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Non-conventional methodologies for transition-metal catalysed carbon–carbon coupling: a critical overview. Part 2: The Suzuki reaction

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Contents

Abbreviations: A, ampere; Ad, adamantyl; aq, aqueous; AFM, atomic force microscopy; BAL, 4-formyl-3-dimethoxyphenyloxymethyl-functionalised polystyrene resin; bbim, 1,3-di-*n*-butylimidazolium; bmim, 1-butyl-3-methylimidazolium; Boc, *tert*-butoxycarbonyl; cat., catalytic; *co*, copolymer; CTAB, cetyltrimethylammonium bromide; CuMeSal, copper(I) 3-methylsalicylate; CuTC, copper(I) thiophene-2-carboxylate; Da, Dalton; DAB, 1,4-diaminobutane; DABCO, 1,4-diazabicyclo[2.2.2]octane; dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPEA, diisopropylethylamine; DMA, *N*,*N*-dimethylacetamide; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; dppb, 1,4-diphenylphosphinobutane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; EDTA, ethylenediamine-*N*,*N*,*N*′,*N*′-tetraacetic acid; emim, 1-ethyl-3-methylimidazolium; IL, ionic liquid; L, ligand; LDH, layered double hydroxide; M, metal; MALDI-TOF, matrix-assisted laser desorption ionisation-time of flight; MCF, methyl chloroformate; MCH, methylcyclohexane; MCM-41, hexagonally packed mesoporous molecular sieves; Mes, mesityl; MOM, methoxymethyl; MW, microwave; NHC, *N*-heterocyclic carbene; PAMAM, poly(amidoamine); PDHC, poly(*N*,*N*-dihexylcarbodiimide); PEG, poly(ethylene glycol); PI, polymer incarcerated; Piv, pivaloyl; PPTS, pyridinium *p*-toluenesulfonate; PS, polystyrene; PTFE, poly(tetrafluoroethylene); PVP, poly(*N*-vinylpyrrolidin-2-one); py, pyridine; rt, room temperature; sc, supercritical; TBAA, tetra-*n*-butylammonium acetate; TBAB, tetra-*n*-butylammonium bromide; TBAC, tetra-*n*-butylammonium chloride; TBAH, tetra-*n*-butylammonium hydroxide; TBDMS, *tert*-butyldimethylsilyl; TEBA, benzyltriethylammonium chloride; TEG, tetra(ethylene glycol); TEOS, tetraethyl orthosilicate; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THEptAB, tetra-*n*-heptylammonium bromide; TIPS, triisopropylsilyl; TOF, turnover frequency (mole of product per mole of catalyst per hour); TON, turnover number (mole of product per mole of catalyst); Tol, tolyl; US, ultrasound; XL-RC, cross-linked resin-captured.

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1. Introduction

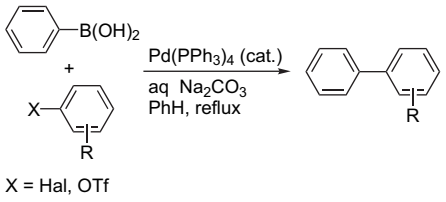
In a previous and recent report,[1] we have highlighted in the introductory section the transition-metal catalysed carbon–carbon bond formation as a fundamental reaction in organic synthesis.[2] In particular, that report dealt with the application of non-conventional methodologies to the Heck reaction and was intended to be written from a critical point of view. Following a similar pattern of contents, we wish to present in this report some of the recent advances involving non-conventional methodologies that have been applied to the Suzuki reaction.

It must be pointed out that there is a vast amount of literature related to the title topic and that numerous reviews have appeared, which independently cover some of the aspects included in this report, most of them until 2002. Therefore, instead of this being a comprehensive review, we will focus mainly on the pioneering work and some selected examples, mostly belonging to the interval 2003–2006. In order to better compare the different methodologies, this study will be limited to the Suzuki cross-coupling reaction leading to biaryl formation, with alkyl, vinyl, benzyl, alkynyl and non-aromatic heterocycles being excluded. An introduction to the different non-conventional methodologies will be omitted here, as these have already been described by us in the above-mentioned report.

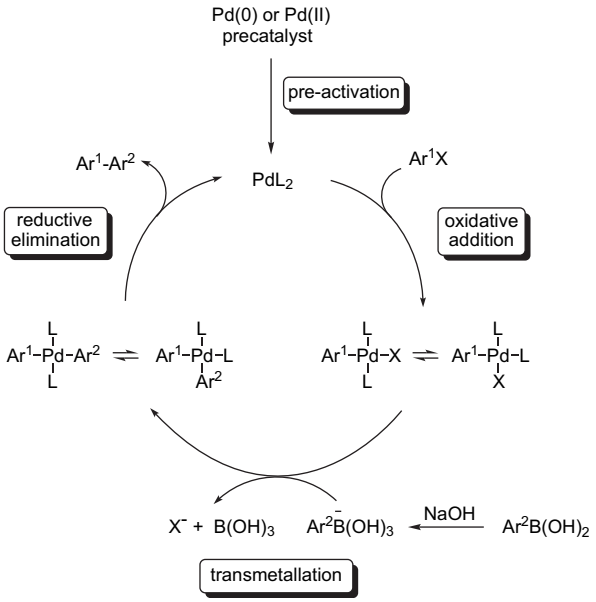
2. The Suzuki reaction

The Suzuki–Miyaura cross-coupling reaction of organoboron compounds and organic halides or pseudohalides can be considered as one of the most efficient methods for the construction of carbon–carbon bonds.[3] In general, the commercial availability of the starting materials, the relatively mild reaction conditions required, the tolerance of a broad range of functionalities, the insignificant effect of steric hindrance, together with the ease of handling and removal of the non-toxic boron-containing by-products, as well as the possibility of using water as a solvent or co-solvent, have widened the scope of this reaction. Because of all these features, it has gained prominence in recent years at an industrial level, mainly in the synthesis of pharmaceuticals and fine chemicals. In academic laboratories, it has been largely applied as the key step in the total synthesis of natural[4] and non-natural products (dendrimers, porphyrins, unusual amino acids and peptides),[31] or in polymer synthesis.[5] Various modifications, however, have been recently introduced involving catalysts, substrates, reaction media, reaction conditions, synthetic techniques, etc. in order to develop environmentally friendly and more efficient Suzuki cross-coupling reactions.[6]

In a typical Suzuki reaction for the preparation of biaryls, phenylboronic acid is cross-coupled with an aryl halide or triflate in the presence of $Pd(PPh_3)_4$ as the catalyst and aq Na_2CO_3 as the base in benzene or toluene (Scheme 1).[7] A general catalytic cycle for this reaction is represented in Scheme 2.



Scheme 1.



Scheme 2.

3. Substrates

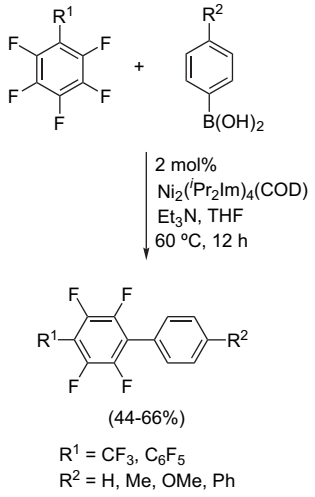
3.1. Alternative electrophilic coupling partners

Aryl bromides and iodides, together with aryl triflates substituted with electron-withdrawing groups, are the most suitable substrates for the Suzuki–Miyaura cross-coupling reaction. Aryl triflates are, however, thermally labile, prone to hydrolysis and more expensive to prepare. The use of aryl tosylates is a better option, since these compounds are easily prepared from phenols, cheaper and more stable than triflates. Aryldiazonium tetrafluoroborates are attractive synthetic alternatives to the corresponding halides and triflates, since they can be prepared from the relatively inexpensive and readily available anilines and they do not need the presence of a base. In addition, they have been found to be more reactive than aryl halides or triflates in this reaction.[8]

Aryl chlorides are, however, more attractive as starting materials because of their lower cost and the wider diversity of available compounds. They suffer, however, from a decreased reactivity that has been attributed to their reluctance towards oxidative addition to Pd(0), due to the strength of the C–Cl bond. Recently, several catalytic systems have been found to facilitate their use in the Suzuki–Miyaura reaction.[2h,9] At any rate, the use of organic halides has some lack of atom economy,[10] since the corresponding inorganic salts that are obtained require proper isolation and treatment. Consequently, the search for novel electrophilic substrates in cross-coupling reactions has been the focus of much attention.[11]

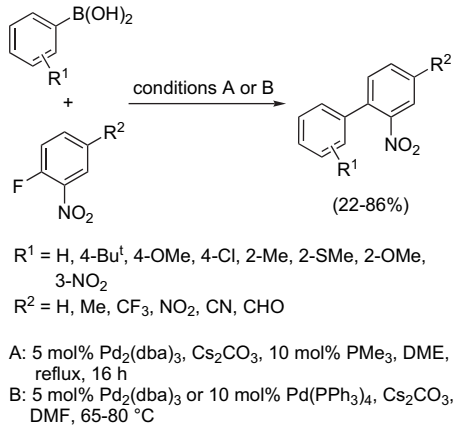
Taking into account the strength of the C–F bond and, therefore, its difficulty in activation,[12] it is worth mentioning the first Suzuki coupling of uncomplexed aryl fluorides, which was independently published in 2003 by the groups of Widdowson[13] and Yu.[14] A main requirement for the reaction to take place is that the aryl fluorides must bear strong electron-withdrawing groups at both the *ortho* and the *para* positions. Very similar reaction conditions were applied by both groups, leading to yields ranging from low to good (Scheme 3). Despite the above-mentioned restriction, this methodology represents an alternative to the use of other aryl halides, especially those which are more expensive than the corresponding aryl fluorides.

More recently, Radius and Schaub reported the synthesis and characterisation of the NHC-stabilised nickel complex $Ni_2(^iPr_2Im)_4(COD)$ [$^iPr_2Im$=1,3-di(isopropyl)imidazol-2-ylidene],[15] which was used in the Suzuki cross-coupling reaction with polyfluorinated arenes as electrophiles.[16] Under the standard reaction conditions (2 mol % catalyst, Et_3N, THF, 60 °C, 12 h), the process was highly regioselective, with only the fluoro substituents in *para* position respect to the CF_3 and C_6F_5 groups being replaced by aryl groups in moderate yields (Scheme 4).

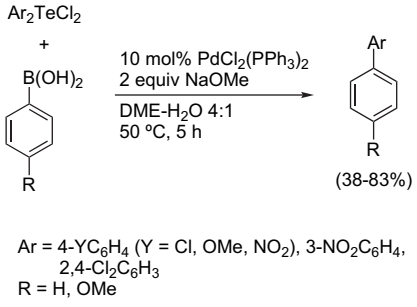


Scheme 4.

The stability of aryl and vinyl tellurides has been used in palladium-catalysed cross-coupling reactions for the preparation of biaryls and stereochemically defined enynes and enediynes. The fact that these reagents work in the presence of sensitive functional groups and under mild reaction conditions makes them interesting substitutes for aryl and vinyl halides and triflates.[17] As an example, various diaryltellurium dichlorides bearing electron-donating and withdrawing groups were allowed to react with phenyl- and 4-methoxyphenylboronic acid in the presence of $PdCl_2(PPh_3)_2$ and NaOMe in DME–H_2O at 50 °C, affording the coupled products in fair-to-good yields (Scheme 5).[18] Unfortunately, diaryltellurium(IV) dihalides are not commercially available and have to be prepared normally



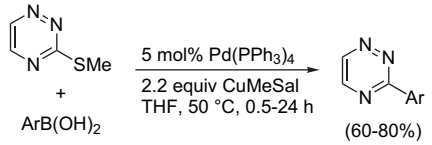
Scheme 3.



Scheme 5.

