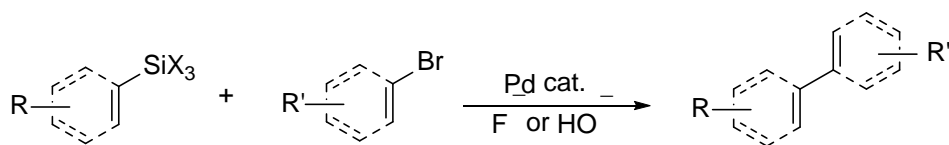


The Hiyama Cross-Coupling Reaction: New Discoveries

Francisco Foubelo,^[a] Carmen Nájera^[a] and Miguel Yus^[a]

Dedicated to Professor Ryoji Noyori

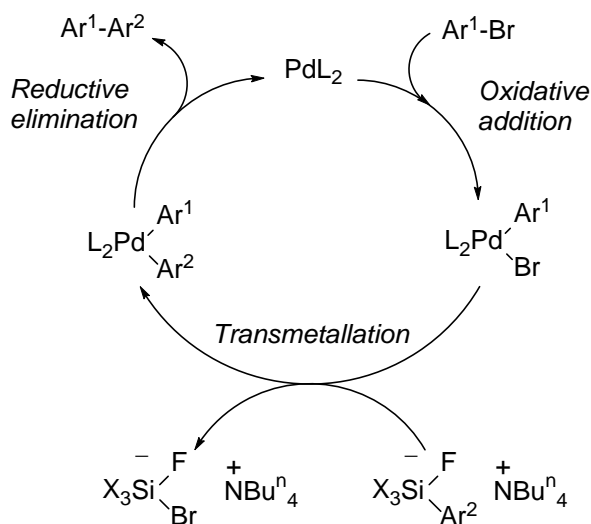


ABSTRACT: In this review article recent developments in the Hiyama cross-coupling reaction from 2010 up today are presented. The most important methodology involves formation of biaryl systems by using aryl bromides or iodides and aryl trialkoxy silanes: other variants are far less studied. The most useful procedures are collected paying special attention to the synthetic application of this methodology in synthetic organic chemistry.

Keywords: Hiyama reaction; silicon compounds; biaryls; cross-coupling; palladium catalysts

1. Introduction

The Hiyama cross-coupling reaction¹ represents one of the most used methodologies for creating new carbon-carbon bonds. This reaction has been mainly used for the formation of Csp²-Csp² bonds, for instance to prepare biaryls, and the accepted mechanism involves in most of the cases an activating reagent such as fluoride for the formation of a pentacoordinate silicon intermediate able to perform the transmetalation step. Previously, an oxidative addition takes place on the palladium(0) catalyst, and finally a reductive elimination gives the coupling product regenerating the active catalytic species (Scheme 1).



Scheme 1. Proposed mechanism for the Hiyama cross-coupling reaction of an aryl bromide and an arylsilane.

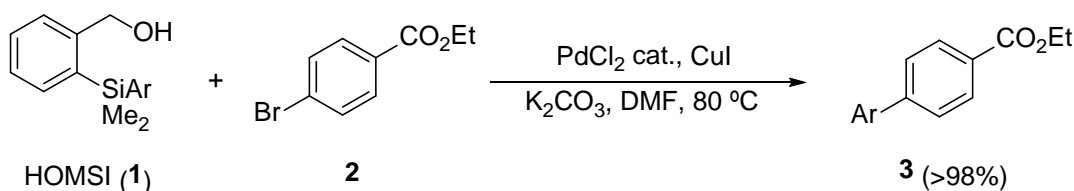
Several review articles have been reported on the Hiyama cross-coupling reaction, the last excellent one being published in 2011 by the protagonist of the chemistry.² Since then, the mentioned methodology has been considered as a part of general accounts on cross-coupling reactions.³ For this reason, and due to our continuous interest in the Hiyama reaction,⁴ we present here the last findings in this process from 2010 up to now, paying special attention to the synthetic applications of this chemistry.

2. Arylation Reactions

As it was mentioned before, the arylation of aryl halides with compounds of the type ArSiX_3 is the most studied Miyaura cross-coupling reaction. Depending on the X group (alkyl, fluoro, alkoxy) the reactivity of the corresponding silicon-containing reagent can be different, so this section will be divided according to that circumstance.

2.1. Alkylated Silicon Reagents

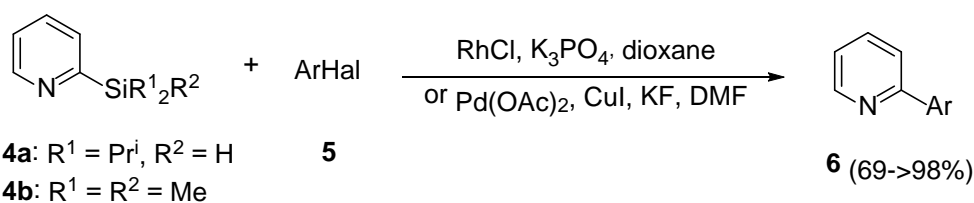
There are few examples of using ArSiR_3 or similar reagents for the cross-coupling with aryl halides. Some years ago⁵ it was described the use of HOMSI (**1**) as reagent for its palladium-catalyzed arylation with ethyl 4-bromobenzoate (**2**) in the presence of copper(I) iodide to give biaryls **3** (Scheme 2).



[Ar = Ph, 4-MeOC₆H₄, 4-ClC₆H₄]

Scheme 2. Cross-coupling between HOMSI (**1**) and ethyl 4-bromobenzoate (**2**).

Other examples of arylation of alkylated silanes involve compounds **4**, which by a rhodium (**4a**)⁶ or palladium (**4b**)⁷ catalysis were arylated with different halides **5** to give the expected products **6** with good results (Scheme 3).



4a: $\text{R}^1 = \text{Pr}^i$, $\text{R}^2 = \text{H}$

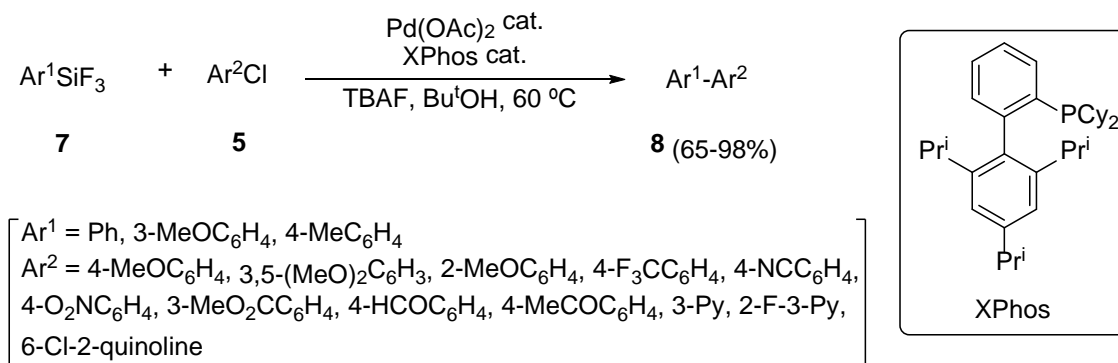
4b: $\text{R}^1 = \text{R}^2 = \text{Me}$

[Ar = Ph, 4-MeOC₆H₄, 4-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-NCC₆H₄,
4-MeO₂CC₆H₄, 4-HCOC₆H₄, 4-H₂NC₆H₄, 4-MeCOC₆H₄, 3-F₃CC₆H₄,
3-EtO₂CC₆H₄, 3-O₂NC₆H₄, 3-FC₆H₄, 3-BrC₆H₄, 3-PhC₆H₄, 3-MeC₆H₄,
3-MeCOC₆H₄, 5-ClPy, 5-MePy, 5-NCPy, 6-(Boc)₂NPy
Hal = Cl, Br, I

Scheme 3. Coupling of silylated pyridines **4** with aryl halides **5**.

2.2. Fluorinated Silicon Reagents

The use of reagents of type Ar^1SiF_3 (**7**) has been reported for the palladium-catalyzed cross-coupling with aryl or heteroaryl chlorides in the presence of the phosphine XPhos as ligand and tetrabutylammonium fluoride (TBAF) as a fluoride source, giving the expected products **8** (Scheme 4).⁸



Scheme 4. Coupling of trifluoro compounds **7** with aryl and heteroaryl chlorides.

2.3. Alkoxyated Silicon Reagents

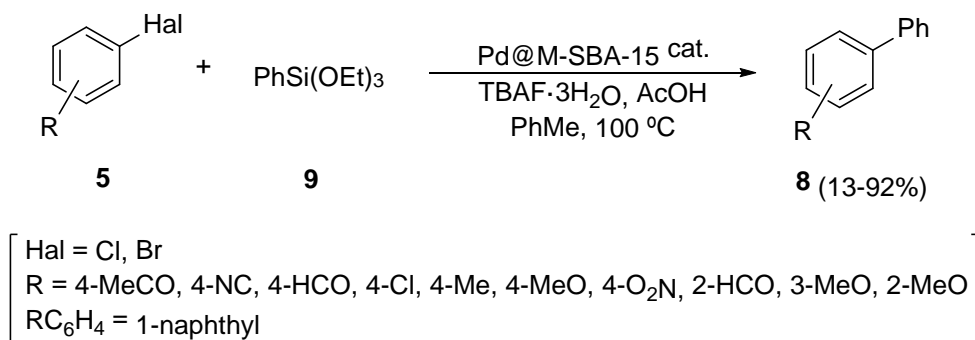
The most important group of reagents used in the Miyaura cross-coupling reaction are of the type ArSi(OR)_3 . In this part we will consider the use of supported palladium catalysts, the role of different ligands on the metal catalysts, the use of metal nanoparticles, and other type of reactions involving different substrates.

