Recent Progress in the Cross-Coupling Reaction Using Triorgano- silyl-Type Reagents

Takeshi Komiyama*  
Yasunori Minami*b  
Tamejiro Hiyama*b

a Department of Applied Chemistry, Chuo University, Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan
thiyama@kc.chuo-u.ac.jp
b Research and Development Initiative, Chuo University, Kasuga, Bunkyo-ku, Tokyo 112-8551, Japan
yminami@kc.chuo-u.ac.jp

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Abstract The silicon-based cross-coupling reaction has attracted much attention over recent decades because there are many advantages in using organosilicon compounds. However, the use of reagents with a triorganosilyl group as a key function remains to be established. This account summarizes our recent progress in cross-coupling chemistry with such silyl reagents.

1 Introduction

The cross-coupling reaction has been developed as a common tool to form carbon–carbon and carbon–heteroatom bonds in π-conjugate systems and allows the construction of a wide variety of frameworks of potent pharmaceuticals, agrochemicals, and electronic materials. To achieve the bond formation, the use of nucleophilic organometallic reagents such as lithium, magnesium, zinc, aluminum, tin, boron, silicon, zirconium, indium and others is essential. Among them, silicon is attractive as it is an earth-abundant element and organosilicon reagents are superior in terms of stability, solubility, ease of handling, and accessibility. Nowadays, many types of organosilicon reagents are available for alkenylation, arylation, alkynylation, and alkylation of organic halides. For successful reactions, a nucleophilic activator such as a fluoride or hydroxide ion is generally employed. To assist the silicon–activator interaction, one to three electronegative heteroatoms such as a halogen or oxygen are often introduced at the silicon center, mainly for the sake of easy formation of the pentacoordinate silicate species responsible for transmetalation to a transition-metal catalyst. As a result, these silicon reagents become reactive enough to accomplish the cross-coupling, but meanwhile they become air- and moisture-sensitive. Therefore, careful attention is required in the preparation and handling of the halo- and oxysilanes.

In contrast, tetraorganosilanes are characterized by their robustness and low toxicity. Accordingly, in terms of stability and ease of handling, they are favorable. However, such reagents generally do not show enough reactivity for the cross-coupling due possibly to inferior silicate formation. In order to find cross-coupling-active alkenyl(triorganosilyl)reagents and appropriate activators, many chemists have made efforts to find a solution. Some triorganosilyl-type reagents are summarized in Figure 1. Hatanaka and Hiyama first discovered that structurally simple vinyl(trimethyl)silanes coupled with aryl iodides upon activation by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF). More than a decade later, Denmark disclosed that 1-alkenyl-1-methyl-silacyclobutanes underwent cross-coupling in the presence of tetrabutylammonium fluoride (TBAF) and observed a ring-opening reaction of the four-membered silacycle by water in TBAF to produce a silanol. They considered that this silanol was the true active species. Similarly, 2-pyridyl, 2-thienyl, benzyl, phenyl, 3,5-bis(trifluoromethyl)phenyl, 3,5-bis(trifluoromethyl)phenyl, allyl, and pentafluorophenyl groups are shown to act as a leaving group to generate cross-coupling-active fluorosilanes and/or silanols in situ. A substituent-induced intramolecular activation strategy is also effective for the coupling. Shindo found that a carboxyl group β-cis to the silicon in alkenyl(trimethyl)silanes promoted the cross-coupling through intramolecular...
activation with Cs₂CO₃. Nakao and Hiyama invented alkenyl[2-(HydroxyMethyl)phenyl]dimethylSi-lanes (alkenyl-HOMSi), which underwent the cross-coupling reaction even in the presence of K₂CO₃.

Cross-coupling-active aryl(triorgano)silanes were also disclosed as in the case with the alkenyl silanes. Such active arylsilanes are summarized in Figure 2. Arylsilanes bearing allyl, 2-(hydroxymethyl)phenyl, or (2-hydroxyprop-2-yl)cyclohexyl groups can be used to connect a wide range of aryl groups to various aryl halides. Simple 2-pyridyl and 2-benzofuryltrimethylsilanes were employed for cross-coupling with aryl iodides in the presence of not only a palladium catalyst, but also a stoichiometric transition-metal mediator. A tert-butyldimethylsilyl group was used in the cross-coupling only in the case of using 8-hydroxy-1-naphthyl as an electrophile. Aryl(triorgano)silanes substituted by a heteroaryl, or 3,5-bistrifluoromethylphenyl group were suggested by Murata, Gevorgyan, and Murai and Takai.

