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Mini Review

Pyridylsilyl group-driven cross-coupling reactions

Kenichiro Itami, Koichi Mitsudo, Toshiki Nokami, Toshiyuki Kamei, Tooru Koike, Jun-ichi Yoshida *

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Kyoto, 606-8501, Japan

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Abstract

Summarized herein are the demonstrations that the use of 2-PyMe$_2$Si group as a removable directing group is a powerful strategy for enhancing the efficiency of otherwise sluggish processes and for steering the course of the reaction by taking advantage of attractive substrate–catalyst interaction in the palladium-catalyzed cross-coupling chemistry. The 2-PyMe$_2$Si group-driven Heck-type coupling, Hiyama-type coupling, Stille-type coupling, and allylic alkylation are described. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Pyridylsilyl group; Removable directing group; Cross-coupling reaction

1. Introduction

The past few decades have witnessed a profusion of highly efficient transition metal-catalyzed carbon–carbon bond-forming process that proceeds with high levels of selectivity (chemo-, regio-, diastereo-, and enantioselectivity) under very mild conditions [1]. Although the novelty of the reaction mode has been one of the central issues in this field, many reactions still suffer from their limitations in the substrate that can be applied. In light that such substrate-limitation would inevitably lead to the product-limitation thereby diminishing the potentiality of a highly efficient bond-forming process, the strategic approaches for expanding the substrate-scope are highly called for.

The tuning of the stereoelectronics of the catalyst by adjusting the ligand field might be a solution for enhancing the reactivity or selectivity [2]. Alternatively, an intramolecular ligand (directing group) provides a powerful strategy for enhancing the efficiency of an otherwise sluggish process and for steering the course of the reaction by taking advantage of attractive substrate–catalyst interaction [3]. In most cases, such reactions are directed by the suitable heteroatoms on the substrate. However, the greatest flaw of the current directed reaction is the difficulty in removing or functionalizing such directing groups after the reaction.

We envisioned that the concept of ‘removable directing group’ should alleviate the problems on substrate limitation [4]. In such strategy, a range of reactions can be directed through the agency of complex-induced proximity effect (CIPE) [5], yet the initial product can still be transformed into a variety of products with the removal of the directing group. In pursuit of this objective, we design a 2-pyridyldimethylsilyl (2-PyMe$_2$Si) group as a candidate for such removable directing group due to the following reasons: (i) coordinating ability of pyridyl group; (ii) high stability of carbon–silicon bond; and (iii) removability and permutability of silyl group (Scheme 1). In this mini-account, we describe our recent works on the palladium-catalyzed cross-coupling reactions that are efficiently driven and directed by the removable 2-PyMe$_2$Si group on the substrates.

2. Palladium-catalyzed Heck-type coupling

The palladium-catalyzed Mizoroki–Heck-type coupling has been well recognized as a powerful method for the preparation of substituted olefins [6]. Although

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* Corresponding author. Fax: +81-75753-5911.

E-mail address: yoshida@sbchem.kyoto-u.ac.jp (J.-i. Yoshida).

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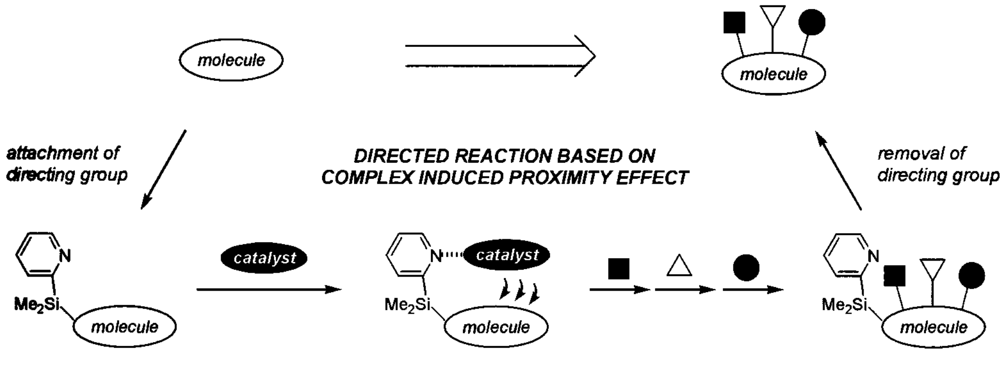