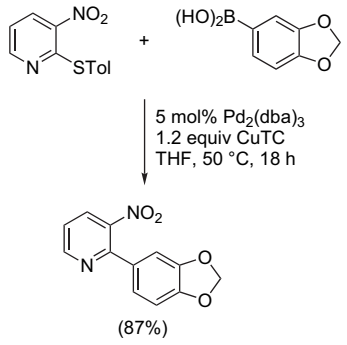
from $TeCl_4$ with activated arenes, arylmercury chlorides or arenediazonium salts.[19] Therefore, the preparation of these compounds represents a major disadvantage that adds to the mutagenic properties of $TeCl_4$ and to the possible toxicity of organotellurium compounds.[20]

In 2002, the groups of Guillaumet and Liebeskind independently described the base-free heteroaromatic thioether–boronic acid cross coupling under palladium catalysis mediated by an organocopper(I) salt. The first group coupled 3-methylthiotriazine with a variety of boronic acids bearing both electron-withdrawing and donating substituents in the presence of copper(I) 3-methylsalicylate (CuMeSal) (Scheme 6).[21] The second group studied a larger series of heterocyclic thioether substrates (with different alkylthio moieties) including substituted pyridines, pyrazines, pyrimidines, benzothiazoles and benzoxazoles (see example in Scheme 7).[22] In this case, copper(I) thiophene-2-carboxylate (CuTC) was used as the copper(I) salt, the presence of additional $Zn(OAc)_2$ being essential in some examples. No reaction was observed in any case under typical Suzuki reaction conditions. Both methodologies involve mild reaction conditions, giving the products in moderate-to-good yields. Taking into account that these substrates are easily synthesised, readily accessible and stable, they are appropriate substitutes for the corresponding aromatic heterocyclic halides. Unfortunately, the organocopper salts must be prepared, leading, after the reaction, to stoichiometric amounts of the corresponding by-products that must be removed and cannot be re-utilised.



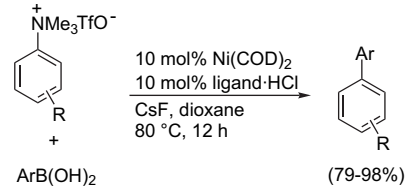
Ar = 2-furyl, 2-thienyl, 3-YC_6H_4 (Y = CF_3, AcNH, Br, NO_2, Ac, NC), 4-$MeSC_6H_4$

Scheme 6.

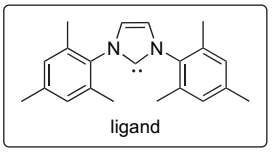


Scheme 7.

The first Suzuki cross coupling of aryltrimethylammonium salts was described by MacMillan and Blakey in 2003.[23] A wide range of boronic acids and aryltrimethylammonium salts, both bearing electron-donating or -withdrawing groups at the *ortho*, *meta* and *para* positions, were subjected to the nickel-catalysed cross-coupling reaction in the presence of a 1,3-bis(2,4,6-trimethylphenyl)imidazole carbene ligand (Scheme 8). All the products were obtained in good-to-excellent yields. The starting aryltrimethylammonium salts were easily prepared from the corresponding *N*,*N*-dimethylanilines, the former being an interesting alternative to the use of aryldiazonium salts in cross-coupling reactions.

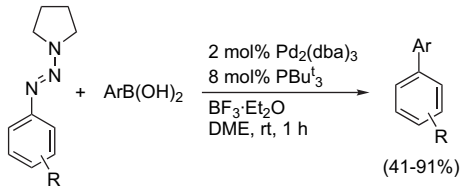


R = 2-Me, 4-Bu^n, 2-OMe, 4-OMe, 4-OBu^n, 3,5-$(OMe)_2$, 3-CO_2Me, 4-CO_2Me, 3-F
Ar = Ph, YC_6H_4 (Y = 2-Me, 3-Me, 4-Me, 2-OMe, 4-OMe, 2-F, 3-F, 4-F, 3-Ac), 2,6-$(MeO)_2C_6H_3$, 1-naphthyl



Scheme 8.

The group of Saeki and Tamao directly coupled, for the first time, aryltriazenes with arylboronic acids using catalytic amounts of a palladium complex, a phosphine ligand and a stoichiometric amount of boron trifluoride (Scheme 9).[24] It is of interest to note that the reaction was fast (with high GC yields in only 10 min) and proceeded at room temperature. In general, aryltriazenes having electron-donating groups furnished the coupled products in higher yields than those having electron-withdrawing substituents, whereas only electron-rich groups attached to the arylboronic acid were reported. Despite the fact that the aryltriazenes must be prepared from anilines and a secondary alkyl amine, this additional step is compensated for by the fast and mild cross-coupling step. Nonetheless, a wider substrate scope in the boronic acid partner would be desirable.

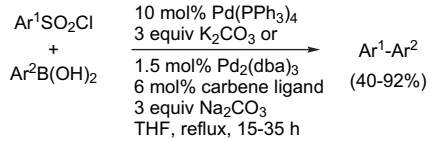


R = 2-Me, 3-Me, 4-Me, 2,4,6-Me_3, 4-F, 4-Cl, 4-Br, 4-OTf, 4-NEt_2
Ar = 4-MeC_6H_4, 4-$MeOC_6H_4$, 1-naphthyl, 2-thienyl

Scheme 9.

Vogel and Dubbaka discovered that sulfonyl chlorides exhibit a reactivity between aryl iodides and bromides in the cross-coupling with boronic acids.[25] Electronically and

structurally diverse sulfonyl chlorides and boronic acids were coupled using two different catalytic systems: $Pd(PPh_3)_4$–K_2CO_3 and $Pd_2(dba)_3$–Na_2CO_3–carbene ligand (Scheme 10). The second catalytic system, which incorporates the carbene ligand shown in Scheme 8, improved the moderate yields obtained with the first catalytic system in those examples in which it was tested. As a drawback, only a few arylsulfonyl chlorides are commercially available, most of which are rather expensive. They are moisture sensitive and those that are not commercially available have to be prepared from the not commercially abundant arylsulfonic acids.



Ar^1 = 4-MeC_6H_4, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 1-naphthyl
Ar^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 3-$HCOC_6H_4$, 4-ClC_6H_4, 3-$NO_2C_6H_4$, 1-naphthyl, 2-furyl

Scheme 10.

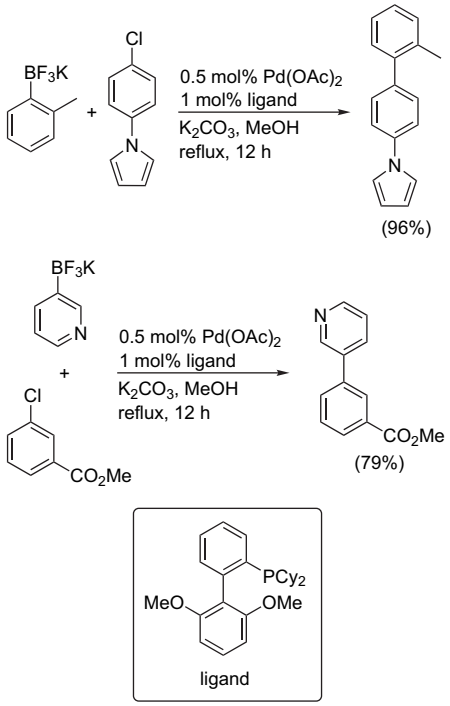
Other electrophilic coupling partners such as aryl phosphates failed in the Suzuki cross-coupling reaction with arylboronic acids [$Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C], the expected biaryl products being obtained in low yields (5–12%), together with the homocoupling product of the boronic acid (10–24%).[26] This behaviour was attributed to the low reactivity of the Ar–OP bond to oxidative addition towards the metal centre. Enol phosphonates were, however, coupled successfully with a variety of arylboronic acids.

3.2. Alternative boron-containing nucleophilic coupling partners

Boronic acids, boronate esters and organoboranes have been utilised for many years as the primary boron source in Suzuki–Miyaura-type reactions. Both boronic acids and boronate esters are highly nucleophilic, exhibit a broad range of functional-group tolerance and are substantially less toxic than the heavy-metal organometallic reagents such as organotins. These organoboron reagents have, however, inherent limitations including: (a) possible hydrolysis of the carbon–boron bond, (b) the boronic acids are often difficult to purify and have uncertain stoichiometry, (c) the boronate esters lack atom economy and thus detract market value and (d) the boranes are limited by their hydroboration method of preparation, are air sensitive and lack functional-group compatibility.

On the other hand, potassium organotrifluoroborates are a special class of organoboron reagents that offer the following advantages over the corresponding boronic acids and esters: (a) they are air- and moisture-stable salts, readily accessible by a variety of high-yielding methods (e.g., treatment of boronic acids with KHF_2), (b) the tractable, crystalline solids are suitable for storage for extended periods of time, (c) the post-reaction by-products are salts readily separated from the desired product and (d) the BF_3K moiety is compatible with sensitive functional groups and is tolerant to reaction conditions such as epoxidation, ozonolysis, osmylation and metal–halogen exchange.[27] Organotrifluoroborates have been shown to be versatile coupling partners and are present as reagents in a vast array of C–C bond-forming reactions. In 1997, Gênet et al. reported the coupling of potassium aryl- and alkenyltrifluoroborates with arenediazonium tetrafluoroborates.[28] In a recent review, Molander et al. have demonstrated their application in Suzuki cross-coupling reactions.[29] Some recent articles that are not included in this review are as follows.

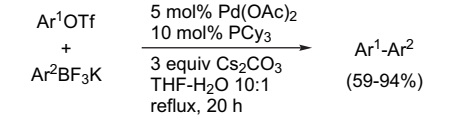
Buchwald and Barder reported a highly efficient Suzuki coupling of aryl and heteroaryl chlorides with potassium aryl and heteroaryl trifluoroborates under mild reaction conditions.[30] 4-*tert*-Butylphenyl and 2-tolyl trifluoroborates were coupled with electron-rich or hindered aryl chlorides in excellent yields (84–96%) at low catalyst loading (0.05–2.00 mol % Pd) and using S–Phos as the ligand (see example in Scheme 11). Interestingly, a variety of nitrogen- and sulfur-containing heteroaryl chlorides were also successfully coupled with 1-naphthyl trifluoroborate and 3-pyridyl trifluoroborate (73–98%) (see example in Scheme 11). It is worthy of note that the reaction conditions were compatible with the presence of the more sensitive ester or aldehyde functionalities. Despite the fact that the presence of different functional groups in the aryl trifluoroborate partner has not been studied yet, this methodology seems to possess a great potential, above all taking into account that it involves the more readily available and less expensive aryl chlorides.



Scheme 11.

As an alternative to the use of aryl halides, Molander et al. have coupled electronically diverse aryl and heteroaryl triflates with aryl and heteroaryl trifluoroborates.[31] Good-to-high

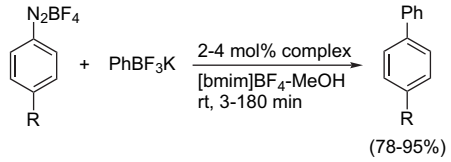
yields of the corresponding products were obtained under palladium catalysis in aq THF (Scheme 12), the reactivity of the aryl electrophiles following the order Br>OTf>Cl. The disadvantages of using aryl triflates as electrophilic coupling partners have already been discussed in Section 3.1.



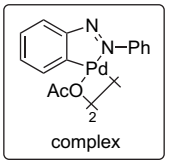
Ar^1 = 4-YC_6H_4 (Y = Me, OMe, NO_2, Cl), 2,5-$Me_2C_6H_3$, 1-naphthyl, 2-naphthyl, 8-quinolyl
Ar^2 = Ph, 4-YC_6H_4 (Y = Me, OMe, CF_3), 1-naphthyl, 2-thienyl

Scheme 12.

The palladium-catalysed cross-coupling of several aryldiazonium tetrafluoroborates with potassium phenyltrifluoroborate in ionic liquids was studied by the group of Mastrorilli.[32] The best results were obtained using a palladacycle complex in a mixture with [bmim]BF_4–MeOH. The reactions were performed at room temperature and in short times, especially using aryldiazonium salts containing an electron-withdrawing group (Scheme 13). Although a 20% excess of 4-tolyldiazonium tetrafluoroborate provided a recyclable catalytic solution, it seemed to be of low efficiency and was only applicable to this substrate.

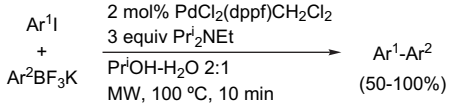


R = Me, OMe, CO_2Et, Br, Cl



Scheme 13.

Kabalka and Al-Masum showed that the palladium-catalysed coupling of potassium aryltrifluoroborates with aryl iodides occurred rapidly under microwave irradiation.[33] Good-to-excellent yields (mostly of about >90%) of the products were obtained with aryl iodides containing either electron-donating or electron-withdrawing groups in an isopropanol–water mixture (Scheme 14). The effect of electron-donating substituents on the potassium aryltrifluoroborates was, however, not studied. Alternatively, aryl triflates were used as the electrophilic partners of the potassium aryltrifluoroborates under similar reaction conditions, but in the absence of base [0.6 mol % $Pd(AcO)_2$, EtOH–H_2O, MW, 95 °C, 15 min].[34] In this case, different electronically substituted aryltrifluoroborates were coupled with aryl triflates to give the corresponding biaryls in good-to-excellent yields. The group of Leadbeater also coupled successfully several organotrifluoroborates with electronically different aryl bromides and iodides under microwave promotion in water, but using ultra-low palladium loadings (2.5 ppm Pd, Na_2CO_3, TBAB, H_2O, MW, 150 °C, 5 min).[35]

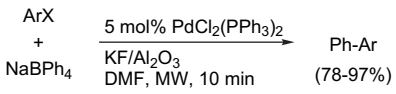


Ar^1 = 4-YC_6H_4 (Y = F, Cl, Ac, OMe), 2,4-$Me_2C_6H_3$, 2-YC_6H_4 (Y = Me, OMe), 1-naphthyl, 3-$NO_2C_6H_4$
Ar^2 = Ph, 4-YC_6H_4 (Y = Me, F, CF_3), 2,4,6-$F_3C_6H_2$

Scheme 14.