As described above, organo-HOMSis are examples of cutting-edge reagents for silicon-based cross-couplings (Scheme 1). This type of cross-coupling reagent is applicable not only to alkenylation and arylation, but also to alkylation. The organo-HOMSi reagents are stable but become highly reactive to effect the cross-coupling upon activation by a weak base such as potassium carbonate. Moreover, the silicon residue, cyclic silyl ether, is recoverable and recyclable to any organo-HOMSi reagents by treatment with an organolithium or organomagnesium reagent.

Protection of the proximal hydroxy group makes the HOMSi totally cross-coupling inactive. Orthogonally removable protecting groups such as tetrahydropyranyl (THP), methoxymethyl (MOM), acetyl (Ac), and silyl (SiR₃) are applicable. This flexibility permits the construction of a

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**Biographical Sketches**

**Takeshi Komiyama** was born in Saitama in 1991, and is a Ph.D. student at Chuo University guided by Professors Tamejiro Hiyama and Yasunori Minami. His research interest is the exploitation of novel synthetic transformations of organosilicon compounds by transition-metal catalysis. He received a Poster Award at the 5th CSJ Chemistry Festa (2015), the Gakuin Kaicho Award from the Head of Chuo University Alumni Association (2016), the Student Presentation Award at the 71th Kanto Branch Symposium organized by the Association of Synthetic Organic Chemistry, Japan (2016), the Shibuya Ken-ichi Award for Encouragement presented by the Director of Chuo University (2017), and the Presentation Award (Industry Division) at the 97th CSJ Annual Meeting (2017).

**Yasunori Minami** was born in Mie prefecture in 1982. He spent three months at the Laboratories of Professor John F. Hartwig (University of Illinois at Urbana-Champaign) as a visiting student in 2009, before receiving his Ph.D. from Osaka University in 2010 under the supervision of Professor Nobuaki Kambe. He then joined RDI at Chuo University as an assistant professor. His current research interests are synthetic organic chemistry using transition-metal catalysts and main group elements.

**Tamejiro Hiyama** was born in Osaka in 1946. He was appointed Associate Professor at Kyoto University in 1972, completed his Ph.D. under the supervision of Professor Hitoshi Nozaki at Kyoto University in 1975, and spent a postdoctoral year at Harvard University working with Professor Yoshito Kishi. In 1981, he started his research as a Principal Investigator at the Sagami Chemical Research Center. In 1992, he moved to the Research Laboratory for Resources Utilization, Tokyo Institute of Technology, as a full professor and then to the Graduate School of Engineering, Kyoto University, in 1997. Since retirement from Kyoto University in 2010, he has been at Chuo University as an RDI Professor. His research stems from the invention of synthetic methods for the synthesis of biologically active agents and liquid crystalline and light-emitting materials.
variety of oligoarenes easily. For example, 2-thienyl-HOMSi undergoes cross-coupling with THP-protected 2-(5-bromo-thienyl)-HOMSi in the presence of a catalyst consisting of palladium, CuI, and RuPhos to give the protected bithienyl-HOMSi, which can be deprotected to give cross-coupling-active bithienyl-HOMSi (Scheme 2).

A similar idea of intramolecular activation was also developed by Tamao, who noted that ortho-oxybenzyl-substituted phenylsilanes generated in situ from cyclic silyl ether with TBAF and KF, and AgNO3 give the protected bithienyl-HOMSi, which can be deprotected to give cross-coupling-active bithienyl-HOMSi (Scheme 2).

As discussed before, some tetraorganosilanes are active for the cross-coupling but lack the generality. Herein, we briefly review our recent progress in the development of synthetic methods for triorganosilyl-type reagents and their cross-coupling chemistry, taking advantage of such silicon reagents.