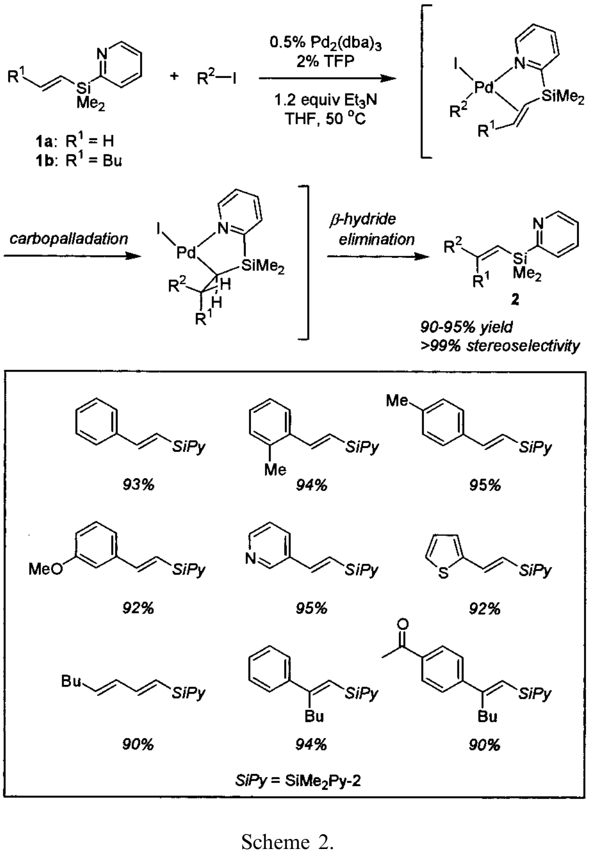
Scheme 1.

Heck-type coupling can in principle be applied to any kinds of alkene and alkyne, significant gap still exists in the scope of this reaction especially in the intermolecular reaction. Vinylsilane is a substrate that possesses several difficulties upon the Heck-type coupling [7]. For example, the treatment of vinylsilane with aryl iodide in the presence of $Pd(OAc)_2$, PPh_3, and triethylamine (typical Heck reaction conditions) affords exclusively a styrene derivative as a result of carbon–silicon bond cleavage [8]. Usually, the Heck-type coupling of vinylsilane requires the addition of an equimolar amount of silver nitrate [9,10]. By taking advantage of efficacious CIPE through the coordination of the pyridyl group to the catalyst palladium, we expected the occurrence of the Heck-type reaction of 2-pyridyldimethyl(vinyl)silane (**1**) without the need of silver salt [11].

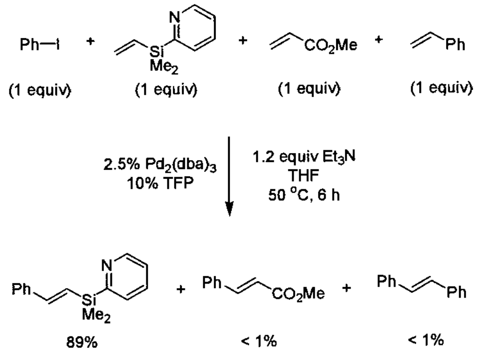
As expected, Heck-type coupling of **1** with aryl iodide took place in the presence of a palladium catalyst and a base giving the β-substituted vinylsilane **2** (Scheme 2) [12]. The catalyst–ligand combination of $Pd_2(dba)_3$ and tri-2-furylphosphine (TFP) gave rise to extremely high yield of the coupling product **2**. It may be reasonable to assume that the coordination of pyridyl group to palladium might render the carbopalladation event kinetically and/or thermodynamically favorable (Scheme 2). The stereoselectivity was in agreement with the mechanism of the Heck reaction (stereospecific *syn* carbopalladation and *syn* β-hydride elimination) [6]. However, under the identical reaction conditions, Heck-type coupling did not take place with aryl bromides or aryl triflates. Noteworthy features of this process are that (1) the formation of styrene derivatives (C–Si bond cleavage) was completely suppressed, (2) the coupling occurred under mild conditions (50 °C) and at low catalyst loading (as low as 0.1 mol%), (3) virtually complete stereoselectivity (> 99% *E*) was observed in all cases examined, and (4) the regio- and stereoselective coupling occurred even with the β-substituted vinylsilane **1b**.

To evaluate the relative reactivity of 2-pyridyldimethyl(vinyl)silane, competitive reaction was carried out with methyl acrylate and styrene, the most commonly used reactive substrates in Heck-type coupling reaction (Scheme 3) [12]. The reaction was carried out with **1a** (one equivalent), methyl acrylate (one equivalent), styrene (one equivalent), iodobenzene (one equivalent), and triethylamine (1.2 equivalent) in the presence of $Pd_2(dba)_3$/TFP catalyst (5 mol% Pd). To our surprise, the only product detected in the reaction mixture was the Heck-type product of **1a** (89% yield), which clearly signifies the high reactivity of 2-pyridyldimethyl(vinyl)silane toward the Heck-type coupling.