Aryltellurides of the type ArTeBu have been recently found to be more reactive than aryl halides in the cross-coupling reaction with potassium aryltrifluoroborates [10 mol % $Pd(PPh_3)_4$, Et_3N, 2 equiv Ag_2O, MeOH, reflux].[36] The products were obtained in moderate-to-high yields with tolerance for a variety of functional groups. Ag_2O (2 equiv) was, however, required as an additive to re-oxidise Pd(0) to Pd(II). The disadvantages of organotellurium compounds have been mentioned above.

Sodium tetraphenylborate is a commercially available reagent, an alternative to phenylboronic acid, which has found application in the Suzuki reaction, especially in aqueous solutions.[37] More recently, Wang et al. discovered that, under microwave irradiation, the cross-coupling of sodium tetraphenylborate with aryl halides proceeded 144-fold faster than that under conventional heating in the presence of a palladium catalyst and KF–Al_2O_3.[38] Interestingly, the reaction was applied to aryl chlorides, bromides and iodides, providing the biaryl products in high yields (Scheme 15). Unfortunately, only one of the four phenyl groups was transferred from sodium tetraphenylborate, making the process less efficient.

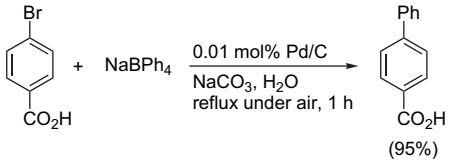


X = Cl, Br, I
Ar = Ph, 4-YC_6H_4 (Y = Me, OMe, NO_2), 3-MeC_6H_4, 2-$NO_2C_6H_4$, 2,5-$Me_2C_6H_3$, 1-naphthyl, 2-naphthyl

Scheme 15.

Sodium tetraphenyl- and tetrakis(4-tolyl)borate were subjected to the ligandless palladium on charcoal-catalysed Suzuki reaction of bromoaryl and bromobenzyl carboxylic acids in water.[39] The reactions were fast and performed under air with low catalyst loading in a simple and green reaction medium (see example in Scheme 16). It is noteworthy that, in this case, the four phenyl groups were transferred from sodium tetraphenylborate and that the recovered Pd–C could be re-used, although with a gradual decrease in catalytic activity [95% (fresh) to 76% (fourth run)]. Concerning the use of tetraarylborates as substitutes of arylboronic acids, it should be

pointed out that sodium tetraphenylborate is only slightly more expensive than phenylboronic acid, but it is light sensitive and toxic. In addition, sodium tetraphenylborate is apparently the only commercially available tetraarylborate, any other compounds of this type requiring preparation from the corresponding aryl Grignard reagent and BF_3, $NaBF_4$ or boron trialkyl esters. Nonetheless, their use in aqueous media can be recommended, due to their higher solubility in water in comparison with the corresponding arylboronic acids.



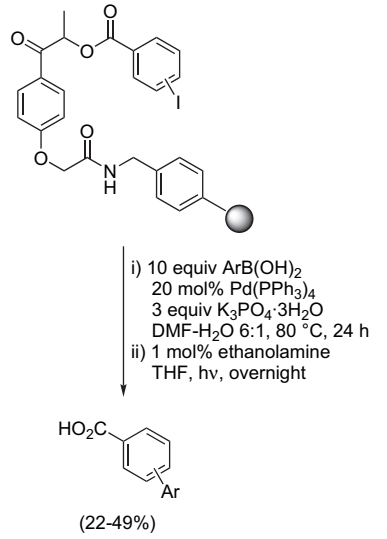
Scheme 16.

Sodium tetraphenylborate has been recently coupled with hypervalent iodonium compounds under microwave irradiation in water without base in the presence of $PdCl_2$ as catalyst.[40] High product yields in short reaction times were obtained, but the results did not differ significantly from those obtained in the absence of a catalyst (see introduction to Section 4).

3.3. Supported substrates

In recent years, increasing interest has been shown to the possibility of anchoring the substrates to a solid support, facilitating their use in automated parallel synthesis in a combinatorial manner. The main advantages of these solid-phase transformations are the avoidance of tedious work-up procedures, the quasi high-dilution effect (high yields by employing an excess of reagent), amenability to automation and the non-interference of various functionalities in the building blocks on a solid support. Carbon–carbon bond-forming solid-phase reactions have been extensively studied, including the Suzuki reaction.[41] The pioneering work in this field was simultaneously carried out by Friesen and Frenette[42] and Ellman and Backes[43] in 1994 using aryl halides bound to a Merrifield and sulfonamide-derivatised aminomethylated resin, respectively.

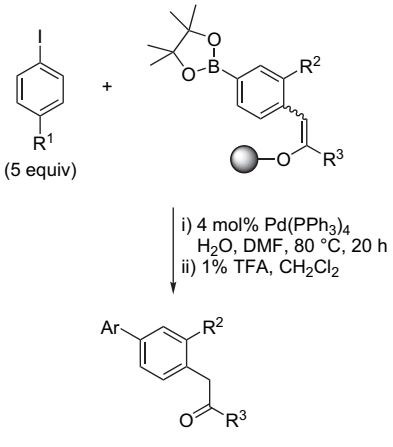
In the more recent literature, it is of interest to note the methodology developed by Waldmann and Gerdes that has allowed the direct mass spectrometric monitoring of the solid-phase Suzuki reaction of iodobenzoic acids with several boronic acids.[44] This methodology was based on the use of a photolabile phenacyl ester linker attached to polystyrene, which could be cleaved by a short laser pulse. A commercial MALDI-TOF spectrometer equipped with a laser emitting at 337 nm was utilised, releasing negatively charged carboxylates upon irradiation that could be recorded as strong peaks. Irradiation with a mercury vapour lamp or nucleophilic cleavage using hydrazine hydrate in dimethyl formamide released the products from the solid support in moderate yields (Scheme 17). This technique could not be applied, however, to compounds with pronounced photoreactivity. In addition, the fact that the procedure to support the substrate is not straightforward, together with the relatively large amounts of boronic acid and palladium catalyst employed, can curtail its application.



Ar = 4-C_6H_4COMe, 3-C_6H_4COMe, 4-C_6H_4OMe

Scheme 17.

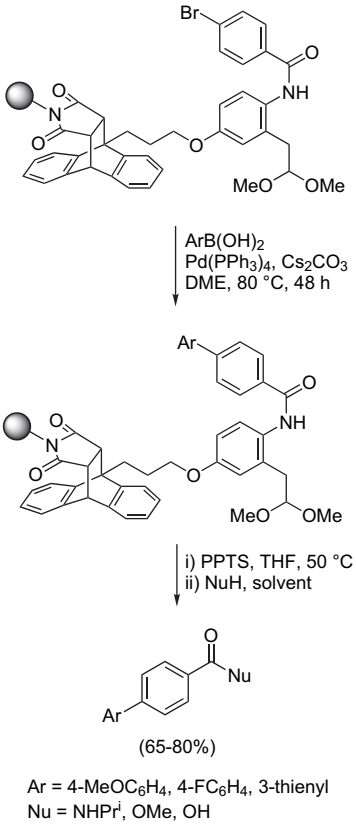
Merrifield resin-bound esters were reacted with titanium benzylidene derivatives bearing a boronate moiety at the *para* position to give the corresponding enol ethers. The latter ethers were subjected to cross-coupling with several aryl iodides, giving, after resin washing and cleavage, the expected ketones in moderate yields (Scheme 18).[45] This is one of the few examples in which the boron-containing substrate is on a solid support. Treatment of the ketone products with 10% HCl–MeOH furnished a variety of 2,5-disubstituted benzofurans. The starting titanium benzylidenes were prepared from the corresponding thioacetals, the preparation of which involved five synthetic steps.



Ar = 4-$R^1C_6H_4$
R^1 = Me, OMe, NO_2
R^2 = H, OMOM
R^3 = Ph$(CH_2)_2$, Me_2C=CH, 4-$MeOC_6H_4$

Scheme 18.

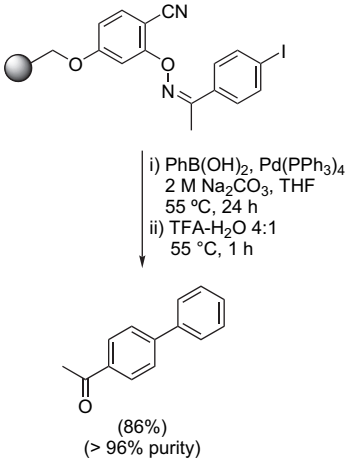
A maleimide resin-bound *p*-bromobenzenecarboxamide was subjected to the Suzuki coupling with three different boronic acids under the conditions depicted in Scheme 19.[46] Under these conditions, competing reduction of the aryl bromide did not occur to any significant extent. By treating the resulting resins with PPTS, the corresponding indolylamides were obtained and subsequently subjected to cleavage in the presence of three different nucleophiles to afford the desired products. The products were obtained in high purity and good yields, but the linker is rather sophisticated and had to be prepared in four steps from the non-commercially available 9-(3-iodopropyl)anthracene.



Scheme 19.

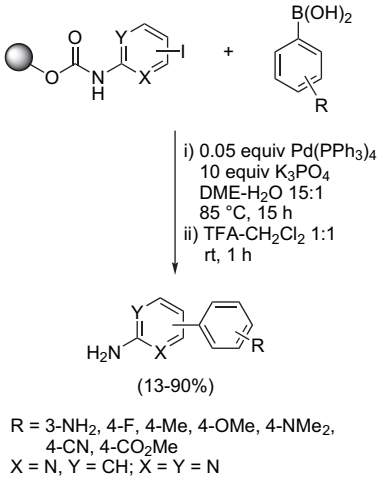
In a study on the application of aryloximes as solid-phase ketone linkers, a *p*-iodoaryloxime attached to a Merrifield resin was treated with phenylboronic acid under aqueous basic Suzuki coupling conditions.[47] No palladium catalyst was specified, but, most probably, $Pd(PPh_3)_4$ was used, following some reported conditions. After resin cleavage, the desired biaryl ketone was obtained in high isolated yield and purity (Scheme 20). This methodology is interesting because of the novel ketone linker used, but not as a very useful approach to the synthesis of biaryls. Five synthetic steps are required to prepare the supported aryl iodide in order to obtain, finally, a biaryl ketone more easily accessible by other solution routes.

Iodo-substituted anilines, 2-aminopyridines and 2-aminopyrimidines attached to the Wang resin with a carbamate linker underwent a Suzuki coupling reaction with differently substituted arylboronic acids under standard conditions, but



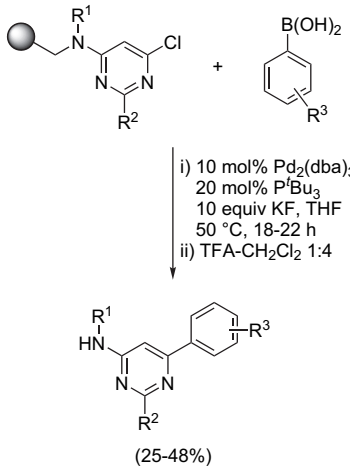
Scheme 20.

with a large excess of the base (Scheme 21).[48] Unfortunately, most of the yields of the resin-free products were <50% and were especially low in the case of 4-iodoaniline (17–37%) and 2-amino-5-iodopyrimidine (13–39%) derivatives. This behaviour was attributed to the premature cleavage of the carbamate linkage during the reaction sequence. Similar Wang-resin-supported chloro- and iodopyrimidines were applied to the solid-phase synthesis of endothelin receptor antagonists through the Suzuki coupling with several arylboronic acids.[49]



Scheme 21.