Scheme 1 HOMSi reagents as cross-coupling nucleophiles

Scheme 2 A HOMSi as a cross-coupling nucleophile
2 Preparation of HOMSi Reagents from Aryl Bromides and Disilanes

The reaction of the cyclic silyl ether 1 with organometallic reagents in Scheme 1 is a typical procedure to prepare any HOMSi reagent. However, it is not suitable in the case of reagents containing a reactive functional group such as formyl or cyano. To overcome this drawback, transition-metal-catalyzed silylation of aryl electrophiles with hydro-silanes,26 disilanes,27 or silylboranes28 is feasible. Indeed, Kondo reported that the Pd-catalyzed silylation of aryl bromides with protected HOMSi-type disilanes could be used to prepare various protected aryl-HOMSi reagents.

In the case of DavePhos as a ligand, Ar-HOMSi reagents 5ea–ia with an electron-neutral or electron-deficient substituent such as CF3, CN, Cl, Ac, and CHO were obtained in moderate to good yields (Scheme 4), whereas the reagent with an NO2 group was hard to prepare by the present method.

Bis-HOMSi reagents were also successfully prepared. For example, 2,7-dibromo-9,9-dioctylfluorene was doubly silylated smoothly under conditions similar to those in Scheme 3 and gave THP-protected bis-HOMSi reagents 6a in 73% yield. This method allows the preparation of phenyl-HOMSI reagents containing any electron-donating or electron-withdrawing reactive functional group. RuPhos was effective for arenes with an electron-donating aryl group and DavePhos for those with an electron-withdrawing group. When RuPhos was used, HOMSi reagents with OMe, NPh2, and NHBoc groups at para positions (5ba–da) were obtained in good yields, whereas the synthesis of a HOMSi reagent with a CF3 group did not proceed effectively; the example with a bulky 2-tolyl aryl group reduced the reactivity to afford low yields of the product.
3 HOMSi Reagents from Heteroaromatics and Hydrosilanes

In contrast to the preparation of Ar-HOMSi reagents starting with aryl halides, catalytic C–H silylation of aromatic hydrocarbons is more attractive in view of green chemistry.32 This type of transformation is made possible by C–H silylation of arenes catalyzed by a transition-metal complex,33 t-BuOK,34 B(C₆F₅)₃,35 or a Brønsted acid.36 HOMSi-type hydrosilanes, H-HOMSi, accessible by hydride reduction of 1 followed by protection of the resulting OH group, are an appropriate form for the straightforward synthesis of Ar-HOMSi. The total transformation is considered a sustainable silicon cross-coupling protocol (Scheme 5). Therefore, we decided to develop the straightforward synthesis of Ar-HOMSi reagents.37

According to Falck’s protocol,33c we first examined the reaction of benzothiophene with MOM-protected hydrosilanes 7MOM using the [Ir(OMe)cod]₂/4,7-di-tert-butyl-bipyridyl (dtbpy) catalytic system and isolated the desired product in <10% yield. Optimization of the conditions led to the isolation of THP-protected benzothienyl-HOMSi 5ja in 89% yield: [Ir(OMe)(cod)]₂ (5 mol%), Me₄phen (10 mol%), norbornene (1.5 equiv) in (i-Pr)₂O (8 equiv) at 80 °C (Scheme 6). An acetyl group is also a pertinent protecting group. Five-membered heteroaromatics such as benzofuran, indole, and 2-bromo-3-dodecylthiophene gave C₂-silylated products in good to excellent yields. The carbon–bromine bond did not interfere with this silylation, whereas pyridine, pentafluorobenzene, and 1,4-dimethoxybenzene failed to undergo silylation.

Using three equivalents of 7THP and norbornene, disilylation was successfully effected to give Ar(HOMSi)_2. Indeed, Ar(HOMSi)_2 reagents 6b–e were readily accessible, originating from 3-bromothiophene, benzodithiophene, 3,4-ethylenedioxythiophene, and 4,7-dithienylbenzothiadiazole (Figure 3) under the conditions in Scheme 6. The resulting Ar(HOMSi)_2 compounds are potential monomers for the synthesis of π-conjugated polymers used for organic electronics.
4 Cross-Coupling Polymerization with HOMSi Reagents