As we recently reported, the additional benefit of using the 2-PyMe_2Si group is that it can also be utilized



Scheme 2.



Scheme 3.

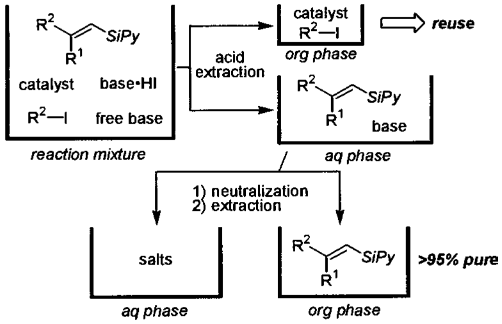


Fig. 1. Acid–base extraction process for the purification of coupling product and the recovery of palladium catalyst.

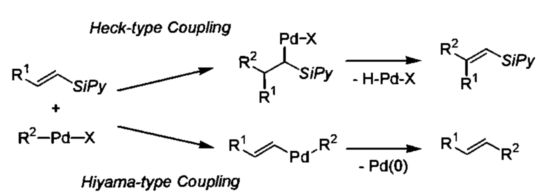
as a phase tag [13], which enables easy purification [14]. By taking advantage of this phase tag property of the 2-PyMe$_2$Si group, all products were isolated by simple acid–base extraction (Fig. 1). The yield of **2** using this acid–base extraction is generally higher (ca. 5%) than that using silica gel chromatography and is slightly lower (ca. 3%) than that determined by GC analysis of the reaction mixture. Importantly, the purities of the products are over 95% in all cases as judged by NMR and GC analysis. This easy separation/purification protocol without using any chromatographic isolation technique is notable [15].

Another interesting aspect in this acid–base extraction process is that the palladium catalyst can be easily recovered from the initial organic phase (Fig. 1). The recovery of the palladium catalyst was almost quantitative so that the catalyst may be used for the next reaction. Indeed, the thus-recovered catalyst can be used several times without any significant loss of catalytic activity and stereoselectivity [12]. This implies that the recovery of the metal catalyst does not necessarily have to rely on the polymer-supported catalyst, and clearly paves the way for the strategic catalyst recovery in the solution-phase synthesis.

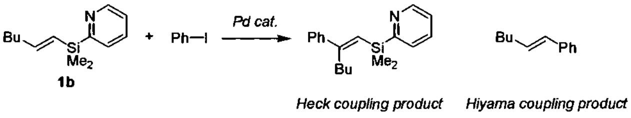
3. Palladium-catalyzed Hiyama-type coupling

Next, we became interested in the multiform reactivities of 2-pyridyldimethyl(vinyl)silanes, which can potentially react with organic halides and palladium catalyst in two mechanistically different modes (Scheme 4). As already mentioned in the previous section, the arylation at C=C bond exclusively took place to give the Heck-type coupling product in extremely high yield. Alternatively, however, arylation can potentially occur at the C–Si functionality affording Si-free alkenes (Hiyama-type cross-coupling products) [16]. It would be of great importance in organic synthesis if these two reaction pathways were perfectly controlled, ideally with slight changes of additive or reaction conditions, because sequential integration of these two reactions should pave the way for the stereoselective synthesis of multi-substituted olefins. Thus, we searched for the catalyst- or additive-controlled switching of the above-mentioned two reaction pathways [17].

As a model substrate, we selected 2-pyridyldimethyl(hexenyl)silane (**1b**) because such β-substituted vinylsilanes are good substrates for addressing the regioselectivity issue [18]. As already stated, the Pd$_2$(dba)$_3$/TFP catalyst system promoted the Heck-type coupling of **1b** with iodobenzene [12]. Although various palladium catalysts were examined, the only product detected was the Heck-type coupling product. This may be due to the strong directing effect of the pyridyl group and the poor transmetalation ability of silicon. Thus, we followed the lead of Hiyama [16] who has established that the transmetalation from silicon to palladium can be accelerated by adding a fluoride ion [19]. We subjected **1b** and iodobenzene to the action of palladium catalyst and fluoride source at 60 °C in THF. By adding tetrabutylammonium fluoride (TBAF) to the Pd$_2$(dba)$_3$/TFP catalyst system, the course of the reaction changed to the Hiyama-type coupling and the Heck-type coupling was completely suppressed (Scheme 5). Moreover, we found that phosphine-free palladium complexes were



Scheme 4.



catalyst	additive	ratio (yield)
Pd$_2$(dba)$_3$/TFP	Et$_3$N	100/0 (94%)
Pd$_2$(dba)$_3$/TFP	TBAF	0/100 (59%)
PdCl$_2$(PhCN)$_2$	TBAF	0/100 (99%)

Scheme 5.