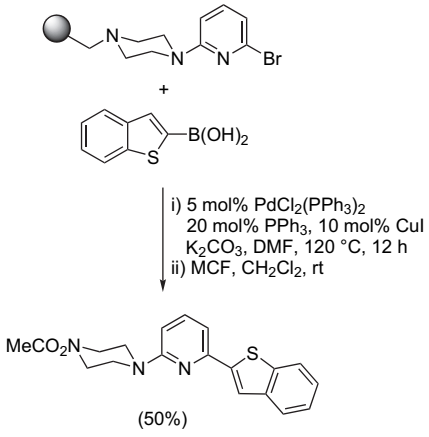
Several resin-supported chloropyrimidines derived from a 4-formyl-3,5-dimethoxyphenoxymethyl resin and primary amines were coupled with some boronic acids containing electron-withdrawing, neutral and electron-donating groups.[50] The reaction proceeded under mild reaction conditions, although a large excess of base was also necessary, giving rise to a library of 4-(substituted amino)-6-arylpyrimidines in high purity, but moderate yields, upon cleavage with acid (Scheme 22). A very similar protocol was applied by Ma et al. for the same purpose, with the advantage that no post-synthesis purification was necessary.[51]



R^1 = Bu^n, $MeO(CH_2)_2$, 2,3-dihydro-1*H*-inden-5-yl, 3-$FC_6H_4(CH_2)_2$, 3,4-$(MeO)_2C_6H_3(CH_2)_2$
R^2 = H, SMe
R^3 = H, 4-Et, 4-OMe, 3-COMe, 3-NO_2, 2-MeO-5-FC_6H_3

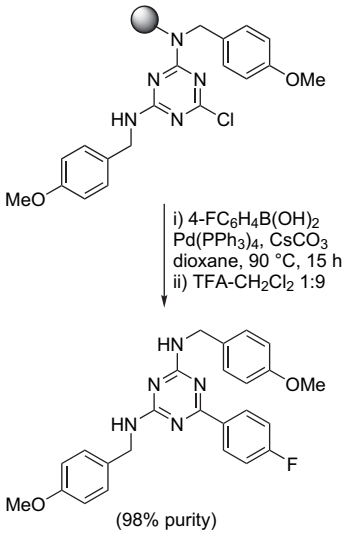
Scheme 22.

Polymer-bound 2-bromopyridylpiperazines reacted with two arylboronic acids (naphth-2-yl- and benzo[*b*]thiophen-2-yl boronic acids) in the presence of a palladium catalyst, PPh_3 and CuI, to give, after resin cleavage with methyl chloroformate (MCF), the corresponding 1-(6-arylpyridin-2-yl)-piperazine carbamates in moderate yields (see example in Scheme 23).[52] Although this methodology gives access to structurally interesting nitrogenated compounds, the boronic acid scope is, apparently, rather limited.



Scheme 23.

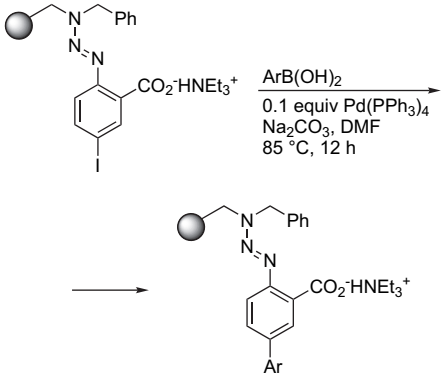
A new synthetic route was developed by Chang et al. in order to introduce the triazene moiety into biaryl systems. This route involved the Suzuki cross-coupling reaction of resin-bound chlorotriazines with a representative range of arylboronic acids (see example in Scheme 24).[53] The final trisubstituted triazene derivatives were obtained in excellent purities after acidic resin cleavage. Although the isolated product yields were not provided, the methodology seems very appropriate to synthesise these particular heteroaromatic biaryl compounds.



Scheme 24.

4-Bromobenzoic esters supported on polystyrene cross-linked with divinylbenzene or bis(4-vinylbenzyl) ether gave moderate conversions (42–55%) and low yields (18–20%) in the Suzuki coupling with 2-thienylboronic acid [$Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, 80 °C, 48 h] after resin cleavage (KO^tBu, H_2O, THF, 65 °C, 48 h).[54] Although the resins were prepared in five simple and high-yielding steps, the low product yields and the long reaction times make the whole process merit little application.

The group of Bräse has prepared a series of triazene carboxylate resins starting from iodo-substituted anthranilic acids and benzylaminomethyl polystyrene.[55] The Suzuki coupling of these resins with several arylboronic acids furnished the corresponding biaryls that were successfully transformed into 6-aryl-3*H*-benzo[*a*][1,2,3]triazinones (Scheme 25). The yields of the biaryl resins were not provided, but the carboxylate moiety remained intact under the reactions conditions. The fact that the nitrogen content of the resin decreased to 70–80% was rationalised in terms of a partial counterion exchange. More recently, the same reaction conditions were applied to (bromophenyl)- and (dibromophenyl)triazene resins

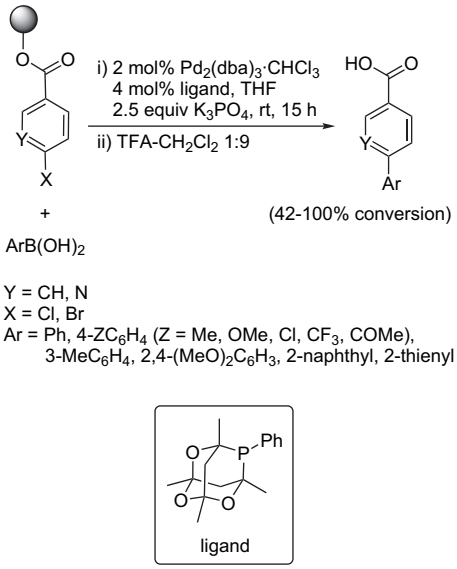


Ar = Ph, 4-YC_6H_4 (Y = Bu^t, Ph, Me, OMe, Br), 3,5-$Cl_2C_6H_3$

Scheme 25.

to give the mono- and disubstituted products, respectively, in moderate-to-good yields.[56]

1,3,5,7-Tetramethyl-2,4,8-trioxa-6-phenyl-6-phosphaadamantane was shown to be a very efficient ligand in the palladium-catalysed Suzuki coupling of *p*-halobenzoic and 6-halonicotinic acids, linked to a commercially available trityl chloride–polystyrene resin, with a variety of arylboronic acids (Scheme 26).[57] It is noteworthy that the reaction proceeded at room temperature and was applicable to both the bromo- and the chloro-substituted aromatic acids, giving the expected biaryls in moderate-to-excellent conversions. The only objections to this procedure may be the rather sophisticated ligand used and the fact that only conversions, but not isolated yields, were reported, the latter giving a better idea of its practical utility.

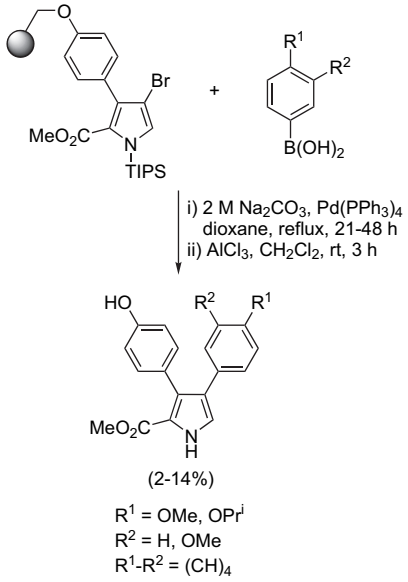


Scheme 26.

More standard Suzuki coupling conditions [$Pd(PPh_3)_4$, K_3PO_4, DMF, 80 °C, 24 h] were successfully applied by Fernández et al. in the coupling of 5-bromonicotinic acid attached to a Wang resin with different arylboronic acids.[58] The corresponding 5-aryl-substituted nicotinic acids were isolated in good yield (75–89%) and purity (78–96%) after resin cleavage. By incorporating 5-bromonicotinic acid onto Rink and alkylamino-BAL resins, small libraries of 24 (>80% purity) and 180 nicotinamides (71–96% purity, 75–85% yield), respectively, were prepared under similar reaction conditions [$Pd(PPh_3)_4$, Na_2CO_3, EtOH–PhMe, 90 °C, 24 h].

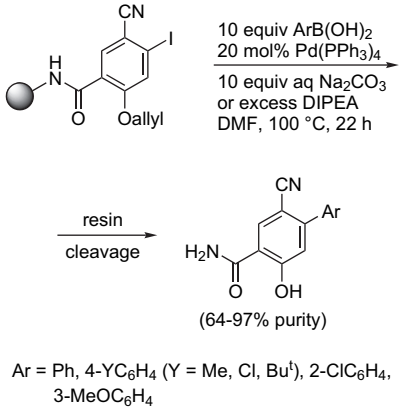
The Suzuki reaction was one of the key steps in a solid-phase synthesis of the pyrrole-based alkaloids lamellarins Q and O.[59] The cleavage of the Merrifield resin was carried out with $AlCl_3$, with concomitant N-deprotection of the pyrrole ring. Although this approach to the synthesis of lamellarins Q and O is elegant, the yields obtained after these two steps are rather poor (Scheme 27).

The Rink amide resin was used in the solid-phase synthesis of novel biphenyl tetrazole precursors based on the Suzuki cross-coupling reaction.[60] Little biphenyl formation was



Scheme 27.

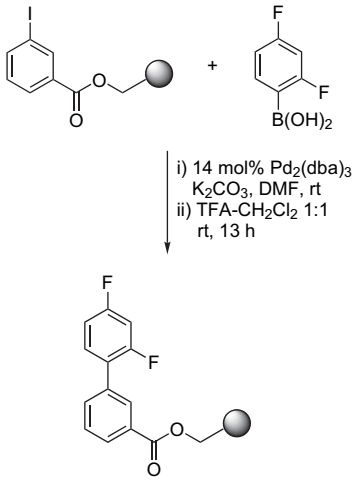
observed under the standard aqueous or anhydrous conditions. In order to obtain better results, 20 mol % of catalyst and a large excess of both arylboronic acid and DIPEA (or aq Na_2CO_3) was necessary (Scheme 28). The same solid support was used for the synthesis of 2-aryl-substituted melatonin derivatives by coupling the resin-bound 2-iodomelatonin moiety with 2-thienyl and 2-benzofuraneboronic acids under Suzuki conditions [K_2CO_3, $Pd(OAc)_2$, dioxane–H_2O, 110 °C or MW].[61] Partial conversion was observed in most cases, even for long reaction times or under microwave irradiation. Nonetheless, 65–77% isolated yields were obtained after resin cleavage and purification by flash chromatography.



Scheme 28.

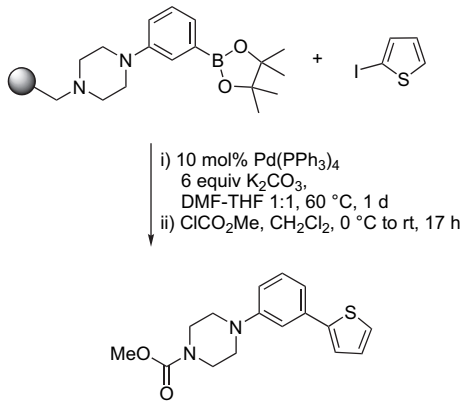
Following the methodology of Guiles et al.,[62] the group of Kelly successfully prepared a diflunisal analogue by coupling a Wang-resin-derived 3-iodobenzoic acid with 2,4-difluorophenylboronic acid followed by resin cleavage (Scheme 29).[63] The coupling took place at room temperature, giving the expected product in 100% isolated yield. The reaction time for the cross-coupling was not provided, but the numerous washings

with different solvents (DMF, H_2O, CH_2Cl_2 and MeOH) make the procedure difficult to scale it up, due to the large amount of waste generated. Additional flash chromatography was necessary after the resin cleavage.



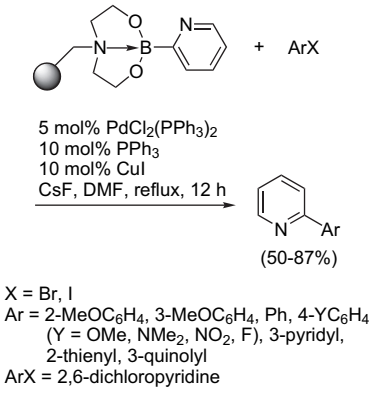
Scheme 29.

