

Palladium-catalyzed cross-coupling reaction of organometalloids through activation with fluoride ion

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Activation of organosilicon compounds with fluoride ion produces a transient pentacoordinate silicate, which is capable of transmetalation with a catalytic organopalladium complex and achieves cross-coupling reaction. Mono-, di- or trifluorosilanes can deliver alkenyl, aryl, or alkyl group, respectively. The reaction, characterized by high chemo- and stereoselectivity, was successfully applied to synthesis of HMG-CoA reductase inhibitor NK-104 and functionalized biaryls for liquid crystals. The stereochemical aspects are discussed.

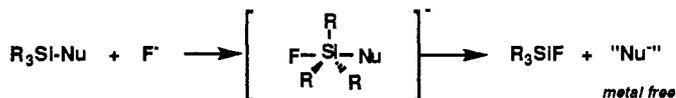
INTRODUCTION

Cross-coupling reaction is the reaction of an organometallic reagent R-M with an organic compound R'-X wherein X is a leaving group and is catalyzed often by a complex of transition metal like nickel or palladium (ref. 1).



Chronologically speaking, the reaction of Grignard reagent/Ni catalyst was the first example as reported in 1972. Since then, many organometallic reagents of Li, B, Al, Zr, Zn and Sn were found to undergo this sort of reaction, but examples of organosilicons are few, because C-Si bond is much less polarized than the above organometals. Although pentafluorosilicates undergo the palladium-catalyzed coupling reaction (ref. 2), the reaction required rather forcing conditions and was not useful enough for organic synthesis. The same conditions were applied to trimethylvinylsilane with limited success (ref. 3). We consider the reaction pathway of these silicon-based reactions is different from those of the cross-coupling reactions using main group metals.

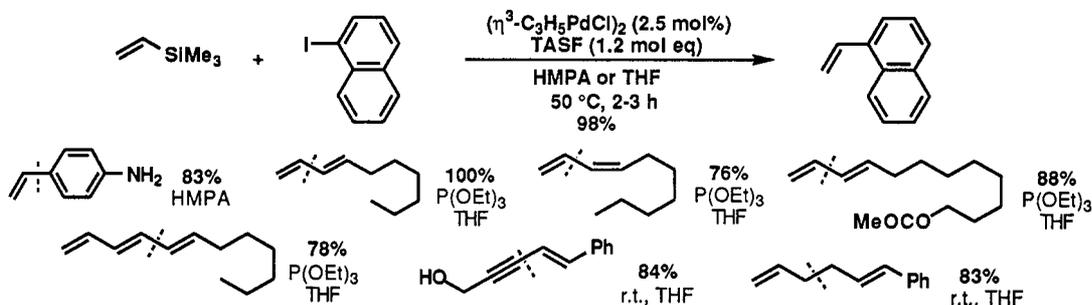
For some years we have been studying the synthetic reactions using fluoride ion and organosilicon compounds (ref. 4). Fluoride ion can attack organosilicon compounds to afford pentacoordinate species and thus activating C-Si bond. This can liberate anion Nu⁻ species if the negative charge is well-stabilized by delocalization. We have studied the synthetic reactions of R₃Si-Nu and found the activation of Si-Nu bond using TBAF or TASF remarkably improved the reactivity, selectivity and stability of Nu⁻ and thus could achieve novel selective synthetic reactions. We have applied this sort of activation to the coupling reaction and have found it really works.



Nu: SiMe₃, CH₂CH=CF₂, CF=CF₂, CHCl₂, CCl₃, C₆F₅, H F⁻: (nBu)₄N⁺F⁻ [TBAF], (Et₂N)₃S⁺Me₃SiF₂⁻ [TASF]