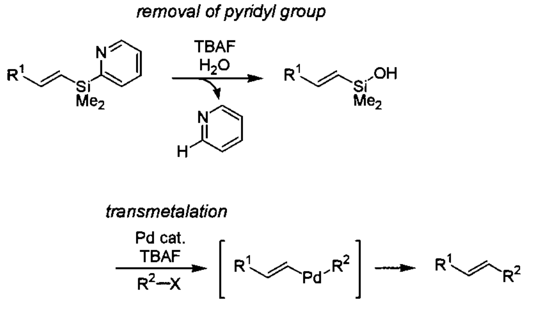
more active catalysts giving the Hiyama-type coupling product in extremely high yield. Among them, $PdCl_2(PhCN)_2$ was found to be the most active catalyst for the Hiyama-type coupling.

Mechanistic studies revealed that the pyridyl group on silicon was selectively removed by the action of TBAF to produce the corresponding silanol in situ [20]. It seems plausible to deduce that the perfect switch of the reaction course (Heck-type coupling vs. Hiyama-type coupling) stems from the selective removal of the Heck-coupling-directing pyridyl group and the introduction of an electronegative group that activates silicon as a leaving group (Scheme 6).

With the feasibility of the selective Hiyama-type coupling established, a survey of the substrate scope was undertaken (Scheme 7) [17]. Various electronically and structurally diverse aryl and alkenyl halides were found to cross-couple with 2-pyridyl-substituted vinylsilanes in good to excellent yields. The advantage of using 2-pyridyl-substituted vinylsilanes as coupling components is apparent, as they are readily available in stereoisomerically pure form by the aforementioned Heck-type coupling [12], the hydrosilylation of alkyne with 2-$PyMe_2SiH$ [21], or the Peterson-type olefination of carbonyl compounds with $(2\text{-}PyMe_2Si)_2CHLi$ (Scheme 8) [22].

4. Palladium-catalyzed one-pot sequential Heck/Hiyama coupling

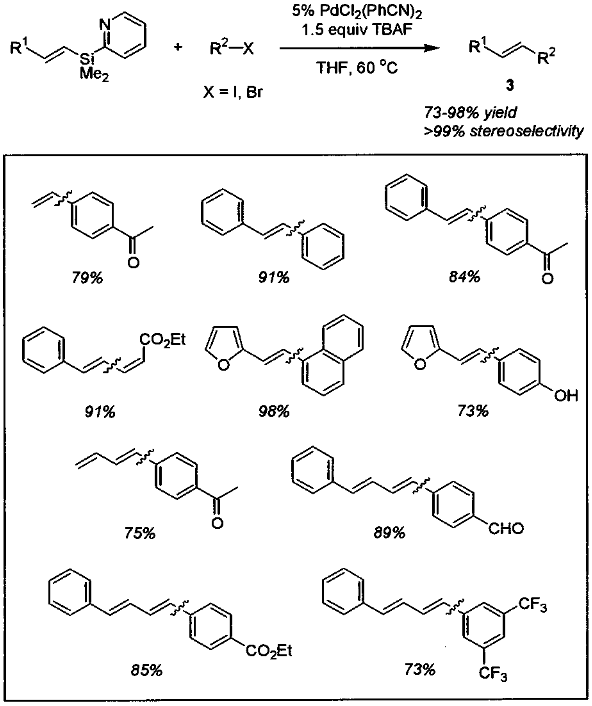
In light of the ability of 2-pyridyldimethyl(vinyl)-silanes to cross-couple with organic halide in two mechanistically different modes (Heck-type coupling and Hiyama-type coupling), we next embarked on a one-pot sequential cross-coupling, in which the Heck-type coupling occurs first and the Hiyama-type coupling takes place thereafter (Scheme 9) [17]. In our preliminary screening of the reaction conditions, we established that $Pd(OAc)_2$, instead of $Pd_2(dba)_3$ or $PdCl_2(PhCN)_2$, is superior palladium source for this one-pot process. The β-substituted vinylsilane **1b** was initially cross-coupled with aryl iodide in the presence of Pd/TFP catalyst. After the initial reaction completed, another aryl iodide and TBAF were added to the mixture to obtain cross-coupling product **4** in 71% yield. Interestingly, the regioisomer **5** can be obtained in 79% yield by simply changing the order of addition. In both cases, the reaction proceeded in virtually complete regio- and stereoselective fashion.