Boronic esters derived from a Merrifield resin-bound piperazine were coupled with different aryl bromides and iodides to give the corresponding resin-bound bi- and terarylpiperazines under Suzuki conditions.[64] Cleavage of the resins was effected with methyl chloroformate as the last step of a sequence that comprised three consecutive palladium-catalysed cross-coupling reactions. The isolated yields after six steps were acceptable, but the amount of solvents used to wash the resins was really prohibitive, e.g., washing of the resin resulting from the Suzuki coupling reaction shown in Scheme 30, in which 1.05 g of the starting resin-bound boronic ester was used, involved DMF (2×300 ml), CH_2Cl_2 (3×300 ml), MeOH (1×300 ml), THF (2×300 ml), MeOH (1×300 ml) and CH_2Cl_2 (3×300 ml), making a total amount of 3.6 l of solvent waste.



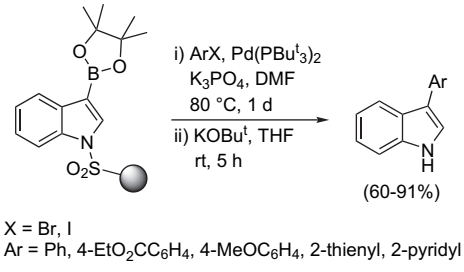
Scheme 30.

Fort et al. have reported the first stable polystyrene-supported 2-pyridylboronate as an efficient reagent that allowed the synthesis of pyridine-containing biaryls by Suzuki coupling with a wide range of aryl and hetaryl halides.[65] The presence of CuI was necessary in order to avoid homocoupling of the aryl halide. Aryl iodides and bromides (bearing a wide range of substituents) and one aryl chloride furnished the corresponding biaryls in moderated-to-good yields after filtration and purification by column chromatography (Scheme 31). Polystyrene-supported 2-pyridylboronate was prepared in three steps and could be stored in an argon-flushed flask, maintaining its efficiency after 5 months.



Scheme 31.

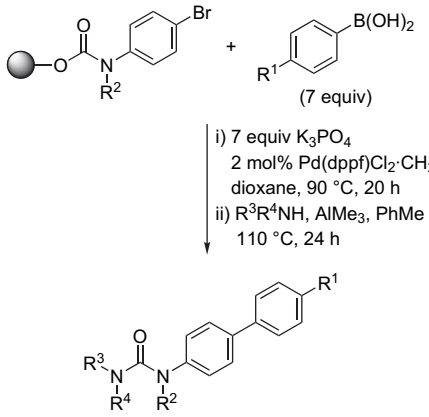
More recently, an immobilised indolylboron derivative was prepared from indole by iodination, immobilisation using chlorosulfonylated polystyrene and borylation following Murata's protocol [pinacolborane, $PdCl_2$(dppf), Et_3N, dioxane, 80 °C].[66] The palladium-catalysed cross-coupling reaction of this immobilised indolylboron compound proceeded smoothly in the presence of $Pd(P^tBu_3)_2$ for both electron-rich and -poor aryl iodides and bromides (Scheme 32). Better results for heteroaryl halides were obtained with $Pd(PPh_3)_4$. The products were obtained in moderate-to-high yields and are important candidates for serotonin 5-HT_2 antagonists.



Scheme 32.

Janda et al. synthesised a library of biaryl ureas from an array of polymer-bound carbamates, derived from the hydroxymethyl JandaJel resin, through a Suzuki reaction and aluminium-promoted resin cleavage in the presence of an amine.[67] Although a considerable excess of both the boronic acid and the base was necessary, the products were obtained in high yield and purity (see examples in Scheme 33). The resin-cleavage conditions are most probably incompatible

with the presence of more reactive substituents on the aryl ring. The same group has also applied the Suzuki reaction to generate a library of bisaryl-linked hexapeptides using a monomethoxy poly(ethylene glycol) as a soluble polymer support to attach the two tripeptides containing an iodoaryl and a phenylboronic moiety.[68]

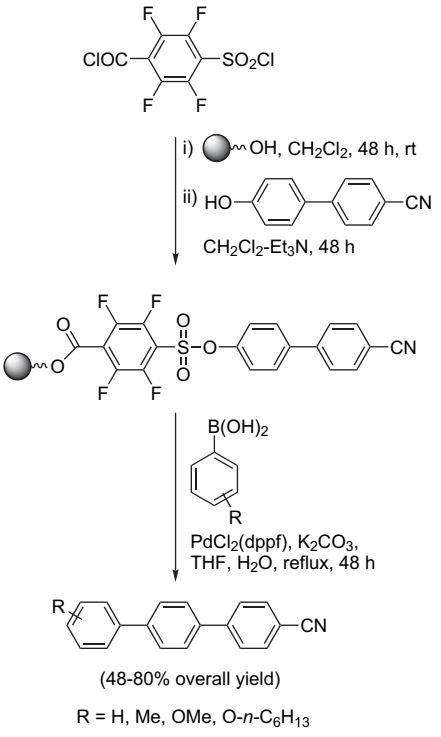


Scheme 33.

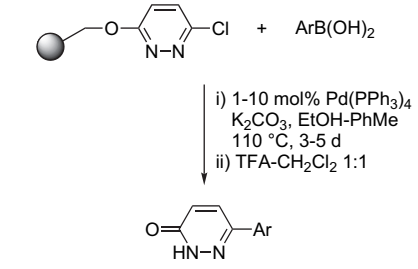
A solid-phase triflate-group equivalent based on an electron-poor arylsulfonate was prepared from two commercial hydroxy supports, Novasyn® TG hydroxy resin and hydroxymethyl polystyrene, with an excess of a diacid chloride.[69] The resulting polymers were reacted with 4-hydroxybiphenyl-4′-carbonitrile and subjected to Suzuki coupling with several boronic acids (Scheme 34). Although, in principle, the cross-coupling reaction was used as a release strategy to remove the product, the corresponding *p*-teraryls were obtained in good overall yields.

Turck et al. immobilised the 3-chloropyridazine moiety onto a Wang resin that was subsequently reacted with various arylboronic acids under Suzuki conditions.[70] Long reaction times (3–5 days) were, however, needed in order to obtain the corresponding resins in high purity (Scheme 35). Acid cleavage of these resins yielded 6-arylpyridazin-3(2*H*)-ones as a mixture of the free base and its trifluoroacetate. Although the combination of both yields led to high values, an additional step to completely release the free base is required.

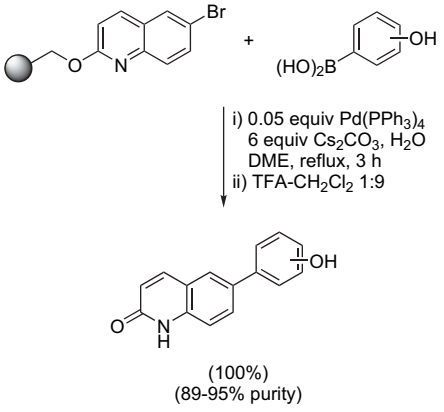
In a study directed towards nuclear hormone receptors, a solid-phase synthesis of a 6-phenylquinolin-2(1*H*)-one library was conducted based on the Suzuki coupling of a 6-bromo-2-alkoxyquinoline attached to a Wang resin with hydroxyphenylboronic acids (Scheme 36).[71] The reactions proceeded relatively rapidly to give, after resin cleavage, the expected products in excellent purity and yield. The only disadvantage of this synthesis seems to be the tedious washing protocol for the resin and therefore, excessive amount of solvent waste



Scheme 34.



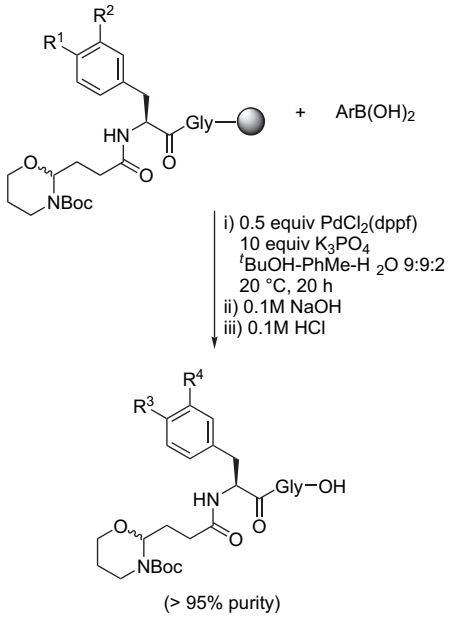
Scheme 35.



Scheme 36.

generated (2×DME, 3×20% satd aq NH_4Cl in THF, 2×20% water in THF, 3×THF and 3×CH_2Cl_2).

Solid-supported masked peptide aldehydes containing 3- or 4-iodophenylalanine moieties were coupled with arylboronic acids bearing different electron-rich and -poor substituents (Scheme 37).[72] The resulting products, once free of the $PEGA_{800}$ resin, were obtained with >95% purity as precursors of pharmacologically interesting aryl-substituted pyrroloisoquinolines. Unfortunately, no yields of the isolated products were provided. The work-up after the Suzuki reaction also involved a particular washing protocol for the resins with unspecified amounts of solvents (6×CH_2Cl_2, 6×DMF, 6×H_2O, 3×DMF and 6×CH_2Cl_2).

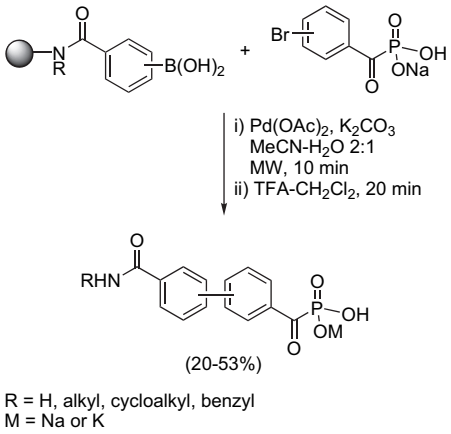


R^1 = H, R^2 = I, R^3 = H, R^4 = Ar
R^1 = I, R^2 = H, R^3 = Ar, R^4 = H
Ar = Ph, 4-YC_6H_4 (Y = Me, CHO, OBu, SMe, OMe, Cl), 2-$MeOC_6H_4$, 3-$F_3CC_6H_4$, 3-$NO_2C_6H_4$, C_6F_5, 4-MeO-3-ClC_6H_3, 3,4-$(OCH_2O)C_6H_3$, 3-CHO-4-$MeOC_6H_3$

Scheme 37.

More recently, sodium bromobenzoyl phosphonates have been found to be good substrates for the Suzuki coupling with resin-bound boronic acids derived from ArgoPore Rink-NH_2 resin and 3- or 4-carboxyphenylboronic acid.[73] The coupling was carried out in an aqueous medium under microwave irradiation, furnishing, after resin cleavage, the corresponding biaryl products in low-to-moderate yields (Scheme 38). The low yields observed were attributed to the poor recovery of these highly polar compounds during the HPLC purification.

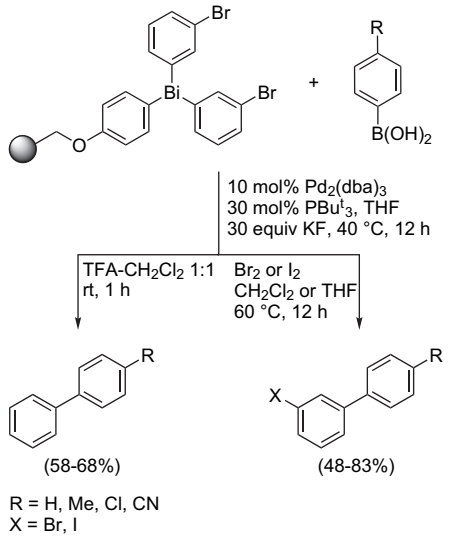
A resin-bound dibromophenylbismuthane, prepared by Ruhland et al. from 1,3-dibromobenzene (three steps, 74% yield),[74] was used in the Suzuki cross-coupling with several arylboronic acids under mild reaction conditions (Scheme 39).[75] Besides both triarylbismuthanes and boronic acids acting as donors in palladium-catalysed cross-coupling reactions with aryl bromides, immobilisation of the bromophenylbismuthane



R = H, alkyl, cycloalkyl, benzyl
M = Na or K

Scheme 38.

on the solid phase apparently prevents the bismuthane from coupling with the resin-bound aryl bromide. Mild reaction conditions were required in order to suppress side reactions of the immobilised bismuthane. Larger amounts of the palladium catalyst, promoter and base were, however, needed in comparison with similar cross-coupling reactions in solution. The versatility of this methodology resides in the fact that the resin cleavage could be effected in a traceless (with TFA−CH_2Cl_2, affording the corresponding biphenyls) or multidirectional manner (with iodine or bromine, giving the halogen-substituted biphenyls). Additionally, both aryl groups of the bismuth linker can be utilised in the product formation, resulting in a high resin loading.

