and handling, stability toward air/moisture, and low toxicity compared to other organometallic reagents (especially tin and zinc), organosilicon compounds and Hiyama reaction in particular, have been applied with great success in recent years.[2]

Apart from the classical advantages referred to easy purification, solid-phase chemistry has grown in interest in cross-coupling reactions since immobilization of one of the substrates makes its homodimerization a less favorable process because of the site isolation, while the homocoupling resulted from the soluble substrate can be eliminated by a simple filtration (Scheme 1).[3,4]

Despite these advantages, so far only two closely related papers dealing with the solid-phase version of Hiyama coupling have been disclosed.[5,6] In these articles, Hiyama and co-workers described the use of aryl(alkyl)difluorosilanes for coupling with immobilized aryl iodide in the presence of catalytic Pd(PPh$_3$)$_4$ and TBAF.[7]

The reason for the limited development of Hiyama coupling in solid-supported chemistry, especially when compared with the Stille and Suzuki reactions, is probably due to the intrinsic resistance of the organosilicon compounds to undergo cross-coupling reactions in the absence of a significant polarity at the C−Si bond. However, recent advances in Hiyama reaction, markedly the use of silicon species containing oxygen atoms, have expanded its use to a wide range of substrates[8] and promoted our interest in developing a general application of solid-phase chemistry to Hiyama coupling.[9]

Clearly, the main target of Hiyama coupling is the preparation of biaryl moieties, which are present in natural products,[10] pharmaceutical[11] and polymer compounds,[12] sensors,[13] and in ligands for transition-metal catalysts.[14] Hence, we decided to study the synthesis of unsymmetrical biaryl compounds (**4**), starting from a Wang resin-supported aryl halide (**1**) that reacts with aryl(triethoxy)silanes (**2**) in the presence of palladium catalyst and a fluoride source (Scheme 2). Among the oxygen-containing organosilicon species,

Scheme 1. Solid-Supported Version of Cross-Coupling Reactions[a]
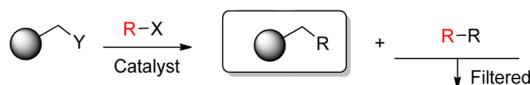
[a]By-products generated during the reaction can be eliminated by filtration.

Scheme 2. Solid-Phase Hiyama Reaction between Aryltriethoxysilanes and Immobilized Aryl Halides
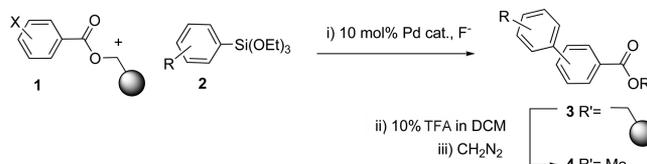
Table 1. Optimization of Conditions for the Solid-Phase Version of Hiyama Coupling Using Phenyltrimethoxysilane
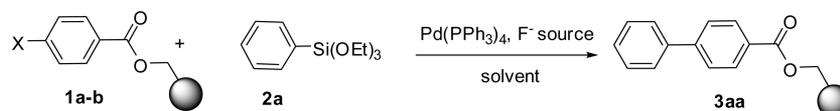
entry	immobilized haloaryl derivative	fluoride source (equiv)	equiv of siloxane	mol % of Pd(PPh$_3$)$_4$	solvent	additive (equiv)	time (h)/ temp (°C)	yield (%)[a]
1	X = I (1a)	TBAF (6)	6	6	THF		18/80	76
2	X = I (1a)	TBAF (6)	6	6	THF		48/80	39
3	X = I (1a)	TBAF (6)	6	6	THF		7/80	84
4	X = I (1a)	TBAF (5)	5	6	THF		7/80	91
5	X = I (1a)	TBAF (5)	5	10	THF		7/80	quant. (77)[b]
6	X = I (1a)	TBAF (5)	5	6	DMF		7/80	nd[c,d]
7	X = I (1a)	CsF (5)	5	6	THF		7/80	42[b]
8	X = I (1a)	TBAF (5)	5	6	THF	CuI (0.5)	7/80	21[b]
9	X = I (1a)	TBAF (5)	5	6	THF	CuI (1)	7/80	35[b]
10	X = I (1a)	CsF (5)	5	6	DMF	CuI (1)	5.5/80	nd[c,d]
11	X = Br (1b)	TBAF (5)	5	10	THF		7/80	55[b]

[a]Yield, after TFA cleavage and esterification with CH$_2$N$_2$, calculated on the basis of the manufacturer's loading of Wang resin. [b]Yield after TFA cleavage, esterification with CH$_2$N$_2$, and purification by column chromatography. Yield calculated on the basis of the manufacturer's loading of Wang resin. [c]Not determined. [d]Methyl 4-iodobenzoate, coming from the immobilized starting material, was the major component of the crude material.