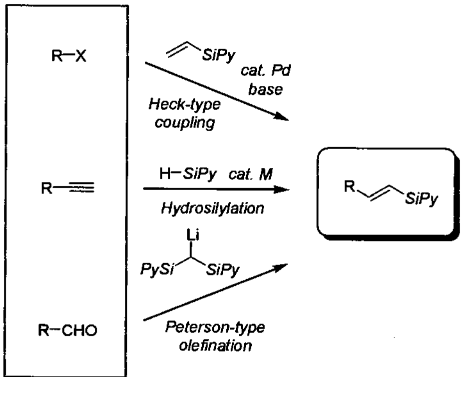
Scheme 6.

5. Palladium-catalyzed Stille-type coupling

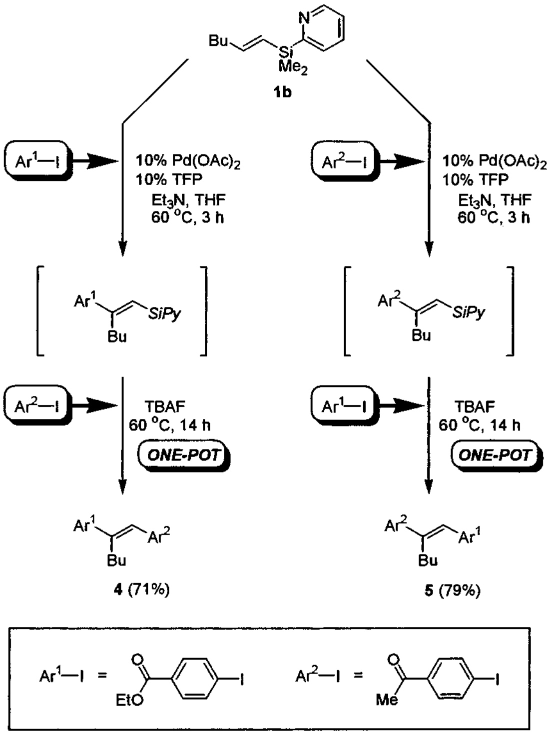
The palladium-catalyzed cross-coupling reaction of organotin compounds with organic halides (Migita–Kosugi–Stille coupling) has also emerged as an important method for the catalytic carbon–carbon bond



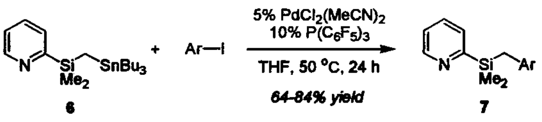
Scheme 7.



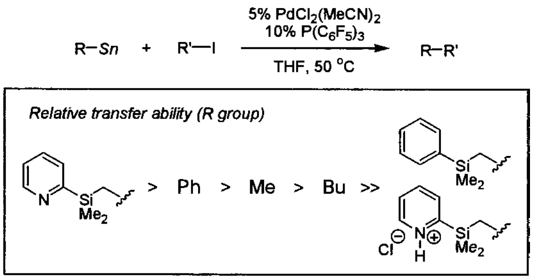
Scheme 8.



Scheme 9.



Scheme 10.

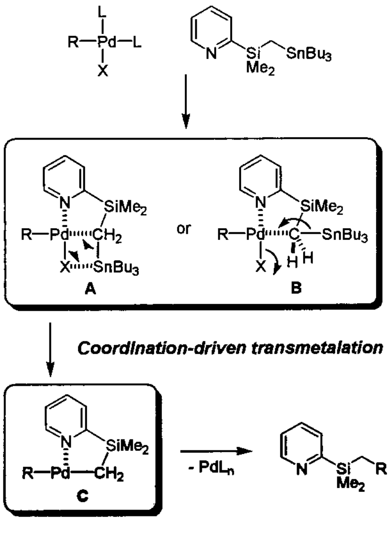


Scheme 11.

formation [23]. Although, the Stille coupling has been well recognized as a powerful method for natural product synthesis in recent years [24], there are still several serious limitations associated with this methodology, namely the low transfer ability of the alkyl group from tin [23]. Especially, synthetically useful silylmethyl groups exhibit extremely low transferring ability and, thus, are not transferred from tin usually. If the silylmethyltin reagents could be effectively cross-coupled with alkenyl or aryl halides, availability of synthetically useful allyl- and benzylsilanes, which bear various functional groups, should be enormously enhanced.