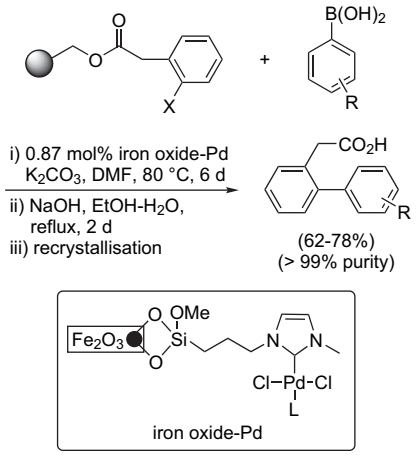


R = H, Me, Cl, CN
X = Br, I

Scheme 39.

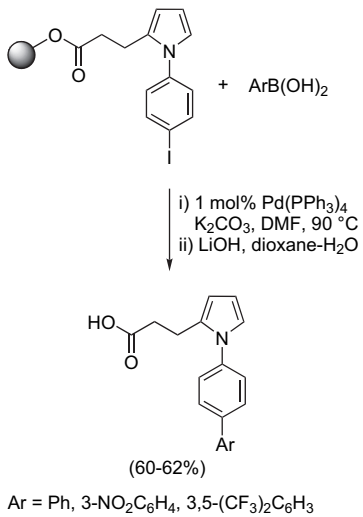
Gao et al. reported for the first time the use of a magnetic nanoparticle-supported palladium catalyst to promote the solid-phase Suzuki cross-coupling of aryl halides on a resin with arylboronic acids in solution (Scheme 40).[76] Organosilanes were utilised to immobilise the Pd−NHC complexes onto the surface of the maghemite nanoparticles (4-nm iron oxide). The aryl halides were also immobilised onto a 1%

divinylbenzene-cross-linked polystyrene resin. It is worthy of note that the work-up is a chromatography-free process involving: (a) iron oxide–Pd magnetic concentration and removal from the resins by applying an external permanent magnet (about 83% recovery, it can be re-used), (b) Suzuki product separation (70% average yield, >99% purity) by resin filtration, saponification and recrystallisation and (c) recovery of the remaining arylboronic acid (>99% purity) by filtrate acidification and extraction with toluene. This methodology, although original, needs to address two important issues: (a) the low reaction rates (>6 days) attributed to the slow diffusion of iron oxide–Pd into and out of the resin pores and (b) the solubility of the iron oxide–Pd in organic media that necessitates repeated magnetic separation steps to completely remove the catalyst from the resins.



Scheme 40.

Hyperbranched polyglycerol was utilised as a soluble polymer to attach *N*-(4-iodophenyl)-2-pyrrolepropanoic acid, which was subjected to the Suzuki reaction, affording several *N*-biphenyl derivatives in acceptable yields (Scheme 41).[77] The preparation of the polyglycerol-bound aryl iodide was not so straightforward, involving an anodic oxidation and dialysis within a total of five steps. No comment was made concerning the possible recovery of the support.



Scheme 41.

4. Catalytic systems

It is obvious that the selection of a proper catalytic system is fundamental for achieving the best efficiency in a given Suzuki reaction. It should be understood, however, that the catalyst efficiency is not only uniquely related to its catalytic activity or selectivity, but also to the possibility of recovery and re-utilisation of its components. At the same time, it is also desirable in every case to minimise the generation of waste and the environmental impact, especially for possible applications on an industrial scale. According to these very basic principles, significant efforts have been made in recent years to develop more simple, but efficient, catalytic systems.

In this sense, and in spite of the title of this report, the so-called 'transition metal-free' Suzuki reaction deserves a brief comment. In 2003, Leadbeater and Marco discovered a microwave-promoted coupling methodology that did not require the addition of a palladium catalyst.[78] This spectacular finding surprised the organic chemists' community and it was a subject of debate and controversy for some time.[79] Further experiments, however, provided conclusive evidence that Leadbeater group's reactions were palladium catalysed after all by the action of very low levels of palladium (20–50 ppb) contained in the commercially available sodium carbonate used.[80] Nonetheless, it was learned from this research that it is possible to carry out the Suzuki reaction with ultra-low catalyst loadings and in the absence of any ligand, under the conditions and for the substrates reported by this group (more examples are discussed in Section 6.1.1).[35] It would be valuable to know more about the properties and morphology of the palladium contained in sodium carbonate that makes it more effective than the added palladium with an identical loading.

The Suzuki-type reactions studied by Yan et al. involving sodium tetraphenylborate with iodanes in water at room temperature in the absence of a base,[81] the catalyst-, solvent- and base-free coupling of sodium tetraphenylborate with hypervalent iodonium salts[82] and iodanes[83] under microwave irradiation and the catalyst- and base-free coupling of sodium tetraphenylborate with hypervalent iodonium salts and iodanes in water[84] and under microwave irradiation, can all be considered to be strictly catalyst free.[81b,85] These reactions, that generally proceed in good yields, are, however, limited to the use of only one boron-containing nucleophilic coupling partner (Ph_4BNa) and show a low atom economy, since it is used in excess with incorporation of only one phenyl group into the electrophilic coupling partner.

In view of the above discussion, it may be concluded that there is always a need for transition metal-catalysed Suzuki reactions, because they can offer more versatility, chemo- and regio-selectivity, functional-group tolerance and milder reaction conditions, among other advantages.

4.1. Ligands: ligand-free catalytic systems

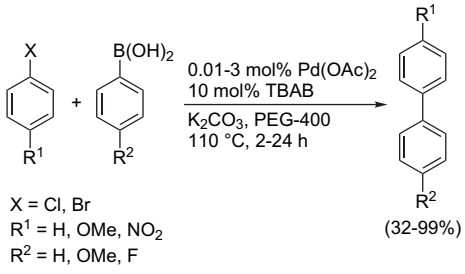
Phosphane-based palladium catalysts are generally used in the Suzuki reaction since they are stable on prolonged heating. In particular, triarylphosphanes are excellent ligands to stabilise the palladium species. They are, however, usually toxic, unrecoverable and frequently hamper the isolation and purification of the desired product, as well as the performance of consecutive catalytic steps of a total synthesis. In addition, there is an undesirable side reaction of the aryl–aryl interchange between palladium- and phosphane-bound aryls (especially in electron-rich haloarenes), leading to the coupling product of phosphane-bound aryls. In 1994, Wallow and Novak showed that high Suzuki reaction rates could be achieved by using palladium catalysts in the absence of a phosphane ligand.[86] Phosphane-related side reactions such as the aryl–aryl exchange in triarylphosphanes and phosphonium salt formation were eliminated.

In spite of the fact that phosphane ligands have been substituted by other ligands, the high ligand sensitivity to air and moisture, their tedious multistep synthesis, the high cost of the ligands and the use of various additives curtail their applications. An operationally, economically and environmentally more advantageous catalytic system is desirable. The ligandless approach for the carbon–carbon cross-coupling reaction was pioneered independently by Beletskaya[87] and Jeffery.[88] Although the ligandless catalysed Suzuki reaction often achieves significantly fast coupling in aqueous media, complete conversion cannot always be possible, especially for the slow reactions of electron-rich and sterically hindered haloarenes.

Some information until 2003 about the ligandless catalytic systems in the Suzuki reaction can be found in the reviews of Kotha's[31] and Rossi's[3r] groups. A selection of more recent information follows, some special conditions (supported catalysts, aqueous media, microwaves, etc.) being tackled in the corresponding sub-sections below.

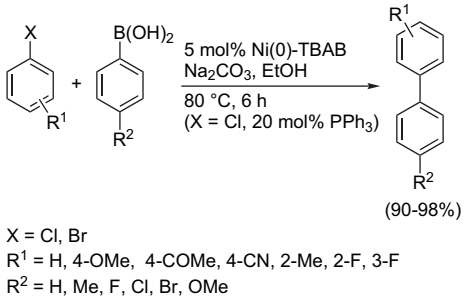
It is worth mentioning the simple catalytic system developed by Shen et al. in 2004 composed of ligandless $PdCl_2$ and K_2CO_3 in pyridine.[89] Aryl bromides containing electron-withdrawing and -donating substituents were coupled using low catalyst amounts (0.3 mol %) at reflux to afford the corresponding biaryl products in 90–100% isolated yield. An additional advantage of this methodology was the recovery of the solvent, pyridine, in >90% under vacuum.

More recently, it has been found that the Suzuki cross-coupling reaction can occur under ligand-free conditions at a loading of 0.01–3 mol % Pd using 10 mol % TBAB as an activator and PEG-400 as the medium.[90] These reaction conditions provided moderate yields for aryl chlorides and good-to-excellent yields for aryl bromides containing different functional groups (Scheme 42). Furthermore, this system could be re-used at least three times without significant loss in catalytic activity. In the absence of TBAB but using a H_2O–PEG 2000 solvent system and Na_2CO_3 as base, aryl bromides and iodides reacted at 50 °C in excellent yields.[91] The catalytic system was also re-usable after product extraction with diethyl ether. Moreover, the simple catalytic system composed of $PdCl_2$ (5 mol %), K_2CO_3 and PEG 300 allowed the Suzuki reaction of a large variety of aryl chlorides and several arylboronic acids at room temperature.[92] Apparently, in this case the catalytic system could not be re-utilised.



Scheme 42.

Ni(0) colloids stabilised by TBAB catalysed the Suzuki reaction of differently substituted aryl iodides and bromides with arylboronic acids under phosphine-free reaction conditions.[93] Excellent yields of the expected biphenyls were obtained for all the aryl bromides tested, although 20 mol % PPh_3 was needed for the reaction with aryl chlorides to take place (Scheme 43). The nickel metal on TBAB was re-used in the same reaction flask for six consecutive cycles without significant loss in activity. This is a clear example of how a cheaper metal, nickel, can be an appropriate substitute for palladium in carbon–carbon coupling reactions. In fact, this nickel-based methodology at 80 °C showed comparable results to that with palladium at 110 °C described above.



Scheme 43.

4.2. Catalysts: supported catalysts

It is worthwhile developing new heterogeneous catalysts or heterogenised homogeneous catalysts that, generally, simplify the catalytic system and the purification step, and that can be recycled and re-used without significant loss of activity.[94] Among the heterogeneous catalysts, the supported metal catalysts, zeolite-encapsulated catalysts, colloid-nanoparticles and intercalated metal compounds may be mentioned. The homogeneous metal complex catalysts can be heterogenised using modified silica catalysts, polymer-supported catalysts, biphasic catalysts, supported liquid-phase catalysts, non-ionic liquid solvents, perfluorinated solvents and re-usable homogeneous

complexes. All these types of catalysts can be easily recovered from the reaction mixture and recycled, if they do not deactivate too quickly under duty.

Since an important part of this topic has already been covered in diverse reviews, we will discuss mainly some selected examples of the most recent literature covering the study of catalysts supported on carbon, metal oxides, molecular sieves, clays, zeolites, polymeric and dendrimeric materials.

4.2.1. Carbon

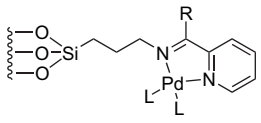
Palladium on carbon (Pd–C) is one of the most frequently investigated catalysts for the Suzuki reaction. In 1994, a group from Hoffmann–La Roche discovered that Pd–C was a good substitute for $Pd(PPh_3)_4$ in the coupling of aryl halides with arylboronic acids.[95] The optimised reaction conditions (5% Pd^0–C or 10% Pd^{II}–C, Na_2CO_3, EtOH, 80 °C) were successfully applied to a variety of electronically different aryl bromides and iodides, although aryl chlorides underwent hydrogenolysis rather than coupling. In general, the Pd^0–C catalyst showed better behaviour, since with Pd^{II}–C, dimerised by-products were detected. The authors presented strong evidence that, under the above reaction conditions, the coupling reactions occurred by heterogeneous catalysis. It is still the subject of debate as to whether this type of reaction takes place on the solid palladium surface or whether the true catalyst is the dissolved palladium that has been leached from Pd–C, which acts simply as a palladium reservoir.

We do not propose to include any more examples of the Pd–C-catalysed Suzuki reaction, since very recently, two comprehensive reviews have been published on this topic.[96] Nonetheless, it is worth highlighting the advantages of Pd–C in this reaction, as summarised by the authors of one of these reviews: (a) it is an inexpensive source of palladium, (b) it is easily separated from the reaction mixture by simple filtration, (c) it can sometimes be recycled and good yields can be maintained with a progressive increase of the temperature, (d) it can be used without ligands and (e) although catalytically less active than the last generation of homogeneous catalysts, it is compatible with a large variety of substrates, including aryl chlorides.