Polyarylenes play a significant role in organic electronics. To construct such \(\pi\)-conjugated molecules, cross-coupling using organoboron or organotin reagents is the standard approach at present.\(^{38}\) When organoboron monomers are reacted using organoboron or organotin reagents is the standard approach at present.\(^{38}\) When organoboron monomers suffer from low solubility owing to their planar and rigid skeletons, organotin reagents containing alkyl chains on the tin center are preferably employed. However, organotin reagents are toxic in general so that they are not suitable for mass production in industry. In contrast, organosilicon compounds are in general stable and easy to handle with- out such toxicity problems. However, silicon-based polymerization leading to polyarylenes has remained almost un- explored except for a few efforts.\(^{39}\) To achieve successful polymerization using organotin reagents containing alkyl chains on the tin center are preferably employed. However, organotin reagents are toxic in general so that they are not suitable for mass production in industry. In contrast, organosilicon compounds are in general stable and easy to handle without such toxicity problems. However, silicon-based polymerization leading to polyarylenes has remained almost un- explored except for a few efforts.\(^{39}\) To achieve successful high-molecular-weight-polymer synthesis, we applied the HOMSi-based cross-coupling. However, the reaction conditions shown in Scheme 2 require strictly stoichiometric organometallic reagents based on organic halides, whereas the original HOMSi-based coupling requires loading of silicon regents in a slight excess. Therefore, we pursued optimization of the reaction conditions to achieve cross-coupling polymerization using Ar-HOMSi reagents and examined double cross-coupling reactions using stoichiometric amounts of Ar-HOMSi and dibromoarenes. As a result, 2.1 equivalents of phenyl-HOMSi turned out to doubly couple with dibromoarenes in the presence of \(\text{Pd[P(o-tolyl)]_2} \) (2 mol%), DPPF (2.1 mol%), CuBr·SMes (3.0 mol%), Cs\(_2\)CO\(_3\) (4.2 equiv), 3 Å MS, and THF/NMP co-solvent in high efficiency (Scheme 7). For instance, 1,4-dibromo-2,5-dihexylbenzene, 2,7-dibromo-9,9-diocetylfluorene, and 2,5-dibromothiophene were applicable to the coupling of Ph-HOMSi and gave products 8a-c in yields higher than 90%. Moreover, 4,7-dibromothiophene smoothly reacted with 2-thienyl-HOMSi, 4-diphenylaminophenyl-HOMSi, and 9,9-diocetyl-2-fluorenyl-HOMSi to furnish teraryls 8d-f in good to excellent yields.

Bis-4,7-(fluorenylene)HOMSi 9 underwent double coupling with 4-bromothiophene to give teraryl 8g in an excellent yield (Equation 4).

With optimized coupling conditions in hand, we next studied the synthesis of polyarylenes. Cross-coupling polymerization of 9 with 4,7-dibromothiophene produced in a quantitative yield poly(9,9-diocetyl-fluorene-co-benzothiadiazole),\(^{40}\) also known as light-emitting material F8BT (Equation 5).

Combined with this double-coupling protocol and the straightforward disilylation described in Section 3, the linear synthesis of an \(\text{o-aryl(arylene)-based bis-HOMSi}\) was easily achieved via a net C–Br/C–H coupling (Scheme 8).

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**Equation 4**

\[
\text{HO} + \text{Br} \rightarrow \text{Si} \quad \text{(2.1 equiv)}
\]

**Scheme 7** Pd-catalyzed double cross-coupling of aryl dibromides with Ar-HOMSi

**Equation 5**

\[
\text{Si} + \text{Br} \rightarrow \text{8g}, 91\%
\]
tected 5-bromo-4-dodecyl-2-thienyl-HOMSi 5ma (see Scheme 6), withstanding the steric repulsion between the dodecyl groups, to produce the coupled product 6f. This oligoarene unit is a part of a polymer for a solar cell.41

5 Cross-Coupling with Aryl(triethyl)silanes

During the studies described in Sections 2, 3, and 4, we were challenged repeatedly to prepare 4,7-benzothiadiazole-based bis-HOMSi reagents by lithiation followed by the reaction with 1, Pd/Cu-catalyzed silylation of bromobenzothiadiazoles as described in Section 2, and Ir-catalyzed silylation of benzothiadiazoles, but all attempts failed. A great deal of effort led to the Ir-catalyzed C–H silylation of 5,6-difluorobenzothiadiazole using triethylsilane as a silylation reagent (Equation 6). Since the cross-coupling of aryl(triethyl)silanes had no precedent, we decided to find appropriate catalytic conditions for the cross-coupling of aryl(triethyl)silanes.

