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Metal-catalyzed silylation of  $sp^3C-H$  bondsBin Li<sup>a\*</sup> and Pierre H Dixneuf<sup>b\*</sup>Received 00th January 20xx,  
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Metal-catalyzed activations of inert  $sp^2C-H$  and  $sp^3C-H$  bonds have recently brought a revolution in the synthesis of useful molecules and molecular materials. Among them the catalytic silylation of  $sp^3C-H$  bonds has been developed due to the interest of the formed  $sp^3C-SiR_3$  silanes, stable organometallic species, for further functionalizations that  $sp^3C-H$  bonds cannot reach directly. Besides many examples of  $sp^2C-H$  bond catalytic silylations, metal-catalyzed silylations of  $sp^3C-H$  bonds have been mostly discovered during the last decade in spite of the  $sp^3C-SiR_3$  group high reactivity. This review will present all the methods of metal-catalyzed silylations of  $sp^3C-H$  bonds into  $sp^3C-SiR_3$  functions, discuss the catalytic mechanisms according to various metal-catalysts, and illustrate their applications in synthesis. The review describes successively the intermolecular  $sp^3C-H$  bond silylations directed first by N-containing heterocycles with silanes with various Ru, Rh, and Ir catalysts and then directed by an amide type function with Pd(II) catalyst and  $R_3Si-SiR_3$  reagent. The catalytic intramolecular silylations of  $sp^3C-H$  bonds can be performed after catalytic formation of  $CH-OSiR_2H$  or  $CH-N(R)SiR_2H$  groups from alcohols, ketones, esters, or amine NH bonds by catalytic hydrosilylation with  $R_2SiH_2$ . Both catalytic processes can be performed with Ir(I) and Rh(I) catalysts with an alkene to capture the formed  $H_2$ . This reaction with Rh(I) and Ir(I) catalysts can be applied to the formation of 5-membered cyclic silanes from aryl silanes and from alkyl silanes arising from hydrosilylated terminal  $C=C$  bonds of alkenes. Oxidation of the cyclic silane derivatives easily leads to 1,3- and 1,4-diols, from alcohol or ketone precursors and to 1,2-amino alcohols from amines. Several methods show how to transform various heteroatom-methyl groups  $X-CH_3$ : B- $CH_3$ , O- $CH_3$ , Si- $CH_3$ , N- $CH_3$ , Ge- $CH_3$  and S- $CH_3$  into their reactive functionalized  $X-CH_2SiR_3$  group, using various Ru(0), Ir(I), pincer-Ru(II), or Y catalysts. Examples are shown of catalytic transformations of allylic moiety  $CH_3-C(R)=CH_2$  into their silylated  $CH_2=C(R)-CH_2SiR_3$  form via i) Pd(II) allyl activation, ii) silyl radical generation with photocatalyst and iii) dual Ir(I) and Fe(II) catalysts for hydrosilylation of alkanes, via alkene formation, isomerization and hydrosilylation. Finally a Ru(II)-catalyzed  $sp^3C-H$  silylation of a methyl group of arylphosphine, directed by P(III) atom, will be presented.

## 1. Introduction

During the last two decades metal-catalyzed activation and functionalization of C-H bonds have tremendously improved the syntheses of a variety of functional useful molecules and molecular materials, often via cross-couplings of C-C bonds with better atom economy.<sup>1-13</sup> Due to the high reactivity of C-SiR<sub>3</sub> bonds efforts have been recently made to regioselectively transform C-H bonds into more reactive and versatile C-Si bonds via successive metal-catalyzed C-H bond activation and silylation. The C-Si bonds are used as temporary functional groups to further promote transformations leading to molecules difficult to reach directly from C-H bonds. In addition C-Si bonds are rather stable thus the formed silanes can tolerate functional groups and be handled more easily than many reactive organometallic derivatives containing a more polar C-M bond.

The regioselective catalyzed silylations of  $sp^2C-H$  bonds into  $sp^2C-SiR_3$  groups has been first developed and several reviews already

illustrate the successes of catalyzed silylation of  $sp^2C-H$  bonds and the usefulness of this approach. Chatani in 2003<sup>14</sup> and Goldman in 2011<sup>15</sup> have discussed early examples of silylation of  $sp^2C-H$  bonds with ruthenium and iridium catalysts. Marciniec in 2005<sup>16</sup> has gathered the catalyzed silylations of alkene C-H bonds and in 2012<sup>17</sup> Hartwig has compared borylations and silylations of  $sp^2C-H$  bonds. In 2015 several reviews on catalytic silylation of  $sp^2C-H$  bonds were presented by J. F. Hartwig<sup>18</sup>, U. Sharma<sup>19</sup>, C. Wang<sup>20</sup>, and Z. Xu<sup>21</sup>, and the three first of them<sup>18-20</sup> included the first examples of catalyzed  $sp^3C-H$  bond silylations. Shang and Liu<sup>22</sup> gathered in 2016 the silylations of  $sp^2C-H$  bonds via radical processes. Noteworthy M. Oestreich has presented in 2017 all the Friedel-Crafts  $sp^2C-H$  bond silylations,<sup>23</sup> and recently he reviewed the various emerging strategies for C-H bond silylations, and briefly discussed the  $sp^3C-H$  bond silylations.<sup>24</sup>

In spite of the usefulness in synthesis of reactive  $sp^3C-Si$  bonds<sup>25</sup> their catalytic formations directly from  $sp^3C-H$  bonds has been much less developed than from  $sp^2C-H$  bonds. However  $sp^3C-SiR_3$  groups allow their easy transformation by oxidation into alcohols<sup>26-27</sup> or into carboxylates directly from  $CO_2$ <sup>28</sup>. They also give cross-coupling reactions with suitable electrophiles<sup>29-30</sup>, amination<sup>31-32</sup> or halogenation<sup>33-34</sup> including fluorination.<sup>35-36</sup> In addition the direct catalytic formation of a reactive  $sp^3C-Si$  bond directly from a  $sp^3C-H$  bond offers a greener alternative to produce reactive silanes rather

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than from silylhalides, from lithium or grignard reagents or from hydrosilanes with alkylchlorides.<sup>25</sup>

This review will present the known metal-catalyzed  $sp^3C-H$  bond silylations, discuss the catalytic mechanisms, and show the usefulness of the produced silane derivatives. Some early examples obtained in 2014 and before have been presented in the early 2015 reviews by J. F. Hartwig<sup>18</sup>, U. Sharma<sup>19</sup>, C. Wang<sup>20</sup>. After pointing out these first examples this review will discuss in more details all recent examples of metal-catalyzed  $sp^3C-H$  bond silylations since 2015. The following sequence will be used to present the successful examples and will focus on the recent updates.

-After a few early and non directed examples of  $sp^3C-H$  bond silylations, the metal-catalyzed *intermolecular* silylations of  $sp^3C-H$  bonds with silane directed by N-containing heterocycles, which take place mostly with Ir, Rh, Ru catalysts, and the metal-catalyzed *intermolecular* silylations of  $sp^3C-H$  bonds directed by amide type groups with Pd(II) catalysts, will be described first.

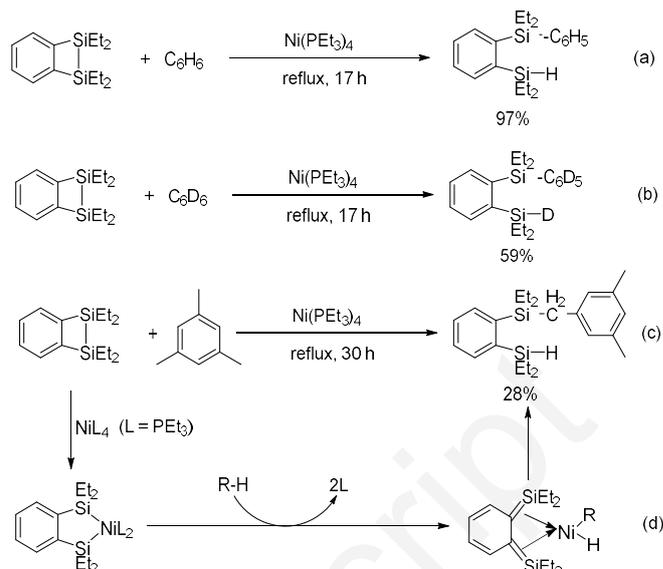
-Then will be presented successively i) the catalyzed *intramolecular* silylations of  $sp^3C-H$  bonds directed by silylated hydroxy group, resulting from dehydrosilylation of alcohols, or hydrosilylation of ketones, with Ir(I) or Rh(I) catalysts, ii) the catalyzed *intramolecular*  $sp^3C-H$  bond dehydrosilylation directed by N-SiR<sub>2</sub>H groups with Ir(I) catalyst and hydrogen acceptor and iii) the *intramolecular* silylations of unactivated  $sp^3C-H$  bonds but in proximity with Si-H bonds of arylsilanes and alkylsilanes with Ir(I) catalyst.

-The *intermolecular* catalyzed  $sp^3C-H$  bond silylations of X-CH<sub>3</sub> groups into X-CH<sub>2</sub>SiR<sub>3</sub> groups (X = B, Si, O, N, Ge, S), will be then discussed. They are mostly promoted by Ru(II) and Ir(I) catalysts in the presence of alkene, with the exception of Yttrium catalyst for SCH<sub>3</sub> group silylation and Copper catalysts for alkylsulfonamide silylation. Finally formal silylations of allylic C-H bonds and the unique and promising example of catalyzed methyl  $sp^3C-H$  bond silylation directed by phosphine will be presented.

## 2. The first steps in non directed catalytic silylations of $sp^3C-H$ bonds

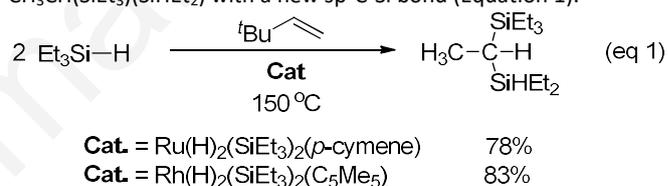
The first examples of catalytic silylation of a  $sp^3C-H$  bond were observed without the assistance of a directing group, but with modest efficiency. As early as 1992 Ishikawa *et al.*<sup>37</sup> studied the Ni(0)-catalyzed transformation of benzo-1,2-disilacyclobutene and observed the activation/cleavage of benzene  $sp^2C-H$  and mesitylene  $sp^3C-H$  bonds to form related C-Si bonds (Scheme 1).

The benzo-1,2-disilacyclobutene with Ni(PEt<sub>3</sub>)<sub>4</sub> catalyst in refluxing benzene led to the cleavage of one benzene  $sp^2C-H$  bond and to the formation of one Si-C( $sp^2$ ) and one Si-H bonds (Scheme 1a). The same reaction performed in deuterated benzene led to the disilyl product with Si-C<sub>6</sub>D<sub>5</sub> and Si-D bond formation (Scheme 1b). By contrast the use of mesitylene as solvent led to one methyl  $sp^3C-H$  bond activation and then silylation with formation of Si-C( $sp^3$ ) and Si-H (Scheme 1c). The catalytic functionalization of C-H and C-D bonds are explained via their oxidative addition to disilyl-Nickel intermediate followed by formation Si-C and Si-H bonds (Scheme 1d).

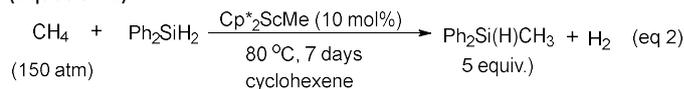


**Scheme 1.** Ni(0)-catalyzed silylation of  $sp^3C-H$  bond with benzo-1,2-disilacyclobutene.

In 1994 an example of  $sp^3C-H$  bond silylation was observed by Berry *et al.*,<sup>38</sup> in their study of hydrosilylation of an alkene <sup>t</sup>BuCH=CH<sub>2</sub> with Et<sub>3</sub>SiH in the presence of Ru and Rh catalyst at 150 °C. Actually they observed besides the low production of silylated alkene, the high yield of dihydrogenative dimerization of 2 Et<sub>3</sub>SiH into CH<sub>3</sub>CH(SiEt<sub>3</sub>)(SiHET<sub>2</sub>) with a new  $sp^3C-Si$  bond (Equation 1).



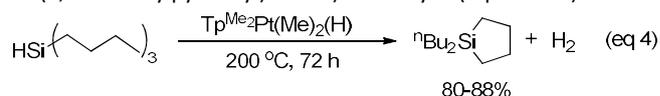
Another unique non directed silylation of  $sp^3C-H$  bond was observed by Don Tilley<sup>39</sup> in 2003 during the reaction of methane (150 atm) with H<sub>2</sub>SiPh<sub>2</sub> at 80 °C with Scandium catalyst Cp\*<sub>2</sub>ScMe (Equation 2).



Cp\*<sub>2</sub>ScSiH<sub>2</sub>Mes has been shown to react with CH<sub>4</sub> to give Cp\*<sub>2</sub>SiCH<sub>3</sub> and MesSiH<sub>3</sub> and then Cp\*<sub>2</sub>ScH and MesSi(CH<sub>3</sub>)H<sub>2</sub> (Equation 3) but it is not clear yet which species Cp<sub>2</sub>\*ScSiH<sub>2</sub>Mes or Cp<sub>2</sub>\*Sc-H activates the methane C-H bond before silylation.



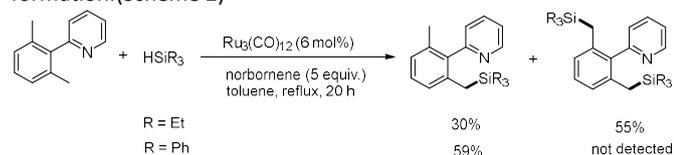
Hartwig in 2005 developed the first *intramolecular* dehydrogenative regioselective coupling of a silane Si-H bond with aliphatic  $\delta$ -C-H bond to generate the 5-membered cyclic organosilane in 80-88% yield by using Tp<sup>Me2</sup>PtMe<sub>2</sub>H (Tp<sup>Me2</sup> = hydrido tris(3,5-dimethylpyrazolyl)borate) as catalyst. (Equation 4)<sup>40</sup>



It was the first observation of a three step process: initial formation of a Si-Metal bond from Si-H bond, activation by the Metal site of one  $sp^3C-H$  bond coming at its proximity followed by Si-C bond formation.

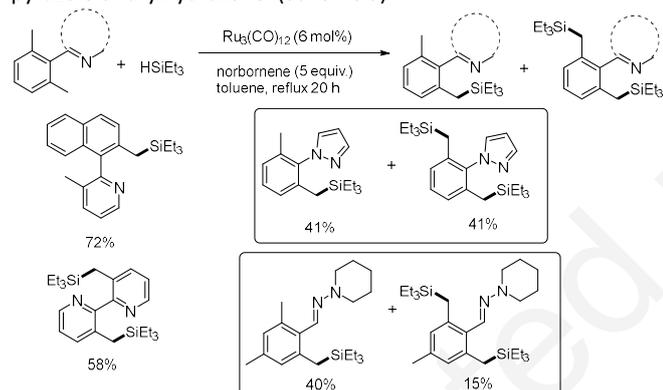
### 3. Metal-catalyzed intermolecular silylations of sp<sup>3</sup>C-H bonds directed by N-containing heterocycles.

An early example of catalytic sp<sup>3</sup>C-H bond silylation directed by pyridine was reported by Chatani in 2004.<sup>41</sup> Ru<sub>3</sub>(CO)<sub>12</sub> was shown to catalyze benzylic silylation with triethylsilane of 2-arylpyridines containing a methyl group at aryl *ortho* position only, not at *para* position, thus showing the directing role of pyridine nitrogen atom. The reaction took place in toluene at reflux in the presence of norbornene for hydrogen capture with norbornane formation. (Scheme 2)<sup>41</sup>



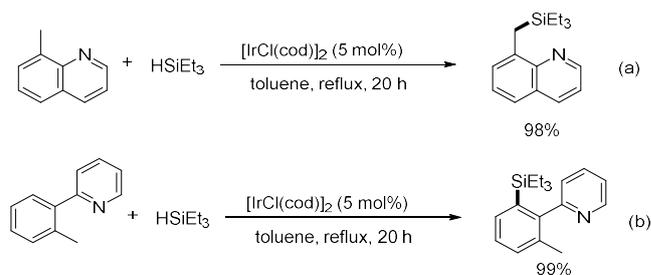
**Scheme 2.** Ru(0) catalyzed silylation of sp<sup>3</sup>C-H bond directed by pyridine.

However the silylation of an aryl *ortho* sp<sup>2</sup>C-H bond is faster than that of an *ortho* methyl sp<sup>3</sup>C-H bond with HSiEt<sub>3</sub> and the silylation of an *ortho* ethyl group of arene does not take place. Under similar conditions the silylation of *ortho* methyl groups of arenes can be directed by other N-containing heterocycles such as quinoline, pyrazole or arylhydrazone. (Scheme 3)<sup>41</sup>



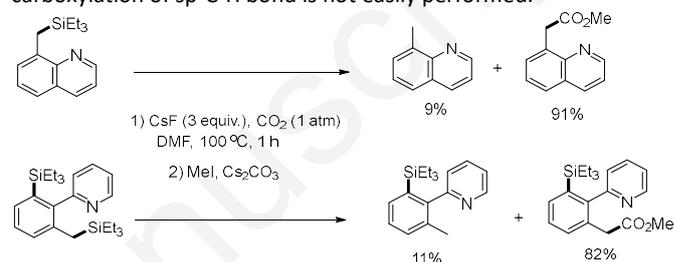
**Scheme 3.** Ru(0) catalyzed silylation of sp<sup>3</sup>C-H bonds directed by N-heterocycles.

In 2012 Sato *et al.*<sup>42</sup> showed that [IrCl(COD)]<sub>2</sub> could catalyze the regioselective silylation of sp<sup>3</sup>C-H bonds of arene methyl groups directed by quinolone but this time without the presence of the hydrogen trap norbornene (Scheme 4 (a)).<sup>42</sup> Ru<sub>3</sub>(CO)<sub>12</sub> catalyst led to the same product in 93% under similar conditions but in the presence of norbornene. It is shown that with this Ir(I) catalyst the *ortho* aryl sp<sup>2</sup>C-H bond silylation is faster than that of a sp<sup>3</sup>C-H bond when it is directed by pyridine, likely because of a more easily generated 5-membered metallacycle intermediate with respect to the 6-membered intermediate required for *ortho* methyl activation (Scheme 4 (b)).<sup>42</sup>



**Scheme 4.** Catalytic benzylic C(sp<sup>3</sup>)-H silylation with Ir(I) catalyst directed by pyridine group.

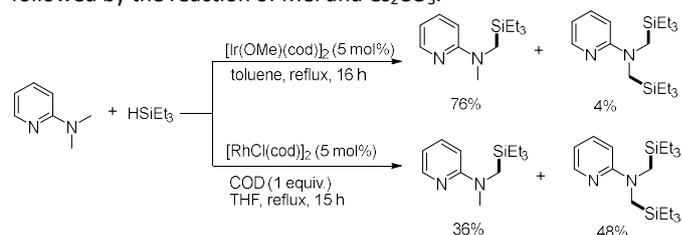
The importance of the sp<sup>3</sup>C-H benzylic silylation was shown by Sato<sup>42</sup> for the direct access to carboxylates from the silylated products by action of CO<sub>2</sub> in the presence of fluoride, whereas the sp<sup>2</sup>C-Si bond is inert toward carboxylation (Scheme 5).<sup>42</sup> This reaction motivates the search for benzylic silylation when the direct carboxylation of sp<sup>3</sup>C-H bond is not easily performed.