2.3.1. Supported Catalysts

As in many other cases, the possibility of supporting the catalyst, in most of the cases a palladium one, would facilitate enormously the recovery and reuse of the catalyst, which plays a fundamental role in industrial applications of this chemistry.

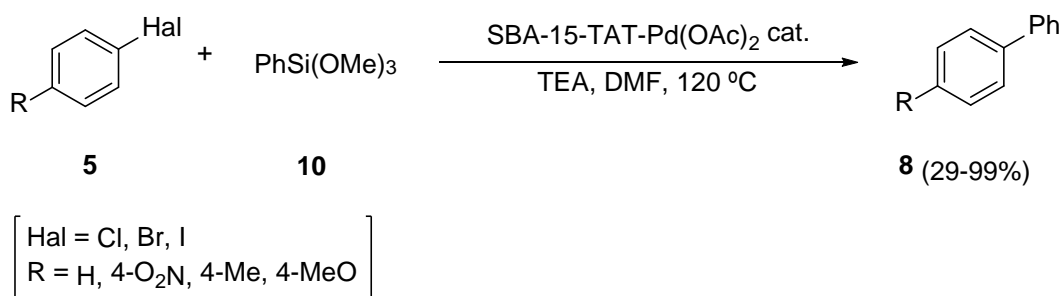
Silica as support

Palladium nanoparticles supported on SBA-15, a mesoporous silica, was successfully used for the cross-coupling of aryl chlorides or bromides **5** with phenyltriethoxysilane **9** in the presence of TBAF yielding the expected biaryls derivatives **8** with variable results (Scheme 5).⁹



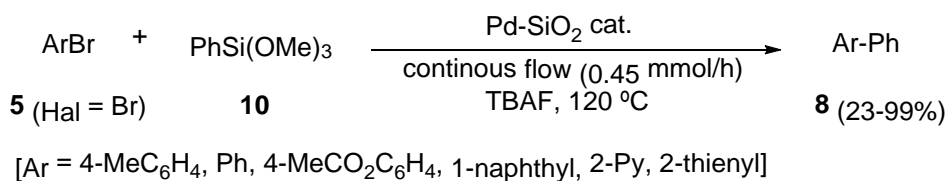
Scheme 5. Cross-coupling between aryl halides **5** and the silane **9**.

The same support SBA-15, but in combination with a triazine derivative (TAT) was in general very efficient for anchoring palladium acetate and used for the coupling between aryl halides **5** with phenyltrimethoxysilane (**10**) to yield products **8** (Scheme 6).¹⁰



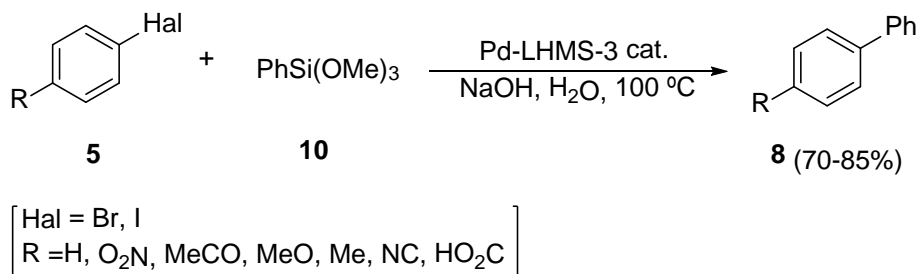
Scheme 6. Coupling between aryl halides **5** and the silane **10**.

The catalyst Pd(OAc)_2 was supported on silica and used for the coupling of aryl bromides and the trimethoxysilane **10** under continuous flow conditions, so the expected products **8** were obtained with variable yields (Scheme 7).¹¹



Scheme 7. Coupling between aryl bromides **5** and the silane **10** under continuous flow conditions.

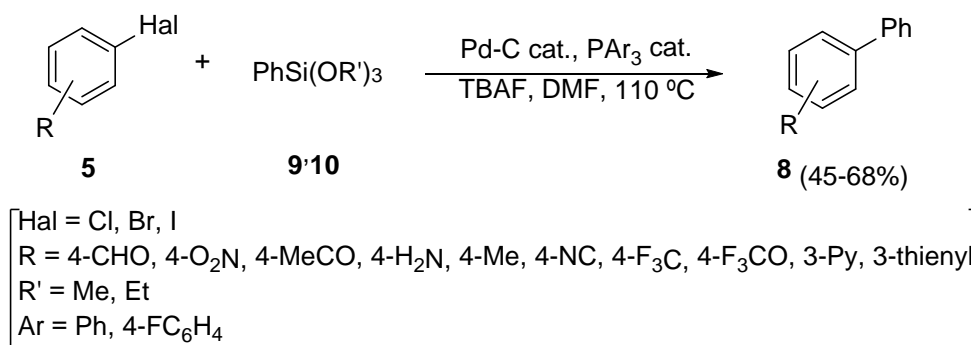
Water was the green solvent of choice for the coupling of several aryl halides **5** with the silane **10** promoted by a heterogeneous palladium-grafted periodic mesoporous organosilica (LHMS-3) under basic conditions, giving the expected products **8** with very good results (Scheme 8).¹²



Scheme 8. Coupling of aryl halides **5** with the silane **10** under aqueous conditions.

Carbon as support

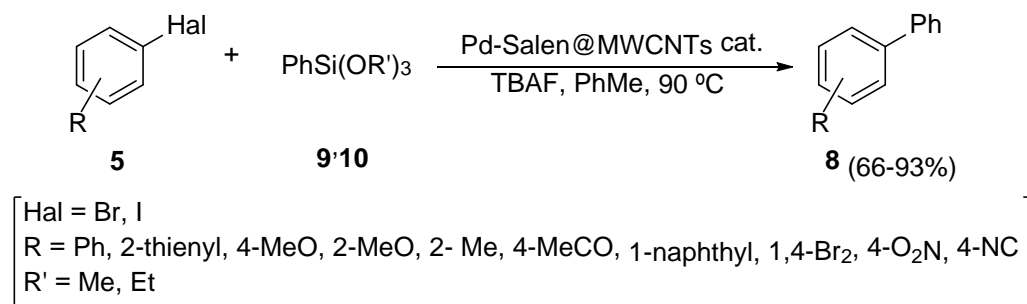
One of the most used supports for palladium is carbon (Pd/C), which can be used in combination with TBAF as activating additive or in few cases with sodium hydroxide. Thus, the reaction of aryl halides **5** with silanes **9** or **10** in the presence of TBAF gave the expected biaryls **8**, in some cases being necessary to use a catalytic amount of a phosphine as additive (Scheme 9).¹³



Scheme 9. Coupling of aryl halides **5** with silanes **9**, **10**.

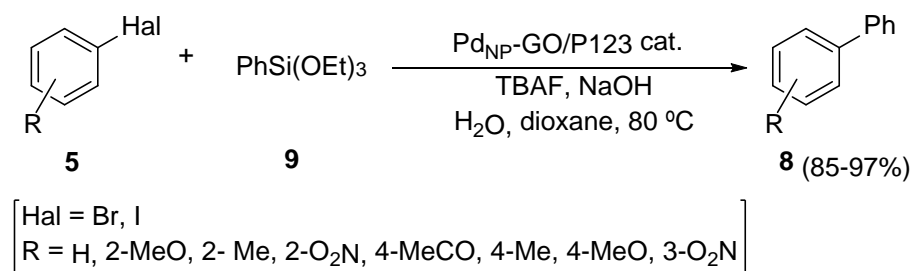
The same process shown in Scheme 9 was also carried out in the absence of a fluorine source and in the presence of sodium hydroxide to activate the silicon reagent.¹⁴

An especial case of a carbonaceous support is the use of multiwalled carbon nanotubes, on which a palladium(II) Salen complex was anchored (Pd-Salen@MWCNTs) and used successfully in the coupling of aryl bromides or iodides with the alkoxy silanes **9**, **10** in the presence of TBAF to yield products **8** (Scheme 10).¹⁵



Scheme 10. Coupling of aryl halides **5** with alkoxy silanes **9, 10** using carbon nanotubes as support.

Recently, exfoliated palladium decorated graphene oxide nanosheets ($\text{Pd}_{\text{NP}}\text{-GO/P123}$) has been reported to be efficient in the coupling of halides **5** with the triethoxysilane **9** (Scheme 11).¹⁶



Scheme 11. Coupling of aryl halides **5** with the silane **9** using a Pd-modified graphene as support.