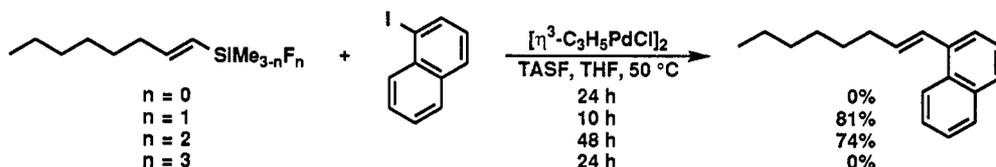
CROSS-COUPLING OF ALKENYLSILANES

We first studied the coupling reaction of commercially available trimethylvinylsilane with 1-iodonaphthalene and found η^3 -allylpalladium chloride dimer was an excellent catalyst to give 1-vinylnaphthalene. TASF in hexamethylphosphoric triamide (HMPA) was proved to be the most effective activator. KF or CsF was not effective. For the coupling with iodo olefins, tetrahydrofuran (THF) solvent and triethylphosphite were preferable. The phosphite ligand probably accelerated the reductive elimination step of the catalytic cycle. As readily seen, stereochemically defined terminal conjugated dienes or trienes were readily prepared. For the coupling of ethynyl- or allylsilanes, TASF in THF was enough. As organosilicon compounds are inert towards various functional groups, protection of ketone, ester carbonyls, amino and hydroxyl groups is not needed (ref. 5).

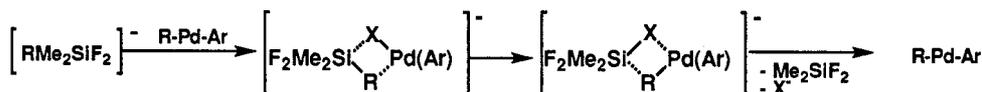


The mechanism of the cross-coupling reaction should follow the well-accepted catalytic cycle. Namely, (1) Pd(0) catalyst generated by unknown pathway undergoes *oxidative addition* to give R-Pd-X complex; (2) *transmetalation* with pentacoordinate silicate $[\text{CH}_2=\text{CHSiFMe}_3]^-$ gives a requisite complex R-Pd-CH=CH₂; (3) *reductive elimination* of this complex affords the coupling product R-CH=CH₂ and regenerates the Pd(0) catalyst. It is often said that transmetalation is the rate-determining step. Although the mechanism of oxidative addition and reductive elimination is well-studied, that transmetalation step remained much less studied.

When we applied the reaction to 1-trimethylsilyl-1-octene, we were disappointed to find it did not work at all. To induce the polarization of Si-C bond, we replaced one to three methyl(s) on Si by fluorine(s) and were pleased to find that mono- or difluorosilyl group was reactive enough (ref. 6).



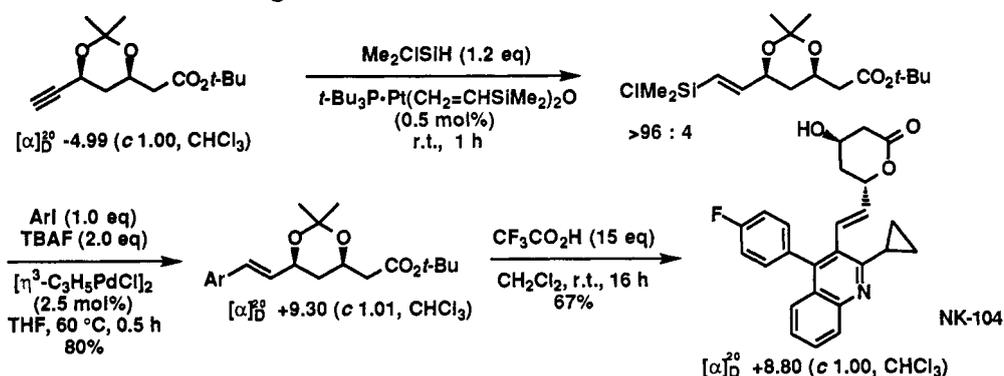
We were surprised to find that trifluorosilyl group was totally ineffective and assumed in this case an inactive hexacoordinated silicate was produced. In cases of mono- or difluorosilanes coordinatively unsaturated species, pentacoordinated silicate, would have been produced in so much as to undergo transmetalation effectively. Accordingly, it appears to be reasonable to assume that transmetalation proceeds through a four-centered transition state.



