

Special The Hiyama Cross-Coupling Reaction at Parts Per Million Levels of Pd: In Situ Formation of Highly Active Spirosilicates in Glycol Solvents

Shun Ichii, Go Hamasaka, and Yasuhiro Uozumi*^[a]

Abstract: A palladium NNC-pincer complex at a 5 mol ppm loading efficiently catalyzed the Hiyama coupling reaction of aryl bromides with aryl(trialkoxy)silanes in propylene glycol to give the corresponding biaryls in excellent yields. This method was applied to the syntheses of adapalene and a biaryl-type liquid-crystalline compound, as well as to the derivatization of dextromethorphan and norfloxacin. ESI-MS and NMR analyses of the reaction mixture suggested the formation of pentacoordinate spirosilicate intermediates in situ. Preliminary theoretical studies revealed that the glycol-derived silicate intermediates formed in situ are quite reactive silicon reagents in the transmetalation step.

Palladium-catalyzed cross-coupling reactions are recognized as an indispensable class of organic transformations in modern synthetic chemistry.^[1] A variety of organometallic reagents have been utilized in C-C bond-forming processes. Among these, the Suzuki-Miyaura cross-coupling reaction of organoboron compounds is the most widely employed in the fields of pharmaceuticals, agrochemicals, and materials chemistry,^[2] because it generally proceeds with excellent functional-group tolerance under mild conditions without producing hazardous waste. Despite these advantages of the Suzuki-Miyaura reaction, Hiyama cross-coupling has emerged as a viable alternative for efficient C-C bond-forming processes, because of the striking features of organosilicon compounds, such as their low toxicity, low cost, and ready availability and because of the rich natural abundance of silicon as an element. However, organosilicon compounds are generally less reactive than organoboron compounds owing to the low degree of polarization of the Si-C bond. Consequently, high loadings of palladium catalyst (mol% levels) are inevitably required to bring about efficient Hiyama coupling reactions, leading to serious problems of contamination of the resulting products by toxic palladium metal.^[3] This drawback has limited the range of industrial appli-

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We recently reported that the palladium NNC-pincer complex 1 is a good catalyst precursor for the generation of highly active monomeric palladium(0) species and we have described its applications in the allylic arylation of allyl acetates with sodium tetraarylboronates^[7] and in the Heck reaction of aryl halides with activated alkenes.^[8] Encouraged by these successful results, we attempted to apply this catalyst system to the Hiyama coupling reaction at an extremely low catalyst loading. Here, we report a successful example of a Hiyama coupling reaction in the presence of a ppm loading of the palladium catalyst. A 5 mol ppm loading of complex 1 catalyzed the Hiyama coupling reaction of a wide variety of aryl bromides with aryl(trialkoxy)silanes in propylene glycol. ²⁹Si NMR and ESI-MS experiments revealed that glycol-derived pentacoordinate spirosilicates were formed in situ from the widely available aryl(trialkoxy)silanes. These silicate intermediates play a crucial role in realizing the efficient coupling reaction.

We began our studies with the optimization of the reaction conditions (Table 1). 4-Bromotoluene (2a) and trimethoxy(phenyl)silane (3 a) were chosen as substrates, and the reaction was initially performed under typical Hiyama coupling conditions by using Pd(OAc)₂ and PPh₃ as the catalyst system and tetrabutylammonium fluoride (TBAF) as the base in DMF (Table 1).^[9] The reaction in the presence of 1.0 mol% of the catalyst gave the coupling product 4aa in 87% yield (entry 1), whereas reducing the catalyst loading to 0.1 mol % significantly lowered the yield of 4aa to 2% only (entry 2). This result clearly showed the difficulty involved in reducing the catalyst loading under the classical Hiyama coupling conditions. During the screening of various solvents, we found that glycol solvents were very effective in this transformation (see Supporting Information for details). When ethylene glycol or propylene glycol was employed as the solvent, the yield increased to 45 and 69%, respectively (entries 3 and 4).^[10] Moreover, potassium fluoride (KF) was found to be a more suitable base, affording the desired product in a higher yield (entries 5 and 6). Under these reaction conditions, the catalyst loading was successfully reduced to 100 molppm without a decrease in the yield (entry 7). However, in the reaction at a 10 mol ppm loading of



the catalyst, then yield of **4aa** fell markedly to 3%, even on prolonging the reaction time to 12 hours (entry 8). We therefore decided to apply the palladium NNC-pincer complex **1** in the Hiyama coupling reaction. When the reaction was carried out in the presence of a 10 mol ppm loading of **1**, the yield improved significantly to 65% (entry 9). Furthermore, the yield increased further on changing the amount of **3a** to 1.2 equivalents and that of KF to 3.0 equivalents (entry 10). Finally, the reaction proceeded in quantitative yield with a 5 mol ppm loading of **1** when the reaction temperature was raised to 100°C (entry 12).