Other supports

Amberlite XAD-4, a nanoporous commercial resin, was impregnated with palladium nanoparticles and used as catalyst for the coupling of aryl chlorides **5** and the silane **10** under basic conditions, so the corresponding coupling products were isolated with excellent yields (76-96%).¹⁷ In the same way, palladium(0) was supported on a phosphine-derived polystyrene and used in the coupling of aryl iodides (**5**, Hal = I) with trimethoxysilanes **10** giving biaryls **8** with variable yields (60-99%).¹⁸

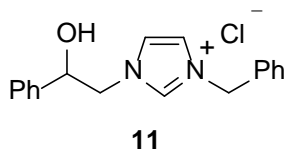
Other supports useful to anchor palladium nanoparticles are aluminium¹⁹ and zinc oxides.²⁰ These catalysts have shown to be effective in the coupling of aryl halides **5** and the trimethoxysilane **10**, affording the coupling products **8** with variable yields (50-96%).

PAMAM dendrimers of generations G2 and G3 have been used to bind palladium(0) nanoparticles and used in the coupling of aryl bromides and iodides (**5**, Hal = Br, I) with the triethoxysilane **9** to give modest yields in the coupling products **8** (32-52%).²¹

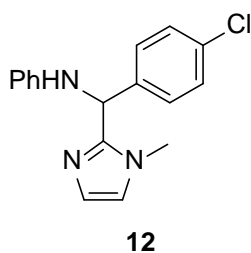
Finally, palladium nanoparticles have been supported on magnetite ($\text{Pd}/\text{Fe}_3\text{O}_4$), so giving a magnetically recoverable catalyst for the coupling of aryl bromides (**5**, Hal = Br) with trialkoxysilanes (**9**, **10**) under basic aqueous conditions, being remarkable that the use of potassium fluoride as silicon activator gave very low yields. Products **8** were isolated with very good yields (65-92%).²²

2.3.2. Different Ligands

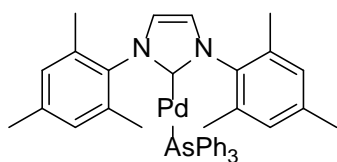
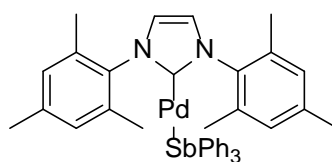
In many cases, a complex between a palladium compound and a ligand has been used successfully for catalyzing the Hiyama-type reaction. Among possible ligands, NHC ones have been efficiently employed, for instance the precursor **11** works properly in the fluoride-free $\text{Pd}(\text{OAc})_2$ -catalyzed coupling between aryl chlorides or bromides **5** with the trimethoxysilane **10** under microwave heating to give the expected biaryls **8** (18-90%).^{4f,g}



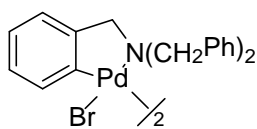
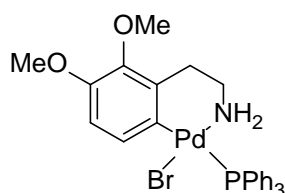
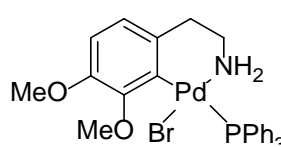
The same reaction mentioned above was also carried out with the precursor **12**, which under the same reaction conditions gave the expected coupling products with variable results (30-89%).^{4h}



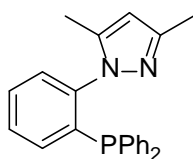
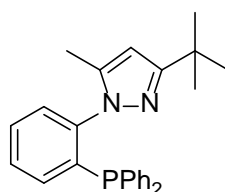
Isolated arsine or stilbine-stabilized *N*-heterocyclic carbene palladium complexes such as compounds **13** and **14** are efficient for the coupling aryl chlorides **5** (Hal = Cl) and the trimethoxysilane **10** in the presence of TBAF to form the corresponding biaryls of the type **8** with excellent results (70-89%).²³

**13****14**

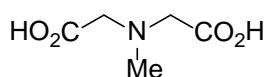
Another class of palladium complexes used in the cross-coupling reaction is the family of *ortho*-palladated catalysts. Among them, complexes **15**,²⁴ **16**,²⁵ and **17**²⁶ have been reported to be very active in the cross-coupling between aryl halides (**5**, Hal = Cl, Br, I) and the triethoxysilane **9** in the presence of TBAF as silicon activator yielding the expected products of the type **8** with good-to-excellent yields (60-97%).

**15****16****17**

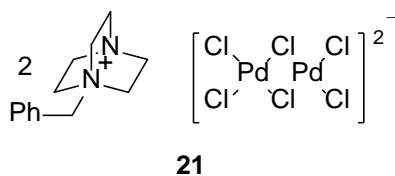
A pyrazole-tethered phosphine ligand **18** or **19** in combination with Pd₂(dba)₃ was used in the presence of TBAF for the coupling between several aryl bromides (**5**, Hal = Br) and the triethoxysilane **10** to give the corresponding biaryls **8** with very good results (58-93%).²⁷

**18****19**

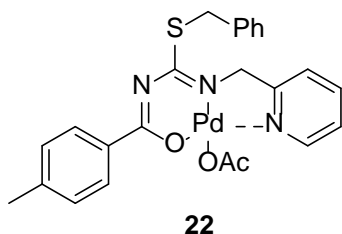
The simple *N*-methyliminodiacetic acid (**20**, MIDA) in combination with PdCl₂ acts as an effective catalyst for the coupling aryl bromides (**5**, Hal = Br) with trimethoxysilane **10** and its 4-substituted derivatives (4-Me, 4-MeO) under basic reaction conditions yielding biaryls **8** with good results (62-97%).²⁸

**20**

The ionic complex **21** was very efficient for the coupling of aryl halides (**5**, Hal = Cl, Br, I) and the trimethoxysilane **9** in the presence of CsF to afford the corresponding coupling products with excellent results (68-98%).²⁹

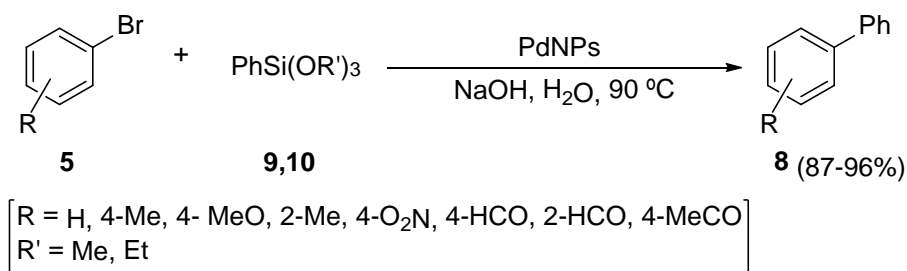


Finally, the complex **22**, prepared by mixing a thiopseudourea and Pd(OAc)₂, was used for several cross-coupling reactions, among them the coupling of 4-bromotoluene and the trimethoxysilane **10** under basic conditions to give the expected biaryls with high yield.³⁰



2.3.3. Nanoparticles as Catalysts

Some catalytic palladium nanoparticles were already considered in the section 2.3.1 for supported ones. For non-supported palladium nanoparticles (PdNPs), it was recently reported the use of an aqueous extract of *Euphorbia thymifolia* L. for their generation and their use in the coupling of aryl bromides (**5**, Hal = Br) with the alkoxy silanes **9** and **10** under basic aqueous conditions, yielding biaryls **8** with excellent yields (Scheme 12).³¹



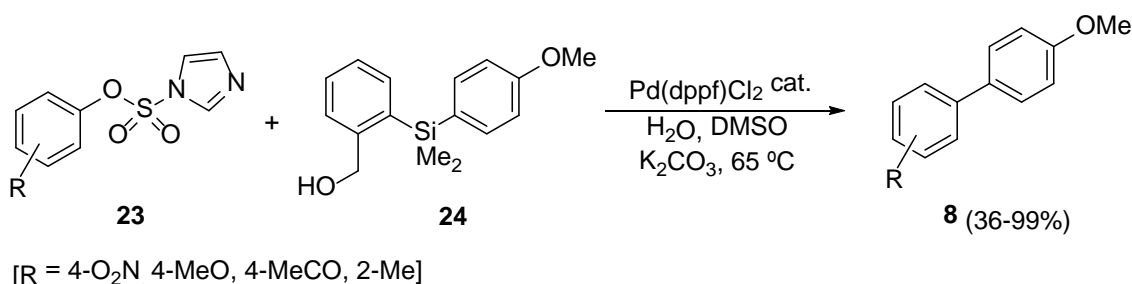
Scheme 12. Coupling of aryl bromides **5** with alkoxy silanes **9** and **10**.

The same process has been described using colloidal palladium nanoparticles stabilized by PVP and under microwave heating, yields being in any case excellent.³²

Nanoparticles derived from palladium and gold have been activated photochemically to act as catalysts in the coupling of 3-methylphenyl iodide with the trimethoxysilane **10**, giving a 71% yield of the coupling product of type **8**. The same process in the dark gave only 7% yield.³³ In addition, gold nanoparticles have emerged as an attractive choice for the process shown in Scheme 12, working in water and with microwave heating.³⁴

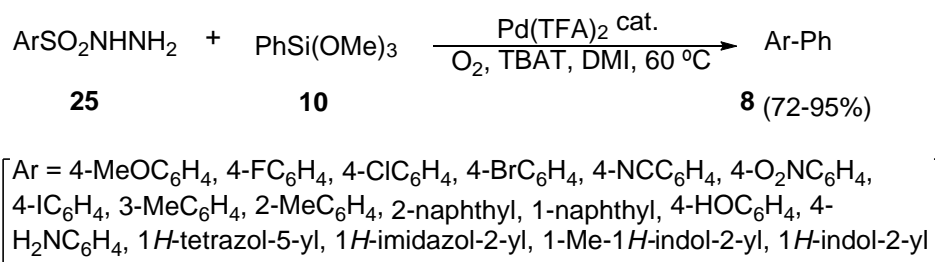
2.3.4. Other Substrates

Apart of commonly used aryl halides (**5**), other substrates have been used in the cross-coupling reaction. For instance, aryl imidazol-1-yl sulfates (**23**) are efficient in the palladium-catalyzed coupling with the silane **24** under aqueous basic conditions (Scheme 13).³⁵



Scheme 13. Coupling between sulfonates **23** and the silane **24**.