**Scheme 5.** Carboxylations of silylated benzyl groups with CO<sub>2</sub>.

Sato has also shown that Ir(I) and Rh(I) catalysts [Ir(OMe)(COD)]<sub>2</sub> and [RhCl(COD)]<sub>2</sub> were able in the presence of HSiEt<sub>3</sub> to silylate a sp<sup>3</sup>C-H bond of a methyl group bonded to the nitrogen atom of 2-dimethylaminopyridine, thus directed by pyridine nitrogen itself (Scheme 6).<sup>43</sup> The Rh(I) catalyst operates only in the presence of the additive cyclooctadiene COD (1 equiv.) to eliminate the formed hydrogen whereas the later is not needed with the Ir(I) catalyst which is then not deactivated by in situ generated hydrogen.

However, the Rh(I) catalyst is more active for the silylation of N-H bond than of NCH<sub>3</sub> C-H bond of 2-methylaminopyridine.<sup>43</sup> The resulting N-CH<sub>2</sub>SiEt<sub>3</sub> groups can also be transformed into the carboxylate group N-CH<sub>2</sub>CO<sub>2</sub>Me on reaction with CO<sub>2</sub> and CsF followed by the reaction of MeI and Cs<sub>2</sub>CO<sub>3</sub>.<sup>43</sup>

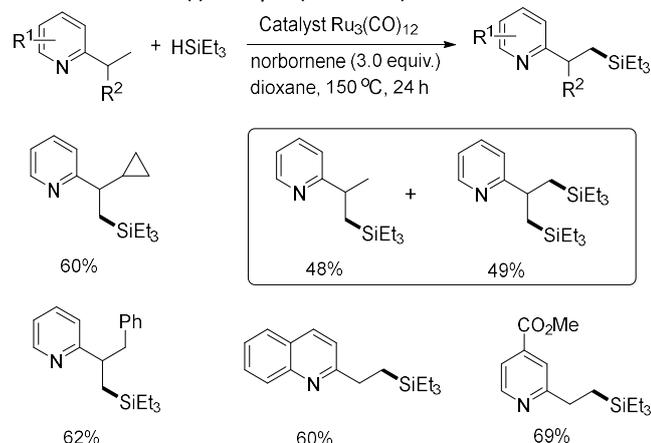


**Scheme 6.** Ir(I) and Rh(I) catalyzed silylation of C(sp<sup>3</sup>)-H bonds adjacent to a nitrogen atom and directed by pyridine.

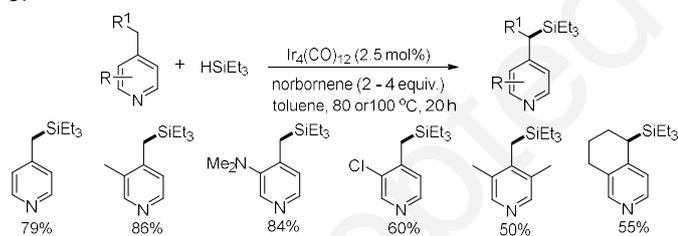
Sato also showed that the same catalyst [Ir(OMe)(COD)]<sub>2</sub> could promote the silylation with HSiEt<sub>3</sub> of the alkyl group at *beta* carbon of 2-ethyl and 2-isopropyl pyridine but with low yield, 20 and 34% respectively.<sup>43</sup>

By contrast using the Ru<sub>3</sub>(CO)<sub>12</sub> catalyst Jingsong You in 2016<sup>44</sup> succeeded to activate and silylate sp<sup>3</sup>C-H bonds of the alkyl group of 2-alkyl pyridines at the *beta* carbon in the presence of 3 equiv. of norbornene as hydrogen trap (Scheme 7).<sup>44</sup> The reaction shows that the silylation is favoured at alkyl *beta* carbon position and tolerates

functional groups on the pyridine ring (OMe, CO<sub>2</sub>R, Ph). Mechanism studies reveal that sp<sup>3</sup>CH bond cleavage is reversible and not the rate-determining step<sup>44</sup>. However this catalytic system was not operative for the sp<sup>3</sup>CH silylation of 2-dimethylaniline as previously described with Rh(I) catalyst. (Scheme 6)<sup>43</sup>

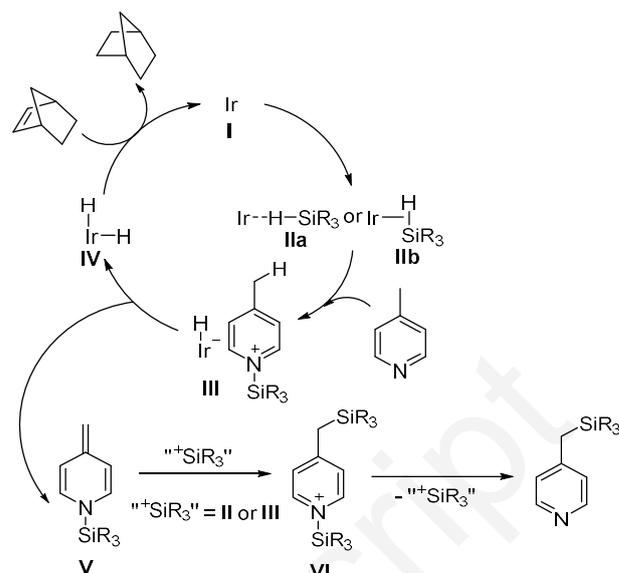


Chatani in 2017<sup>45</sup> has succeeded to silylate the sp<sup>3</sup>CH bond of methyl groups at the *para* position of pyridine derivatives. Ir<sub>4</sub>(CO)<sub>12</sub> was used as catalyst precursor with HSiEt<sub>3</sub> and in the presence of norbornene in toluene at 80-100 °C (Scheme 8).<sup>45</sup> The reaction does not involve silylation of methyl at 3-position. It tolerates -NMe<sub>2</sub>, -Cl, -Br, -OMe groups on the pyridine and is regioselective at the *alpha* carbon of the alkyl chain. The silylation of 2,4-dimethyl pyridine requires more drastic conditions (120 °C, 48h) to produce 12% of silylated product at 4-Methyl group. Pyridine does not play the directing group role in that case but favours the 4-alkyl sp<sup>3</sup>C-H bond activation by deprotonation as shown in the mechanism on scheme 9.<sup>45</sup>



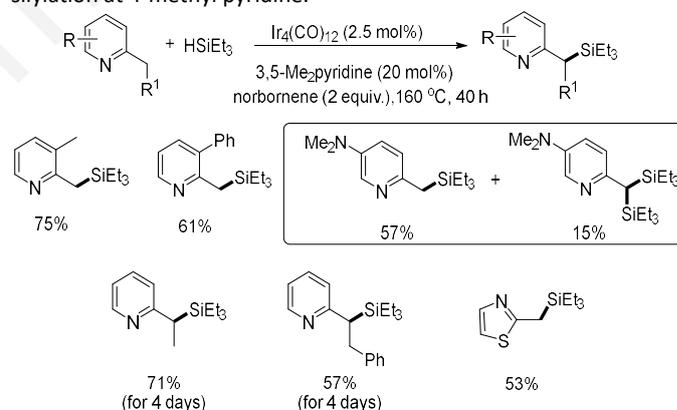
Beside Ir<sub>4</sub>(CO)<sub>12</sub>, Ir(acac)(CO)<sub>2</sub> is also active at 80 °C (20h) for the same reaction to produce 74% of 4-triethylsilylmethylpyridine with 15% of disilylated compound. [Ir(OMe)(COD)]<sub>2</sub> is also operative but under one atmosphere of carbon monoxide.

The proposed mechanism by Chatani (Scheme 9)<sup>45</sup> is based on deuteration studies with DSiEt<sub>3</sub>. It suggests initial oxidative addition of the H-Si bond to the Ir(0) species **I** derivative of Ir<sub>4</sub>(CO)<sub>12</sub> which leads to a [Ir-H]<sup>-</sup> species and silylation of the pyridine nitrogen **III**. The [Ir-H]<sup>-</sup> hydride deprotonates the 4-methyl group to give the enamine **V** which is silylated to give the intermediate **VI** which then affords the 4-silylmethyl pyridine. The *in situ* formation of IrH<sub>2</sub> species **IV** allows the insertion of the norbornene double bond and reductive elimination to produce norbornane and to regenerate the Ir(0) catalytic species.<sup>45</sup>



**Scheme 9.** Proposed mechanism for Ir<sub>4</sub>(CO)<sub>12</sub> catalyzed silylation of 4-alkyl pyridines.

By contrast Chatani recently described the catalytic sp<sup>3</sup>CH bond regioselective silylation at the benzylic position of 2-alkylpyridines leading only to 2-(1-silylalkyl)pyridines. The silylation is performed with HSiEt<sub>3</sub> and Ir<sub>4</sub>(CO)<sub>12</sub> as catalyst in the presence of norbornene as hydrogen trap but in the presence of 3,5-dimethylpyridine ligand (Scheme 10).<sup>46</sup> Thus the 3,5-dimethylpyridine modifies strongly by coordination the Ir(0) catalyst which without this ligand favours silylation at 4-methyl pyridine.<sup>45</sup>



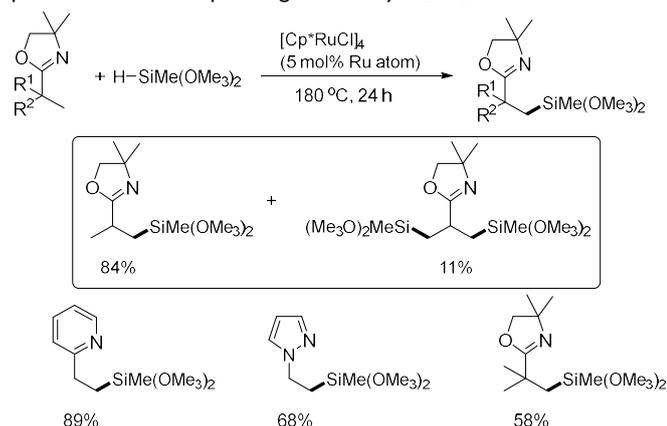
**Scheme 10.** Ir<sub>4</sub>(CO)<sub>12</sub> catalyzed benzylic sp<sup>3</sup>C-H bond silylation of 2-alkylpyridine.

A mechanism similar to that described in Scheme 9 is proposed for this reaction and based on the initial formation of [Ir-H]<sup>-</sup> and (pyridine)N-SiEt<sub>3</sub><sup>+</sup> cation, then on the deprotonation of 2-methylpyridine methyl group and silylation of the resulting methylene group.

Several other catalytic dehydrogenative silylations of sp<sup>3</sup>C-H bonds have been directed by the nitrogen atom of heterocycles such as oxazolines, azoles and quinolines with Ru(II), Ir(III) and Ru(III) respectively, for which the nature of key ligands on the metal catalysts play a crucial role.<sup>47-49</sup>

An excellent example was described by Murata<sup>47</sup> in 2016 who showed that the oxazoline nitrogen atom could direct the silylation of sp<sup>3</sup>C-H bond of the 2-alkyl group but regioselectively at the  $\beta$ -

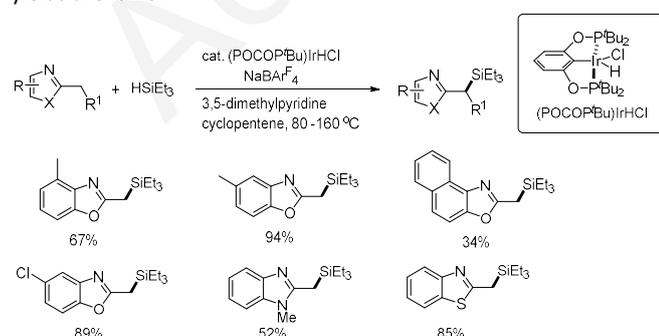
carbon atom. The reaction is performed only efficiently with  $\text{HSiMe}(\text{OSiMe}_3)_2$  in the presence of a Ru(II) catalyst  $[\text{Cp}^*\text{RuCl}]_4$  at 180 °C in cyclohexane. The Ru(III) derivatives  $[\text{Cp}^*\text{RuCl}_2]_2$  and  $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$  also display a rather good catalytic activity for this reaction which also allows disilylation at the alkyl  $\beta$ -carbon atoms. (Scheme 11)<sup>47</sup> However the nature of the silane is crucial as  $\text{HSiEt}_3$  and  $\text{HSiMe}_2(\text{OMe})$  are not efficient for this reaction. The silylation can be extended efficiently to 2-ethylpyridine (89%) and 1-ethylpyrazole (68%). The interest of the  $\beta$ -silylated 2-ethylpyridine is demonstrated using the Fleming-Tamao oxidation reaction with  $\text{H}_2\text{O}_2/\text{KHF}_2$  which produced the corresponding alcohol  $\text{PyCH}_2\text{CH}_2\text{OH}$ .



**Scheme 11.** Ru(II)-catalyzed  $\text{sp}^3\text{C-H}$  silylation at  $\beta$ -carbon of 2-alkyloxazolines.

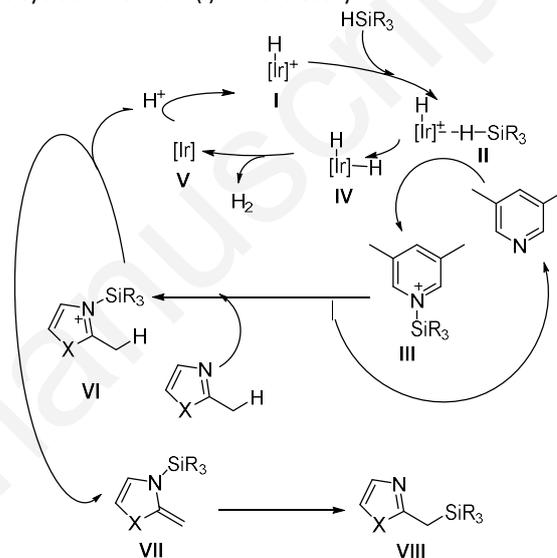
To understand the mechanism DFT calculations were made using  $\text{HSiMe}_3$  and Ru-H as the initial reagents.<sup>47</sup> They showed the easy interaction of one  $\beta$ -C-H bond with H-Ru-N(heterocycle) intermediate to eliminate  $\text{H}_2$  and to form a Ru(II)-cyclometalate. By contrast the oxidative addition of the H-Si bond to the (cyclometalate)Ru species and  $\beta$ -Carbon silylation require higher energy ( $\Delta G^\ddagger = 35.9 \text{ kcal. Mol}^{-1}$ ).

By contrast Fukumoto and Chatani in 2018 using a pincer H-Ir(III) catalyst showed that the  $\alpha$ - $\text{sp}^3\text{C-H}$  bond silylation of 2-alkyl-1,3-azoles was readily performed in the presence of cyclopentene, 3,5-dimethylpyridine ligand, but also of the salt  $\text{NaB}(\text{C}_6\text{F}_5)_4$  or  $\text{NaB}(\text{C}_6\text{H}_3(\text{CF}_3)_2)_4$  containing non coordinating anion (Scheme 12).<sup>48</sup> The silylation is performed with  $\text{HSiEt}_3$ . By contrast when  $\text{HSiEt}_2\text{Me}$  or  $\text{HSiEtMe}_2$  are used the disilylation of the  $\alpha$  carbon is favored. It is observed that when the azole nitrogen is sterically hindered the yields are lower.



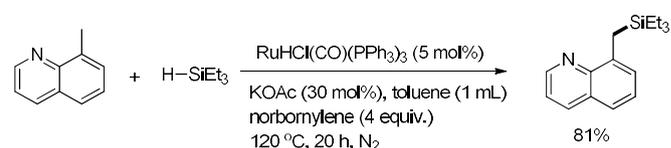
**Scheme 12.** Pincer hydride-Ir(III)-catalyzed silylation of 2-alkyl azoles at alkyl  $\alpha$ -carbon.

The plausible mechanism in the absence of hydrogen trap is shown on scheme 13.<sup>48</sup> The  $[\text{Ir-H}]^+$  species arising from chloride displacement of the pincer Ir(III) complex in the presence of a bulky coneranion is expected to trap the silane hydride to give the  $(\text{H})_2\text{Ir}(\text{III})$  intermediate (IV) and the N-silylated 3,5-dimethylpyridine cation III can transfer the  $\text{R}_3\text{Si}^+$  cation to the azole nitrogen forming (VI) thus favoring the methyl deprotonation to give VII. The migration of the silyl group to the methylene carbon affords the silylated product VIII. The catalytic species I is regenerated by protonation of Ir(I) intermediate V with the cationic compound VI. In the presence of alkene (cyclopentene) as  $\text{H}_2$  trap a similar mechanism takes places but alkene inserts into one Ir-H bond of IV to give alkyl-Ir-H intermediate which after reductive elimination offers cycloalkane and Ir(I) V more easily.



**Scheme 13.** A plausible reaction mechanism in the absence of alkene as a hydrogen acceptor.

Finally during the evaluation of  $\text{sp}^2\text{C-H}$  silylation of 2-aryl *N*-heterocycles with  $\text{HSiEt}_3$  in the presence of norbornylene, as hydrogen acceptor, and with the efficient Ru(II) catalyst  $\text{RuH}(\text{Cl})(\text{CO})(\text{PPh}_3)_3/\text{KOAc}$ , Bin Li<sup>49-51</sup> showed in 2019 that the silylation conditions applied to 8-methylquinoline preferentially led to the  $\text{sp}^3\text{C-H}$  bond silylation of the 8-methyl group (Scheme 14).<sup>49</sup> For this reaction the role of KOAc is crucial to generate a Ru(H)(OAc) intermediate on which oxidative addition of H-SiR<sub>3</sub> bond is possible.

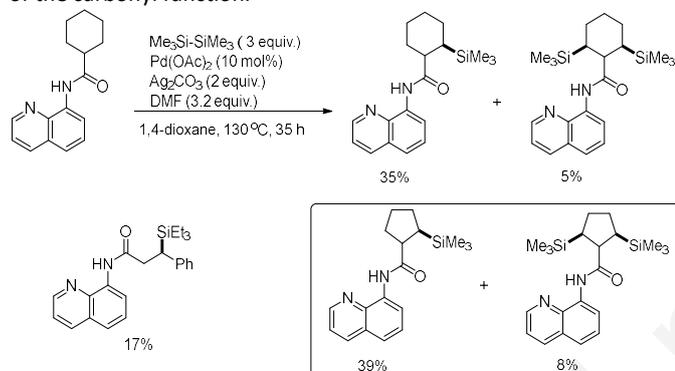


**Scheme 14.**  $\text{sp}^3\text{C-H}$  bond silylation with H-SiEt<sub>3</sub> of 8-methylquinoline with a Ru(II) catalyst.