As discussed previously, the coupling with trialkylsilyl-type reagents has been a long-standing synthetic challenge; a successful outcome would be anticipated to enhance the availability of not only organosilicon chemistry but also synthetic organic chemistry. Thus, we focused on the development of the cross-coupling reaction with trialkylsilarenes with aryl halides. We were soon pleased to find that CuBr₂ was a crucial catalyst for the targeted reaction.42 For example, the reaction of 4,7-bis(triethylsilyl)-5,6-difluorobenzothiadiazole (10) with 4-idoanisole and 4-iodobromobenzene took place in the presence of CuBr₂ (10 mol%), Ph-DavePhos (10 mol%), CsF (2.5 equiv) in 1,3-dimethyl-2-imidazolidinone (DMI) to give teraryl 8h and 8i in excellent yields (Scheme 9). The coupling of 10 with 3-iodocarbazole produced 8j in a good yield using KF, 18-crown-6 (18C6), and cyclopentyl methyl ether (CPME) instead of CsF and DMI. Double cross-coupling of 2,5-bis(triethylsilyl)-3,4-ethylenedioxythiophene and 1,4-bis(triethylsilyl)tetrafluorobenzene, both prepared by the Ir-catalyzed C–H silylation, proceeded to give 8k and 8l.

Scheme 8 Linear synthesis of an oligoarylene-Bis-HOMSi by a sequential protocol involving Ir-catalyzed C–H silylation and double cross-coupling

Equation 6

Scheme 9 Cu-catalyzed double cross-coupling of bis(triethylsilyl)arenes
The results of the mono-coupling of aryl(triethyl)silanes with 4-iodoanisole are summarized in Figure 4. 2-Benzothienyl, 2-indolyl, 2- and 3-pyridyl-, 3,5-bis(trifluoromethyl)phenyl-, and 4-cyanophenyl(triethyl)silanes gave the corresponding biaryls in moderate to excellent yields. Whereas 2-pyridylboronic acids and esters were not sufficiently stable to effect the Suzuki–Miyaura coupling, 2-pyridyl(trimethyl)silane is stable and easy to handle, and smoothly participates in the cross-coupling. We should note that electron-neutral and electron-rich arylsilanes such as 2-naphthyl-, 4-biphenyl-, and 4-diphenylaminophenyl(triethyl)silanes failed to react, probably due to the low electrophilicity of the silicon center.

In addition to 4,7-bis(triethylsilyl)-5,6-benzothiadiazole (10), its phenyldimethylsilyl analog 10′ cross-couples with 4-iodoanisole to give 4,7-(di-4-anisyl)benzothiadiazole 8h in 63% yield along with 4-methoxybiphenyl (4% yield) (Equation 7). Probably a more electron-deficient aryl group on the silicon center was transmetalated to the Pd center faster than an electron-rich one. This reactivity order contrasts sharply to that in transmetalation in the Pd-catalyzed cross-coupling.

We propose the catalytic cycle shown in Scheme 10, which consists of three steps: (1) single-electron transfer from Ar′(fluoro)silicate to CuX2 (X = Br, I) to generate radical species II and/or III and Cu(I)X, (2) oxidative addition of Ar′I to Cu(I)X to form Ar′–Cu(III), and (3) coupling of II and/or III with Ar′–Cu(III) to form the coupled Ar′–Ar product and reproduce Cu(II)X2.