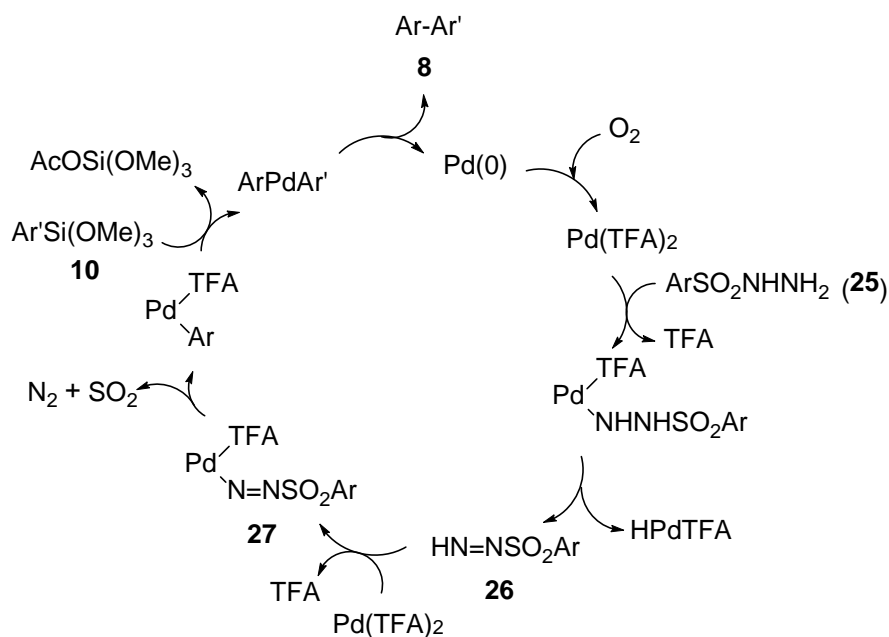
Other substrates used for the coupling with trimethoxysilane **10** are arylsulfonyl hydrazines **25** under aerobic palladium catalysis and in the presence of tetrabutylammoniumdifluorotriphenylsilicate (TBAT) and with 1,3-dimethyl-2-imidazolidinone (DMI) as solvent (Scheme 14).³⁶



Scheme 14. Coupling between hydrazines and the silane **10**.

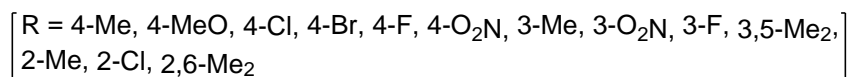
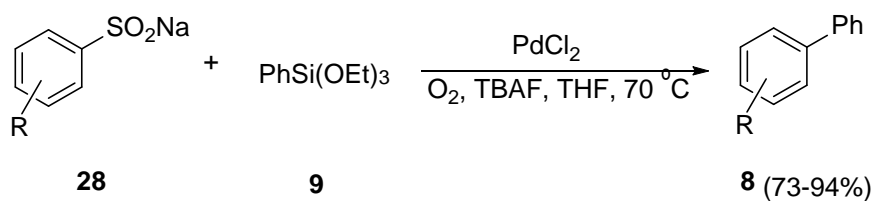
The proposed mechanism for the process shown in Scheme 14 is included in Scheme 15: in the first step Pd(0) is oxidized to Pd(II), which by reaction with the hydrazine and β -elimination of a palladium hydride to give a sulfonyldiimine **26**. This intermediate reacts with Pd(TFA)₂ to give another intermediate **27** that suffers N₂ and SO₂ extrusion giving a new

species which suffers from arylation with the silane **10** to give, after reductive elimination, the final product **8** recovering the Pd(0) precatalyst (Scheme 15).



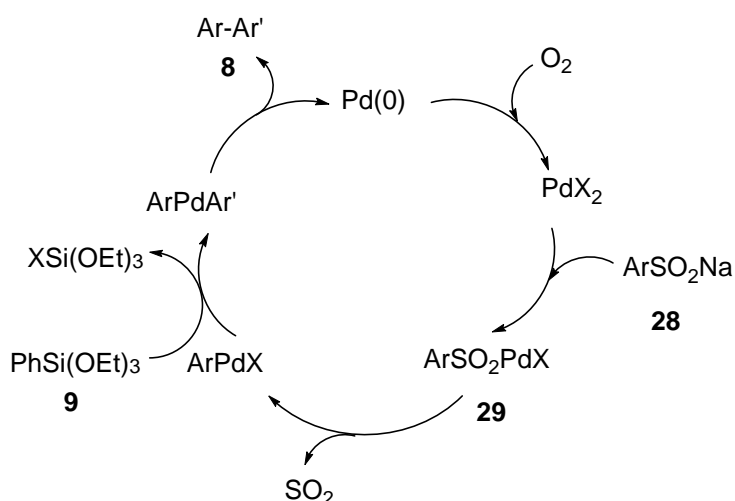
Scheme 15. Proposed mechanism for the coupling between hydrazines and the silane **10**.

Arenesulfonates **28** are suitable substrates for the palladium-catalyzed oxidative cross-coupling with the triethoxysilane **9** in the presence of TBAF (Scheme 16).³⁷



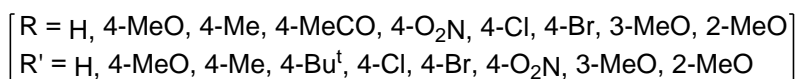
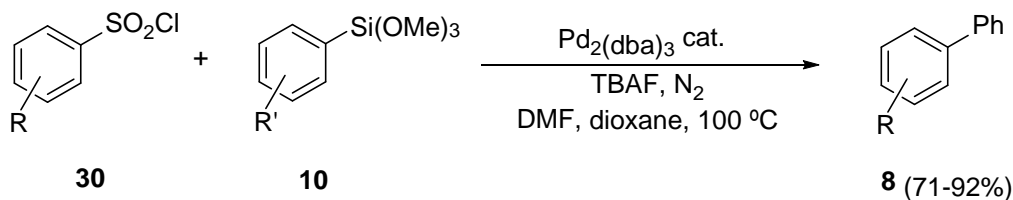
Scheme 16. Coupling of sulfonates **28** with the triethoxysilane **9**.

In this case, also an oxidation of Pd(0) to Pd(II) is proposed: after reacting with the sulfonate **28** and intermediate **29** is generated, which suffers SO₂ extrusion to give a new Pd intermediate, which after arylation and reductive elimination gives the biaryls **8** and the Pd(0) precatalyst (Scheme 17).



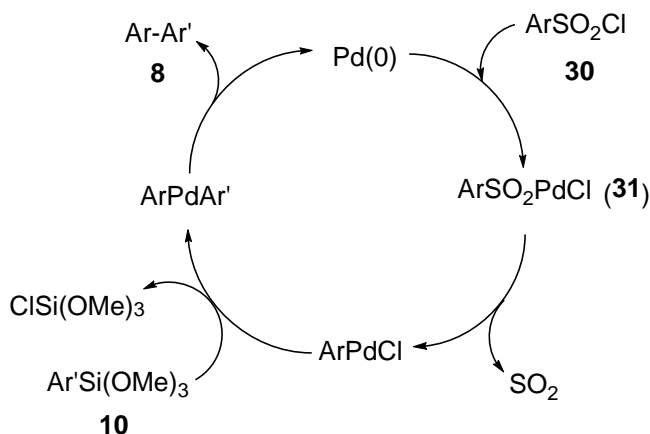
Scheme 17. Possible mechanism for the oxidative coupling between a sulfinate and the silane **9**.

Also sulfonyl chlorides **30** can suffer desulfonative cross-coupling reactions with substituted trimethoxysilanes **10** under palladium-catalysis and in the presence of TBAF to give excellent results of the corresponding biaryls **8** (Scheme 18).³⁸



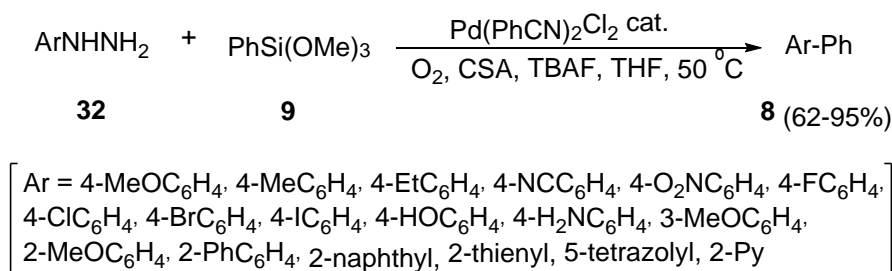
Scheme 18. Coupling of sulfonyl chlorides **30** with silanes **10**.