SYNTHETIC APPLICATIONS OF ALKENYL CROSS-COUPLING

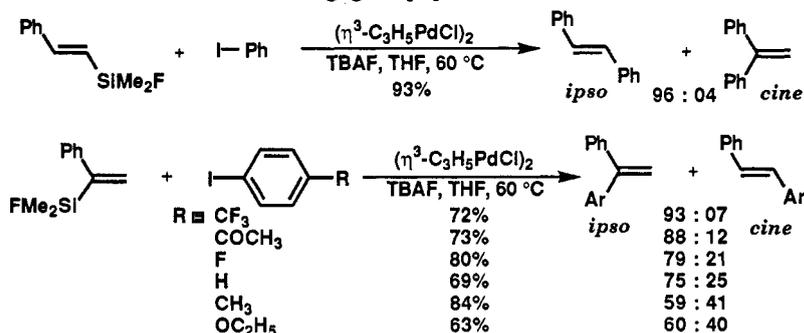
Many types of aryl and alkenyl halides can undergo cross-coupling with 1-monofluorosilyl-1-alkenes. Representative examples are conjugate diene synthesis. Reaction ($(\eta^3\text{-C}_3\text{H}_5\text{PdCl})_2$ (2.5 mol%), TASF (1.5 mol), THF, 50 °C) of (*E*)-1-octenyl(fluoro)dimethylsilane with (*E*)- or (*Z*)-iodoalkene gave (*E, E*)- or (*E, Z*)-dienes. (*Z*)-Octenylsilane turned out to be sluggish under the same conditions, but we soon could find that $\text{Pd}(\text{PPh}_3)_4$ (5 mol%) in DMF (50 °C) was highly effective to complete the reaction, and thus (*Z, E*) and (*Z, Z*)-dienes were obtained in synthetically useful yields with excellent stereochemical purities (ref. 6).

A successful application is the synthesis of artificial HMG-CoA reductase inhibitor. The starting acetylene was allowed to react with chlorodimethylsilane using Lappert-type Pt catalyst to afford (*E*)-alkenylsilane with selectivity over 96 : 4. Cross-coupling reaction of the alkenylchlorosilane with 2-cyclopropyl-3-iodo-4-(4-fluorophenyl)quinoline under the standard conditions using 2 mol eq of TBAF afforded the desired (*E*)-olefin in 80% isolated yield. Deprotection and lactonization afforded the target molecule, NK-104 (ref. 7).



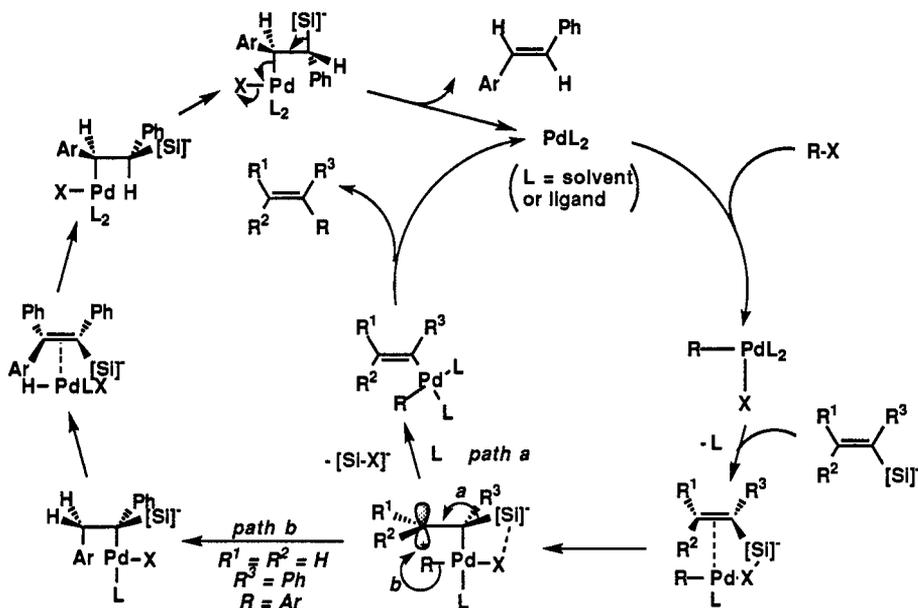
MECHANISM OF ALKENYL CROSS-COUPLING

When *trans*- β -fluorodimethylsilylstyrene was allowed to react with iodobenzene, in addition to the expected *trans*-stilbene (*ipso*-substitution product), we obtained a small amount of 1,1-diphenylethene (*cine*-substitution product). α -Silylstyrene gave a 75 : 25 mixture of *ipso*- and *cine*-substitution products. An electron-withdrawing group was found to favor the *ipso*-substitution, whereas an electron-donating group preferred *cine*-substitution (ref. 8).