#### 4. Palladium(II) catalyzed intermolecular silylations of $sp^3C-H$ bonds with amide type directing groups.

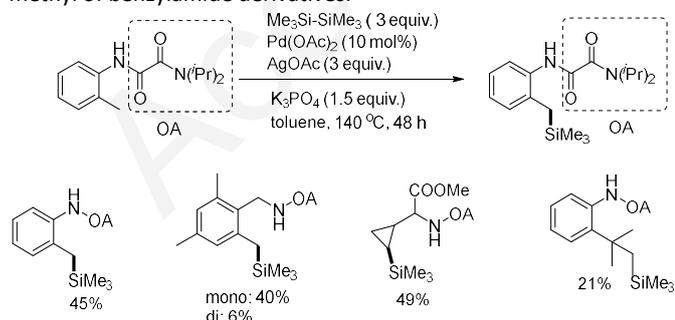
Since 2014 several reports gave evidence that amide functions  $RNHCO-alkyl$ ,  $R_2NCOCONH-alkyl$  or  $ArCONH-alkyl$  could direct metal catalyzed silylations via directed alkyl  $sp^3C-H$  bond activation and *intermolecular* silylation with  $R_3Si-SiR_3$ . The metal catalysts are based mostly on Palladium(II) catalysts  $Pd(OAc)_2$  or  $Pd(OPiv)_2$ . One rare example of  $\alpha$ -silylation of benzamides with  $tBuMgCl/dtbpv$  will be also presented but it involves a [1,5]-hydrogen transfer.

Kuninobu and Kana<sup>52</sup> were the first to report in 2014 that the simple  $Pd(OAc)_2$  catalyst could promote the silylation of aryl  $sp^2C-H$  bonds of  $RNHCO-aryl$  with  $R_3Si-SiR_3$ . At the same time they showed a few examples of alkyl  $sp^3C-H$  bond silylation with  $Me_3Si-SiMe_3$  of carboxamides directed by 8-aminoquinoline in (heteroaryl) $NHCO-alkyl$  derivatives with  $Pd(OAc)_2$  catalyst and  $Ag_2CO_3$  in DMF (Scheme 15)<sup>52</sup> These 8-aminoquinoline derivatives were able to direct  $sp^3C-H$  bond activation and functionalization of the alkyl group at  $\beta$ -carbon of the carbonyl function.



**Scheme 15.**  $Pd(OAc)_2$  catalyzed  $sp^3C-H$  silylation of carboxamide alkyl groups with hexamethyldisilane.

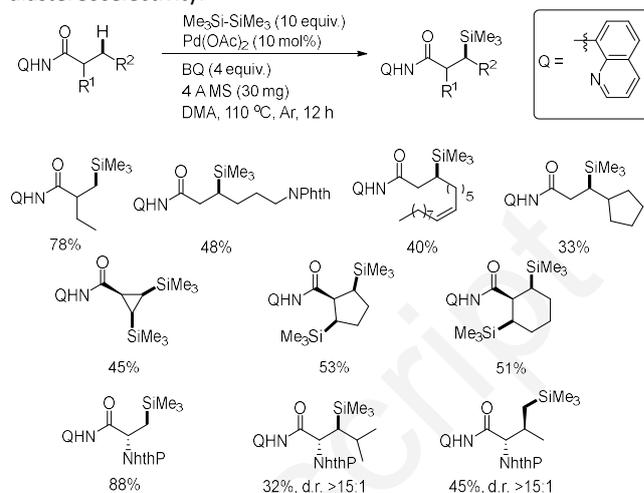
Just after, Y. Zhao<sup>53</sup> reported in 2015 that the oxalyl amide group could favour the  $sp^3C-H$  bond silylation, with  $Me_3Si-SiMe_3$  and  $Pd(OAc)_2$  catalyst of alkyylanilines in the presence of 3 equiv.  $AgOAc$  and  $K_3PO_4$  at 140 °C (Scheme 16).<sup>53</sup> The oxalyl amide group thus directs  $sp^3C-H$  bond activation with  $Pd(OAc)_2$ . The silylation takes place at the *ortho* methyl group of *ortho* methylaniline derivatives or of the cyclopropyl group of amide ester group. The  $\delta$ -silylation takes place when no hydrogen is present at  $\gamma$ -position or at the *ortho* methyl of benzylamide derivatives.



**Scheme 16.** Palladium catalyzed  $sp^3C-H$  silylation with oxalyl amide directing groups.

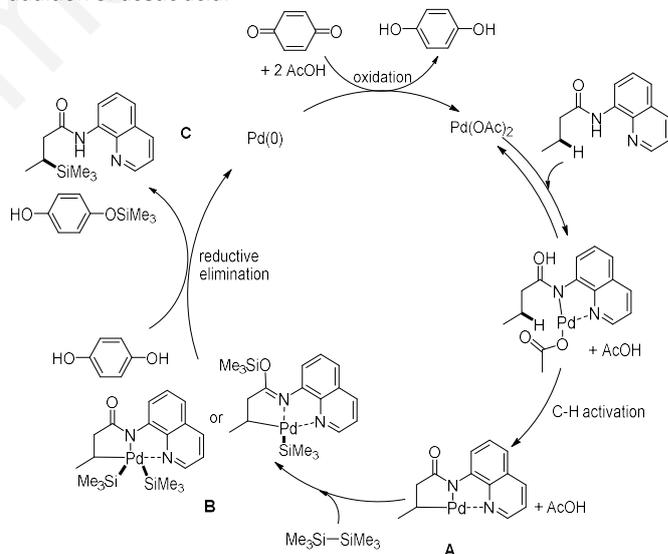
S.-Y. Zhang in 2016 succeeded to silylate with hexamethyldisilane remote  $sp^3C-H$  bonds at  $\beta$ -carbon of 8-aminoquinoline amide

derivatives as directing groups. The reaction catalyzed by  $Pd(OAc)_2$  needs an oxidant such as benzoquinone (BQ) at 110 °C in DMA (Scheme 17).<sup>54</sup> This silylation can be applied to *N*-Phthalimide (Phth) protected chiral amino acid derivatives with good diastereoselectivity.



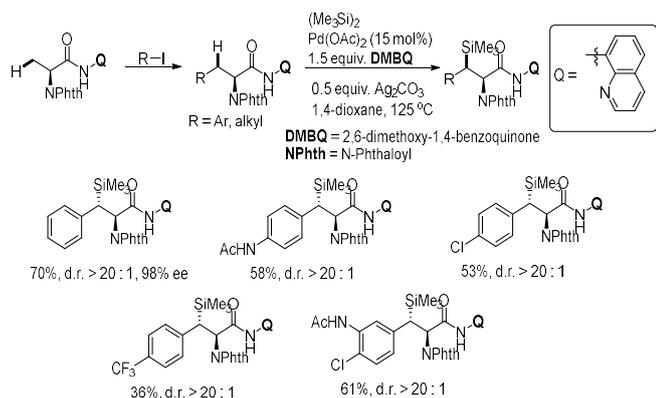
**Scheme 17.**  $sp^3 C-H$  bond silylation at  $\beta$ -carbon of carboxamides derived from 8-amino quinoline.

The proposed mechanism is shown on scheme 18,<sup>54</sup> and involves the bicyclic metalate **A** formation by  $N-H$  and  $C_\beta-H$  deprotonation, and its disilylation at  $O$  and  $Pd$  atoms or at  $Pd$  site only in intermediate **B**. After reductive elimination with  $C-Si$  bond formation to give product **C** the  $Pd(0)$  is reoxidized into  $Pd(OAc)_2$  with benzoquinone and addition of acetic acid.



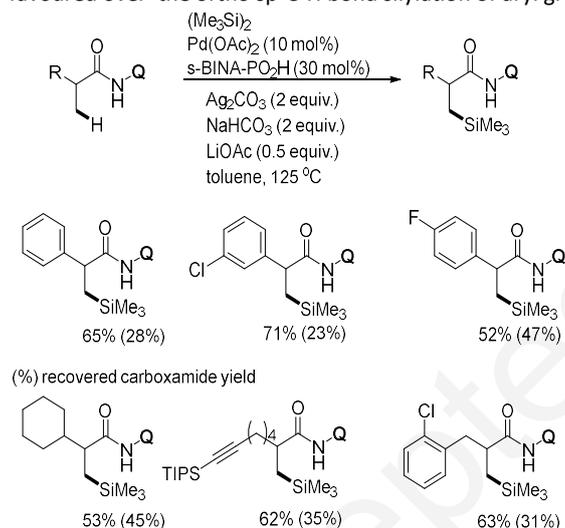
**Scheme 18.** Proposed mechanism for silylation of  $\beta$ -carbon of carboxamides.

Bing-Feng Shi et al. have found in 2016 the  $Pd$ -catalyzed intermolecular silylation of unactivated primary and secondary  $sp^3C-H$  bonds of *N*-Phthaloyl (PhTh) protected  $\alpha$ -amino acids but containing the directing group 8-aminoquinoline (AQ), which is easy to be removed by action of  $BF_3 \cdot Et_2O$  in MeOH. A variety of chiral  $\beta$ -silylamino acids can be prepared with retention of configuration and high *diastereoselectivity* using  $Me_3SiSiMe_3$ ,  $Pd(OAc)_2$  catalyst  $Ag_2CO_3$  (0.5 equiv.) and DMBQ = 2,6 dimethoxy-1,4-benzoquinone as oxidant to regenerate the  $Pd(II)$  catalyst (Scheme 19).<sup>55</sup>



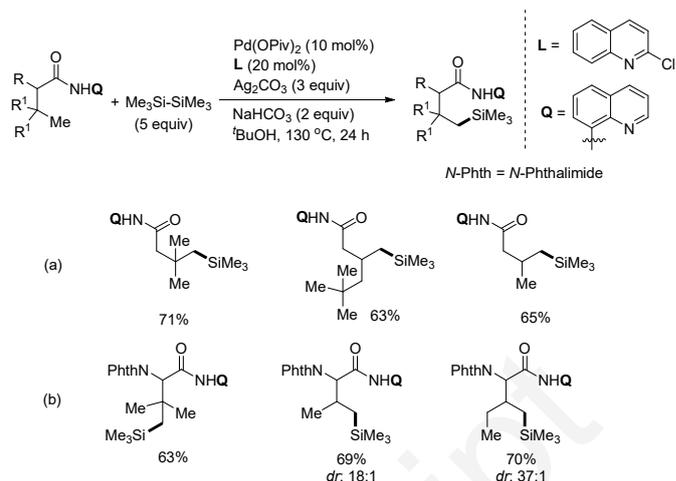
**Scheme 19.** Synthesis of chiral TMS-amino acid derivatives via Pd(II) catalyzed silylation.

2-Aryl propionic acids were treated by Bing-Feng Shi under slightly different conditions using Pd(OAc)<sub>2</sub> catalyst but with S-BINAPO<sub>2</sub>H (30 mol%) and Ag<sub>2</sub>CO<sub>3</sub> (2 equiv.) and silylation occurred at the β-methyl group (Scheme 20).<sup>55</sup> Stoichiometric reactions show that the isolated bicyclic cyclometalate arising from deprotonation of NH and one methyl C-H bond is thermodynamically more stable than the N,N cyclometalate arising from deprotonation of NH group only. Importantly for this silylation the sp<sup>3</sup>C-H silylation of alkyl group is favoured over the ortho sp<sup>2</sup>C-H bond silylation of aryl group.



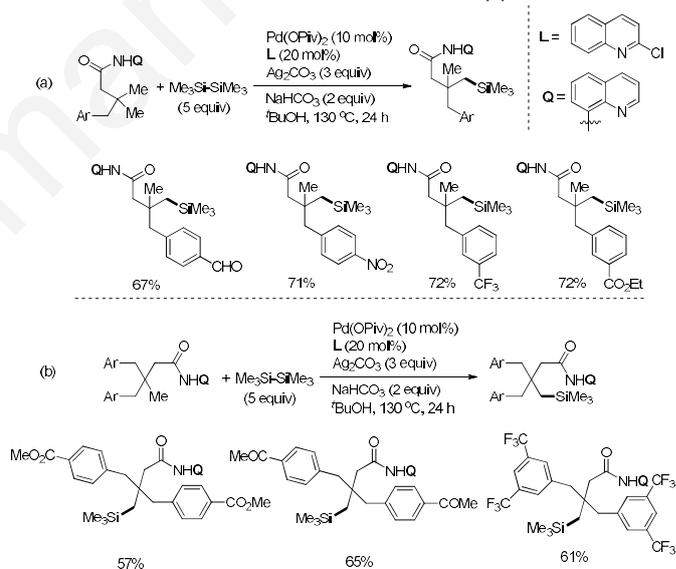
**Scheme 20.** Pd(II)-catalyzed silylation of primary C-H bonds of 2-aryl propionic acids.

Debrabata Maiti has succeeded in 2017<sup>56</sup> to perform the regioselective γ-silylation with hexamethyldisilane of amide derivatives of amino acids and 8-aminoquinoline (Scheme 21a).<sup>56</sup> Pd(OPiv)<sub>2</sub> appears to be the best catalyst partner when associated to the ligand 2-chloroquinoline L in the presence of Ag<sub>2</sub>CO<sub>3</sub> and NaHCO<sub>3</sub>. Several N-Phthalimide protected natural α-amino acid derivatives were also γ-silylated under similar conditions such as the derivatives of L-valine, L-isoleucine and tert-butyl leucine (Scheme 21b).<sup>56</sup>



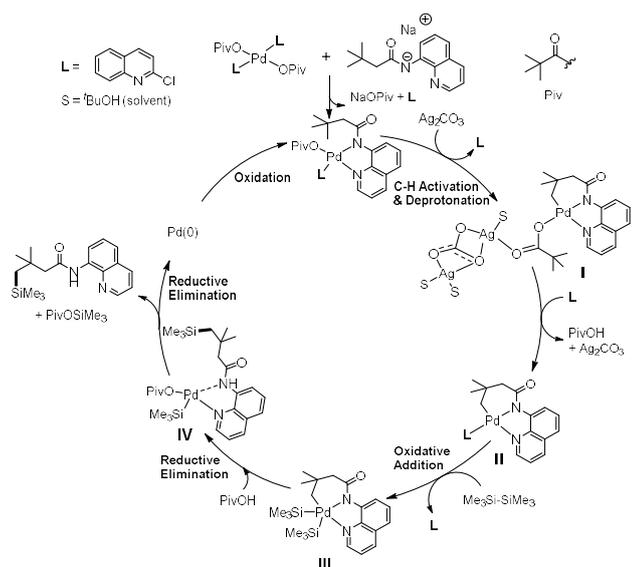
**Scheme 21.** Aliphatic γ-sp<sup>3</sup>C-H bond silylation of 8-aminoquinoline derivatives of amino acids.

The same reaction applied to γ-arylated amides, derivatives of 8-aminoquinolones, with Pd(OPiv)<sub>2</sub> catalyst and associated to the ligand 2-chloroquinoline furnishes only the sp<sup>3</sup>C-H bond γ-silylated products (Scheme 22a).<sup>56</sup> The similar γ-diarylated products under the same conditions only lead to the γ-silylation of the remaining methyl group (Scheme 22b).<sup>56</sup> The germylation with Me<sub>3</sub>Ge-GeMe<sub>3</sub> of the same amino acid derivatives was also successfully performed.<sup>56</sup>



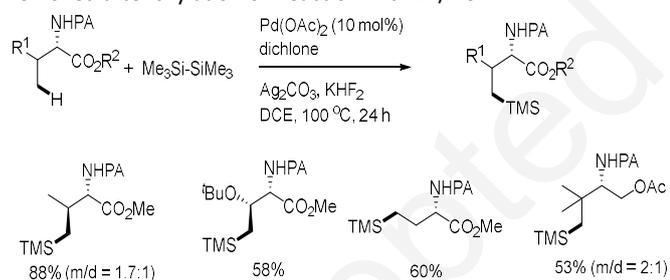
**Scheme 22.** γ-sp<sup>3</sup>C-H silylation of γ-mono and diarylated quinolamides.

The plausible mechanism of the reaction is presented on Scheme 23.<sup>56</sup> It is based on H/D kinetic studies and assisted by computational studies. It involves the γ-C-H methyl activation via deprotonation step first and the initial formation of the 6-membered cyclometalates I and II. The oxidative addition of Me<sub>3</sub>Si-SiMe<sub>3</sub> to the Pd(II) intermediate gives III. Then the reductive elimination to give the C(γ)-SiMe<sub>3</sub> bond leads to IV, and the reductive elimination leading to the γ-silylated product releases PivOSiMe<sub>3</sub> and Pd(0) species which needs to be reoxidized by Ag<sup>+</sup>.



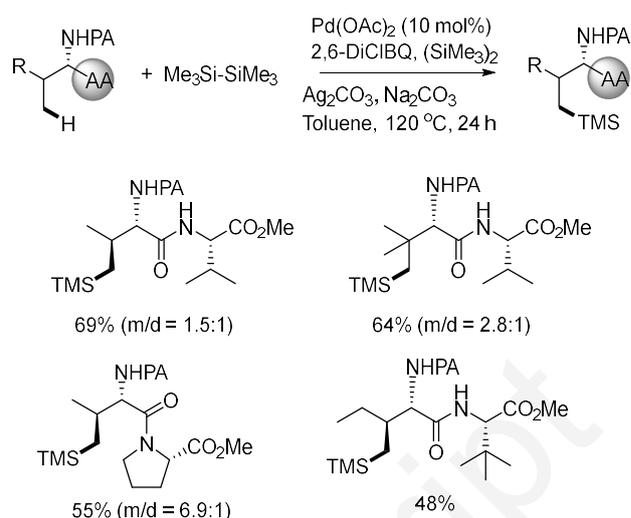
**Scheme 23.** Mechanistic cycle for palladium-catalyzed  $\alpha$ -silylation of quinolamide derivatives.

Recently in 2019 Bing-Feng Shi has succeeded to perform the  $\alpha$ - $sp^3C$ -H bond silylation of peptides and  $\alpha$ -amino acids, with  $Me_3Si-SiMe_3$  and  $Pd(OAc)_2$  catalyst, but assisted by a picolinamide (PA) directing group. This silylation has been applied to various amino acids valine, leucine-2-aminobutyric acid and to amino alcohol derivatives (NHPA :  $-NCO(2-Pyridine)$ ) (Scheme 24).<sup>57</sup> The reaction requires the presence of  $Ag_2CO_3$  and  $KHF_2$  and is improved by the presence of benzoquinone derivative such as dichlone as oxidant to regenerate the  $Pd(II)$  catalyst. The picolinamide group is easily removed after silylation on reaction with  $Zn/HCl$ .



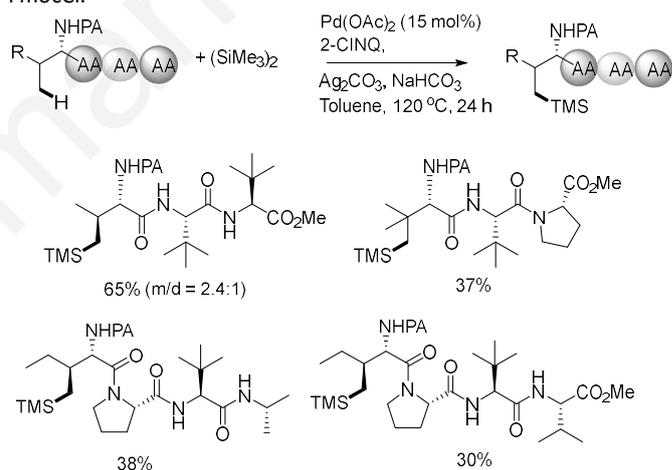
**Scheme 24.**  $\alpha$ -methyl silylation of  $\alpha$ -amino acids and  $\alpha$ -amino alcohols.