The proposed mechanism involves the formation of a sulfonyl palladium intermediate **31**, which suffers SO_2 extrusion giving a new Pd-intermediate ready to be arylated with the silicon reagent, followed by reductive elimination yielding the biaryl product and completing the catalytic cycle (Scheme 19).



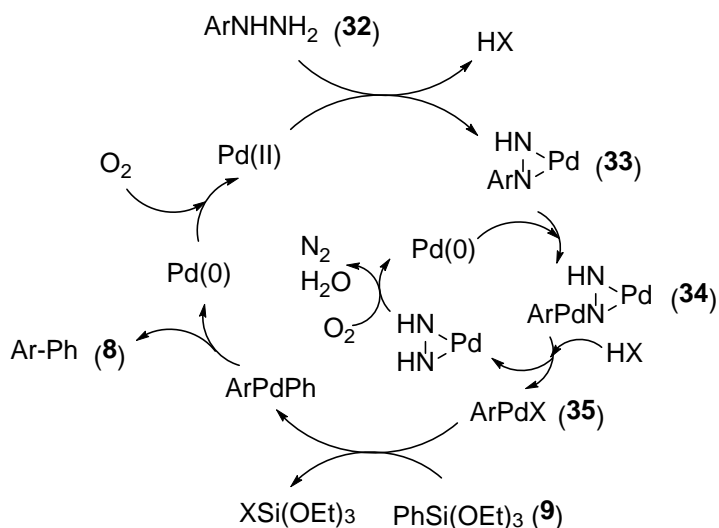
Scheme 19. Proposed mechanism for the coupling between sulfonyl chlorides **30** and silanes **10**.

Arylhydrazines **32** could be efficiently used as substrates for the palladium-catalyzed oxidative cross-coupling with the trimethoxysilane **9** in the presence of camphorsulfonic acid (CSA) and TBAF, so the corresponding coupling products **8** were isolated (Scheme 20).³⁹



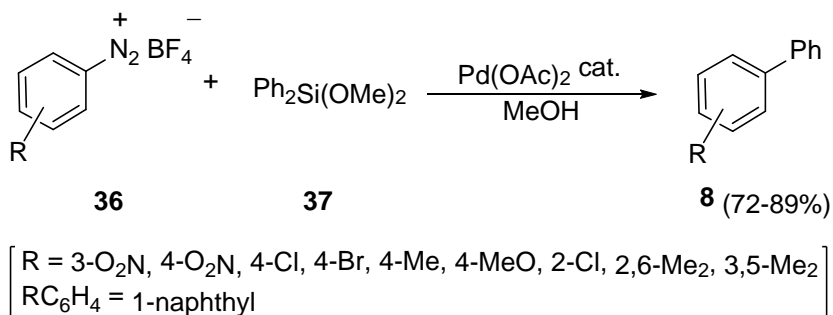
Scheme 20. Coupling of hydrazines **32** with the silane **9**.

The proposed mechanism for this reaction is a little bit complex involving an initial interaction between the hydrazine and Pd to give an intermediate **33**, which inserts another atom of Pd generating the species **34**. This intermediate regenerates the Pd(0) catalyst and reacting with acid gives an arylpalladium compound **35**, which is arylated by the silicon reagent **9**, suffering reductive elimination rendering the biaryls **8** and Pd(0), that is oxidized to Pd(II) reinitiating the catalytic cycle (Scheme 21).



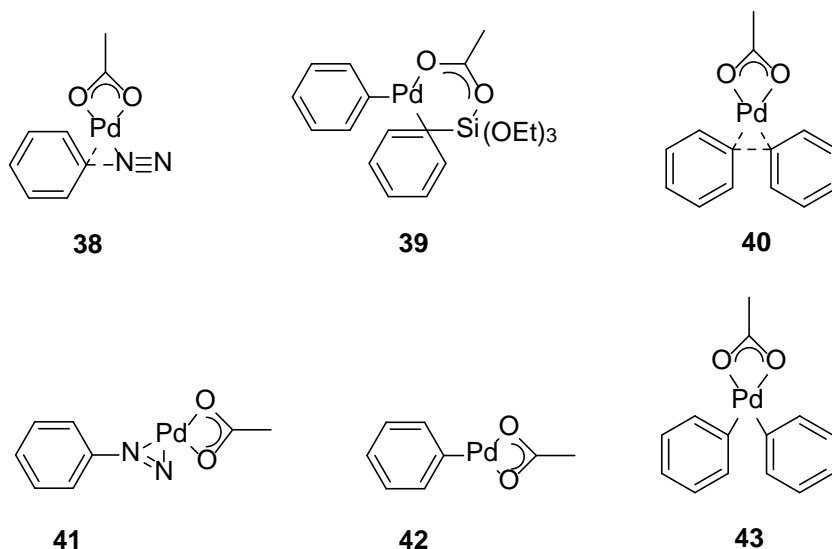
Scheme 21. Proposed mechanism for the coupling between hydrazines **32** and the trimethoxysilane **9**.

Other substrates that have been used efficiently for the palladium-catalyzed cross-coupling reaction are arenediazonium salts **36**. Their reaction with the dimethoxydiphenylsilane (**37**) gave the expected biaryls with good results (Scheme 22).⁴⁰

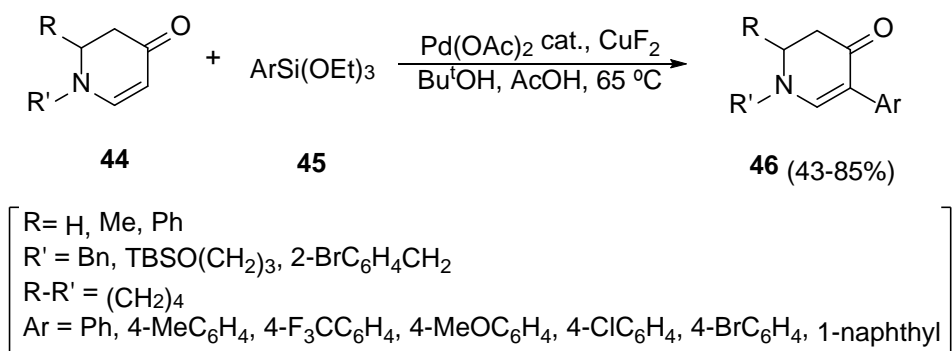


Scheme 22. Coupling of diazonium salts **36** with the silane **37**.

The mechanism of the former reaction was studied computationally and results rather complex, involving at least three transition states **38-40** and three intermediates **41-43**, this being the less energetic reaction pathway.^{40b}

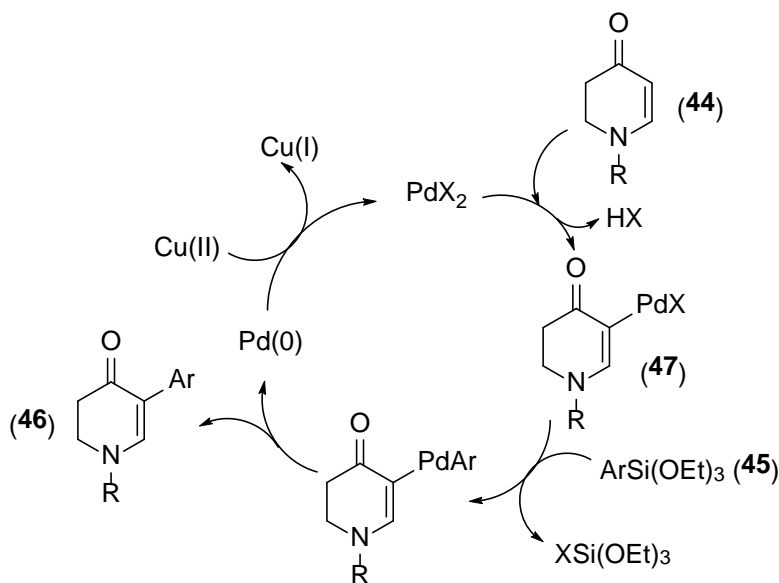


An especial case of cross-coupling starting from non-halogenated materials is the palladium-catalyzed arylation of heterocycles. Thus, cyclic enaminones **44** were successfully arylated with silanes of the type $\text{ArSi}(\text{OEt})_3$ (**45**) in the presence of copper difluoride giving the coupling products **46** (Scheme 23).⁴¹



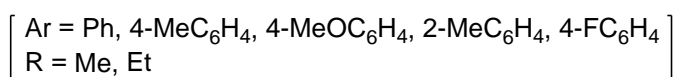
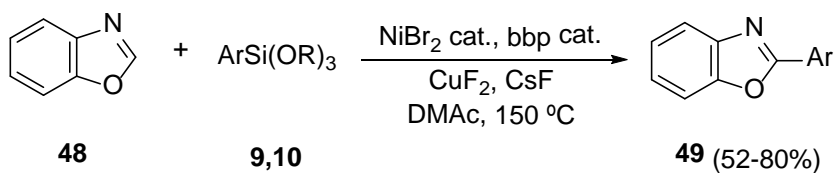
Scheme 23. Coupling of compounds **44** with silanes **45**.

The proposed mechanism in this case involves palladation of the starting material **44** to give the intermediates **47**, which after arylation and reductive elimination gives the arylated product and $\text{Pd}(0)$, that is oxidized by means of the $\text{Cu}(\text{II})$ salt (Scheme 24).