Above observations suggest a mechanism that pentacoordinated silicate undergoes transmetalation with $\text{R-PdL}_n\text{-X}$. The halogen X of palladium complex can coordinate Si of the coordinatively unsaturated silicate to give a coordinatively saturated silicate. Interaction of the bivalent palladium with C=C bond followed by C-Pd bond formation would produce a β -cationic silicate wherein the C-Si σ -bond is electron-rich enough to promote elimination according to path *a* to give a palladium complex responsible for *ipso*-substitution products.

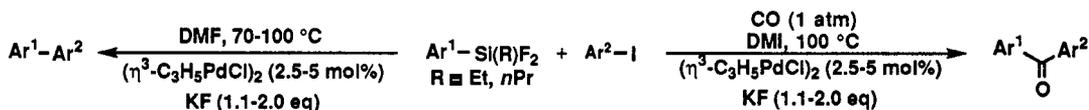
This pathway should be particularly facilitated by cation-stabilizing groups R^1 and/or R^2 and the negatively charged hexacoordinated silicate group (enhanced β -effect). The unusual behavior observed for the α -silylstyrene is ascribed to a 1,3-migration of R from palladium to β -carbon, *i.e.* path *b*.



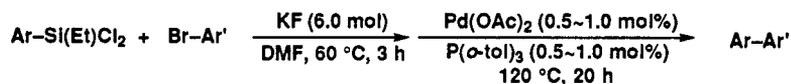
This migration should be favored particularly when the nucleophilicity of R is enhanced by an electron-donating substituent. Carbopalladation, β -elimination, hydropalladation, followed by retro-silyl-palladation give the *cine*-substitution product. The striking feature of organosilicon reagents is that the fully coordinated silicate involved in a catalytic cycle stabilizes effectively the β -cationic carbon to promote path *a* to give *ipso*-substitution product in many cases as exclusive products.

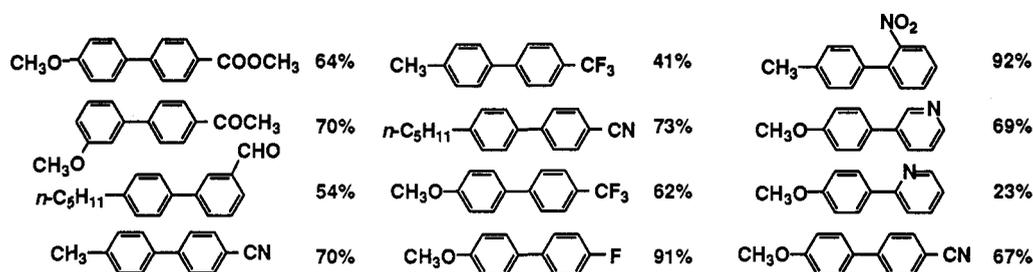
SYNTHESES OF BIARYLS AND DIARYL KETONES

Aryl-aryl coupling is successfully achieved using aryl(alkyl)-difluorosilanes, hereby alkyl group is a dummy ligand, preferably ethyl or propyl, because methyl group competitively underwent the coupling reaction. Herein TBAF, an extremely effective activator, could be replaced by KF. Thus, unsymmetrical biphenyls of various kinds are prepared. Both electron-donating and -withdrawing groups are compatible to the reaction. Again, high chemoselectivity is observed. When the coupling was carried out under carbon monoxide atmosphere in 1,3-dimethyl-2-imidazolidinone (DMI), carbonylative coupling took place to give unsymmetrical diaryl ketones (ref. 9).

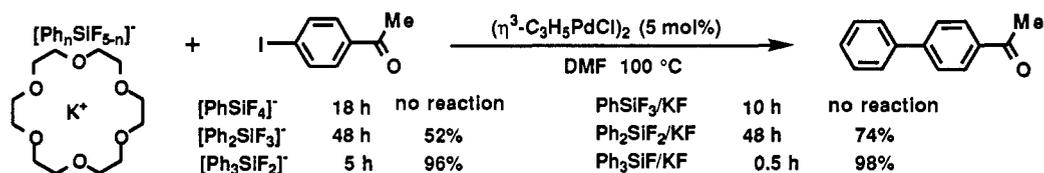


Recently we modified the biaryl synthesis using commercially available chlorosilane, aryl bromide, 2 mol of KF, $Pd(OAc)_2$ catalyst, and tri(*o*-tolyl)phosphine ligand. This process was applied to the synthesis of various unsymmetrical biphenyls shown below (ref. 10).