4.2.2. Metal oxides and other inorganic materials

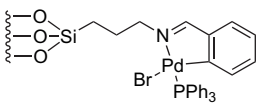
Silica, within the family of metal oxides, has been by far the most utilised support in the Suzuki reaction.[97] The most common methodology involves the immobilisation of imine ligands on a chemically modified silica by the introduction of a 3-aminopropyl moiety followed by palladium complexation.[98]

The original idea was developed by the group of Clark[99] and applied for the first time to the Suzuki reaction independently by Clark et al.[100] (complex **1**, Chart 1) and Bedford et al.[101] (complex **2**, Chart 1) in 2001. All the catalysts showed high catalytic activity in the coupling of phenylboronic acid with aryl bromides in xylene (95–120 °C) or toluene (130 °C). Catalyst **2**, however, lost all its activity after recycling. It was found that catalyst **1** with R=Me, L=OAc was much more active than with R=H, L=OAc and this was applied to the synthesis of polyaryls from polybrominated



1

R = H, Me; L = OAc, Cl

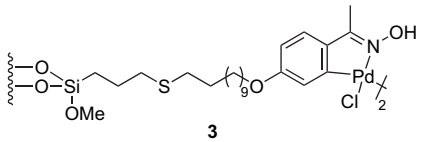


2

Chart 1.

aromatics.[102] In addition, this catalyst exhibited a high stability and could be re-used for at least seven runs with a good performance. Lower yields were observed for the same substrates when the reaction was carried out with catalyst **1** (R=H, L=Cl) or the analogous quinoline derivative using benzene as the solvent at 80 °C.[103] Nonetheless, a reduced amount of palladium was utilised and the process was applied to the more unusual substrates, 9-bromo- and 9,10-dibromoanthracene, giving the corresponding biaryls in moderate yields. Catalyst **1** (L=OAc) also showed the highest rate constants for the above-mentioned reaction within a series of silica-supported palladium catalysts containing 2-substituted pyridyl, thienyl, furyl, anilino, phenoxide and pyrrolyl moieties.[104]

Corma et al. have also actively contributed to the Suzuki reaction catalysed by palladium complexes supported on silica. They found that a preformed oxime–carbapalladacycle complex covalently anchored onto mercaptopropyl silica (Chart 2, **3**) was very active (>99% conversion) in the coupling of 4-chloro- and 4-bromoacetophenone with phenylboronic acid.[105] The main advantages of this methodology were the use of water as the solvent (at reflux) and the catalyst reusability for eight consecutive runs without a noticeable decrease in activity. The catalyst was shown to be superior



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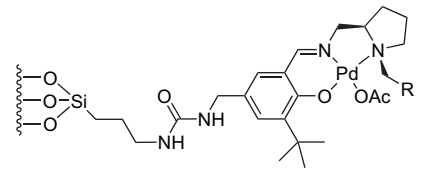
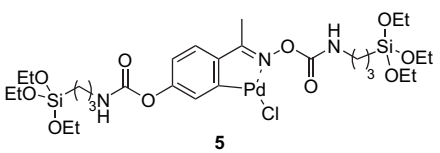


R = Ph, 1-naphthyl, 2-naphthyl

4



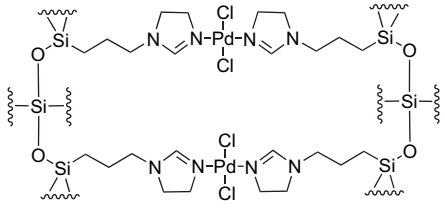
5

Chart 2.

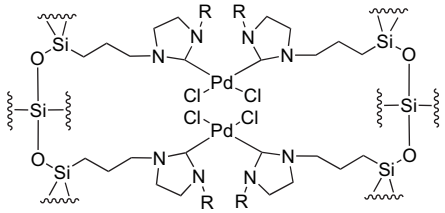
when supported on silica in comparison with mesoporous MCM-41 or polymeric supports derived from styrene or methyl acrylate.[106] Although practically all the other aryl halides studied contained electronically neutral or withdrawing groups and were coupled only with phenylboronic acid, an aryl fluoride (4-fluoro-2-nitrobenzaldehyde) also reacted, giving the expected biaryl in 30% yield. Catalyst **4** (Chart 2) (5 mol %) also catalysed the Suzuki reaction of bromobenzene and phenylboronic acid in *o*-xylene and aq K_2CO_3 at 143 °C. No accurate information about the yields was provided in this case, although silica and MCM-41 seemed to be better supports than delaminated zeolites.[107] The catalyst and its preparation appear to be rather sophisticated, the structure containing a non-utilisable enantiomerically pure chiral moiety.

Periodic mesoporous organosilicas incorporating the carbapalladacycle **5** (Chart 2) were synthesised from tetraethyl orthosilicate (TEOS) and showed an ordering and structure expected for an MCM-41 silica.[108] The activity of this mesoporous catalyst in the Suzuki reaction of aryl bromides with phenylboronic acid (10 mol % Pd, K_2CO_3, H_2O, reflux, 24 h) was much higher than that of the analogous amorphous solids. It was estimated that 50% of the overall catalytic activity was due to leached palladium species coming from a gradual decomposition of the initial oxime carbapalladacycle. This catalyst transformation could explain the progressive decrease in the conversion upon re-use.

Complex **6** (Chart 3) was prepared by heating 3-(4,5-dihydroimidazol-1-yl)propyltriethoxysilane-dichloropalladium(II) with mesoporous silica nanotube particles,[109] and was applied to the coupling of activated and deactivated aryl halides (ArX, X=Cl, Br, I) and phenylboronic acid using Cs_2CO_3 as a base in dioxane at 80 °C. The reactions proceeded quite rapidly (0.5–4 h) and in high yields (82–98%) with a relatively low catalyst loading (1.5 mol %). In all cases where recycling of the catalyst was attempted, however, small decreases in activity were observed from one run to the next. Practically, the same behaviour was observed for the palladium carbene complex grafted onto the surface of amorphous silica **7** (Chart 3), in the coupling of *para*-substituted aryl chlorides with phenylboronic acid under the above reaction conditions.[110]



6



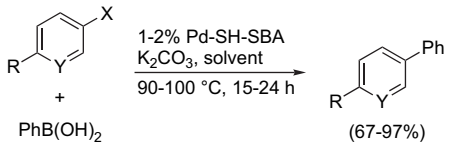
R = 2,4,6-trimethylbenzyl

7

Chart 3.

An FSM-16 mesoporous silica-supported mercaptopropylsiloxane-palladium(II) complex, Pd–SH–FSM, was prepared by stirring mercaptopropyl-functionalised FSM-16 (SH–FSM) with a solution of $Pd(OAc)_2$ in acetone at 25 °C for 12 h.[111] The activity of the catalyst was studied for the coupling of 4-bromoanisole and phenylboronic acid (1 mol % catalyst, K_2CO_3, DMF, 130 °C) and compared with the other supports. The Pd–SH–FSM catalyst prevented Pd metal aggregation, but gave a similar performance when compared with the SH-functionalised amorphous silica (79 vs 76% yield). Lower palladium leaching was observed for Pd–SH–FSM in comparison with Pd–FSM, Pd–Y zeolite or Pd–C, the two latter catalysts showing, however, higher yields of the products (83 and 86%, respectively). Nonetheless, a wider substrate scope would be desirable.

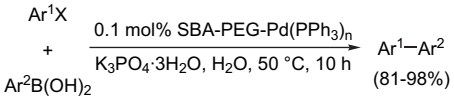
Palladium leaching was reduced to <3 ppb when mercaptopropyl-modified mesoporous SBA-15 silica (Pd–SH–SBA) was used, instead of FSM-16.[112] This catalyst was applied to the coupling of several aryl bromides and chlorides with phenylboronic acid in DMF, H_2O or DMF–H_2O. Moderate-to-excellent yields of the products were obtained at 90–100 °C with virtually no loss of activity after re-use (Scheme 44). Palladium and palladium–gold nanoparticles highly dispersed in functionalised mesoporous silica SBA-15 were also found to catalyse the Suzuki reaction, but the yields, TONs and TOFs were substantially lower than those observed in the solution-phase systems.[113]



X = Br, Y = N, R = H
X = Cl, Br; Y = CH; R = H, COMe, Me, OMe, CHO

Scheme 44.

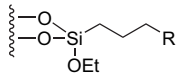
Ma et al. recently prepared a new palladium catalyst supported on PEG-modified mesoporous silica SBA-15 that was shown to be very active in the Suzuki reaction of a variety of aryl bromides, aryl iodides and chlorobenzene with four different arylboronic acids (Scheme 45).[114] Despite the fact that both the mesoporous silica SBA-15 and the silica-supported catalyst had to be synthesised (the latter involving five steps), this effort was more than compensated for by the following remarkable properties of this catalyst: the possibility of carrying out the coupling in neat water in the open air, the high product yields, the catalyst stability (it was effective, even after exposure to air for 6 weeks), its good performance at low catalyst loading and its re-usability without any loss of activity (no leaching was detected). Nevertheless, a wider substrate scope for aryl chlorides would still be desirable.



Ar^1 = Ph, 2,6-$Me_2C_6H_3$, 4-YC_6H_4 (Y = OMe, NO_2), 2-YC_6H_4 (Y = OH, CO_2Me, CN, NO_2)
Ar^2= Ph, 4-YC_6H_4 (Y = OMe,CF_3), 2-NCC_6H_4
X = Br, I
Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$, X = Cl

Scheme 45.

Palladium nanoparticles immobilised onto mesoporous silicas **8**, organically modified by amine functionalities, proved to be active in the coupling of aryl bromides (4-YC_6H_4Br, Y=H, Me, COMe, OMe; 2-YC_6H_4Br, Y=Me, OMe) with phenylboronic acid (K_3PO_4, PhMe, 110 °C, 5 h). Although high reaction conversions were attained, deactivation of the catalyst occurred when used beyond three runs.[115] $PdCl_2$ complexed to a closely related support to **8** [R=$NH(CH_2)_2NH_2$] showed high conversions (82–98%) in the coupling of phenylboronic acids with hydroxy, hydroxymethyl and carboxy groups at the 3- and 4-position with 4-bromophenylacetic acid, 4-iodobenzoic acid and 4-iodoanisole.[116] The reactions were fast (2 h) under the optimum reaction conditions tested (Na_2CO_3, DMA–H_2O, 90 °C). Much lower yields or no coupling was observed for the phenylboronic acids bearing 4-amino, 4-formyl or 4-vinyl substituents. Apparently, the possibility of recycling of the catalyst was not studied.

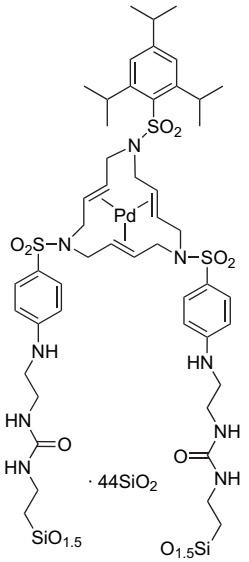


R = $NH(CH_2)_2NH_2$, $NH(CH_2)_2NH(CH_2)_2NH_2$

8

The group of Pleixats prepared a hybrid organic–inorganic material containing a macrocyclic palladium(0) complex covalently bonded to a mesoporous silica matrix obtained from tetraethyl orthosilicate.[117] The resulting catalyst **9** (2.8% Pd) exhibited good activity in the coupling of 4-nitrophenyl iodide and 4-iodoanisole with phenylboronic acid (K_2CO_3 or Cs_2CO_3, PhMe or dioxane, 95–100 °C). The reaction was fast for 4-nitrophenyl iodide (2 h), but rather slow for 4-iodoanisole (48 h). The necessity of anhydrous and degassed solvents as well as an inert atmosphere, the progressive decrease in activity of the catalyst when re-used and the long synthetic pathway (eight steps) are some of the disadvantages of this rather sophisticated supported palladium complex.

Better results were observed for the high-surface hybrid silica materials **10** with a covalently attached di(2-pyridyl)-methylamine–palladium dichloride complex.[118] They showed a remarkable behaviour in the coupling of the activated 4-bromoacetophenone with phenylboronic acid (0.2 mol % Pd, K_2CO_3, DMF–H_2O, 110 °C, 45–60 °C). The reactions were fast, leading to the expected biaryl compound in excellent isolated yields, even after 10 consecutive cycles (100–94% yield). Unfortunately, the coupling of 3-chlorobenzonitrile with phenylboronic acid was much slower, with an incomplete and significant decrease of conversion upon recycling.