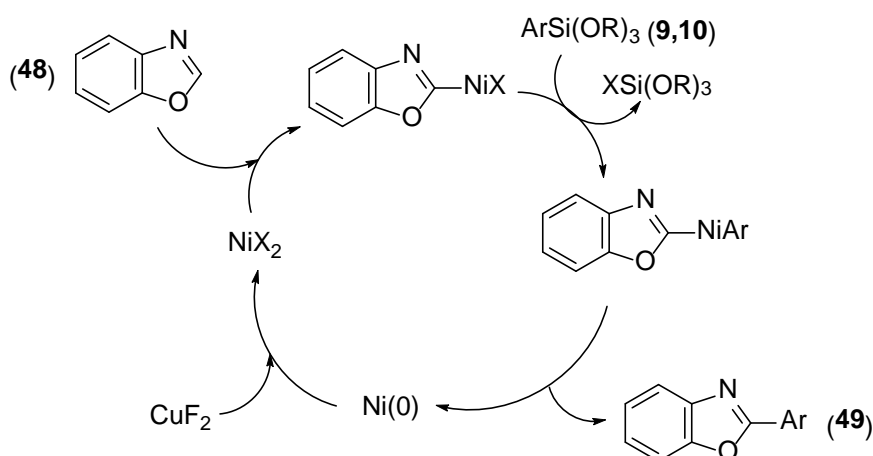
Scheme 24. Proposed mechanism for the arylation of compound **44** with the silane **45**.

In another C-H activation reaction, but in this case catalyzed by nickel, benzoxazole (**48**) was easily arylated with the alkoxy silanes **9** and **10** in the presence of CuF_2 and CsF , yielding the expected products **49** (Scheme 25).⁴²



Scheme 25. Arylation of benzoxazole **48** with silanes **9** and **10**.

The reaction shown in Scheme 25 was also applied to other heterocycles, such as 5- and 6-substituted benzoxazoles, benzotriazole, benzimidazole and 1,3,4-oxadiazole, giving in general good yields. Concerning the possible mechanism, in a first step, a nickelation of the heterocycle was followed by an arylation and reductive elimination (Scheme 26).



Scheme 26. Plausible mechanism for the arylation of benzoxazole **48** with silanes **9** and **10**.

Alkynyl halides (Hal = Cl, Br, I) have been developed for the palladium-catalyzed coupling with aryltrialkoxysilanes (**9**, **10**) in the presence of silver fluoride under basic conditions, so the corresponding arylated alkynes were isolated in moderate-to-good yields. This process represents a reasonable alternative to the Sonogashira reaction using silylated alkynes and aryl halides.⁴³

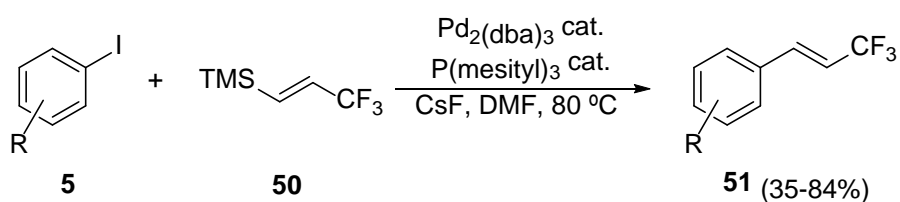
Recently, a study on the role of CuI and a small amount of water in the palladium-catalyzed coupling of silanes of type **9** and aryl bromides has been reported, concluding that both reagents are crucial in order to get good results.⁴⁴

3. Alkenylation Reactions

Even being not so commonly used, compared to the arylation processes studied in the former section, the alkenylation of aromatic halides represents a general approach to functionalized styrenes of great synthetic importance. The corresponding chemistry will be divided depending on the substituents at the silicon atom.

3.1. Alkylated Silicon Reagents

(*E*)-Trimethyl-(3,3,3-trifluoroprop-1-enyl)silane (**50**) was coupled with aryl iodides (**5**, Hal = I) under palladium catalysis and in the presence of CsF and a phosphine, so the corresponding products **51** were isolated with variable yields (Scheme 27).⁴⁵

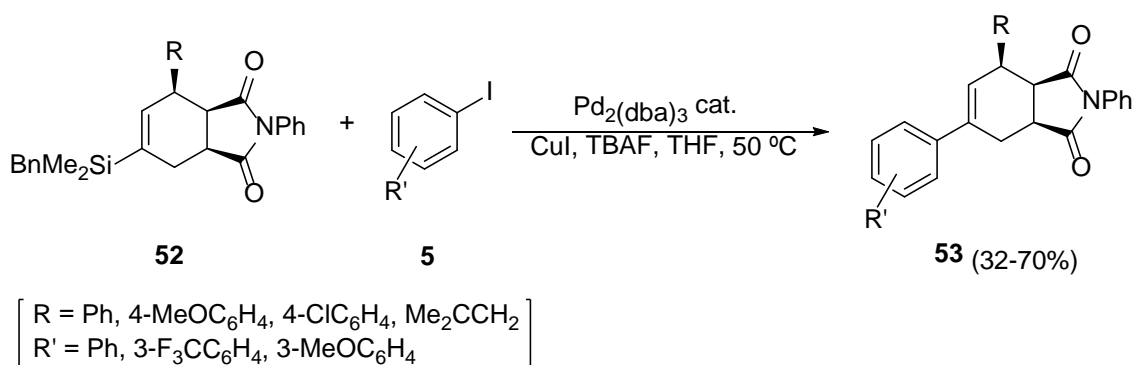


[R = 4-Prⁱ, 4-Ph, 4-PhCH₂O, 4-MeS, 2-MeO, 2-MOMO, 4-EtO₂C]

Scheme 27. Coupling of aryl iodides **5** with the alkenyl silane **50**.

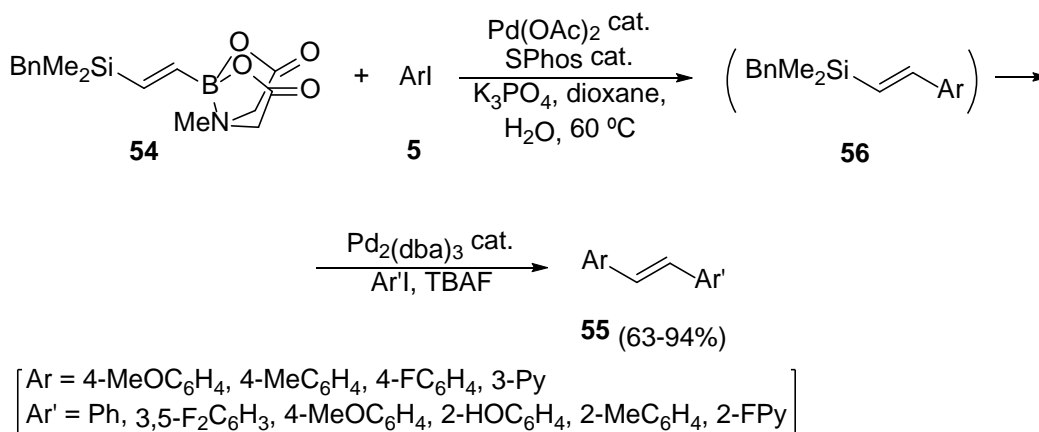
In the case of 2-iodoaniline (**5**, R = 2-NH₂) the obtained products were condensed with different aldehydes in the presence of copper(II) triflate to give 2-substituted-3-trifluoromethylquinolines (37-78%).⁴⁶

The introduction of an aryl group by substitution of the silicon moiety in compounds **52** was easily achieved by palladium catalysis in the presence of copper(I) iodide and TBAF to afford products **53** (Scheme 28).⁴⁷



Scheme 28. Coupling of compounds **52** with aryl iodides **5**.

An especial case of vinyl silanes is the family of MIDA substituted ones because having two possible coupling points, the boron and the silicon moieties, it is possible to perform selective couplings. Thus, starting from the material **54** a sequential Suzuki-Hiyama couplings afforded the stilbenes **55** through the vinylsilanes **56** (Scheme 29).⁴⁸

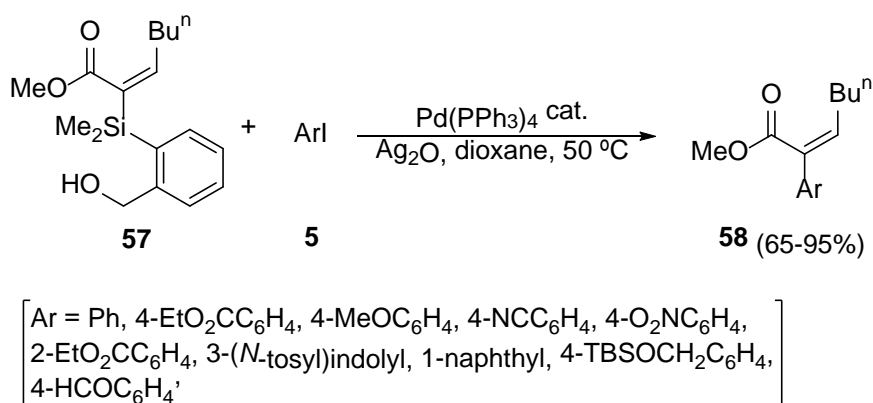


Scheme 29. Tandem Suzuki-Miyaura/Hiyama coupling of MIDA derivatives **54** with aryl iodides ArI and Ar'I.