To gain insight into the reason for the high efficiency of the present method, we performed ²⁹Si NMR and ESI-MS analyses of the reaction mixture (Scheme 1). After the reaction of trimethoxy(phenyl)silane (3a) with KF in ethylene glycol for two hours, the resulting mixture was analyzed by ²⁹Si NMR spectroscopy and ESI-MS. In the ²⁹Si NMR spectra, the signal of **3a** at -57.8 ppm completely disappeared, and a new signal was observed at -93.1 ppm. ESI-MS experiments on the resulting product revealed the formation of an ethylene glycol-derived pentacoordinate spirosilicate 5 (Scheme 1a). A single-crystal xray analysis of silicate 5 clearly confirmed its structure (Scheme 1 b). The propylene glycol-derived pentacoordinate spirosilicate 6 also formed under similar reaction conditions (Scheme 1 c). From these results, the spirosilicates-generated in situ appear to be key intermediates in permitting the Hiyama coupling reaction to proceed efficiently. The structures and re(a) The reaction of **3a** with KF in ethylene glycol



Scheme 1. ²⁹Si NMR and ESI-MS Experiments for a Mixture of Trimethoxy(phenyl)silane and KF in Glycol Solvents.

activities of related catechol-derived pentacoordinate spirosilicates have been studied extensively,^[11] and silicates have recently attracted attention as precursors of alkyl radical in photocatalytic reactions.^[12] Hiyama coupling reactions in the presence of organobis(catecholato)silicates have also been independently reported by the groups of Hosomi^[5a] and DeShong.^[13] Nevertheless, the reactivity of glycol-derived pentacoordinate spirosilicates in C–C bond-forming reactions remains unexplored.

To understand the reactivity of the pentacoordinate spirosilicate intermediates formed in situ, we conducted preliminary theoretical studies on the transmetalation step (Scheme 2). By electrochemical methods, Jutand and co-workers elucidated the roles of fluoride ion in the Hiyama coupling reaction.^[14] Fluoride ions react with [Ar-Pd-X], formed by oxidative addition of ArX to Pd⁰ species, to generate [Ar-Pd-F] species. Transmetalation occurs between [Ar-Pd-F] and PhSi(OMe)₃ via a four-membered cyclic transition state, whereas the fluorosilicate [PhSi(OMe)₃F]⁻ is not reactive. DFT calculations on the transmetalation of $[CH_2=CH-Pd-F]$ with $CH_2=CHSiMe_3$ have been performed by Sakaki and Hiyama and their co-workers.^[15]

In accord with these reports, we set up model reactions of [Ph-Pd-F(PPh₃)] (7) with the silicate intermediate 5 and with PhSi(OMe)₃ (3a). First, the phenyl groups of the arylsilanes 3a and 5 coordinate to the palladium center, and the fluorine ligand of 7 begins to interact with the silyl groups to form the hexacoordinate spirosilicate Int-a and the pentacoordinate sili-

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(a) Transmetalation of 7 with 5



Scheme 2. Results of Theoretical Studies on the Transmetalation Step. (a) Transmetalation of an arylpalladium fluoride **7** with the pentacoordinate spirosilicate **5**. (b) Transmetalation of an arylpalladium fluoride **7** with trimethoxy(phenyl)silane (**3**a). Geometries were optimized at the B3LYP/6-31G(d,p) level for C, H; at the 6-31 + G(d,p) level for O, F, Si, P and K; and at the LanL2DZ level for Pd. Relative Gibbs free energies were obtained by single-point energy calculations at the B3LYP/6-311 + +G(2d,p) level for C, H, O, F, Si, P, and K, and at the SDD level for Pd with the SMD solvation model (DMF).

cate **Int-b**, respectively. Here, a slightly higher activation barrier is required for the formation of **TS-Ia** (11.9 kcalmol⁻¹) compared with that for **TS-Ib** (8.1 kcalmol⁻¹), due to the steric effect of the larger silicate moiety of **5**. Subsequently, a palladium-carbon bond starts to form via **TS-IIa** and **TS-IIb**. The silicon center adopts a hexacoordinated octahedral structure in **TS-IIa**, whereas the geometry around the silicon center in **TS-IIb** is understood to be trigonal bipyramidal. Notably, the palladium-carbon bond formation from **Int-a** occurs with a very low activation barrier of 1.8 kcalmol⁻¹. In sharp contrast, this process with trimethoxy(phenyl)silane (**3 a**) requires a significantly higher activation barrier of 15.2 kcalmol⁻¹. Consequently, these calculation results strongly support the assumption that the glycol-derived pentacoordinate spirosilicates are quite reactive in the transmetalation step.