Table 2. Solid-Phase Hiyama Reaction between Aryltriethoxysilanes and Immobilized Aryl Halides
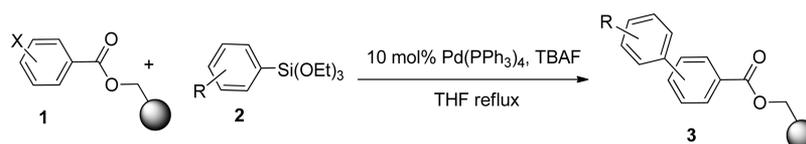
entry	immobilized haloaryl derivative	siloxane (equiv)	fluoride source (equiv)	time (h)/temp (°C)	product	yield (%)[a]
1	X = 4-I (1a)	R = H (2a) (5)	TBAF (5)	7/80	3aa	77
2	X = 4-I (1a)	R = 4-OMe (2b) (5)	TBAF (5)	5.5/80	3ab	62
3	X = 4-I (1a)	R = 4-CF3 (2c) (5)	TBAF (5)	6/80	3ac	71
4	X = 4-I (1a)	R = 4-Cl (2d) (5)	TBAF (5)	5/80	3ad	quant.
5	X = 4-I (1a)	R = 4-Me (2e) (5)	TBAF (5)	7.5/80	3ae	52
6	X = 4-I (1a)	R = 3-OMe (2f) (5)	TBAF (5)	5.5/80	3af	25[b]
7	X = 4-I (1a)	R = 3-OiPr (2g) (5)	TBAF (5)	7/80	3ag	20[b]
8	X = 3-I (1c)	R = H (2a) (5)	TBAF (5)	7/80	3ca	54
9	X = 3-I (1c)	R = 4-OMe (2b) (5)	TBAF (5)	5.5/80	3cb	34
10	X = 3-I (1c)	R = 3-OMe (2f) (5)	TBAF (5)	5.5/80	3cf	8[b]
11	X = 3-I (1c)	R = 3-OiPr (2g) (5)	TBAF (5)	7/80	3cf	5[b]
12	X = 2-I (1d)	R = 4-OMe (2b) (5)	TBAF (5)	5.5/80	3db	29[c]

[a]Yield after TFA cleavage, esterification with CH$_2$N$_2$, and purification by column chromatography, calculated on the basis of the manufacturer's loading of Wang resin. [b]Presence of homocoupling product was observed in crude material. [c]Yield based on crude material.

synthetically accessible aryl(trialkoxy)silanes (2)[15] have demonstrated their utility for the generation of biologically interesting structures.[16]

We initially analyzed the reaction of immobilized 4-halobenzoates 1a−b with phenyltrimethoxysilane (2a) in the presence of catalytic tetrakis(triphenylphosphine)-palladium(0), as a model reaction. Results are summarized in Table 1. The number of equivalents of the siloxane, fluoride source and catalyst were varied to find that 5 equiv of 2a and TBAF, and 10% mol of Pd(PPh$_3$)$_4$ were the best conditions (entry 5). Interestingly, long reaction times led to low yields of the crude product, probably due to some premature loss of resin-bound material (see entries 1−3). The change of solvent from THF to DMF or the use of CsF to replace TBAF, resulted in an incomplete reaction (entries 6−7). The role of cuprous iodide as additive was also tested,[17] however, the consequence was a decrease in reaction yields. The addition of CuI gave only a

35% isolated yield, in the best case (entry 9). These results must largely be due to the difficulty of removing the CuI at the end of the reaction. A direct comparison between immobilized aryl iodide (1a) and aryl bromide (1b) showed that iodide group gave better yield (compare entries 5 and 11).