Under closely related conditions the reaction can be applied to the  $\alpha$ -silylation of 15 various dipeptides, in this case the preferable oxidant is 2,6-dichloro-1,4-benzoquinone (2,6-DiCIBQ) with picolinamide directing group (NHPA :  $-NCO(2-Py)$ ). (Scheme 25).<sup>57</sup>



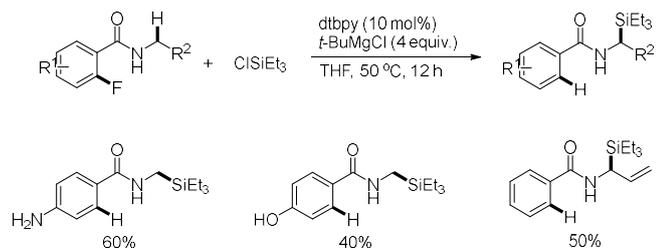
**Scheme 25.**  $Pd(II)$ -catalyzed  $sp^3C$ -H bond  $\alpha$ -silylation of dipeptides.

Bing-Feng Shi showed that this  $\alpha$ -silylation can also be extended to tripeptides and tetrapeptides under similar conditions with  $Pd(OAc)_2$  catalyst, but rather using 2-chloro-1,4-napthoquinone (2-CINQ) as oxidant (Scheme 26).<sup>57</sup> The picolinamide directing group in these peptides is shown to be removed easily by action of  $Zn/HCl$  in THF and replaced by useful protecting Fmoc group on reaction with FmocCl.



**Scheme 26.**  $Pd(II)$ -catalyzed  $sp^3C$ -H bond  $\alpha$ -silylation of tripeptides and tetrapeptides.

Another quite different intermolecular  $sp^3C$ -H bond silylation process of amides was discovered in 2016 by Xiaoming Zeng *et al.*<sup>58</sup> for the functionalization of benzamides in which the amide does not play the role of directing group for C-H bond activation by metal catalyst as previously. They succeeded to prepare  $\alpha$ -silylamides *via*  $sp^3C$ -H bond silylation but involving a [1,5]-hydrogen transfer to the benzamide *ortho* C-F bond. The reaction shown on Scheme 27 is performed with  $ClSiEt_3$ , or other trialkyl silyl chlorides, on reaction with  $tBuMgCl$  and 4,4'-di-tertbutylbipyridine (dtbpy) at only 50°C. The [1,5] hydrogen transfer is demonstrated to occur by study of a  $N-CD_3$  labeled benzamide derivative.

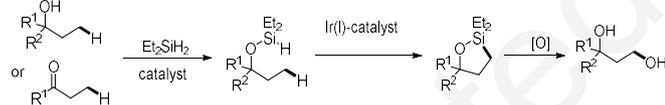


**Scheme 27.** Site-selective silylation of aliphatic C-H bonds at the  $\alpha$ -position through [1,5]-hydrogen transfer.

Kinetic studies suggest that the  $\alpha$ -sp<sup>3</sup>C-H bond cleavage is the rate determining step and that the *ortho* C-F bond is not cleaved in the absence of chlorosilane. To show the advantage of this regioselective silylation the prepared  $\alpha$ -silabenzamides were easily functionalized on reaction of the C-Si bond to give a variety of *N*-formyl (PhCONHCHO),  $\beta$ -hydroxyl (PhCONHCH<sub>2</sub>CHOHR) or  $\beta$ -amino (PhCONHCH<sub>2</sub>CH(NHR)Ph) benzamide derivatives.<sup>58</sup>

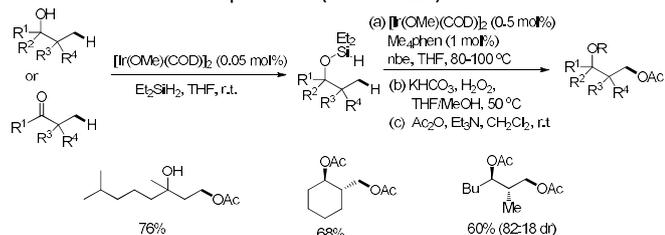
## 5. Metal-catalyzed intramolecular silylations of sp<sup>3</sup>C-H bonds directed by hydrosilylated hydroxy and ketone groups

As early as 2012 Hartwig<sup>59</sup> showed that O-SiH(alkyl)<sub>2</sub> groups, arising from catalyzed dehydrosilylation with silane alkyl<sub>2</sub>SiH<sub>2</sub> of hydroxy group or by hydrosilylation of ketone carbonyl group, could lead to regioselective *intramolecular* silylation of  $\gamma$ -sp<sup>3</sup>C-H bond and hydrogen elimination to form 5-membered oxasiloxane. The efficient catalyst was based on Iridium(I) in the presence of a bulky phenanthroline ligand. One major advantage of this regioselective silylation is that it offers the easy oxidation of the formed oxasiloxanes, with H<sub>2</sub>O<sub>2</sub>, to generate 1,3-diols, or lead to the corresponding 1,3-acetates on further treatment with Ac<sub>2</sub>O. (Scheme 28).



**Scheme 28.** Silylation of alkyl sp<sup>3</sup>C-H bond directed by silylated hydroxy group or ketone.

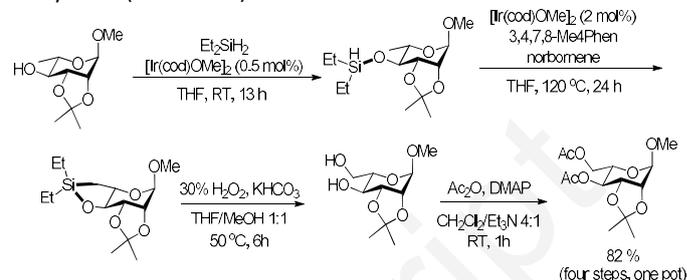
Thus the hydroxy and ketone groups were first dehydrosilylated and hydrosilylated respectively with alkyl<sub>2</sub>SiH<sub>2</sub> in the presence of the catalyst [Ir(OMe)(COD)]<sub>2</sub> in THF. Then the intramolecular dehydrosilylation was performed with the same Ir(I) catalyst but in the presence of 3,4,7,8-tetramethylphenanthroline. The addition of norbornene allowed to trap the generated hydrogen before the C-Si bond formation to form the cyclic oxasiloxanes (Schemes 28, 29). The in situ treatment of the formed oxasiloxane with hydrogen peroxide leads to 1,3-diol which on reaction with Ac<sub>2</sub>O affords the 1,3-diacetate at room temperature (Scheme 29).<sup>59</sup>



**Scheme 29.** Iridium(I) catalyzed silylation of alcohol and ketone

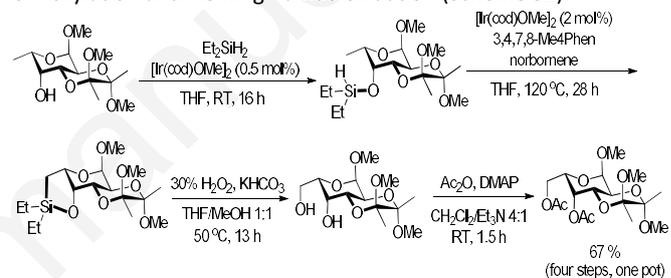
followed by intramolecular  $\gamma$ -sp<sup>3</sup>C-H bond silylation.

The same year, with the Hartwig procedure, Pedersen and Bols<sup>60</sup> developed a one-pot sequence process to synthesize fully protected L-mannoside in 82% yield only using 4 steps from methyl glycoside derivative, including Si-H/O-H cross-coupling reaction, intramolecular sp<sup>3</sup>C-H silylation, Fleming-Tamao-type oxidation, and acetylation (Scheme 30).



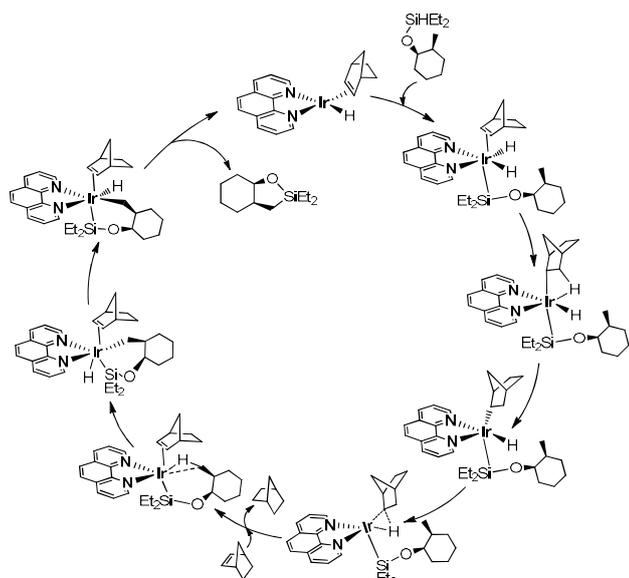
**Scheme 30.** One-pot sequence for the synthesis of fully protected L-mannoside involving an intramolecular  $\gamma$ -sp<sup>3</sup>C-H bond silylation.

Furthermore, this method could be also applied to synthesize fully protected L-galactosides from the corresponding L-fucoside through C-H silylation and Fleming-Tamao oxidation (Scheme 31).<sup>60</sup>



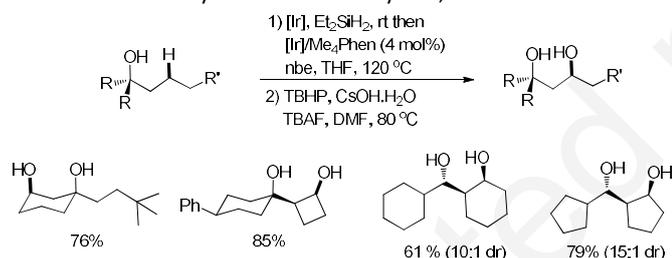
**Scheme 31.** One-pot synthesis of fully protected L-galactoside through C-H silylation and oxidation.

The mechanism of Ir(I)/phenanthroline catalyzed silylation of  $\gamma$ -sp<sup>3</sup>C-H bond of 2-methyl cyclohexanol was studied by Sunoj *et al*<sup>61</sup> using DFT calculations. The proposed mechanism is presented on scheme 32. It is shown that in the presence of SiH<sub>2</sub>Et<sub>2</sub> the [Ir(OMe)(COD)]<sub>2</sub> catalyst alone first performs the silylation of the alcohol. Then the Ir-H(Phen) complex can coordinate norbornene before allowing the Si-H oxidative addition. The alkene allows insertion into Ir-H bond and reductive elimination of alkane. Then C-H bond oxidative addition of the  $\gamma$ -sp<sup>3</sup>C-H bond takes place followed by reductive elimination with C-Si bond formation. The last step of the reductive elimination to form C-Si bond is the rate-determining step of the reaction (TS: 14.6 kcal/mol) whereas the C-H bond activation needs lower energy (TS: 9 kcal/mol).



**Scheme 32.** Mechanism of conversion of (hydrido)silyl ether to oxasilolane catalyzed by neutral  $[\text{IrH}(\text{nbe})(\text{phen})]$ .

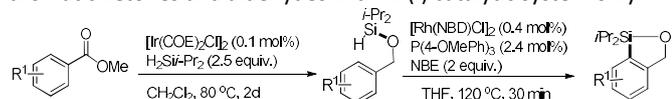
Hartwig<sup>62</sup> has then applied his strategy to generate oxasilane  $\text{O-SiEt}_2\text{H}$  group, from hydroxy group or corresponding ketone, and to direct the intramolecular regioselective  $\gamma$ - $\text{sp}^3\text{C-H}$  bond dehydrosilylation of intermediate  $\text{R}_2\text{C}(\text{OSiEt}_2\text{H})-\text{CH}_2\text{CH}_2\text{CH}_2\text{R}'$  to *in situ* form the oxasilolanes. The later can then be *in situ* oxidized into 1,3-diols with TBHP peroxide (Scheme 33). This dehydrosilylation reaction catalyzed by  $[\text{Ir}(\text{OME})(\text{COD})]_2/\text{Me}_4\text{Phen}$  allows the *diastereoselective* synthesis of a variety of 1,3-diols.



**Scheme 33.** Intramolecular dehydrosilylation of secondary C-H bonds and synthesis of 1,3-diols.

The primary C-D/C-H KIE=2 indicates that the C-H bond cleavage is the rate-limiting step for this directed intramolecular  $\text{sp}^3\text{C-H}$  bond silylation. The catalytic dehydrosilylation of the derivatives  $\text{R}_2\text{C}(\text{OSiEt}_2\text{H})\text{CH}_2\text{CH}_3$  and of  $\text{R}_2\text{C}(\text{OSiEt}_2\text{H})\text{CH}_2\text{CH}_2\text{CH}_3$  show that the silylation of the  $\gamma$ - $\text{CH}_3$  group is 49 times faster than that of the  $\gamma$ -methylene group, thus faster at the primary than at secondary  $\gamma$ -C-H bond.

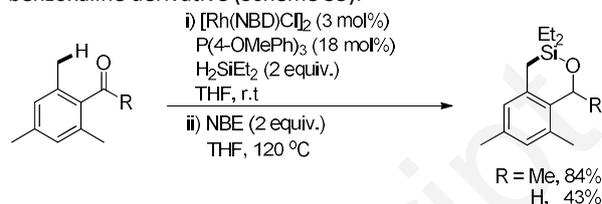
In 2015 Jeon *et al.*<sup>63</sup> have developed a method for initial hydrosilylation of ester, ketone and aldehyde carbonyl groups followed by  $\text{sp}^2\text{C-H}$  bond *ortho* silylation of aromatic systems. The first hydrosilylation of carbonyl group is performed with  $[\text{IrCl}(\text{COE})]_2$  catalyst with  $\text{H}_2\text{SiEt}_2$ . The following intramolecular silylation was catalyzed by  $[\text{RhCl}(\text{NBD})]_2/\text{P}(\text{C}_6\text{H}_4\text{OMe})_3$  in the presence of norbornene (Scheme 34). The same reaction could be applied to aromatic ketones and aldehydes with Rh(I) catalytic system only.



**Scheme 34.** Sequential reductive carbonyl and arene *o*-CH silylations

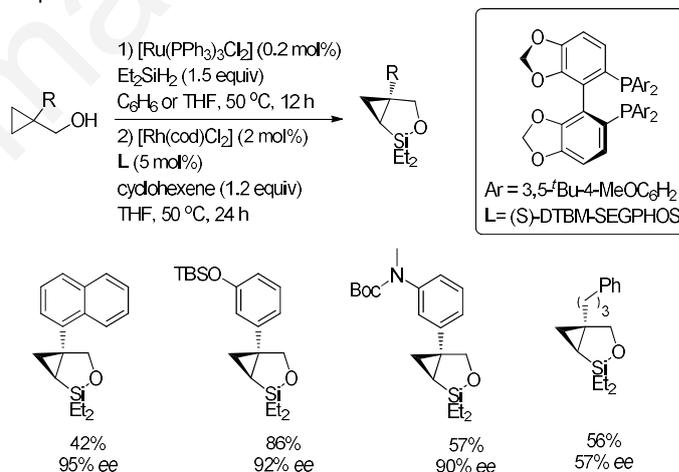
with both Ir(I) and Rh(I) catalysts.

Interestingly, when the reaction was applied to an aromatic ester containing an *ortho* methyl group, the similar successive Ir(I) and then Rh(I) reaction led to the reduction of carbonyl group first and then to the  $\text{sp}^3\text{C-H}$  benzylic bond intramolecular hydrosilylation to afford the benzoxaline derivative. From aromatic ketone and aldehyde containing an arene *ortho* methyl group only the Rh(I)/Phosphine catalyst led to both carbonyl hydrosilylation and then in the presence of NBE intramolecular dehydrosilylation to form the benzoxaline derivative (Scheme 35).



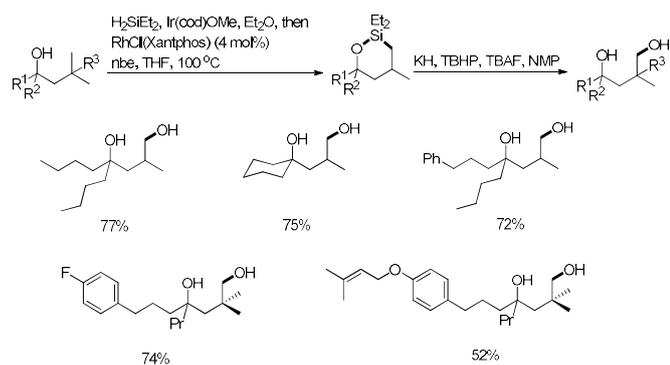
**Scheme 35.** Sequential reductive benzylic  $\text{sp}^3\text{C-H}$  silylation of aromatic esters, ketones and aldehydes with Rh(I) catalyst.

Later on, Hartwig developed the first chiral-rhodium(III) catalyzed highly enantioselective C-H bond silylation of cyclopropyl C-H bond to form a five-membered ring oxasilolane. Up to 89% isolated yield and 95% *ee* of oxasilolane were obtained by using a sequence of  $[\text{Ru}(\text{PPh}_3)_3\text{Cl}_2]/\text{Et}_2\text{SiH}_2$  catalytic system followed by  $[\text{Rh}(\text{cod})\text{Cl}_2]/(\text{S})\text{-DTBM-SEGPHOS}/\text{cyclohexene}$  catalytic system (Scheme 36).<sup>64</sup> The H/D KIE value is 2.1 which indicates that the Rh catalyzed C-H bond cleavage is the turnover-limiting and enantioselectivity-determining step.

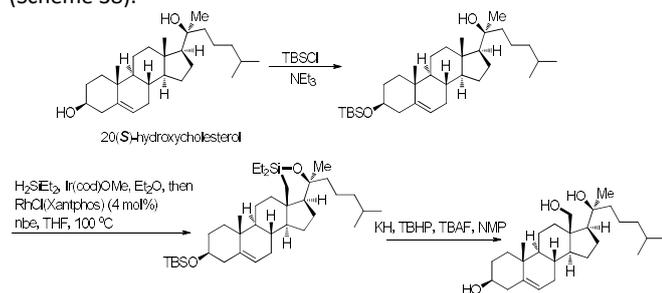


**Scheme 36.** Rh catalyzed enantioselective silylation of cyclopropyl  $\text{sp}^3\text{C-H}$  bonds.

Then the Hartwig group<sup>65</sup> developed a rhodium-catalyzed site selective silylation of alkyl  $\delta$ -C-H bonds, when no C-H bond is present at  $\gamma$ -carbon atom, to form six-membered oxasilolanes with hydroxyl group as the initial directing group. The catalytic reaction takes place in the presence of  $[\text{Rh}(\text{Xantphos})\text{Cl}]$  catalyst with norbornene as the hydrogen acceptor (Scheme 37).<sup>65</sup> The oxidation of the resulting six-membered oxasilolanes led to 1,4-diols in high yields with tolerance of many functional groups. The mechanistic studies show that the  $(\text{Xantphos})\text{Rh}(\text{SiEt}_2\text{OR})(\text{nbe})$  is the key complex for the rate-resting state and that the oxidative addition of the  $\delta$  C-H bond to Rh(I) is the rate-limiting step of the process.