The vinylic coupling between vinylsilanes and vinyl iodides catalyzed by palladium has been successfully applied to the total synthesis of retinoids⁴⁹ and the macrolide (-)-exigualide.⁵⁰

3.2. Arylated Silicon Reagents

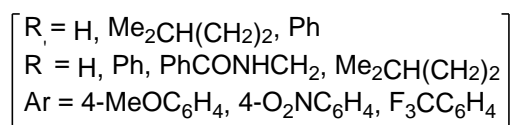
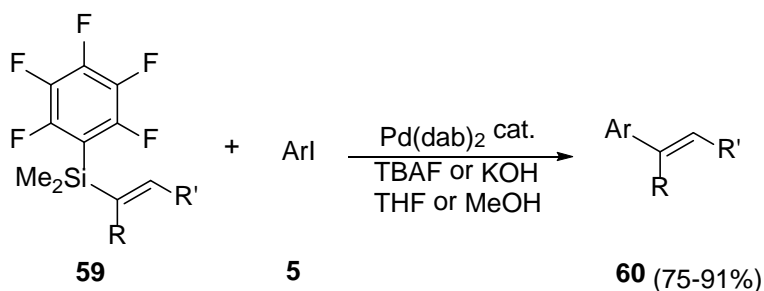
This type of vinylic silicon reagents is less frequent than the corresponding alkylated ones mentioned in the former section. One example is the reagent **57**, which has been coupled with aryl bromides and iodides **5** (Hal = Br, I) through a palladium catalysis in the presence of silver oxide to give products **58** (Scheme 30).⁵¹



Scheme 30. Coupling of silane **57** with aryl iodides **5**.

Another reagent containing a vinyl and aryl substituents at the silicon atom is compound **59**, which is useful transferring the vinyl moiety to aryl iodides **5** (Hal = I) in a

palladium-catalyzed process in the presence of TBAF or KOH giving the coupling products **60** (Scheme 31).⁵² This chemistry was applied to the total synthesis of resveratrol derivatives.

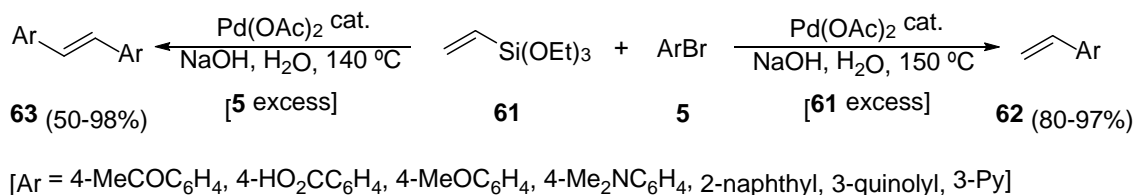


Scheme 31. Coupling between alkenyl silanes **59** and aryl iodides **5**.

Finally, dimethyl-2-thienylvinylsilane was very efficient for the post-functionalization of polyoxometalate platforms under palladium-catalyzed coupling reactions.⁵³

3.3. Alkoxyated Silicon Reagents

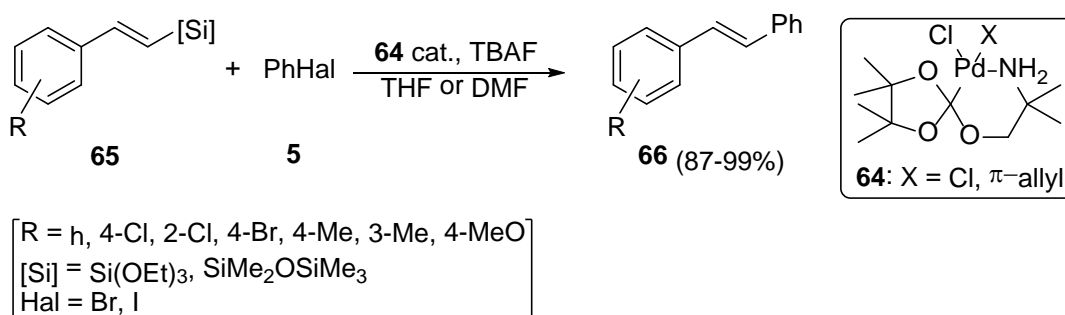
Depending on the stoichiometry, the vinylsilane **61** can be mono (to **62**) or diarylated (to **63**) with aryl bromides (**5**, Hal = Br) in a process catalyzed by palladium under basic conditions (Scheme 32).⁵⁴



Scheme 32. Coupling of the vinyl silane **61** with aryl bromides **5**.

The successive coupling with two different aryl bromides allowed the preparation of unsymmetrically substituted (*E*)-diarylethene compounds of type **63**. Computational studies at the DFT level could explain the obtained results.

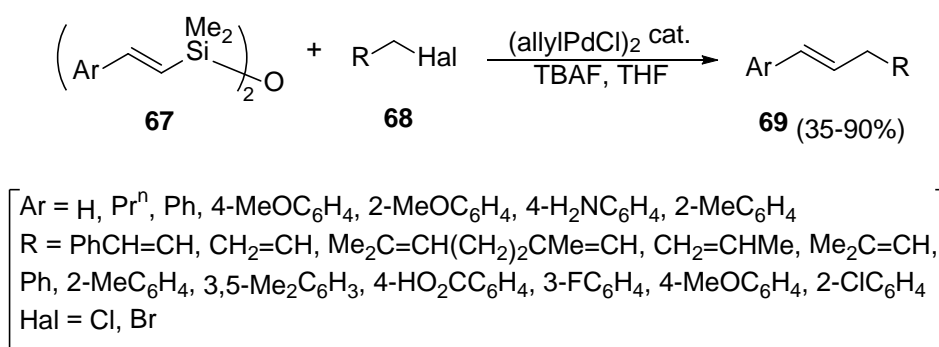
The catalyst **64** was very active for the coupling of vinylsilanes **65** with aryl bromides and iodides **5** (Hal = Br, I) to get the corresponding stilbenes **66** (Scheme 33).⁵⁵



Scheme 33. Coupling of vinylsilanes **65** with phenyl halides **5**.

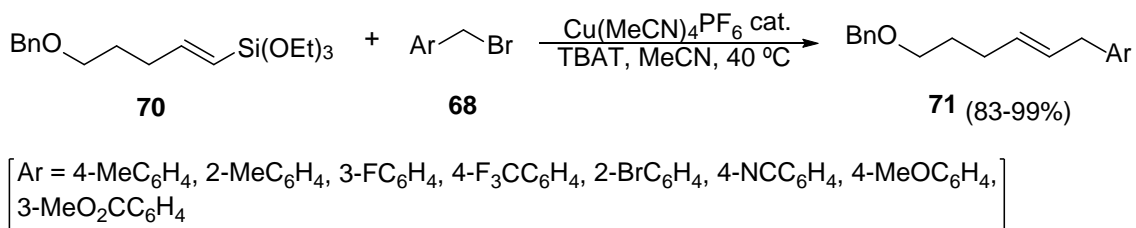
Palladium nanoparticles stabilized by triimidazolium salts (**1-Pd**) have been successfully used for the coupling of the vinylsilane **61** with aryl iodides (**5**, Hal = I) under basic conditions giving the corresponding styrenes with good-to-excellent results (59-93%).⁴¹

Vinylsiloxanes **67** are adequate substrates for the palladium-catalyzed cross-coupling with allyl and benzyl chlorides or bromides **68** to afford the expected products **69** (Scheme 34).⁵⁶



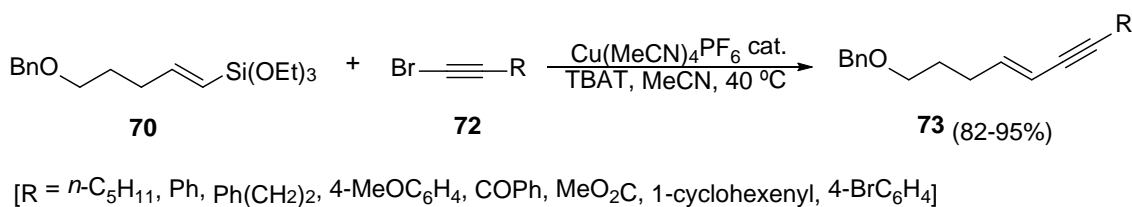
Scheme 34. Coupling between silanes **67** and allyl or benzyl halides **68**.

The same type of benzyl bromides **68** were coupled with the vinylsilane **70** under copper catalysis in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT) to afford the corresponding products **71** (Scheme 35).⁵⁷



Scheme 35. Coupling of the alkenyl silane **70** with benzyl bromides **68**.