Subsequently, the reaction of a variety of aryltriethoxysilanes with immobilized o-, m-, and p-substituted aryl halides under the optimized cross-coupling conditions was examined (Table 2). Although the success of the Hiyama reaction in homogeneous phase solution is remarkable, most of the examples involve 4-substituted aryl halides and (4-substituted-phenyl)triethoxysilanes. The solid-phase reaction performed well for the Wang resin-supported 4-iodobenzoate (1a) when treated with (4-substituted-phenyl)triethoxysilanes (2b−e), giving the biaryl derivatives (3ab−3ae) which, after TFA cleavage and esterification with CH$_2$N$_2$, afforded the corresponding methyl esters in high isolated yield for the whole

synthetic sequence (entries 2−5). Although homocoupling of silanes has been reported for Hiyama coupling in homogeneous phase,[18] this is not an issue in solid-phase synthesis since these byproducts are soluble and will be eliminated by filtration.

Next, we tested the solid-phase Hiyama coupling involving siloxanes bearing aromatic rings substituted by electron-donating groups at the meta position. Thus, reaction of **1a** with triethoxy(3-methoxyphenyl)silane (**2f**) was taken as a model. Under our optimized conditions, using dry THF, product **3af** was obtained in 25% isolated yield after purification by column chromatography (entry 6). The presence of the homocoupling product was detected in the crude material, indicating that the slower rate of cross-coupling could favor the homocoupling reaction.[19] Inspired by previous reports in literature about the effect of the addition of small amounts of water in Hiyama cross-coupling reaction,[20] we either added water to THF (5% v/v) or used nonanhydrous THF, but the reaction did not go to completion and gave lower yields of the purified biaryl **3af**. The change of solvent to DMF or the use of CsF to replace TBAF, resulted also in an incomplete reaction. When the immobilized 3-iodobenzoate (**1c**) was used, reaction with phenyltriethoxysilane (**2a**) was performed in acceptable isolated yield (entry 8). However, if a (4-substituted-phenyl)-triethoxysilane, such as **2b**, was used, yield dropped to 34% (entry 9). Even lower yields were obtained when the meta-substituted iodide linked to Wang resin (**1c**) reacts with (3-substituted-phenyl)triethoxysilanes (entries 10−11). As expected, immobilized ortho-substituted iodide (**1d**) reacted very slowly with (4-methoxy-phenyl)triethoxysilane (**2b**) (entry 12). Interestingly, a very low yield of the crude material was obtained in this case, indicating some premature release of the starting iodide from the resin during reaction. This was corroborated by finding 2-iodobenzoic acid in the reaction filtrate after the Hiyama coupling and before the TFA cleavage. Apparently, because of the very low reaction rate of **1d**, a competitive cleavage process emerges, probably catalyzed by a palladium species.[21]

In summary, we report the first study of the solid-phase version of Hiyama coupling using oxygen-containing organo-silicon species. The developed reaction conditions were found to be applicable to the preparation of unsymmetrical biaryl compounds in high yield for 4′-substituted 1,1′-biphenyl derivatives. In the case of siloxanes bearing aromatic rings substituted at the meta position, solid-phase cross-coupling was less efficient. We think that this study is an important contribution for a more general application of Hiyama cross-coupling to solid-supported organic synthesis. Further studies are in progress to extend of use of this protocol to the generation of libraries of biologically promising compounds, and the results will be detailed in due course.

EXPERIMENTAL PROCEDURES

Representative Procedure for the Solid-Phase Hiyama Cross-Coupling Reaction. Resin-bound arylhalide **1a** (0.1 g, 0.88 mmol/g, 0.088 mmol) was suspended in anhydrous THF (5 mL), and the following were added in sequential order under a nitrogen atmosphere: $Pd(PPh_3)_4$ (0.010 g, 10 mol %), phenyltriethoxysilane (**2a**) (0.115 mL, 0.439 mmol), and TBAF (0.439 mL, 1 M in THF). The flask was fitted with a condenser and the reaction mixture was stirred 7 h at 80 °C. Subsequently, the resin was filtered and washed successively with CH_2Cl_2 (×3), THF (×3), DMF (×3), MeOH (×3), and finally, CH_2Cl_2. After drying under high vacuum, 0.13 g (0.12 mmol)

of the compound linked to the resin was cleaved from the support with 5 mL of a 10% TFA in CH_2Cl_2 for 50 min at room temperature. Then, the mixture was filtered, washed with CH_2Cl_2 (2 × 3 mL) and the filtrate was evaporated under reduced pressure. Esterification with diazomethane afforded the crude product that was analyzed by ^1H NMR and GC/MS and then purified by column chromatography (hexane-EtOAc), yielding 19 mg of pure methyl-4-biphenylcarboxylate (**3aa**) (77%).

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data, consisting of ^1H NMR and ^{13}C NMR spectra. This material is available free of change via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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