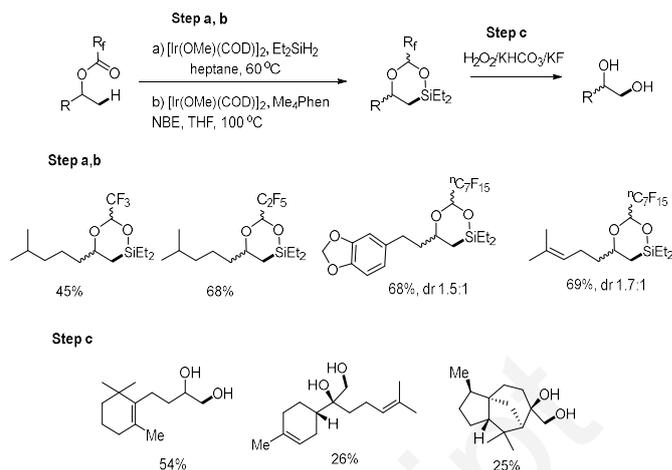
This method could be applied to functionalize the natural oxysterol compound 20(S)-hydroxycholesterol with alcohol-directed oxygenation at the C18 position *via* the [Rh(Xantphos)Cl] catalyzed  $\delta$ -sp<sup>3</sup>C-H bond silylation followed by the Fleming-Tamao oxidation (Scheme 38).<sup>65</sup>



**Scheme 38.** Rh(Xantphos)Cl catalyzed  $\delta$ -C-H silylation of oxysterol.

Hartwig<sup>66</sup> in 2018 has applied his method for intramolecular silylation of sp<sup>3</sup>C-H bonds observed with the Rh(I) catalyst, for regioselective dehydrosilylation of alkyl  $\beta$ -C-H bond directed by a perfluorinated ester group, which was successful with Ir(I) catalyst. First tertiary alcohols were first esterified into perfluorinated esters which were treated with Et<sub>2</sub>SiH<sub>2</sub> with catalyst [Ir(OMe)(COD)]<sub>2</sub> to afford quantitatively the carbonyl hydrosilylation product containing the O-SiEt<sub>2</sub>H group. Then the addition of [Ir(OMe)(COD)]<sub>2</sub>/Me<sub>4</sub>Phen catalyst allowed the regioselective  $\beta$ -C-H bond silylation with dehydrogenation in the presence of norbornene to form the 6-membered dioxasilanes (Scheme 39).

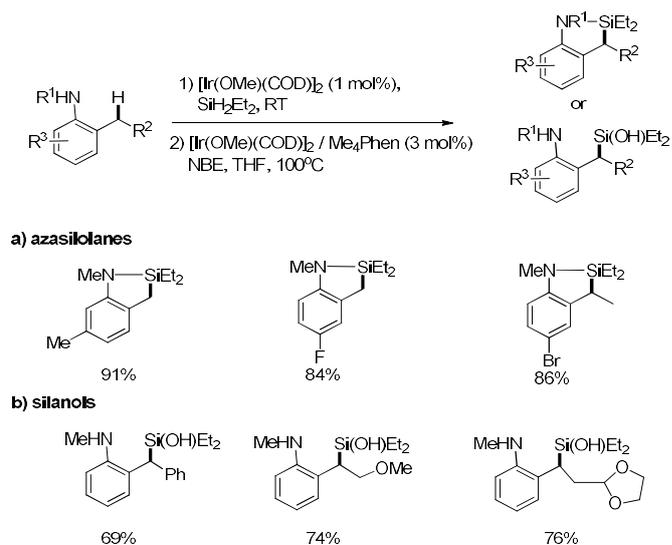
These perfluorinated esters can be used as starting substrates to produce a variety of natural 1,2-diols,<sup>66</sup> by successive Ir(I) catalyzed  $\beta$ -C-H bond silylation and then oxidation with H<sub>2</sub>O<sub>2</sub> according to the Tamao-Fleming reaction.



**Scheme 39.** Hydrosilylation of fluorinated esters, intramolecular sp<sup>3</sup>C-H bond silylation and oxidation.

## 6. Catalyzed regioselective intramolecular sp<sup>3</sup>C-H bond dehydrosilylation of silylated amine NH Bonds

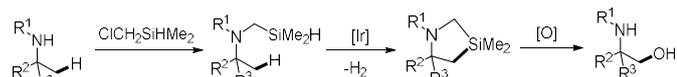
Hartwig has shown in 2014 that secondary aromatic amines could direct the silylation with H<sub>2</sub>SiEt<sub>2</sub> of N-H bond first with [Ir(OMe)(COD)]<sub>2</sub> catalyst alone, followed by the *intramolecular* silylation of aryl *ortho* sp<sup>2</sup>C-H bond using the same catalyst, but with an additional phenanthroline ligand [Ir(OMe)(COD)]<sub>2</sub>/Me<sub>4</sub>Phen catalyst and with the presence of norbornene to eliminate the hydrogen.<sup>67</sup> This principle was then applied to secondary aryl amines containing an *ortho* alkyl group which led to initial Ar(R)N-H transformation into (hydro)silylamines Ar(R)NSiH<sub>2</sub>Et<sub>2</sub> first and then to the intramolecular alkyl sp<sup>3</sup>C-H bond silylation of *ortho* methyl groups and of secondary benzylic sp<sup>3</sup>C-H bond at the  $\gamma$ -position of the N(SiH<sub>2</sub>Et<sub>2</sub>) group to produce a variety of azasilolanes (Scheme 40a).



**Scheme 40.** sp<sup>3</sup>C-H silylation of N-2-alkylanilines and formation of azasilolanes and silanols.

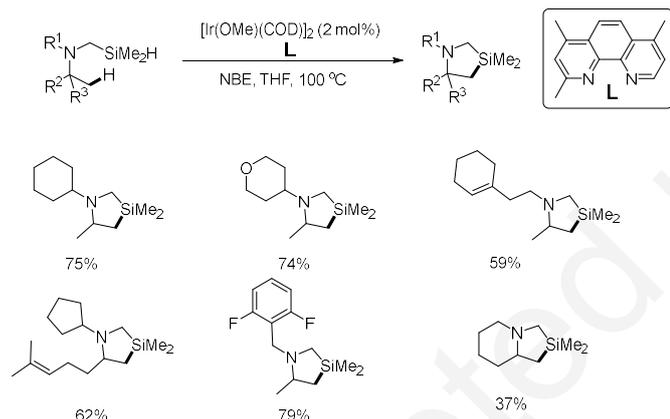
The later azasilolanes during chromatography were opened to produce the corresponding silanols (Scheme 40b). The reaction used successively the same two iridium(I) catalyst systems which tolerated many functional groups (Br, MeO, OSiR<sub>3</sub>, OAc). The silanols can be oxidized easily with H<sub>2</sub>O<sub>2</sub> to form aromatic secondary amines with  $\gamma$ -hydroxy group.

Hartwig has recently reported the intramolecular  $\beta$ -selective silylation of unactivated sp<sup>3</sup>C-H bonds of alkylamines.<sup>68</sup> The reaction requires the initial formation of the N-CH<sub>2</sub>-SiHMe<sub>2</sub> group by reaction of secondary alkyl amine with ClCH<sub>2</sub>SiHMe<sub>2</sub>. Then intramolecular alkyl silylation affords a cyclic silane which can be oxidized into 1,2-aminoalcohol. (Scheme 41)



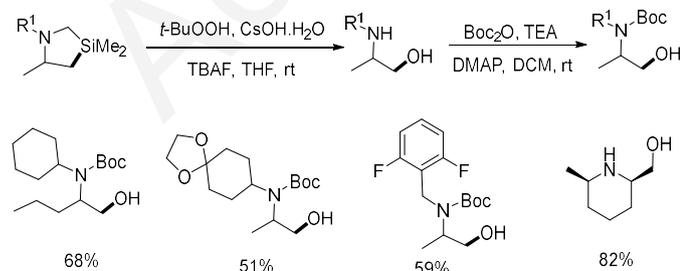
**Scheme 41.** Selective C-H silylation of aliphatic amines and oxidation into 1,2-amino alcohols.

The  $\beta$ -selective intramolecular silylation of amines is performed with [Ir(OMe)(COD)]<sub>2</sub> and a trimethyl phenanthroline ligand **L** in the presence of an hydrogen acceptor (NBE) (Scheme 42)<sup>68</sup>. Many functional groups are tolerated such as alkene, C-F bond or other groups.



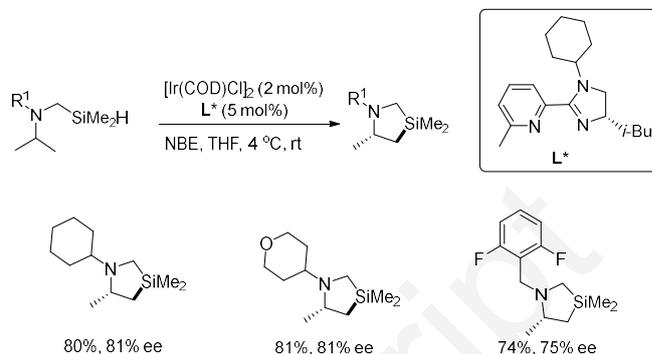
**Scheme 42.** Intramolecular sp<sup>3</sup>C-H silylation of aliphatic amines into silapyrrolidines.

The formed silapyrrolidines can be oxidized easily with *t*-BuOOH to produce 1,2-amino alcohols (Scheme 43). These 1,2-amino alcohols are easily transformed into *N*-protected carbamates by treatment with Boc<sub>2</sub>O (Scheme 43).



**Scheme 43.** Synthesis of 1,2-amino alcohols, derived from sp<sup>3</sup>C-H silylation, and of their *N*-protected carbamates.

Hartwig also performed enantioselective intramolecular dehydrosilylation of silylamines.<sup>68</sup> The silylation reaction has been carried out with [Ir(OMe)(COD)]<sub>2</sub> catalyst but with a chiral pyridylimidazoline ligand **L\***. The chiral ligand **L\*** containing a *N*-alkyl imidazoline has led to good enantioselectivities (Scheme 44).<sup>68</sup>

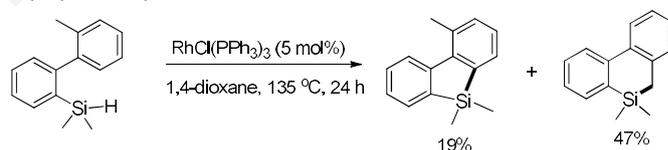


**Scheme 44.** Enantioselective intramolecular C-H silylation of aliphatic amines.

## 7. Intramolecular silylations of sp<sup>3</sup>C-H bonds in proximity with Si-H bonds.

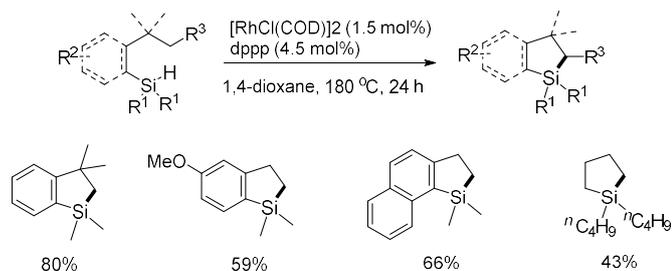
### 7.1 From arylsilanes

The first example of *intramolecular* silylation of sp<sup>3</sup>C-H bond *without directing group* was observed by Kuninobu and Takai with a Rh(I) catalyst RhCl(PPh<sub>3</sub>)<sub>3</sub> in 2013 on reaction of the diphenylhydrosilane containing an *ortho* methyl group (Scheme 45)<sup>69</sup>. Thus the sp<sup>3</sup>C-H intramolecular silylation appeared to be easier than the expected aryl sp<sup>2</sup>C-H silylation.



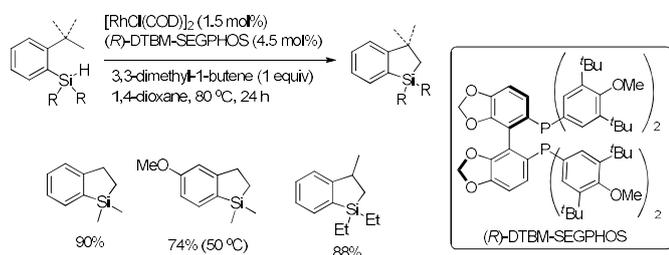
**Scheme 45.** Rhodium(I)-catalyzed silylation of aromatic sp<sup>2</sup>C-H and benzylic sp<sup>3</sup>C-H bonds.

This first example led this group to discover a general intramolecular sp<sup>3</sup>C-H bond silylation of arylsilanes containing an *ortho* alkyl group, to form a 5-membered cyclic silane, with a catalytic system based on [RhCl(COD)]<sub>2</sub> and diphosphine Ph<sub>2</sub>P(CH<sub>2</sub>)<sub>2</sub>PPh<sub>2</sub> (dppp) (Scheme 46).<sup>67</sup> The proposed reaction mechanism suggested the initial insertion of the Rh(I) species into the Si-H bond followed by oxidative addition of the proximal alkyl sp<sup>3</sup>C-H bond to the Rh species followed by dehydrogenation and formation of the sp<sup>3</sup>C-Si bond.<sup>69</sup> Further studies led the same group to propose the catalytic mechanism presented later in Scheme 49. This regioselective reaction can also be performed without aromatic ring such as from H-Si(<sup>*n*</sup>Bu)<sub>3</sub> by silylation of alkyl sp<sup>3</sup>C-H bond,<sup>69</sup> as it was also observed with a platinum catalyst (see Equation 4).<sup>40</sup>



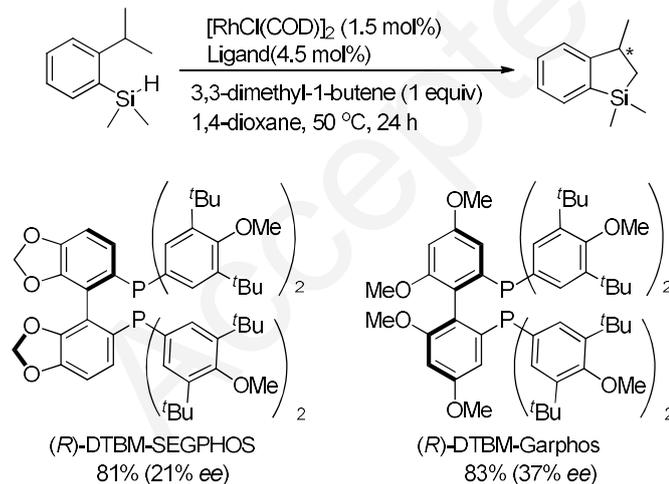
**Scheme 46.** Rhodium-catalyzed intramolecular silylation of unactivated  $sp^3C-H$  Bonds.

Later the same Kuninobu-Takai group<sup>70</sup> showed the strong influence of the phosphine ligand on the efficiency of the  $[RhCl(COD)]_2$  catalyst as well as the required presence of an alkene. For instance (*R*)-DTBM-SEGPHOS and 3,3-dimethyl-1-butene appeared to be excellent partners for intramolecular silylation at  $\beta$ - $sp^3C-H$  bond of the alkyl group as shown in scheme 47.



**Scheme 47.** Rhodium-catalyzed dehydrogenative silylation leading to 2,3-dihydro-1H-benzo[*b*]siloles.

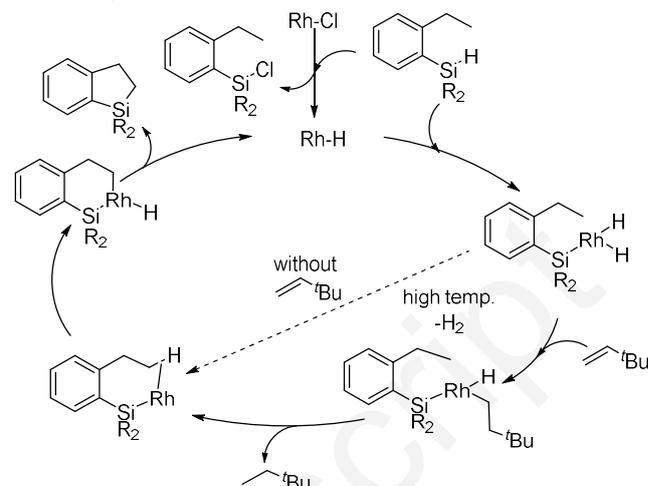
More importantly, the use of chiral SEGPHOS or GARPHOS diphosphine allowed the enantioselective intramolecular methyl silylation of 2-isopropyl phenylsilane although in modest enantiomeric excess. (Scheme 48)<sup>70</sup>



**Scheme 48.** Rhodium-catalyzed enantioselective  $sp^3C-H$  Bond silylation with chiral diphosphines.

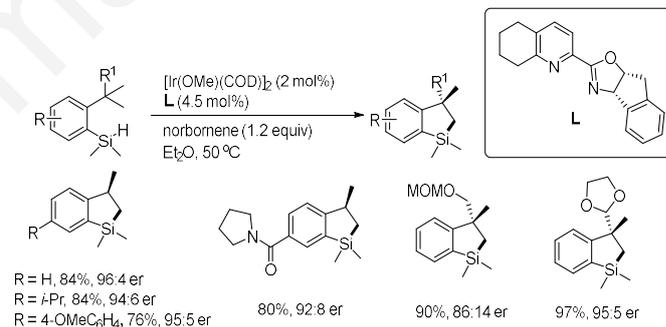
The proposed mechanism of the reaction involves first the initial transformation of the Rh-Cl into the Rh-H bond by reaction with silane followed by oxidative addition of the Si-H bond to the Rh-H moiety. The dehydrogenation with the help of the alkene proceeds

by its insertion into Rh(III)-H bond and alkane elimination. The insertion of the resulting Rh(I) species into the neighbour alkyl  $\beta$ -C-H bond, followed by reductive elimination to form the Si-C bond can then take place (Scheme 49)<sup>70</sup>.



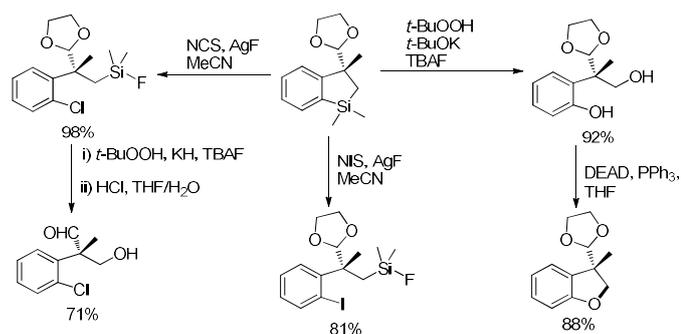
**Scheme 49.** Proposed reaction mechanism for intramolecular silylation of alkyl group with Rh(I) catalyst.

More recently Hartwig *et al.*<sup>71</sup> have applied this reaction for the very efficient enantioselective intramolecular silylation of  $\beta$ -C-H bond of an alkyl group at *ortho* position of arylsilanes using  $[Ir(OMe)(COD)]_2$  catalyst with optically active *N,N* bidentate ligand **L**. (Scheme 50)



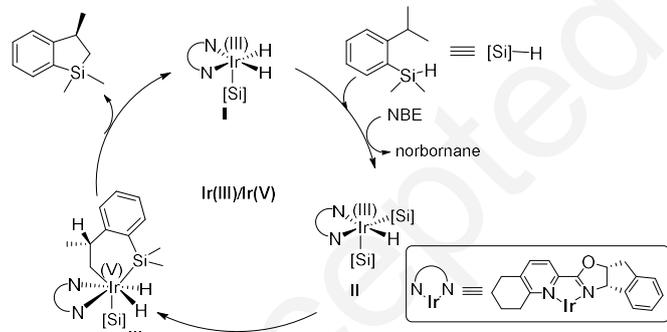
**Scheme 50.** Enantioselective intramolecular silylation of  $sp^3C-H$  bond with chiral Ir(I) catalyst.