We envisioned that the use of the 2-PyMe$_2$Si group might have some interesting effects on the alkyl group transfer from tin in Stille coupling. During the course of this investigation, we unexpectedly discovered that the 2-PyMe$_2$SiCH$_2$ group behaves quite unusually in Stille coupling where the intramolecular ligand (2-PyMe$_2$SiCH$_2$ group) itself transfers from tin [25]. Treatment of 2-PyMe$_2$SiCH$_2$SnBu$_3$ (**6**) with 1.2 equivalent of aryl iodide in the presence of 5 mol% of PdCl$_2$(CH$_3$CN)$_2$ and 10 mol% of P(C$_6$F$_5$)$_3$ in THF at 50 °C exclusively afforded the 2-PyMe$_2$SiCH$_2$ transferred product 2-PyMe$_2$SiCH$_2$Ar (**7**) in good yield (Scheme 10). The butyl group transferred product was produced only in a trace amount. This result was in a sharp contrast to the original report of Stille, in which the methyl group was selectively transferred from tin when Me$_3$SiCH$_2$SnMe$_3$ was used as an organotin nucleophile. Moreover, the intramolecular competition experiments revealed that the relative transfer ability of the organic group from tin is 2-PyMe$_2$SiCH$_2$ $>$ Ph $>$ Me $>$ Bu $\gg$ PhMe$_2$SiCH$_2$ (Scheme 11).

It seems that the coordination of the pyridyl group to tin is not a viable explanation for the selective 2-PyMe$_2$SiCH$_2$ group transfer on the basis of the ^{119}Sn-NMR study of **6**. Instead, we favor the mechanistic rationale based on the pyridyl-to-palladium coordination at the transmetalation step (Scheme 12) [26]. The coordination of the pyridyl group to palladium brings tin into the proximity of the palladium and renders the subsequent transmetalation intramolecular in nature, thereby facilitating the transfer of the bridging 2-PyMe$_2$SiCH$_2$ group (**A** or **B**) [27]. In addition to this kinetic preference, stabilization of the palladium(II) intermediate (**C**) by complexation with the pyridyl group might also contribute to accelerate the 2-PyMe$_2$SiCH$_2$ group transfer [28]. Such pyridyl-to-palladium coordination was validated in the palladium



Scheme 12.

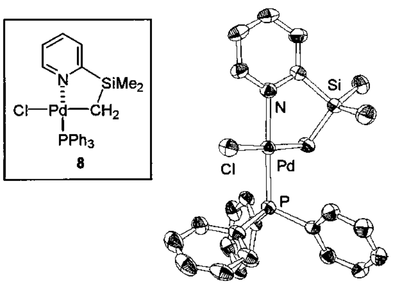


Fig. 2. X-ray crystal structure of **8**.

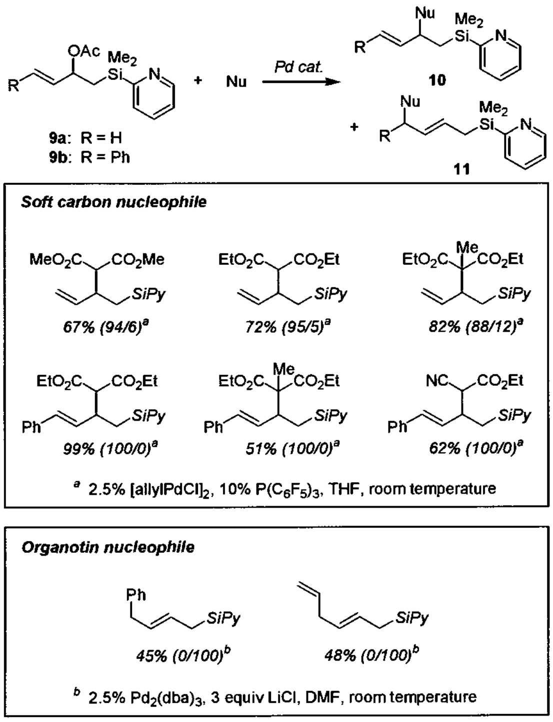
complex **8** by ^{1}H-NMR and X-ray crystal structure analysis (Fig. 2). We believe that the coordination-driven transmetalation demonstrated herein may be a useful alternative to the hypervalent organotin strategy [29] for enhancing the transfer of otherwise non-transferring organic groups from tin in Stille coupling.

6. Palladium-catalyzed allylic alkylation

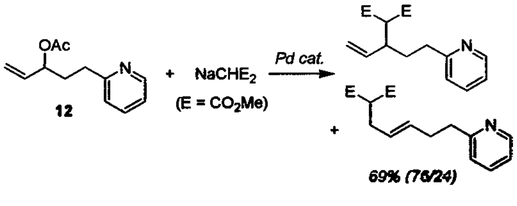
In ongoing efforts to exploit the 2-PyMe$_2$Si group in the metal-catalyzed reactions, we next turned our attention to the regioselectivity problem in the palladium-catalyzed allylic alkylation [30]. It has been well known that, in the palladium-catalyzed allylic alkylation chemistry, the nucleophiles are preferentially introduced into the allylic terminus that is sterically less hindered when unsymmetrically substituted allylic substrates are used. Therefore, we thought of using the 2-PyMe$_2$Si group as a removable directing group to solve the regioselectivity problem in this chemistry [31,32].