6 Amination of Aryl Halides with N-TMS-Amines

The concept of the silicon-based cross-coupling is applicable to formation of not only C–C bonds, but also carbon–heteroatom bonds including C–S, C–O, and C–N bonds. For C–N bond-forming reactions, the Buchwald–Hartwig amination is well described, which generally requires the use of a strong base. On the other hand, Pd-catalyzed amination using an N-silylamine takes place upon activation with a base such as a fluoride ion. Indeed, Smith observed that N-TMS-amines couple with aryl bromides in the presence of a palladium catalyst and Cs2CO3 or CsF in supercritical carbon dioxide. This observation is seminal but it is a drawback to use a pressure bottle for supercritical CO2. In addition, the reactivity of silylamines remains to be improved. Thus, we decided to improve the conditions for the C–N bond-forming cross-coupling reaction using N-TMS-amines. Other N-TMS-amines can be prepared by lithiation of N-H-azines followed by reaction with chlorotrimethylsilane.

After screening the reaction conditions, we found that amination of 4-bromotoluene took place with N-TMS-diphenylamine (1.1 equiv), Pd(dba)2 (1 mol%), XPhos (2 mol%), CsF (1.5 equiv), and DMI as a general organic solvent (Scheme 11) to give 4-methyltriphenylamine in 97% yield. Various bromoarenes such as 4-BrC6H4NPh2, 2-BrC6H4Me, and 1- and 2-bromonaphthalenes were applicable to the reaction, whereas 2- or 3-bromothiophene, 3-bromopyridine, and bulky 1-bromo-2,6-dimethylbenzene proved unreactive. It is noteworthy that 4-chlorotoluene undergoes the amination without any serious problems.
amines such as N-TMS-N-methylaniline, N-TMS-aniline, N-TMS-morphine, and N-TMS-carbazole are applicable to this amination. Although an N-arylcarbazole unit is an important motif in organic electronics, 51 N-TMS-carbazole could only be applied to the reaction with electron-deficient aryl bromides under the palladium catalytic conditions. We compared the reactivity of N-TMS-amines with respect to the rate of amination of 4-bromotoluene using TMS-NPh₂, TMS-NMePh, TMS-NHPh, and N-TMS-morpholine. The results are shown in Figure 5, which shows that the reaction rates are in the order of TMS-NPh₂ > TMS-NMePh ≈ TMS-NHPh > N-TMS-morpholine. In contrast, diarylamines are less reactive in the Buchwald–Hartwig amination than alkyl(aryl)amines and monoaryl amines. 52 The opposite reactivity order of N-TMS-amines is attributed to the basicity of amines, which may contribute to the smooth activation of silicon by a fluoride ion.

The present C–N bond-forming coupling was applied to poly(arylene-imine) 53 synthesis (Scheme 12). Under the optimized conditions, 2,7-dibromo-9,9-diocetylfluorene reacted with N,N-bis(TMS)-anilines or N-TMS-N′-TMS-para-phenylenediamine to produce the corresponding polymers, which might be employed as organic electron-conducting materials. 54

As mentioned above, the Pd-catalyzed amination protocol does not work well with N-TMS-carbazole and electron-rich aryl bromides. We were pleased to find that nickel catalysis is especially effective for the amination of aryl bromides with N-TMS-carbazole. 55 In fact, N-TMS-carbazole coupled with both electron-rich and electron-deficient aryl bromides.
bromides using an SIPr-ligated nickel(0) complex generated in situ (Scheme 13). This novel amination proceeds in the presence of a weak base, sodium acetate.

![Scheme 13](image)

**Scheme 13** Pd-catalyzed C–N bond-forming cross-coupling of aryl bromides with N-TMS-amines

7 Conclusion and Perspective

Recent contributions to silicon-based cross-coupling chemistry are briefly reviewed mainly from our viewpoint. Sections 2, 3 and 4 demonstrate that a wide variety of HOMSI reagents are readily accessible via two catalytic approaches and that they are applicable to teraryl and polyarylene synthesis. Section 5 shows that simple trialkylsilylethers can be utilized for the cross-coupling with iodoarenes in the presence of a copper(II) catalyst. Section 6 deals with the amination of aryl halides with N-TMS-amines. This transformation is an alternative procedure for triarylmethane synthesis because such reactions proceed in the presence of a fluoride ion. The C–C and C–N bond-forming procedure will provide stable tetraorganosilanes that are potentially applicable to various transition-metal-catalyzed reactions, allowing the possibility for novel methodologies to construct complex molecules such as π-conjugated organic materials and nitrogen-linked compounds.

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