The use of the chiral tetrahydroquinoline **L** led to high enantioselectivity (*e.r.* = 92.8 to 98.2) and good yield of the 5-membered cyclic dihydrobenzosiloles at 50° C but in the presence of norbornene as hydrogen trap. The reaction can be performed at a gram scale. The kinetic isotopic effect KIE of  $kH/kD = 1.9$  for intramolecular silylation with the  $CH(CH_3)_2/CH(CD_3)_2$  *ortho* alkyl groups suggested that the C-H bond cleavage is the rate determining step. The formed chiral dihydrobenzosiloles can be transformed easily by classical reactions of silanes into polyfunctional derivatives as some are illustrated in Scheme 51.<sup>71</sup>



**Scheme 51.** Transformations of the enantioenriched dihydrobenzosiloles.

Recently the Genping Huang group<sup>72</sup> has studied the mechanism of Hartwig's reaction<sup>71</sup> on intramolecular silylation of  $sp^3C-H$  bond in *ortho*-alkyl silyl arenes with the help of DFT calculations. First they showed that the  $[\text{Ir}(\text{OMe})(\text{COD})]_2$  precursor on reaction with the chiral  $N^*N^*$  ligand and silane (*o*-alkyl)ArSiMe<sub>2</sub>H led to the Ir(III) ( $N^*N^*$ )Ir(H)<sub>2</sub>[Si] catalytic active species **I** (Scheme 52). The coordination of norbornene C=C bond allows its insertion into Ir-H bond and the resulting alkyl group interact with the remaining Si-H bond to eliminate the norbornane and to form the Ir-SiMe<sub>2</sub>(aryl) intermediate **II**. The next key step involves the alkyl C-H bond interaction with the Ir(III) center, followed by C-H bond oxidative addition to form the Ir(V) intermediate (**III**). The reductive elimination with C-Si bond formation leads to the product and the catalytic species **I**. The reductive elimination from **III** cannot take place directly but occurs after initial Ir-hydride silyl group Ir-H...[Si] interaction. The DFT calculation shows that both electronic and steric effects contribute to create the enantioselectivity.

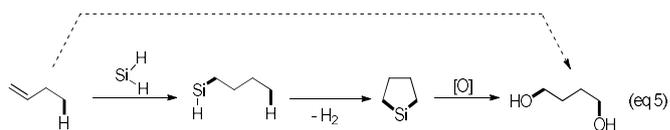


**Scheme 52.** Catalytic cycle based on DFT calculations of intramolecular silylation of  $sp^3C-H$  bond.

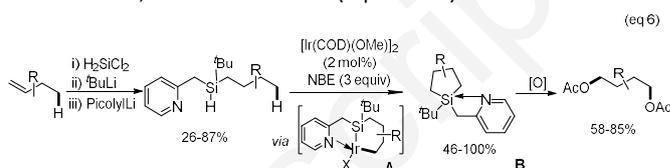
Another recent example of intramolecular silylation of azylsilanes with Ru(II) catalyst will be described later (Scheme 60)

## 7.2 From alkylsilanes arising from in situ hydrosilylation of C=C bonds

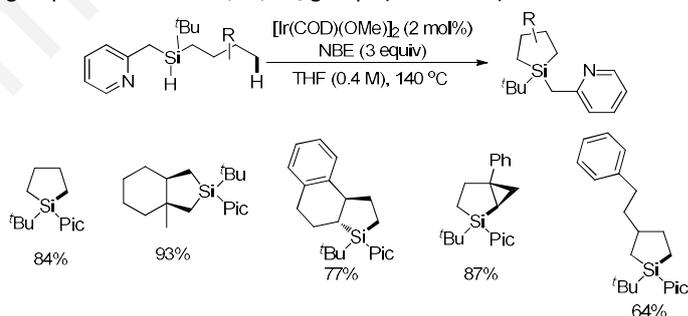
Gevorgyan *et al.*<sup>73</sup> have contributed to formally transform an alkene into a 1,4-diol *via* hydrosilylation of the alkene C=C double bond first with  $\text{R}_2\text{SiH}_2$ , followed by regioselective  $sp^3C-H$  bond intramolecular dehydrosilylation at the  $\delta$ -carbon of the resulting alkylsilane, to form a 5-membered silolane which on oxidation selectively leads to 1,4-diol. (Equation 5)



The silylation reactions are promoted by  $[\text{Ir}(\text{OMe})(\text{COD})]_2$  as catalyst. The success required first the introduction of a picolyl directing group at the silicon atom to allow the oxidative addition of the neighbour Si-H bond at the picoline coordinated Ir(I) center and then the efficient oxidation. Then the  $\delta$   $sp^3C-H$  bond activation at the Iridium center is expected to release hydrogen, trapped by norbornene (NBE), to give intermediate **A** followed by C-Si bond formation to give cyclic silolane **B**. Then the oxidation of the silolane leads to the 1,4-diol or diacetate. (Equation 6)

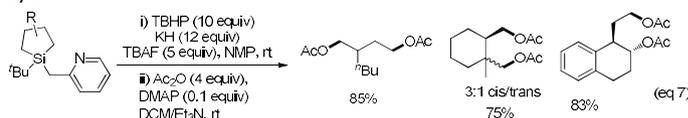


Thus a variety of silolanes have been produced from the silane containing the H-SiCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub> arrangement and the picolyl (Pic) directing group. The presence of <sup>t</sup>Bu group linked to silicon allowed the stability of the silane. The activation of primary  $\delta$ -CH<sub>3</sub> is favoured versus that of  $\delta$ -CH<sub>2</sub>Ar and the silylation of  $\delta$ -C-H bond of a cyclopropyl group is possible. The reaction tolerates many functional groups such as Ar-X: Cl, Br, CF<sub>3</sub> groups (Scheme 53).

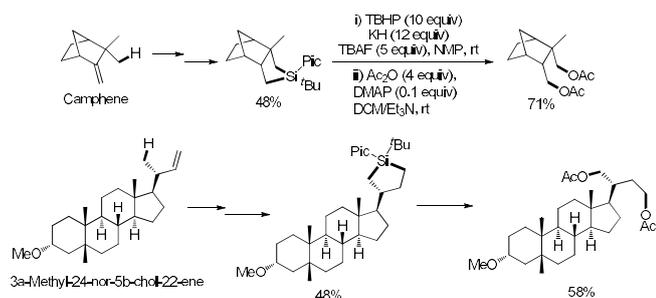


**Scheme 53.** Ir(I)-catalyzed  $\delta$ -C-H dehydrogenative silylation reaction and formation of silolanes.

The oxidation of the silolanes by TBHP/KH and then the treatment with  $\text{Ac}_2\text{O}$  allow the selective formation of 1,4-diacetates. (Equation 7).<sup>73</sup>



Similarly Camphene, 2-methylenebornane and a derivative of lithocholic acid were selectively transformed into their 1,4-diacetate derivatives (Scheme 54).<sup>73</sup>



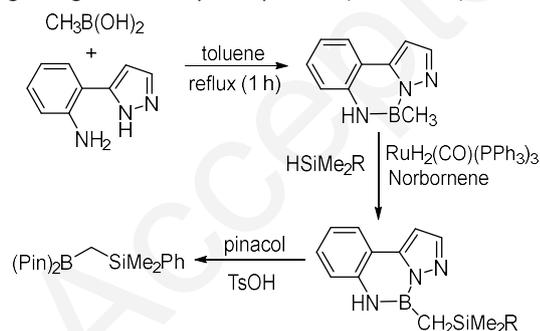
**Scheme 54.** 1,4-oxygenation of alkene containing natural products via hydrosilylation, silylation of  $sp^3C-H$  bond and oxidation.

## 8. Intermolecular catalyzed $sp^3C-H$ bond silylation of $X-CH_3$ into $X-CH_2SiR_3$ groups ( $X = B; Si; O; N; S$ )

A variety of  $sp^3C-H$  bond silylations of groups of type  $X-CH_3$  ( $X = B; Si; O; N; S$ ) has been performed, either directed by a functional group or without. The resulting products of type  $X-CH_2SiR_3$  thus allow a variety of functionalizations into  $X-CH_2-FG$  derivatives which cannot be reached directly from the  $X-CH_3$  group. This part will describe such  $X-CH_3$  silylations and some of the related functionalizations.

### 8.1 Directed silylation of the $B-CH_3$ group

*Directed silylation of the  $B-CH_3$  group* was performed by Suginome as soon as 2011<sup>74</sup>. He first succeeded to silylate the methyl group linked to the boron in boronic acid  $CH_3B(OH)_2$  with a ruthenium catalyst but using 2-(1H-pyrazol-3-yl)aniline (PZA) as a removable *ortho* directing group. Thus the resulting methyl boronic derivative reacts with a variety of trialkylsilanes, promoted by  $RuH_2(CO)(PPh_3)_3$  catalyst which easily affords a classical  $Ru(0)$  species via dehydrogenation. The reaction takes place in the presence of norbornene as hydrogen scavenger to give the  $\alpha$ -silylated product (Scheme 55).



**Scheme 55.**  $\alpha$ -functionalization of methylboronic acid via introduction of a  $N^N$  directing group with Ruthenium catalyst.

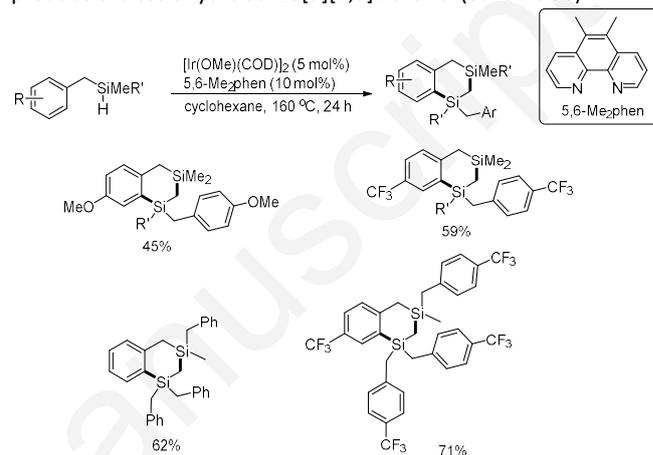
Analogous efficient directing groups can be used from 2-(1H-pyrazol-3-yl)phenol or anthranilamide for this reaction. The formed primary silylation products were treated with pinacol and TsOH to give the corresponding pinacol esters (Scheme 55).<sup>74</sup>

Under similar conditions the silylation of the PZA derivative of ethylboronic acid led to  $\alpha$ - and  $\beta$ -silylation of the ethyl group in similar yield. It is noteworthy that these pinacol esters derived from  $\alpha$ -silylmethyl boronic acid  $(Pin)_2B-CH_2SiMe_2Ph$  are good reagents for

the Suzuki-Miyaura C-C cross-couplings with arylbromides with  $Pd(0)$  catalyst to afford  $Aryl-CH_2SiMe_2Ph$  derivatives.

### 8.2 Silylation of the $Si-CH_3$ group with Ir(I) catalyst

*Directed silylation of the  $Si-CH_3$  group* was recently observed in 2017 by Takai<sup>75</sup>. They performed the novel combination of two molecules of  $PhCH_2SiHMe_2$  by intermolecular silylation of a  $SiCH_3$  group via initial  $sp^3C-H$  bond silylation of one  $SiCH_3$  group to produce first the intermediate  $PhCH_2(Me)_2Si-CH_2Si(H)(Me)CH_2Ph$  and formation of hydrogen in the presence of  $IrCl(CO)(PPh_3)_2$  catalyst. The catalyst  $[Ir(OMe)(COD)]_2$  with  $Me_2Phenanthroline$  after the formation of  $PhCH_2(Me)_2Si-CH_2Si(H)(Me)CH_2Ph$  further promoted the intramolecular silylation of the *ortho*  $sp^2C-H$  bond of one phenyl to produce the tetrahydrobenzo[*d*][1,3]disilane. (Scheme 56).

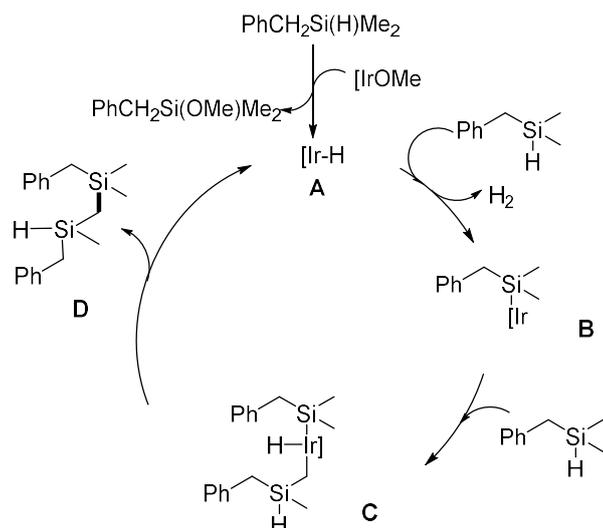


**Scheme 56.** Ir-catalyzed dehydrogenative dimerization of benzylmethylsilane.

It was shown that when the Vaska complex  $IrCl(CO)(PPh_3)_2$  was used as catalyst the silylation of one  $Si-CH_3$  group was observed first and the resulting product in the presence of  $[Ir(OMe)(COD)]_2/Me_2Phen$  catalyst gave the disilane derivative (Equation 8). This shows the easyness of silylation of the methyl group and the importance of catalyst nature for successive intermolecular silylations of  $sp^3C-H$  bond and intramolecular silylation of  $sp^2C-H$  bond.<sup>75</sup>

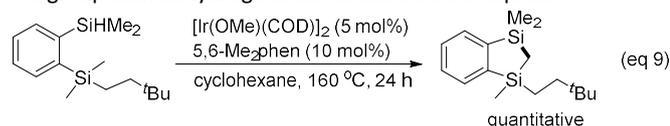


The proposed mechanism involves first the formation of Ir-H species **A** from the  $Ir-X(Ln)$  catalyst and silane to give the formation of  $Ir^I-SiMe_2CH_2Ph$  moiety **B** on elimination of  $H_2$ . Then the oxidative addition of  $H-C$  (methyl) bond of  $HSiMe_2CH_2Ph$  to  $Ir^I-SiMe_2CH_2Ph$  is expected to form the intermediate **C** which on reductive elimination forms the product **D** and regenerates the catalyst **A** (Scheme 57). Then the insertion of the Ir(I) center of  $IrH(Phen)Ln$  into the  $Si-H$  bond of **D**, elimination of  $H_2$  and classical *ortho*  $sp^2C-H$  bond activation by the  $Ir(I)(Phen)$  moiety should lead to  $sp^2C-Si$  bond formation by reductive elimination to give the disilane derivative.

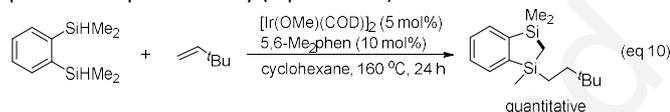


**Scheme 57.** Proposed mechanism for dehydrogenative dimerization of benzylmethylsilane.

The same catalyst  $[\text{Ir}(\text{OMe})(\text{COD})]_2/5,6\text{-Me}_2\text{Phen}$  could be used by Takai<sup>75</sup> to perform the *intramolecular*  $\text{sp}^3\text{C-H}$  bond silylation of a Si-Me group with dehydrogenation as described in equation 9.



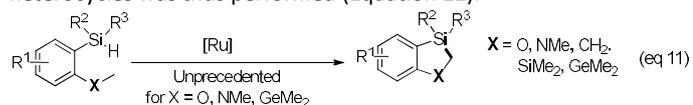
The intramolecular  $\text{sp}^3\text{C-H}$  bond silylation of one methyl of 1,2-bis(dimethyl silyl)benzene with the same  $\text{Ir}(\text{I})/5,6\text{-Me}_2\text{Phen}$  catalytic system in the presence of 3,3-dimethyl butene could also be performed quantitatively (Equation 10).<sup>75</sup>



It is important to note that the above silylation reactions are efficient only for a  $\text{SiCH}_3$  moiety as when one  $\text{-SiHMe}_2$  group of 1,2-bis(dimethylsilyl)benzene is replaced by  $\text{OMe}$  or  $\text{NMe}_2$  (Equation 10) the  $\text{OCH}_3$  and  $\text{NCH}_3$  group are not silylated.<sup>75</sup>

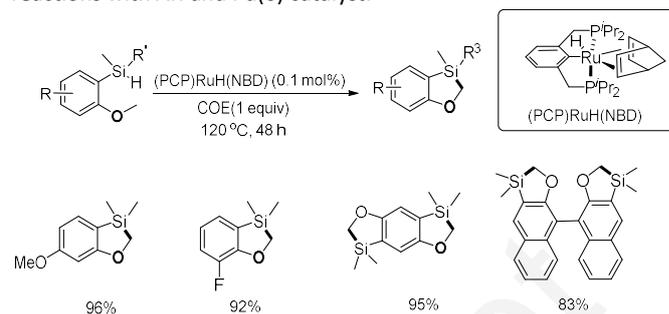
### 8.3 Silylation of the O-CH<sub>3</sub>, N-CH<sub>3</sub>, Si-CH<sub>3</sub> and Ge-CH<sub>3</sub> groups with Pincer Ru(II) catalyst.

*Directed silylation of the O-CH<sub>3</sub>, N-CH<sub>3</sub>, Si(CH<sub>3</sub>)<sub>2</sub> and Ge(CH<sub>3</sub>)<sub>2</sub> groups* has recently been solved with a Ru(II) catalyst. The previous problem of absence of intramolecular silylation by a  $\text{H-SiR}_2$  *ortho* group of a  $\text{sp}^3\text{C-H}$  bond of an *ortho*  $\text{OMe}$  or  $\text{NMe}_2$  group has been solved in 2017 by Zheng Huang who introduced a pincer ruthenium(II) catalyst for catalytic silylations. The fast synthesis of [1,3]-oxasilolanes, azasilolanes, germsilolanes and [1,3]-disilaheterocycles was thus performed (Equation 11).<sup>76</sup>



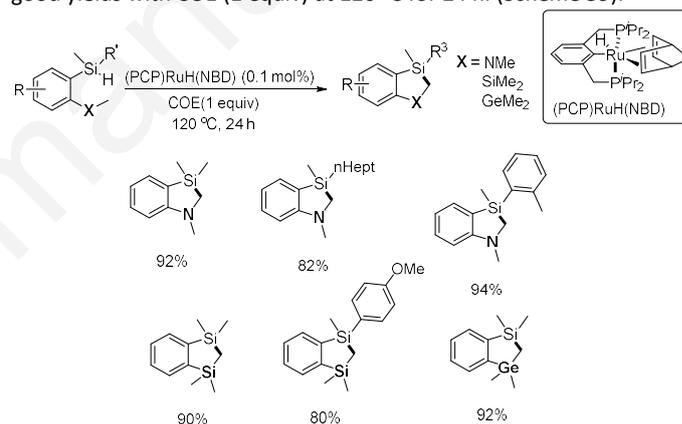
As shown in scheme 58 a low loading of pincer Ru(II) complex  $(\text{PCP})\text{RuH}(\text{NBD})$  (0.1 mol%) allows the intramolecular  $\text{sp}^3\text{C-H}$  bond silylation and formation of various [1,3]-oxasilolanes. The reaction takes place with hydrogen acceptor cyclooctene (COE) at 120 °C.