Subjection of 2-PyMe$_2$Si-substituted allylic acetate **9** and NaCH(CO$_2$Me)$_2$ to the action of [allylPdCl]$_2$/P(C$_6$F$_5$)$_3$ catalyst led to the predominant production of **10** as the result of nucleophilic attack at more substituted carbon of the allylic moiety (Scheme 13). This unusual inner-site selective allylic alkylation was found to be a general phenomenon for the stabilized carbon nucleophiles. Quite interestingly, the use of organotin compound as a nucleophile [33], on the other hand, gave rise to complete switch of the regioselectivity of the reaction, in which the nucleophilic attack occurred at the allylic terminus remote from the silyl group (Scheme 13). To the best of our knowledge, such regioselectivity switch has never been observed in the (π-allyl)palladium chemistry.

In general, the palladium-catalyzed allylic substitution occurs at the less substituted carbon of the allylic moiety [30]. Indeed, Szabó has established in the related allylic substitution of β-silyl allylic acetates that the nucleophilic attack selectively occurs at the allylic terminus remote from the silyl group because of the steric and electronic reasons [34]. The allylic acetate **12**, which has 2-PyCH$_2$ group instead of 2-PyMe$_2$Si group, underwent the alkylation with good regioselectivity (76/24) favoring the nucleophilic attack at more hindered allylic carbon (Scheme 14). This result, together with the work of Szabó, clearly implies that the unusual regioselectivity observed for **9** (Scheme 13) is primarily attributed to the effect of pyridyl group.

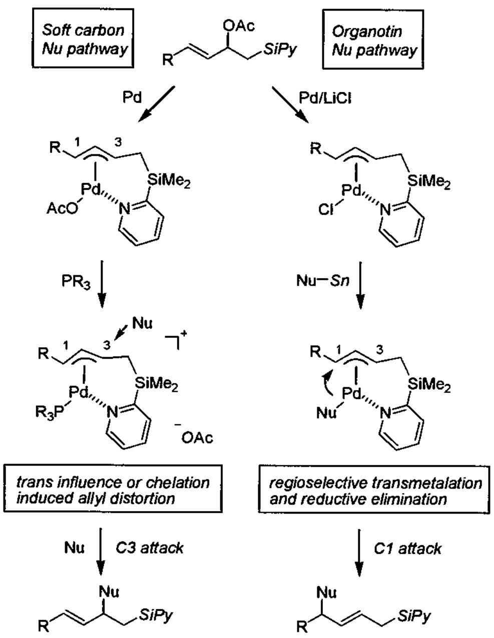


Scheme 13.



Scheme 14.

The mechanistic rationale for this unusual regioselectivity-control is of special interest. The observed inner-site selective allylic alkylation for the stabilized carbon nucleophiles is most likely attributed to the *trans* influence [35] and/or chelation-induced distortion of allylic moiety, in which the soft carbon nucleophile preferentially attacks the longer and, accordingly, more reactive Pd–C bond (Scheme 15) [36]. The pyridyl-to-palladium coordination and the distortion of allylic moiety was validated in the (π-allyl)palladium complex **13**, which was prepared by the reaction of **9a** with Pd$_2$(dba)$_3$·CHCl$_3$ and LiCl, by X-ray crystallographic analysis (Fig. 3). The Pd–C bond *trans* to chlorine (Pd–C3 = 2.183 Å) is substantially longer than the Pd–C bond *trans* to nitrogen (Pd–C1 = 2.089 Å).



Scheme 15.

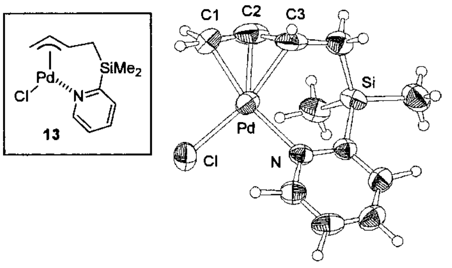
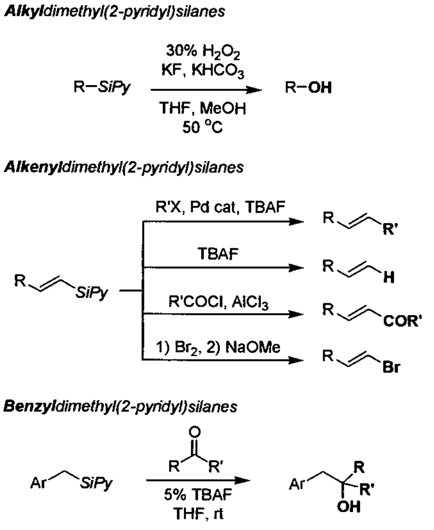


Fig. 3. X-ray crystal structure of **13**.