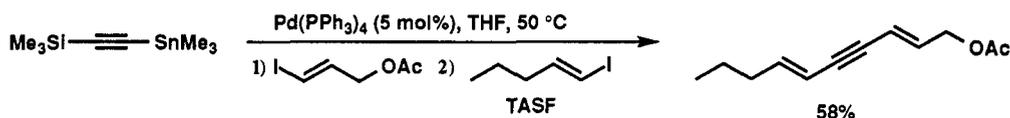


In order to get an insight into the mechanism of aryl-aryl coupling, we used 18-crown-6 complexed potassium phenylfluorosilicates for the reaction with *p*-iodoacetophenone. Although $[\text{PhSiF}_4]^-$ failed to give 4-acetylbiphenyl, $[\text{Ph}_2\text{SiF}_3]^-$ and $[\text{Ph}_3\text{SiF}_2]^-$ gave the biaryl in 52% and 96% yield, respectively. The reactivity order is exactly the same as that of the expected pentacoordinate silicates derived from the corresponding tetragonal phenylfluorosilanes and KF (ref. 11).



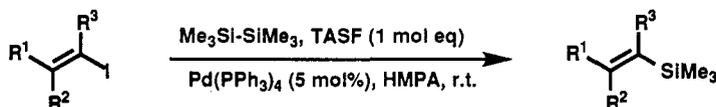
THREE COMPONENT COUPLING

Since organotin compounds undergo coupling reaction with a palladium catalyst, a substrate which contains both Me_3Sn and Me_3Si can couple sequentially with two different iodides using the same catalyst in a single flask. For example, 3-acetoxy-1-iodopropene reacted with trimethylsilyl(trimethylstannyl)ethyne in the presence of $\text{Pd}(\text{PPh}_3)_4$. After the first coupling was completed, (*E*)-1-iodo-1-pentene as well as TASF was added to effect the second coupling. Thus, an inhibitor of photosynthesis was prepared by one-flask reaction (ref. 12).

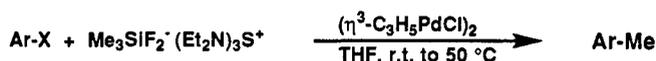


TRIMETHYLSILYLATION AND METHYLATION

Trimethylsilyl anion generated from hexamethyldisilane and TASF undergoes palladium-catalyzed silylation of iodo olefins. The reaction is stereospecific and thus allows us to prepare stereodefined vinylsilanes (ref. 13).

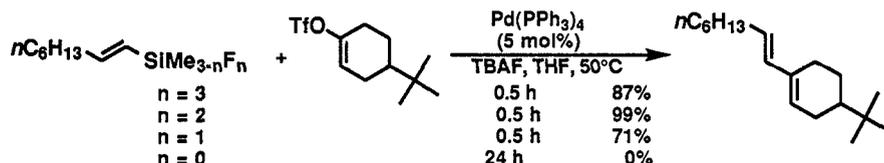


In the absence of organosilanes, TASF itself reacts as a coupling partner and methylates various aryl and vinyl iodides. This is another example that a well-characterized pentacoordinated silicate can undergo the coupling reaction.



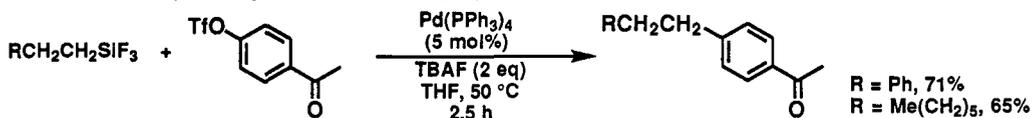
CROSS-COUPLING REACTION OF TRIFLATES

As a coupling partner, alkenyl triflates and aryl triflates are applicable. To find the optimum number of fluorine on silyl group, we studied the reactivity of 1-Me_{3-n}F_nSi-substituted 1-octene. Me₃Si was inactive but Me₂FSi, MeF₂Si and F₃Si groups could achieve the coupling reaction in the presence of Pd(PPh₃)₄ and TBAF at 50 °C. Of these three, F₂MeSi was proved to be the most reactive, and thus we studied the coupling reaction of various F₂MeSi-substituted alkenes with various triflates.