Other selected catalysts based on pincer Ir(III) complex offer low yield for silylation. This reaction could produce in one step 7.6 g of simple [1,3]-oxasilolane which can easily lead to cross coupling reactions with  $\text{ArI}$  and  $\text{Pd}(0)$  catalyst.<sup>76</sup>



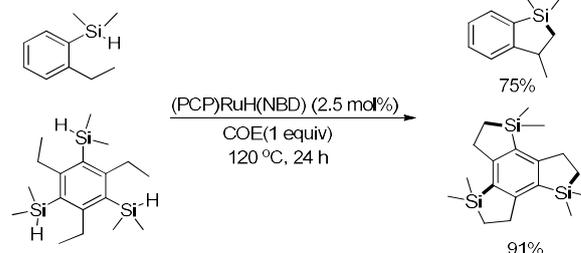
**Scheme 58.** Pincer-Ru(II)-catalyzed intramolecular silylation of  $\text{sp}^3\text{C-H}$  bonds  $\alpha$  to O-atom.

Previously the silylation of  $\text{NCH}_3$  group was reported by Sato<sup>43</sup> but the  $\text{C-H}$  bond activation was assisted by pyridine as directing group (Scheme 6). The *intramolecular* silylation of methyl  $\text{sp}^3\text{C-H}$  bonds of  $\text{-NRCH}_3$ ,  $\text{-Si(CH}_3)_3$  and even  $\text{-Ge(CH}_3)_3$  groups was performed, without assistance of a directing group, with the same pincer-Ru/COE catalyst by Zheng Huang<sup>76</sup>. However the loading of catalyst had to be increased for  $\text{Si(CH}_3)_3$  (5 mol%) and for  $\text{Ge(CH}_3)_3$  (10 mol%) to reach good yields with COE (1 equiv) at 120 °C for 24 h. (Scheme 59).



**Scheme 59.** Pincer Ru-catalyzed intramolecular silylation of  $\text{sp}^3\text{C-H}$  bonds  $\alpha$  to N-, Si-, or Ge-atom.

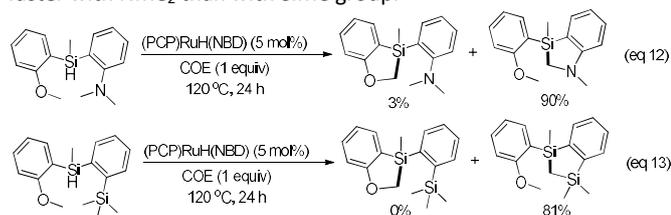
The silylation with pincer-Ru catalyst could also be performed at methyl primary  $\text{sp}^3\text{C-H}$  bond of *ortho* alkyl group not attached to a hetero atom element in proximity with the  $\text{Si-H}$  bond (Scheme 60).<sup>76</sup> The intramolecular silylation of *ortho* alkyl of 2-alkyl arylsilanes was also observed previously using  $\text{Rh}(\text{I})$  catalysts (see Schemes 45,46).<sup>69</sup>



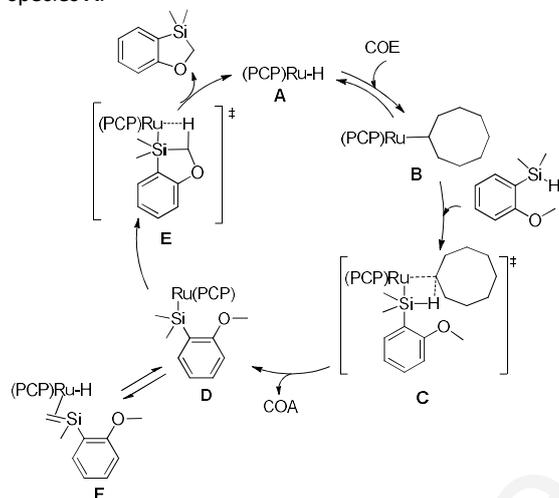
**Scheme 60.** Ru(II)-catalyzed intramolecular silylation of  $\text{sp}^3\text{C-H}$  bonds at *ortho* alkyl  $\beta\text{-C}$ -atom of arylsilanes.

To establish the relative reactivity of these  $(\text{X-CH}_3)$   $\text{C-H}$  bonds, experiments were performed with this pincer Ru(II) complex (5

mol%) with COE (1 equiv) at 120 °C for 24 h and show that intramolecular silylation is faster with NMe<sub>2</sub> than OMe group (Equation 12) and faster with SiCH<sub>3</sub> than OCH<sub>3</sub> (Equation 13), and faster with NMe<sub>2</sub> than with SiMe group.<sup>76</sup>



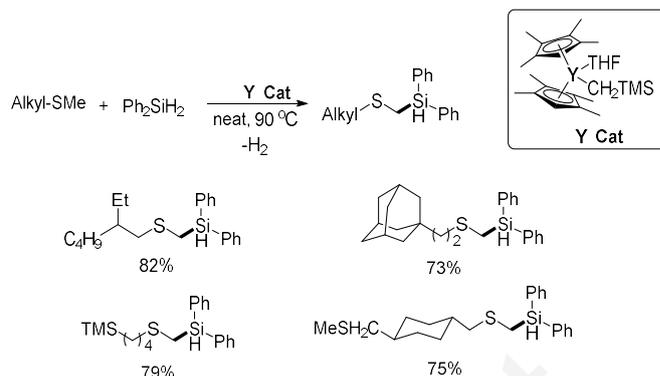
The observed H/D KIE of 3.9 suggests that the C-H bond cleavage is the rate determining step. The proposed mechanism based on exchange experiments is presented in scheme 61.<sup>76</sup> The formed cyclooctyl group from **B** assists in **C** the H-SiMe<sub>2</sub>Aryl hydride elimination to give cyclooctane and **D**. Then the intramolecular interaction of (CH<sub>3</sub>O)C-H bond with Ru-Si bond in **E** leads to C-H bond activation and Si-CH<sub>2</sub>O bond formation to release the Ru-H catalyst species **A**.



**Scheme 61.** Proposed mechanism for the intramolecular sp<sup>3</sup>C-H silylation of *ortho* O-CH<sub>3</sub> group.

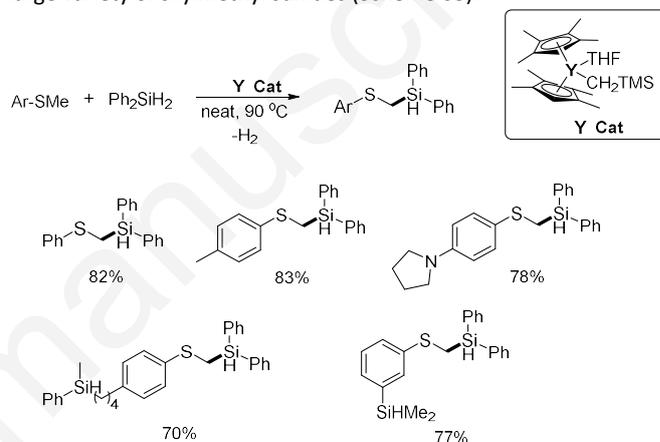
#### 8.4 Silylation of the S-CH<sub>3</sub> group with Yttrium catalyst

*Directed silylation of the S-CH<sub>3</sub> group* was observed in 2018 for the first time by Zhaomin Hou *et al.*<sup>77</sup> The catalytic silylation of a sp<sup>3</sup>C-H bond of methyl sulfides RSCH<sub>3</sub> with H-SiR'<sub>3</sub> to produce RSCH<sub>2</sub>SiR'<sub>3</sub> derivatives has been performed *intermolecularly* by using metallocene yttrium catalyst (C<sub>5</sub>HMe<sub>4</sub>)<sub>2</sub>Y(CH<sub>2</sub>SiMe<sub>3</sub>)(THF) which appeared as the best catalyst precursor for this S-methyl C-H silylation. The catalyst precursor *in situ* gives in the presence of H<sub>2</sub>SiR<sub>2</sub> the binuclear complex (C<sub>5</sub>HMe<sub>4</sub>)<sub>2</sub>Y(μH)<sub>2</sub>Y(C<sub>5</sub>HMe<sub>4</sub>)<sub>2</sub> as revealed for *n*-C<sub>5</sub>H<sub>11</sub>SCH<sub>3</sub> methyl silylation with PhMeSiH<sub>2</sub>.<sup>77</sup> The same catalyst was the most efficient for the silylation of alkyl-SCH<sub>3</sub> sulfides *without alkene* as H<sub>2</sub> acceptor (Scheme 62).



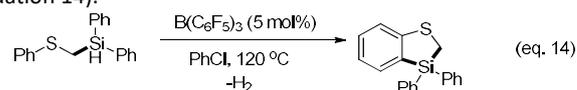
**Scheme 62.** Silylation of alkyl methyl sulfides with diphenylsilane and yttrium catalyst.

The same reaction with Yttrium catalyst can be applied to aryl methyl sulfides with diarylsilanes to give in neat medium at 90 °C a large variety of silylmethyl sulfides (Scheme 63).<sup>77</sup>

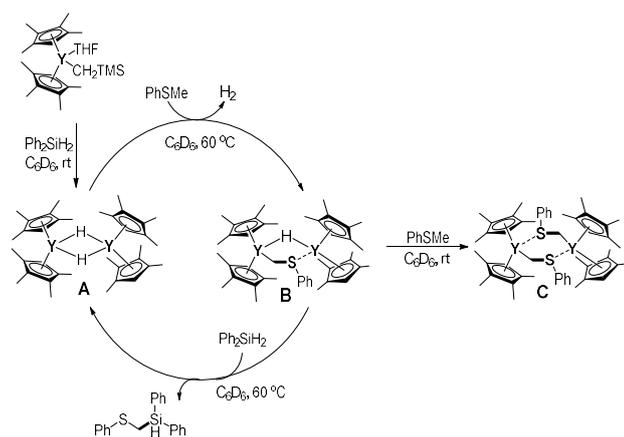


**Scheme 63.** Silylation of aryl methyl sulfides with diphenylsilane with metallocene yttrium catalyst.

The prepared silylmethyl sulfides can be used for further intramolecular silylation of *ortho* aryl sp<sup>2</sup>C-H bond to generate 5-membered annulated products in the presence of Lewis acid B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> (Equation 14).<sup>77</sup>



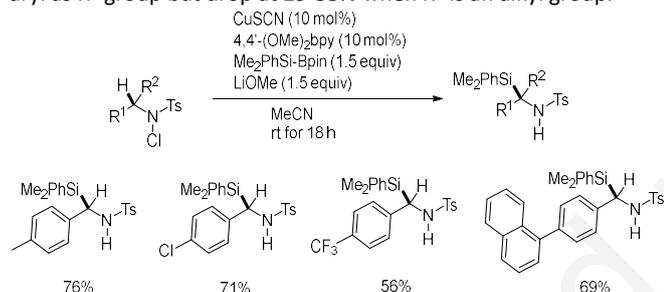
The proposed mechanism (Scheme 64) is based on stoichiometric reactions with silane with the catalyst precursor. With an excess of Ph<sub>2</sub>SiH<sub>2</sub> at room temperature the formation of bimetalocene **A** containing bridged hydrides is observed. Complex **A** reacts at 60 °C with PhSCH<sub>3</sub> to give the characterized intermediate **B** with a Y-CH<sub>2</sub>S(Ph)-Y bridge. The intermediate **B** can further lead to **C** with two identical -CH<sub>2</sub>S(Ph)- bridges. Both **B** and **C** react with 5 equiv of Ph<sub>2</sub>SiH<sub>2</sub> at 60 °C to give the PhSCH<sub>2</sub>SiHPh<sub>2</sub> silane and to regenerate **A**.



**Scheme 64.** Mechanism for silylation of  $sp^3C-H$  bond of phenyl methyl sulfide with Yttrium catalyst.

### 8.5 Directed silylation of the $\alpha-C-H$ bond of (sulfonamide)XN-CHR<sub>2</sub>.

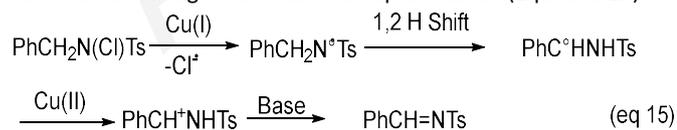
Recently Oestreich<sup>78</sup> has demonstrated the silylation of  $sp^3C-H$  bond adjacent to amide nitrogen atoms with  $R_3Si-Bpin/alkoxide$ . The reaction is catalyzed by  $CuSCN/4,4'-(OMe)_2bpy$  (10 mol%). The silylation occurred easily with *N*-chloro sulfonamides and with  $MePh_2Si-Bpin$  (Scheme 65). The yields are in the range 50–76% with aryl as  $R^1$  group but drop at 29–35% when  $R^1$  is an alkyl group.



**Scheme 65.** Copper-catalyzed silylation of  $sp^3C-H$  bonds adjacent to a *N*-chloro sulfonamide *N* atom.

Although the reaction presented here corresponds to the formation of a  $sp^3C-Si$  bond, it does not involve the formal silylation of  $sp^3C-H$  bond. Control experiments show that the initial step is the formation of the imine  $PhCH=NTs$  in the presence of  $LiOMe$  and the catalytic system  $CuSCN/(MeO)_2bpy$ . This imine in the presence of  $Me_2PhSi-Bpin$  at room temperature gives the  $\alpha$ -silylated product *via* classical  $Cu$ -catalyzed 1,2 addition of the silicon nucleophile.

It is possible that the imine formation, usually arising from base mediated  $\beta$ -elimination, is formed *via* initial formation of the radical  $PhCH_2N^{\bullet}Ts$ , by action of  $Cu(I)$ , rearranging into  $PhCH^{\bullet}NHTs$  radical which can give, by action of  $Cu(II)$ , the cation intermediate  $PhCH^+NHTs$  leading to the imine on deprotonation (Equation 15).

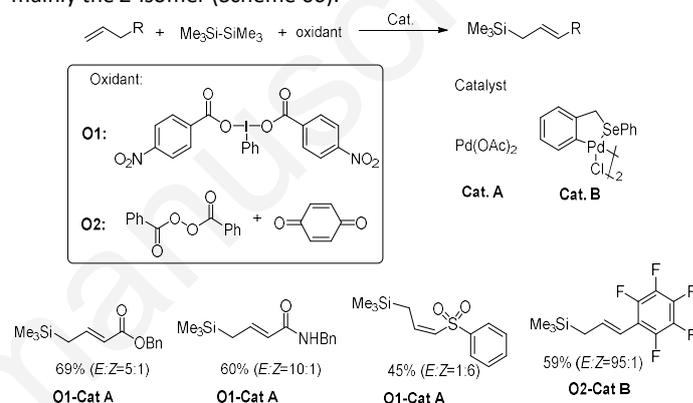


## 9. Silylation of allylic and alkane C-H bonds producing terminal $CH_2-SiR_3$ function

Some silylations leading to  $sp^3CH_2-SiR_3$  bond formation will be presented here, although they do not involve a real  $sp^3C-H$  bond

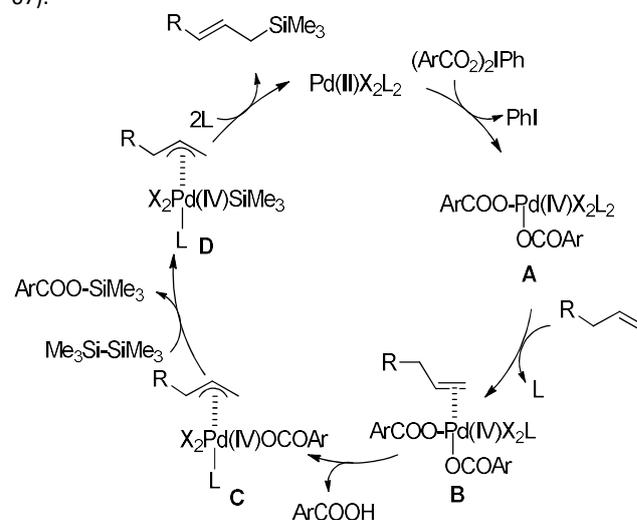
catalytic silylation. Three different examples reported by Swabó,<sup>79</sup> Peng-Fei Xu<sup>80</sup> and Zheng Huang<sup>81</sup> will be presented here as they constitute useful approaches to produce reactive  $sp^3CH_2-SiR_3$  from allylic compounds and from initial alkane dehydrogenation. The first one involves a classical  $Pd(II)/Pd(IV)$  activation of alkene into allyl derivatives,<sup>79</sup> the second one involves a silyl radical formation able to regioselectively add to allylic  $C=C$  bond<sup>80</sup> and the third presents the dehydrogenation of alkanes followed by isomerization and hydrosilylation of resulting alkenes.<sup>81</sup>

In 2011 Swabó described the catalytic silylation with  $Me_3Si-SiMe_3$  of a functional allylic group with  $sp^3C-Si$  bond formation.<sup>79</sup> The reaction was catalyzed by  $Pd(OAc)_2$  or a  $Pd(II)$ -cyclometalate complex but the reaction needed a strong oxidant such as hypervalent iodine reagent  $(ArCO_2)_2IPh$ , but also  $PhOCO-COOPh$  with benzoquinone or 4-nitro benzoic acid. This oxidant prevents the use of a hydrogen acceptor such as an alkene. The reaction at 80 °C for 48 h offers preferably the stereoselective formation of the *E*-isomer, except for the allyl sulfones and the allylsulfonamides which provide mainly the *Z*-isomer (Scheme 66).



**Scheme 66.** Synthesis of allylsilanes by catalytic C-H silylation.

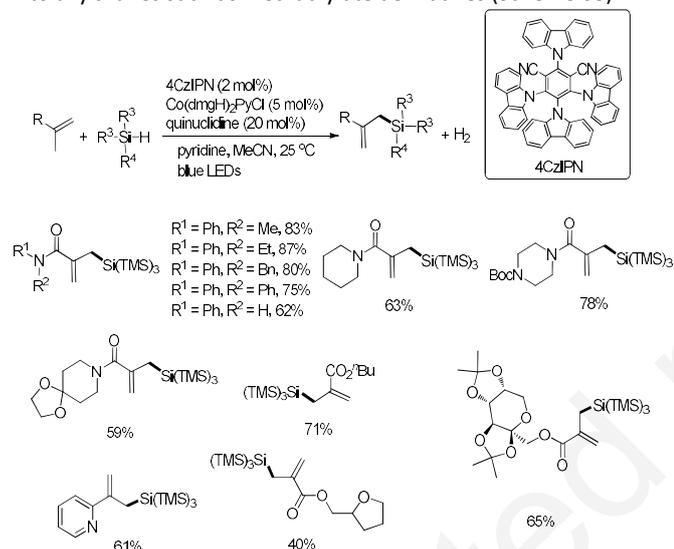
The proposed mechanism (Scheme 67) suggests the initial formation of a  $Pd(IV)$  intermediate **A** on oxidation of  $Pd(II)$  with  $(ArCO_2)_2IPh$ . Coordination of the allyl double bond in **B** is followed by  $\pi$ -allyl ligand formation in **C** on C-H bond deprotonation with a carboxylate. Then transmetalation with  $Me_3Si-SiMe_3$  leads to the intermediate **D** which is subject to reductive elimination with  $sp^3C-Si$  bond formation with the less substituted allylic carbon to generate the silylated functional allyl derivative and  $Pd(II)$  catalyst. (Scheme 67).