We next investigated the scope of the reaction of various aryl bromides with trimethoxy(phenyl)silane (3 a) (Scheme 3). Bromobenzenes 2 bearing an electron-donating substituent coupled efficiently with trimethoxy(phenyl)silane (3a) in the presence of a 5 molppm loading of complex 1 in propylene glycol to give the corresponding biaryls 4ba, 4ca, and 4da in high yields. The reactions of substrates with halo or carbonyl groups also proceeded well to furnish products 4 fa-4 ma in good yields. Under our reaction conditions, the chloro group in 4 fa remained completely intact. Unfortunately, bromobenzenes bearing highly electron-withdrawing substituents, such as cyano or nitro groups, were less reactive in this transformation; higher catalyst loadings were required to promote the reaction efficiently, and the coupling products 4na and 4pa were then obtained in yields of 95 and 93%, respectively. 4-Bromobenzonitrile substituted with an electron-donating 3methoxy group coupled smoothly to furnish 4oa, even with a 5 mol ppm loading of 1. Sterically hindered 1-naphthyl and 2tolyl bromides were also compatible with this reaction. However, 2-bromo-1,3-dimethylbenzene required a 100 mol ppm loading of the catalyst to afford the corresponding product **4sa** in a reasonable yield. Notably, heteroaromatic bromides were also suitable substrates, affording the corresponding products **4ta**–**4za** in high yields.

Next, we focused on the scope with respect to aryl- or alkenyl(triethoxy)silanes (Scheme 4). Aryl- or (alkenyl)triethoxysilanes were chosen as silicon reactants instead of trimethoxysilanes because of their ready availability. Indeed, triethoxy(phenyl)silane exhibited a similar reactivity to that of 3a, affording the coupling product 4 aa in 91% yield. Electron-rich and electronically neutral arylsilanes coupled efficiently with 4-bromotoluene (2a) in the presence of a 5 mol ppm loading of the catalyst to give the corresponding biaryls 4ab-4ah in yields of 72 to 99%. On the other hand, electron-deficient aryl(triethoxy)silanes 31, 3j, and 3k were less reactive owing to their low nucleophilicity, so that a 100 mol ppm loading of the catalyst was required to promote their coupling reactions efficiently. Additionally, alkenyl(triethoxy)silanes also served as good substrates in the transformation, providing the desired products 4qm and 4an in high yields.

To further demonstrate the utility of our reaction system, we examined several of its synthetic applications. The method was applied a synthesis of adapalene (**10**)^[16] on about a sevengram scale. The target molecule was successfully synthesized in 93% yield without chromatographic purification (Scheme 5). Moreover, this method was applicable to the derivatization of drug molecules. The reaction of an aryl bromide-tethered nor-floxacin^[17] with 4-[4-(triethoxysilyl)phenyl]morpholine proceeded nicely to furnish the derivative **11** in 85% yield. A triethoxy-

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Scheme 3. Scope of Aryl Bromides.^[a] [a] Reaction conditions: 1 $(2.5 \times 10^{-6} \text{ mmol})$, 2 (0.5 mmol), 3 a (0.6 mmol), KF (1.5 mmol), propylene glycol (1.0 mL), 100 °C, 12 h. Isolated yields are reported. [b] 1 (0.1 mol%). [c] 1 (100 mol ppm).

silylated dextromethorphan^[18] also coupled readily with 1bromo-3,5-bis(trifluoromethyl)benzene to give product **12** in 90% yield. Additionally, the liquid-crystalline compound **13**^[19] was also synthesized under the same reaction conditions (Scheme 6).

In summary, we have developed a simple, efficient, and general method for performing the Hiyama coupling reaction at ppm levels of a Pd catalyst. A 5 mol ppm loading of complex 1 catalyzed the Hiyama coupling reaction of a wide variety of aryl bromides with aryl(trialkoxy)silanes in propylene glycol to give the corresponding biaryls in excellent yields. NMR and ESI-MS analyses of the reaction mixture suggested the formation of a pentacoordinate spirosilicate intermediate in situ. Preliminary theoretical studies revealed that the glycol-derived silicate intermediates significantly facilitate the transmetalation step. Moreover, this method was successfully applied to a multigram-scale synthesis of adapalene, the synthesis of a liquidcrystalline compound, and the functionalization of two drug molecules.



 $Tol = C_6H_4CH_3-p$

Scheme 4. Scope of Aryltriethoxysilanes.^[a] [a] Reaction conditions: **1** $(2.5 \times 10^{-6} \text{ mmol})$, **2 a** (0.5 mmol), **3** (0.6 mmol), KF (1.5 mmol), propylene glycol (1.0 mL), 100 °C, 12 h. Isolated yields are reported. [b] **1** (100 mol ppm).



Scheme 5. Synthesis of Adapalene on $a \approx 7$ g Scale.

Acknowledgements

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Scheme 6. Functionalization of Drug Molecules and Synthesis of a Liquid-Crystalline Compound.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkoxysilanes • aryl bromides • aryltrialkoxysilanes • Hiyama coupling reaction • pincer complex • spirosilicates

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COMMUNICATION

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A palladium NNC-pincer complex at a 5 mol ppm loading efficiently catalyzed the Hiyama coupling reaction of aryl bromides with aryl(trialkoxy)silanes in propylene glycol to give the corre-

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