Coupling reaction of PhSiF₃, Ph₂SiF₂, or Ph₃SiF with the cyclohexenyl triflate afforded 4-*t*-butyl-1-phenylcyclohexene in 57% (2.5 h), 62% (2.5 h), or 0% (24 h) yield, respectively. Here again, difluorosilyl group turned out to be effective (ref. 15).

Furthermore, 4-acetylphenyl triflate could couple with alkyltrifluorosilanes. Noteworthy is that alkylsilanes having β -hydrogens could be employed for the coupling reaction. This type of reactions is currently being studied thoroughly.



STEREOCHEMISTRY OF CROSS-COUPLING OF ALKYL SILANE

When (*S*)-1-phenylethyltrifluorosilane of 34% ee was allowed to react with 4-acetylphenyl triflate, optically active 1-phenyl-1-(4-acetylphenyl)ethane was isolated. At 50 °C almost complete retention of configuration resulted but at higher temperatures the degree of retention gradually dropped linearly and finally inversion resulted above 75 °C (a in Fig. 1). Similar temperature dependency was observed in case of 3-formylphenyl triflate (b) also.

Solvent effect was obvious. The reaction of 4-acetylphenyl triflate with PhCH(Me)SiF₃ (38% ee, *S*) at 60 °C was retention (31% ee, *S*) in THF, but inversion (8% ee, *R*) in HMPA-THF (1 : 20). In DMF-THF (1 : 10) or DMSO-THF (1 : 10) still retention (16% ee, *S* in both cases) was observed but albeit of low level. Thus, in a nonpolar solvent retention resulted but in a polar solvent system inversion was the stereochemistry of the reaction path (ref. 16).

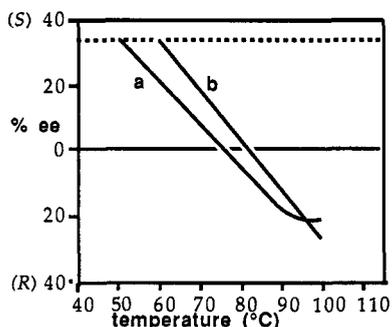
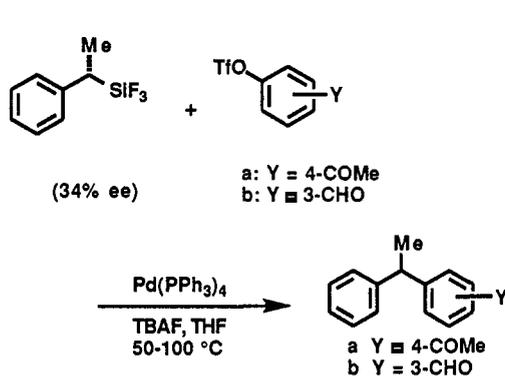
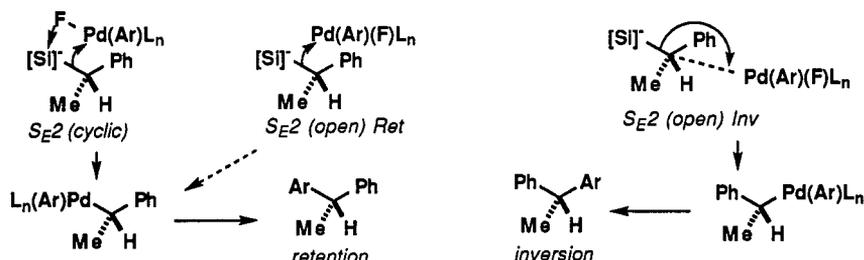


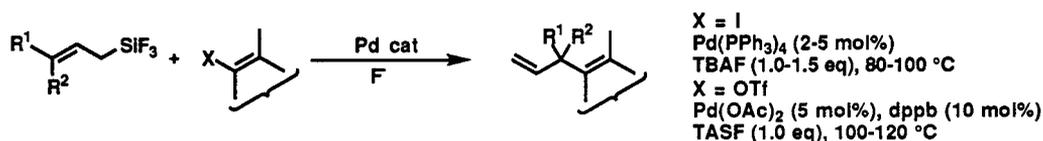
Fig 1. Temperature vs stereochemistry of cross-coupling of (*S*)-PhCH(Me)SiF₃ (34% ee) with a or b

According to the mechanism we discussed so far, fluorine-bridged S_E2 (cyclic), wherein the silicate moiety is originally pentacoordinate, appears to be the best model to explain retention at lower temperatures in THF. S_E2 (open) Ret model is less likely because it should be applicable to hexacoordinated silicate species. This is not our case. At higher temperatures or in polar solvents, the fluorine-silicon bridge would be cleaved to switch to S_E2 (open) Inv model.