**Scheme 67.** Proposed catalytic cycle for silylation of functional allyl

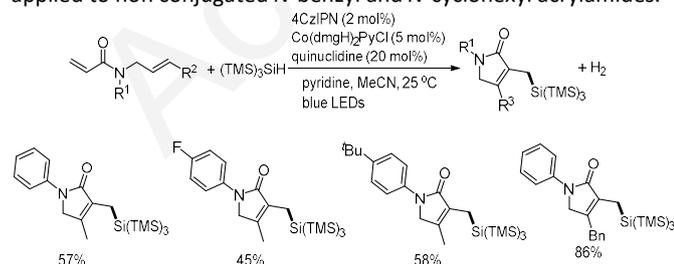
group.

**Photocatalysts** have been successfully used for the selective functionalization of C-H bonds, but mostly till now of  $sp^2$  C-H bonds.<sup>82</sup> However recently Peng-Fei Xu *et al.*<sup>80</sup> have reported a new method to generate substituted allylsilanes by dehydrogenative silylation of alkenes with  $H-SiR_3$ . The silylation does not involve the functionalization of C-H bond but regioselectively takes place by addition of a silyl radical at the terminal carbon of the allyl  $C=C$  bond  $RC(CH_3)=CH_2$  to form a terminal  $CH_2-SiR_3$  bond. The reaction involves the initial generation of a  $R_3Si\cdot$  radical by hydrogen atom transfer (HAT) catalysis and the reaction is promoted by an organic photocatalyst and a Co(II) catalyst  $Co(dmgH)_2Cl(Py)$  (dmg = dimethyl glyoximate) for single electron transfer (SET) (Scheme 68). The dehydrogenative silylation of alkenes was performed with photocatalyst 4CzIPN using blue LEDs with  $Co(dmgH)_2(Py)Cl$  for single electron transfer (SET) and quinuclidine as HAT catalyst in the presence of pyridine as a required base. A large variety of functional alkenes were selectively transformed at room temperature in MeCN, into allylsilanes such as methacrylate derivatives (Scheme 68).



**Scheme 68.** Dehydrogenative radical silylation of alkenes into allylsilanes with multiple catalysis.

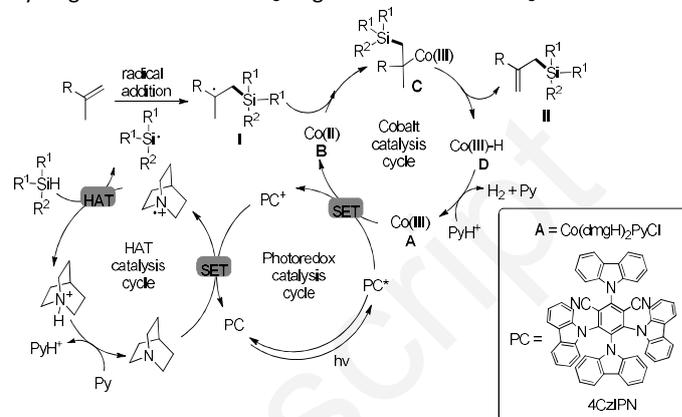
This tricatalytic system was applied to *N*-allyl-*N*-arylacrylamides to produce related cyclic silylated products with a terminal  $CH_2SiR_3$  group: 5-membered  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams *via* 5-exo-trig cyclization (Scheme 69). This general transformation was also performed at the gram scale. However the reaction could not be applied to non conjugated *N*-benzyl and *N*-cyclohexyl acrylamides.



**Scheme 69.** Dehydrogenative radical silylation of *N*-allyl arylamides and 5-exo-trig cyclization.

This transformation involves the formation of radical intermediates as it is inhibited by radical trap TEMPO. The proposed mechanism is

shown on Scheme 70.<sup>80</sup> The reaction requires the presence of a photocatalyst **PC** (4CzIPN) which on excitation with blue LED generates the excited **PC\*** which is oxidized by Co(III) species **A** giving **PC\*** cation and Co(II) species **B**. ( $E_{1/2}^{red} Co(III)/Co(II) = -0.68V$  vs SCE). Then the **PC\*** = 4CzIPN<sup>+</sup> species ( $E_{1/2}^{red} P^+/P = +152V$  vs SCE) oxidizes the HAT catalyst quinuclidine **Q** ( $E_{1/2}^{red} = +1.10V$ ) to give **Q\*** and initial photocatalyst **PC**. The radical cation **Q\*** is able to trap the hydrogen atom from  $H-SiR_3$  to generate the radical  $R_3Si\cdot$ .

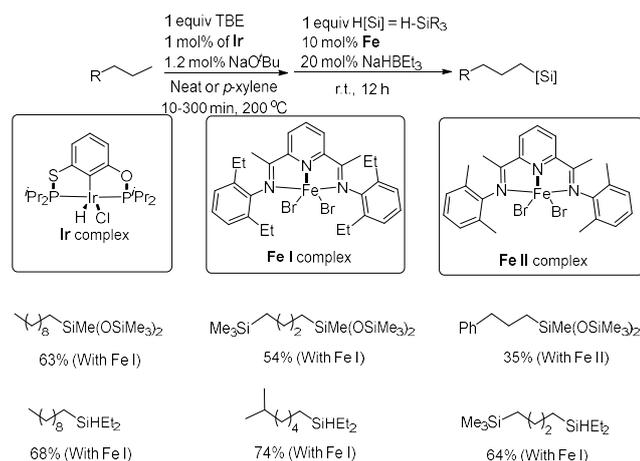


**Scheme 70.** A proposed mechanism for dehydrogenative silylation of alkenes into allylsilanes.

Subsequent addition of the  $R_3Si\cdot$  radical to the terminal carbon atom of the alkene generates the carbon center radical which adds the Co(II) species **B** arising from the reduction of the initial Co(III) species **A** by SET from **PC\***, to give **C**. The later *via* classical beta elimination generates the new alkene with an allyl silyl group **II**. The resulting Co(III)-H species **D** on protonation with  $PyH^+$  releases  $H_2$  and the initial Co(III) catalyst **A**.

This new synergetic catalytic reaction to form  $CH_2=CH(R')-CH_2SiR_3$ , from  $CH_3-CH(R')=CH_2$ , does not involve a direct C-H bond functionalization, but the formation of silyl radical, has a strong potential to produce regioselectively functional allylsilanes and to open new selective silylations.

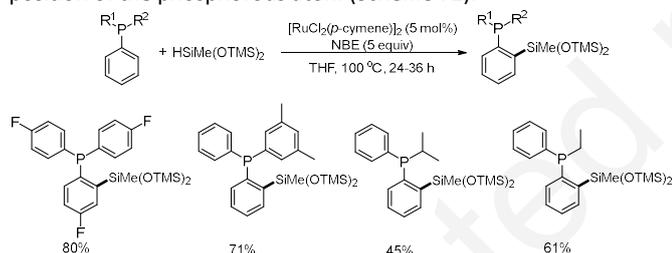
**Linear alkylsilanes** are one of the most important compounds for the wide applications to lead to coatings, silicone rubbers and moulding products. Hydrosilylation of terminal olefins is the most efficient method for the synthesis of linear alkylsilanes, but the direct and selective functionalization of alkanes at primary C-H bonds into a C-Silyl group have been seldom reported in spite of their importance. However, Zheng Huang *et al.* in 2015<sup>81</sup> reported a new method to produce linear alkylsilanes *via* a dual-catalyst system, one pot and three-step alkane silylation. These catalytic systems involve a pincer-ligated Ir(III)-catalyzed alkane dehydrogenation to generate internal olefin and Fe catalyzed successive regioselective olefin isomerization and hydrosilylation (Scheme 71).<sup>81</sup> The (PNN)FeBr<sub>2</sub> complex is ineffective for the hydrosilylation of internal olefins, but plays two important roles for the catalytic system, i) the fast isomerization of internal olefins, produced by Ir catalyzed alkane dehydrogenation, into the terminal olefin and ii) the catalyzed Markovnikov hydrosilylation of the terminal alkenes to yield terminal alkylsilanes.



**Scheme 71.** Catalytic silylation of various alkanes via catalytic alkane dehydrogenation and isomerization–hydrosilylation.

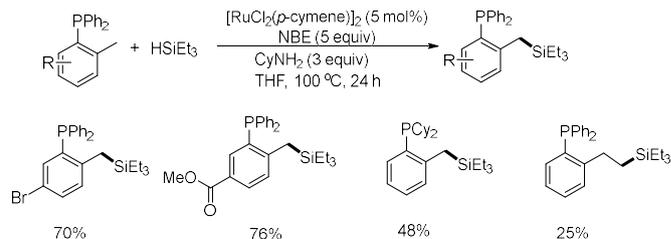
## 10. Catalyzed $sp^3C$ -H bond silylation directed by phosphine P(III) atom

Quite recently Zhuangzhi Shi<sup>83</sup> explored the possibility to silylate aryl  $sp^2C$ -H bond of P(Aryl) $R_2$  phosphines, with H-SiEt<sub>3</sub> or HSiMe(OTMS)<sub>2</sub> and Ru(II) catalyst precursor [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub>. In spite of the difficult formation of a strained 4-membered cyclometalate intermediate, directed by a phosphine phosphorous(III) atom, with P-Ru-C(*ortho*) bond formation and via deprotonation of the *ortho* aryl  $sp^2C$ -H bond, the dehydromonosilylation was efficient in the presence of norbornene as hydrogen acceptor at 100 °C at the *ortho* position of the phosphorous atom (Scheme 72).



**Scheme 72.** Ruthenium(II) catalyzed *ortho* silylation of arylphosphine  $sp^2C$ -H bond.

More importantly, when an *ortho* methyl group was present on the aryl group of the phosphine, the ruthenium(II) catalyzed dehydrosilylation of methyl  $sp^3C$ -H bond with H-SiEt<sub>3</sub> took place easily at 100 °C in THF but with additional CyNH<sub>2</sub> as a base (Scheme 73).<sup>83</sup> The observed silylation shows that the mono silylation of  $sp^3C$ -H bond at *ortho* methyl group is easier than at the *ortho*  $sp^2C$ -H bond as no *ortho*  $sp^2C$ -H arylation was now observed. The *ortho* methyl arylation seems to be favoured by the presence of an electron withdrawing group on the aryl group (Cl, F, Br, CO<sub>2</sub>Me). When an *ortho* ethyl group is present instead of a methyl group, the silylation takes place at primary C-H bond (Me) rather than at the secondary (CH<sub>2</sub>) C-H bond.



**Scheme 73.** Ru-catalyzed  $sp^3C$ -H silylation of *ortho* methyl group in arylphosphines.

The transformation of the *ortho*-CH<sub>2</sub>SiEt<sub>3</sub> group, of the triaryl phosphines prepared as shown in scheme 73, into a CH<sub>2</sub>CH(OH)Ph group can be easily performed on reaction with PhCHO in the presence of the salt N(<sup>t</sup>Bu)<sub>4</sub><sup>+</sup>F<sup>-</sup> at 60 °C.<sup>83</sup>

This mild condition, intermolecular silylation of alkyl group of phosphine ligands likely takes place via deprotonation by CyNH<sub>2</sub> of the methyl or ethyl  $sp^3CH$  bond on interaction with the Ru(II) center to form a 5-membered cyclometalate, or 6-membered cyclometalate from ethyl group, as deprotonation assisted by Ru(II) site requires low energy.<sup>84-85</sup> This simple silylation has potential to modify many useful phosphorous ligands already used in metal-catalyzed reactions.<sup>86</sup>

## Conclusions and Outlook

Several methods of metal-catalyzed activation of  $sp^3C$ -H bonds synchronized with silylation of this  $sp^3C$  carbon to produce  $sp^3C$ -SiR<sub>3</sub> bonds are now efficient to modify functional molecules, ligands to build catalysts or molecular materials, and to offer functionalizations of silicon containing products. *Intermolecular* silylations of a variety of  $sp^3C$ -H bonds can be directed by a N-containing heterocycle in the presence of silane and of various catalysts based on Ru(0), Ru(II), Rh(I), Ir(I) and Ir(III) metal complexes. The transformation is based on heterocycle directed  $sp^3C$ -H bond metal activation and Si-H bond metal activation with hydrogen elimination which can be solved with addition of an alkene as hydrogen trap. This regioselective formation of CH<sub>2</sub>SiR<sub>3</sub> groups allows their easy transformations such as via oxidation and carboxylation. *Intramolecular*  $sp^3C$ -H bond silylation with R<sub>3</sub>Si-SiR<sub>3</sub> can be directed by an amide type function in the presence of Pd(II) catalyst which involves first a  $sp^3C$ -H bond deprotonation and palladacycle formation usually followed by oxidative addition of the silane Si-Si bond and formation of the C-Si bond. This method can be successfully applied to the stereoselective  $sp^3C$ -H bond silylation of aminoacids and peptides.

The *intramolecular* silylation of  $sp^3C$ -H bonds can be performed, after initial formation of a R'CH<sub>2</sub>O-SiR<sub>2</sub>(H) group, by catalytic dehydrohydrosilylation of alcohols or hydrosilylation of ketones with H<sub>2</sub>SiR<sub>2</sub>. The R'CH<sub>2</sub>O-SiR<sub>2</sub>(H) groups lead to 5- or 6-membered oxasiloxanes in the presence of Ir(I) or Rh(I) with an alkene for hydrogen capture. This silylation is currently used for the access to 1,3- and 1,4- diols from alcohols with a  $sp^3C$ -H bond at  $\gamma$  or  $\delta$  position. Similarly initial silylation of amine NH bonds into N-SiR<sub>2</sub>H group allows further *intramolecular* silylation of neighbour  $sp^3C$ -H bond with Ir(I) catalyst with H<sub>2</sub> trap alkene. Both catalytic silylation steps can be performed in one pot with the same Ir(I) catalyst but on addition of alkene for the second intramolecular step. The  $sp^3C$ -H silylation step can be controlled, on addition of chiral diphosphine, to reach good enantioselectivities especially in the functionalization of cyclopropyl derivatives.

Silanes containing a C-SiR<sub>2</sub>H group at the proximity of a CH<sub>2</sub>R group, such as in ortho alkyl arylsilanes can lead to an intramolecular catalytic silylation of one sp<sup>3</sup>C-H bond with formation of 5-membered silanes with Rh(I) or Ir(I) catalyst mostly in the presence of an alkene. The addition of chiral dinitrogen ligand to the Ir(I) catalyst can lead to excellent enantioselectivities. Alkyl silanes arising from initial catalytic hydrosilylation of terminal alkenes leads also to intramolecular silylation into 5-membered cyclic silanes. This reaction on oxidation offers new access to 1,4-diols.

*Intermolecular and intramolecular* sp<sup>3</sup>C-H bond silylation of X-CH<sub>3</sub> into X-CH<sub>2</sub>SiR<sub>3</sub> group can be performed with a variety of heteroatoms X (X = B, Si, O, N, Ge, S). B-CH<sub>3</sub> groups are silylated after addition of a dinitrogen bidentate ligand to boronic acid, with the help of Ru(0) catalyst precursor. Intermolecular silylation of SiCH<sub>3</sub> bond with Ir(I)/Phenanthroline catalyst can be directed for the production of 5- and 6- membered 1,3-disilanes. By contrast pincer-Ru(II)-H catalyst allows the intramolecular silylation of XCH<sub>3</sub> groups (OCH<sub>3</sub>, NCH<sub>3</sub>, Si-CH<sub>3</sub> and Ge-CH<sub>3</sub>) C-H bonds to produce 5-membered cycles with X-CH<sub>2</sub>-Si arrangement. The intermolecular silylation of alkylSCH<sub>3</sub> and arylSCH<sub>3</sub> can now be easily achieved using an yttrium metallocene catalyst.

Formal silylation of allyl group CH<sub>3</sub>-C(R)=CH<sub>2</sub> into useful function CH<sub>2</sub>=C(R)-CH<sub>2</sub>SiR<sub>3</sub> can be performed in several ways although they do not involve direct sp<sup>3</sup>C-H bond silylation. 1) Pd(II) catalysts with an oxidant are used for the silylation with Me<sub>3</sub>Si-SiMe<sub>3</sub> of allyl group, via allyl-Pd(IV) intermediate. 2) A photocatalyst associated to a cobalt(III) catalyst has been used to generate a silyl radical from silane, via hydrogen atom transfer (HAT), which can add to the allyl C=C bond to further produce CH<sub>2</sub>=C(R)-CH<sub>2</sub>SiR<sub>3</sub> derivatives. 3) A 3-step alkane silylation into terminal linear alkyl silane alkyl-CH<sub>2</sub>SiR<sub>3</sub> can be performed using a Ir(III) catalyst to dehydrogenate the alkane into alkenes and a Fe(II) catalyst to isomerize the produced internal alkenes into a terminal alkene and to hydrosilylate this terminal alkene into linear alkylsilane.

Finally a new useful orientation for the silylation of a sp<sup>3</sup>C-H bond has just been performed via the silylation directed by a (phosphine)P(III) atom for the regioselective silylation of an *ortho* methyl of arylphosphine, with a Ru(II) catalyst in the presence of alkene. This new reaction should allow fast modification by sp<sup>3</sup>C-H bond silylation of a variety of phosphine or diphosphine ligands containing alkyl groups.

These successful examples show that classical noble metal catalysts mostly derivatives of Ru, Rh, Ir and Pd metals are required for both the sp<sup>3</sup>C-H bond activation and the Si-H or Si-Si bond activation, for sp<sup>3</sup>C-Si bond formation. Recently many examples of sp<sup>3</sup>C-H bond activation to make sp<sup>3</sup>C-C bond cross-couplings have been discovered with first row metal catalysts (Mn, Fe, Co),<sup>87-90</sup> thus we can expect that these cheap and less toxic metal catalysts will also inspire chemists to perform with them sp<sup>3</sup>C-H bond catalytic silylations.

The first evidence for direct catalytic silylation of a methyl group graphed on an aryl group of phosphine into a aryl-CH<sub>2</sub>SiR<sub>3</sub> group suggests that in the near future useful phosphines or diphosphines, even chiral ones, can be modified by the introduction of a steric hindered group CH<sub>2</sub>SiR<sub>3</sub> or which can be transformed into a new function to quickly reach new functional ligand and their metal catalysts as it is already shown for phosphine sp<sup>2</sup>C-H bond functionalization.<sup>86, 91-92</sup>

This easy transformation of sp<sup>3</sup>C-H bond into CH<sub>2</sub>SiR<sub>3</sub> group has already allowed the direct access to carboxylates, alcohols, diols, esters, or aminoalcohols, sometimes with excellent enantioselectivity. Thus these reactions should allow new

functionalizations leading to natural products but also to modify in one pot reaction monomers for further polymerization or polymers themselves,<sup>93-94</sup> or the physical properties of molecular materials,<sup>95</sup> including luminescence properties.<sup>96-97</sup> One can even expect that in the near future that catalytic sp<sup>3</sup>C-H bond silylation can be applied to directly modify metal-complexes and their optical properties,<sup>98</sup> or to produce more efficient catalysts.

## Conflicts of interest

There are no conflicts to declare.

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