The same silane **70** was also coupled with alkynyl bromides **72** with the same copper catalyst to yield diastereoselectively the corresponding enynes **73** under the same reaction conditions (Scheme 36).⁵⁸

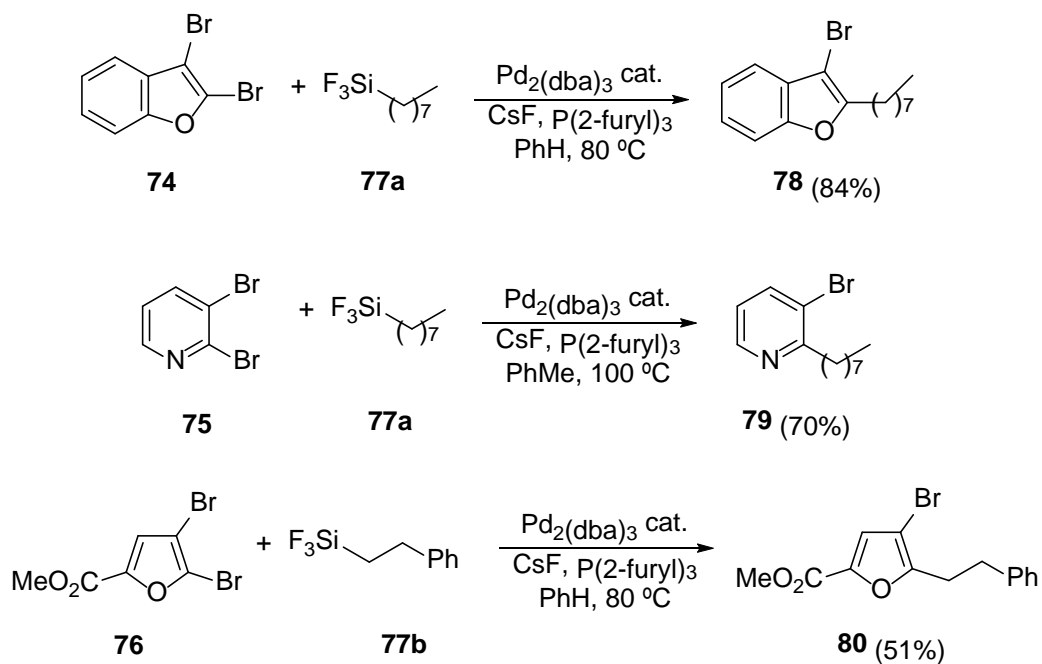


Scheme 36. Coupling of the alkenyl silane **70** with alkynyl bromides **72**.

4. Alkylation Reactions

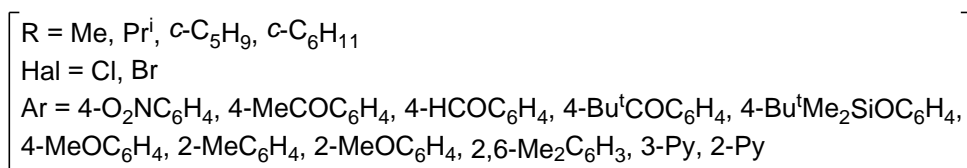
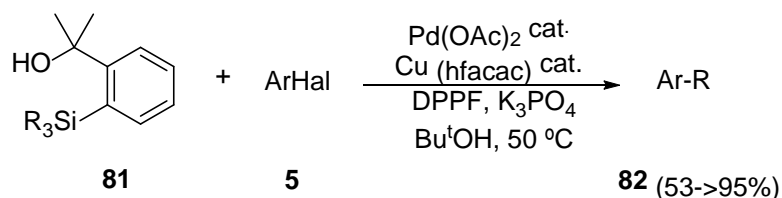
The use of alkylsilanes for the palladium-catalyzed cross-coupling reaction has the problem that after the transmetalation step the palladium intermediate possesses hydrogen atoms at the β-position. That means that the hydride β-elimination competes with the reductive elimination, so only in especial cases the alkylation can be successfully applied to the cross-coupling.

Aliphatic trifluorosilanes were used in the coupling with several heterocyclic bromides in a palladium-catalyzed reaction in the presence of a phosphine and CsF. Scheme 37 shows some examples of the chemistry involving brominated starting materials **74-76** and silanes **77**, so the coupling products **78-80** were isolated with good results.⁵⁹



Scheme 37. Coupling of brominated heterocycles **74-76** with aliphatic silanes **77**.

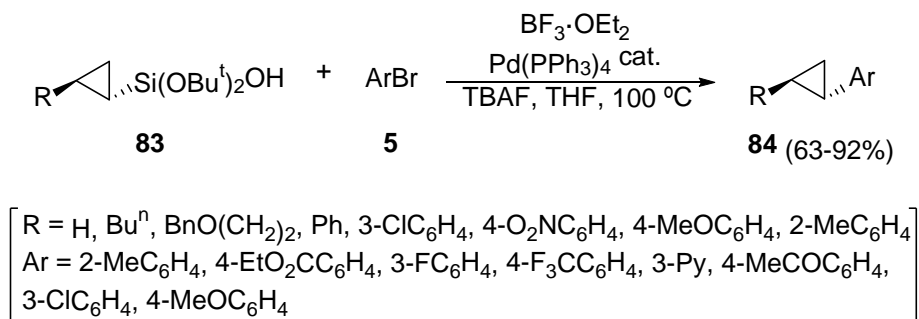
An intramolecular activation allows the alkylation of aryl chlorides and bromides **5** (Hal = Cl, Br) with the silane **81** using a mixed palladium-copper catalyst and a ferrocenylphosphine (DPPF), so the expected products **82** were isolated in general with excellent results (Scheme 38).⁶⁰



Scheme 38 Coupling of the silane **81** with aryl halides **5**.

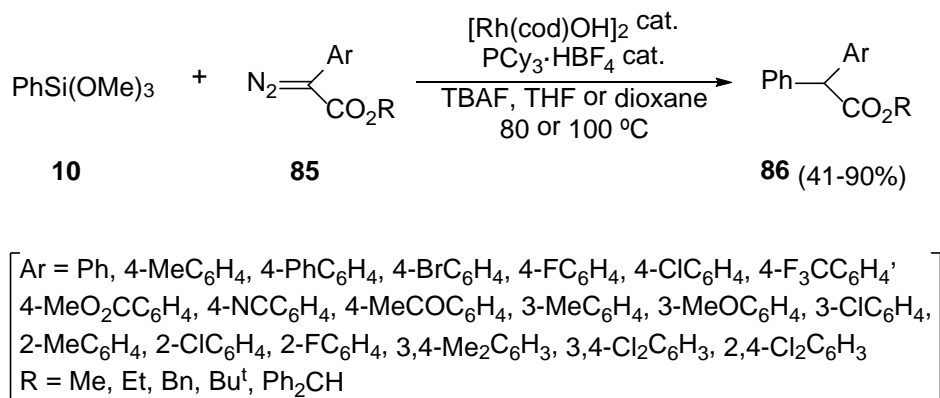
Halogenated quinolines were transformed into the corresponding substituted ones by a palladium-catalyzed alkylation in the presence of a fluoride source.⁶¹

The coupling between cyclopropylsilanes **83** (easily prepared from the corresponding vinylsilanes) and aryl bromides **5** using a palladium catalyst and BF_3 and TBAF as additives gave the corresponding arylated products **84** (Scheme 39).⁶²



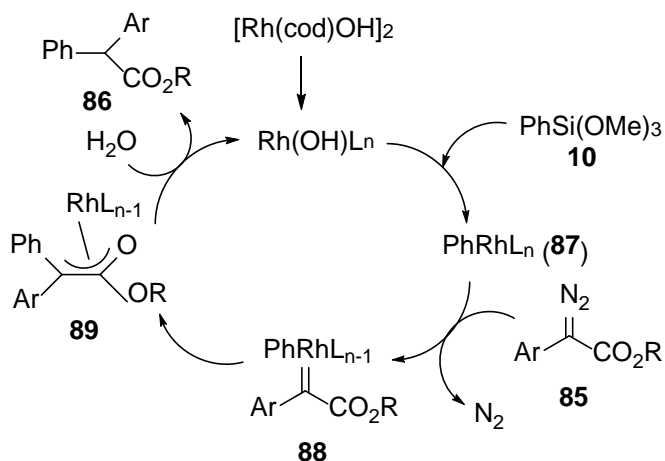
Scheme 39. Coupling of cyclopropylsilanes **83** with aryl bromides **5**.

An especial case of alkylation of a silane **10** used diazoester **85** and a rhodium catalyst yielding the corresponding coupling systems **86** in the presence of TBAF (Scheme 40).⁶³



Scheme 40. Coupling of the silane **10** with diazoesters **85**.

The possible mechanism involves the arylation of the catalyst to give a species **87**, which by reaction with the diazoester **85** gives a rhodium carbene **88** able to suffer a migratory insertion to generate a new intermediate **89** that by protonation gives the reaction product regenerating the active catalyst (Scheme 41).



Scheme 41. Proposed mechanism for the alkylation of the silane **10** with a diazoester **85**.

5. Conclusion

From the chemistry included in this up-dated account on the transition metal-catalyzed cross coupling reaction between silanes and halogenated materials, we conclude that the most used reagents are aryl or vinylsilanes having a trialkoxy substituent at the silicon atom, mainly triethoxy and trimethoxy ones. Concerning the halogenated component, bromides are the most commonly used, the aryl derivatives being the most versatile compounds in this chemistry. As catalysts, the most used ones are palladium(0) or (II) complexes in combination with an activator for the silicon reagent: a fluoride source (normally TBAF or CsF) or sodium or potassium hydroxide are the most employed. In conclusion, this process can be considered one of the most versatile and useful, especially for the formation of unsymmetrical biaryls.

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