The explanation for the regioselectivity observed with the organotin nucleophiles should be mechanistically different (Scheme 15). Whereas soft carbon nucleophiles add to (π-allyl)palladium intermediate directly on the allyl ligand, nucleophilic attack of organotin compounds occurs to the metal (transmetalation) and subsequent reductive elimination process produces the products [37]. In the (π-allyl)palladium complex **13**, chlorine atom sits on palladium *cis* to the allylic C1 atom and the coordination site *cis* to the allylic C3 atom is occupied by the intramolecular pyridyl group. We assume that this regioselective transmetalation and reductive elimination might be responsible for the complete regioselectivity switch.

7. Removal of 2-PyMe$_2$Si group

After the pyridylsilyl group-driven or -directed reactions, the 2-PyMe$_2$Si group can be removed or functionalized by several methods (Scheme 16). For example, the *alkyl*dimethyl(2-pyridyl)silanes can be converted into the corresponding alcohol using the Tamao–Fleming-type oxidation in H_2O_2/KF system [38,39]. The products obtained in the palladium-catalyzed Stille-type coupling or in the palladium-catalyzed allylic alkylation were transformed into the corresponding alcohols with this C–Si oxidation.



Scheme 16.

For the *alkenyl*dimethyl(2-pyridyl)silanes, several methods can be used for further transformation with C–Si bond cleavage. As already mentioned in the previous section, the palladium-catalyzed Hiyama-type coupling can be used for this purpose, providing the substituted olefins as the final products. Subjection of *alkenyl*dimethyl(2-pyridyl)silanes into the action of TBAF leads to the simple protodesilylation. *Alkenyl*dimethyl(2-pyridyl)silanes can also be subjected to the reactions with other various electrophiles [40]. For example, treatment of *alkenyl*dimethyl(2-pyridyl)silanes with acid chlorides in the presence of $AlCl_3$ affords the corresponding α,β-unsaturated enones [22]. The reaction of *alkenyl*dimethyl(2-pyridyl)silanes with bromine and subsequent treatment with NaOMe affords the corresponding alkenyl bromides [22].

The *benzyl*dimethyl(2-pyridyl)silanes, obtained in the palladium-catalyzed Stille-type coupling, add to the carbonyl compounds in the presence of a catalytic amount of TBAF giving the secondary and tertiary alcohols in good yields [41]. Not only simple aldehydes, but also α,β-unsaturated aldehydes and ketones are good electrophiles in this reaction.

8. Other pyridylsilyl group-driven reactions

The pyridylsilyl group-driven or -directed reactions are not limited to the palladium-catalyzed cross-coupling reactions. The 2-PyMe$_2$Si group can also be used as a removable directing group in (i) the rhodium- and platinum-catalyzed hydrosilylation of olefin [13a,21,42], (ii) the deprotonative lithiation of a methyl group on silicon [43–45], (iii) the Peterson-type olefination reaction of carbonyl compound [22], and (iv) the intermolecular carbomagnesation of vinylsilane [46]. Moreover, we recently discovered that the 2-PyMe$_2$Si group efficiently functions as a removable hydrophilic group in the aqueous organic reactions such as the intermolecular Diels–Alder reaction [47].

9. Summary

In summary, we have been able to demonstrate that the use of 2-PyMe$_2$Si group as a removable directing group is a powerful strategy for enhancing the efficiency of otherwise sluggish processes and for steering the course of the reaction by taking advantage of attractive substrate–catalyst interaction in the palladium-catalyzed cross-coupling chemistry. The reactions demonstrated herein not only expand the scope of the existing cross-coupling methodologies but also provide some insights to the mechanism and the implication of the alternative controlling factor in the metal-catalyzed bond-forming processes. Ease of preparation of pyridylsilyl building block (usually one or two steps from 2-bromopyridine), its utility in cross-coupling reactions, and various opportunities for subsequent reactions of coupling products distinguish this chemistry and suggest multiple possibilities for further development. Especially, the integration of the metal-catalyzed cross-coupling (ideally in a one-pot process) would offer an opportunity for the diversity-oriented synthesis which enables the production and screening of a large number of molecules against the target of interest. These studies will be a part of our future work.

Acknowledgements

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