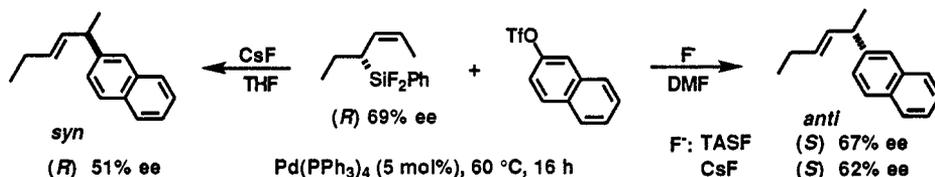


CROSS-COUPLING OF ALLYLTRIFLUOROSILANES

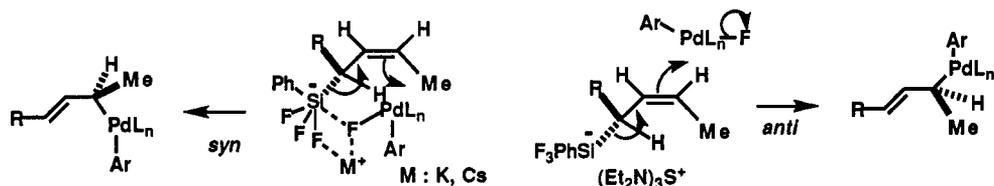
Cross-coupling of allyltrifluorosilanes with aryl iodide takes place at relatively high temperatures in the presence of $Pd(PPh_3)_4$ and TBAF, whereas with triflates with the aid of $Pd(OAc)_2$, diphenylphosphinobutane and TASF. That always γ -carbon reacts is remarkable. Accordingly, starting with 3-methyl-2-butenyltrifluorosilane, quarternary carbon at benzylic or allylic position is readily generated (ref. 17).



Using (*R,Z*)-3-difluorophenylsilyl-2-butene (69% ee), 2-naphthyl triflate, $Pd(PPh_3)_4$ catalyst, and TASF in DMF, we isolated (*S,E*)-2-(2-naphthyl)-3-hexene of 63% ee. Thus, the stereochemistry was proved to be *anti*. This is consistent to the S_E' reaction of allyltrimethylsilanes. When we replaced TASF by CsF , the stereochemical outcome was again *anti*, but the CsF mediated reaction in THF gave *syn*-coupled product. Thus, the solvent and salt effect was striking. To summarize these results, in a polar solvent DMF, the stereochemistry is always *anti*; in an less polar solvent THF with metal fluoride, the stereochemistry is *syn* (ref. 18).

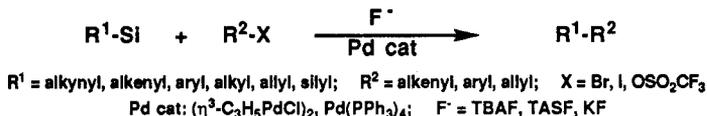


The *anti*-stereochemistry is easily explained by the transition state model shown below. The conformation with methyne hydrogen in a plane of double bond is the most preferred one, and $Pd(II)$ attacks the γ -carbon from *anti*-direction. Herein penta- or hexa-coordinate silicate should accelerate the electrophilic substitution. In contrast, when metal fluoride is present, a complex with Si-F-Pd bridge should be produced which intramolecularly undergoes S_E' reaction to give *syn*-coupled product.



CONCLUSION

Fluorosilanes used herein are readily prepared from the corresponding chlorosilanes, using NH_4F , $(\text{NH}_4)_2\text{SiF}_6$, CuF_2 , ZnF_2 or aq HF (48%). Various types of organochlorosilanes are available commercially. Alternatively these are readily accessible by hydrosilylation of olefins or acetylenes or by Pd-catalyzed silylation of aromatic halides or aroyl chlorides with chlorodisilanes. Accordingly, the Pd-catalyzed cross-coupling reaction of organosilicons will find wide applications particularly in industrial synthesis (ref. 19).



Acknowledgment: Thanks are due to all of my coworkers whose names are listed in the literature below.

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