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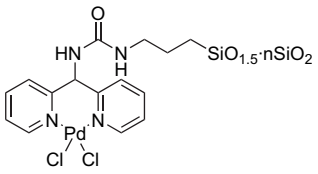
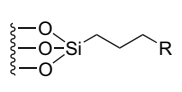


n = 10, 20, 40

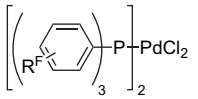
10

Bannwarth et al. developed a strategy to immobilise the perfluoro-tagged palladium catalysts **13**–**17** on a fluorous solid support (**11** and **12**, fluorous reverse-silica gel) (Chart 4) and investigated the performance of the resulting catalysts in promoting different carbon–carbon coupling reactions.[119] Concerning the Suzuki reaction with the support **11** and catalyst **13**, high conversions with no significant loss of activity, at least for two subsequent runs, were obtained for electron-poor aryl bromides and iodides, although a significant decrease in activity was observed using the less-reactive aryl halides (0.1 mol % catalyst, DME, aq Na_2CO_3, 80 °C). The fact that no fluorous solvent was needed in this process is of a great environmental relevance.

Catalyst **13** on support **11** has also found application in the Suzuki reaction in water of water-soluble aryl bromides



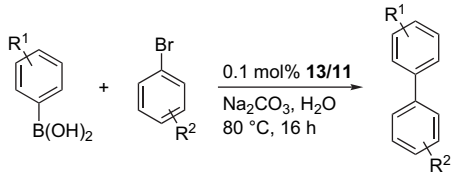
11 R = C_6F_{13}
12 R = $Si(CH_2CH_2C_6F_{13})_3$



13 R^F = 4-$C_8F_{17}CH_2CH_2$
14 R^F = 3-$C_8F_{17}CH_2CH_2$
15 R^F = 4-C_8F_{17}
16 R^F = 4-$C_7F_{15}CH_2O$
17 R^F = H

Chart 4.

(Scheme 46).[120] Except in the case of 3-bromobenzoic acid [30% yield with $PhB(OH)_2$], the yields of the biaryls were high, with even a slight increase in activity upon recycling. The results suggested that the catalyst was operating by a homogeneous mechanism and did not depend upon a soluble aryl halide for the generation of the active species from the precatalyst. Although a wide range of water-soluble aryl bromides were studied, only phenylboronic acid and methoxy-substituted phenylboronic acids were used as the coupling partners.



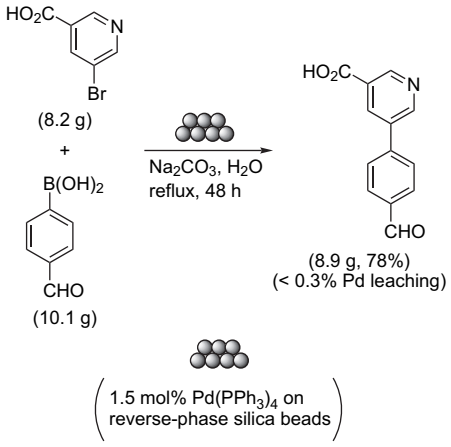
R^1 = H, 2-OMe, 4-OMe
R^2 = 4-CH(OH)CO_2H, 4-CO_2H, 3-CO_2H, 4-CH_2CO_2H, 4-$CONHCH_2CO_2$H, 3-$CONHCH_2CO_2$H

Scheme 46.

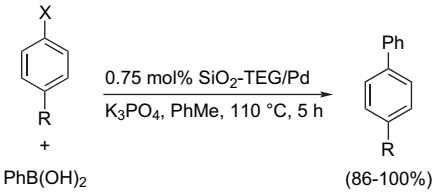
The re-usability of the palladium complexes in Chart 4 and some other perfluoro-tagged palladium complexes with mono- and bidentate ligands on fluorous or unmodified silica gel in organic solvents and in water was investigated more recently.[121] In organic solvents, the activity decreased upon recycling, which was attributed to catalyst decomposition rather than to catalyst leaching. On the other hand, higher cumulative TONs were observed in water, the activity remaining at a high level upon re-use of the supported complex. Therefore, this methodology represents significant progress in the Suzuki coupling of hydrophilic substrates using neat water as the solvent.

In this context, Williams et al. have employed reverse-phase glass (silica) beads as a support for the palladium-catalysed Suzuki reaction of several boronic acids with a large variety of water-soluble aryl iodides and bromides in neat water.[122] In general, the reactions were completed in 1.5–4 h, with low palladium leaching and with the formation of variable amounts of the homocoupling products in some cases. No appreciable loss of activity was observed after a second run with the re-used catalyst. Unfortunately, a very low yield or no product was obtained in the coupling of aryl chlorides. Nonetheless, it is noteworthy that this methodology could be extended to a larger-scale synthesis (Scheme 47).

Palladium nanoparticles, generated from $Pd(PPh_3)_4$ in a mixture of tetra(ethylene glycol) and tetramethoxysilane, were encapsulated in a silica matrix by treatment with water and applied to the Suzuki reaction of phenylboronic acid with several activated aryl halides.[123] High yields of the corresponding biaryls were obtained for the aryl iodides and bromides, but the aryl chlorides practically did not react under these conditions (Scheme 48). Interestingly, the catalyst could be used three times without loss of activity, although its application seems to be limited to aryl bromides and iodides



Scheme 47.

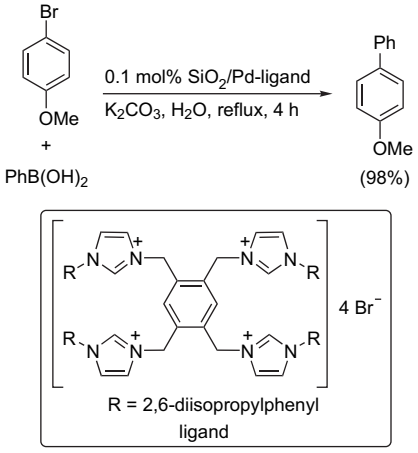


X = Br, I
R = H, CHO, CO_2Me, CF_3

Scheme 48.

bearing electron-withdrawing groups. The effect of different substituents in the arylboronic acid was not reported.

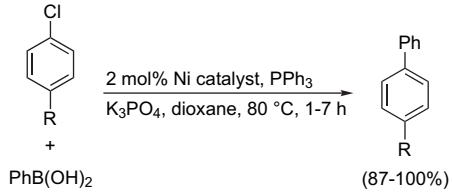
The group of Zhang developed a silica-supported NHC–carbene palladium catalyst for the cross-coupling of aryl bromides with phenylboronic acid in neat water under air.[124] In this case, electron-rich substrates such as methoxy-substituted aryl bromides, as well as several nitrogenated heteroaryl bromides, gave the expected biaryls in moderate-to-excellent yields (52–98%, see example in Scheme 49). It is worth noting that the solid-supported complex could be stored for more than 2 months without significant loss of activity and re-used 2–3 times in refluxing water under air.

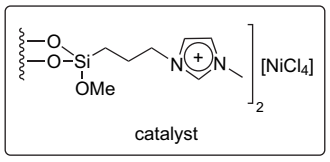


Scheme 49.

The reduced 1.39% Pd–MCM-41 catalyst provided high conversions in the coupling of phenylboronic acid with bromobenzene, 1-bromonaphthalene and 4-bromobenzonitrile (97–100%; Cs_2CO_3, TBAC, DMF–H_2O, 100 °C, 4 h). Significant changes in the catalyst performance were achieved by adding TBAC to the reaction medium.[125] 3-Bromopyridine gave the corresponding biaryl in 63% conversion, whereas very low conversions were obtained for 4-bromoanisole (8%) and 4-bromochlorobenzene (17%). It would be of interest to know more about the substrate scope, the isolated yields and the catalyst recyclability, in order to have a more accurate idea about the potential of this catalyst.

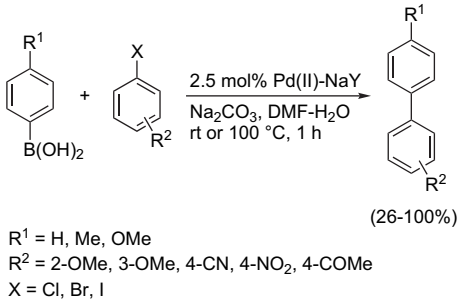
Very interesting is the recent report by Iwasawa et al., who, unlike the majority of researchers on the Suzuki reaction involving palladium catalysts, prepared a new catalyst based on a nickel ion-containing ionic liquid immobilised onto the silica surface.[126] In spite of the rather tedious preparation of the catalyst, it was successfully applied to the coupling of a representative variety of aryl chlorides with three different arylboronic acids under relatively mild reaction conditions (see examples in Scheme 50). Most of the biaryls were obtained in yields ranging from 87 to 100% (GC) and short reaction times, albeit a pre-treatment with sodium *tert*-butoxide for 30 min and the presence of PPh_3 was necessary in order to obtain good results. Recycling of the catalyst by filtration and washing led to 94, 69 and 64% yield for three consecutive runs, attributed to a decrease in the relative content of the catalyst.





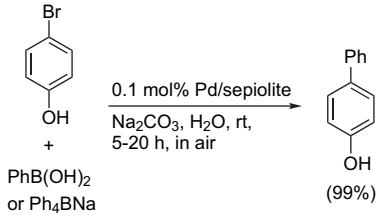
Scheme 50.

To the best of our knowledge, only the group of Artok has used a Pd(II)-exchanged NaY zeolite for the Suzuki reaction under very mild reaction conditions.[127] Aryl bromides and iodides were coupled, in moderate-to-high yields, with three different arylboronic acids in a DMF–H_2O mixture for only 1 h at room temperature (Scheme 51). Two activated aryl chlorides could also be coupled at 100 °C with modest yields. The authors demonstrated that the reaction was heterogeneous and that it did not take place within the zeolite. The catalyst preparation is rather laborious and it needs re-calcination under oxygen in order to recover the activity to be re-used. Nevertheless, this methodology can be considered among the mildest to perform this kind of reaction.



Scheme 51.

Sepiolite is a fibrous natural clay mineral with the formula $Si_{12}Mg_8O_{30}(OH)_4 \cdot 8H_2O$ that was used by Shimizu et al. as a support for the palladium-catalysed Suzuki reaction. Several aryl bromides, iodobenzene and 4-chloroacetophenone reacted with phenylboronic acid using this catalyst (K_2CO_3, 100 °C, 20–24 h), giving the corresponding biaryls in 23–91% GLC yield.[128] The catalyst was prepared in a simple manner and could be recycled without losing its activity. It has also found application in the coupling reaction of 4-bromophenol with phenylboronic acid or sodium tetraphenylborate (Scheme 52).[129] Interestingly, the reaction proceeded smoothly at room temperature in aqueous media and air. In addition, the catalyst could be re-used three times, whilst maintaining the original activity.

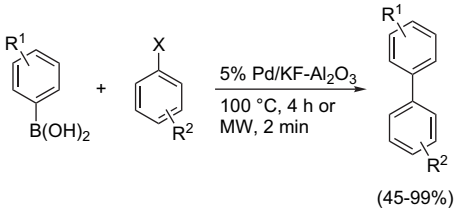


Scheme 52.

A sodium-exchanged sepiolite-containing $PdCl_2$ also catalysed the Suzuki coupling of iodobenzene and phenylboronic acid in the absence of an extrinsic base (*o*-xylene, 145 °C, 24 h, 92%).[130] In this case, however, a considerable decrease in activity (38% yield) was observed in a second cycle after filtration. This decrease in activity was mainly due to depletion of the solid basic sites, which could be reactivated in part by the use of a flow of steam to assist desorption of the hydrohalogen acid.

Besides silica, other metal oxides and inorganic compounds have proved to be useful supports for palladium and other transition metals in Suzuki reactions. Kabalka et al. described the Suzuki coupling reaction on palladium-doped potassium fluoride–alumina.[131] KF–Al_2O_3 is commercially available and proved to be an efficient support for palladium in the coupling of several aryl iodides and bromides with a variety of arylboronic acids under solvent-free conditions with normal or microwave heating (Scheme 53). The reactions were very fast in the latter case and the catalyst remained active through six cycles. In addition, it would have been instructive to study the effect of electronically different substituents on the aryl

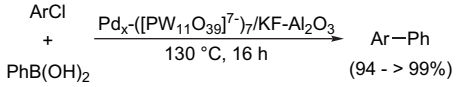
halide partner. Pd–Al_2O_3 has also been used for the microwave-assisted coupling of 4-bromobenzonitrile and phenylboronic acid in a continuous-flow capillary reactor (see Section 7.2).[132]



R^1 = 2-Me, 4-Me, 4-F, 4-Cl, 4-Br, 4-OMe
R^2 = H, 4-Me, 2-F, 3-F, 2-MeC_6H_4CO
X = Br, I

Scheme 53.

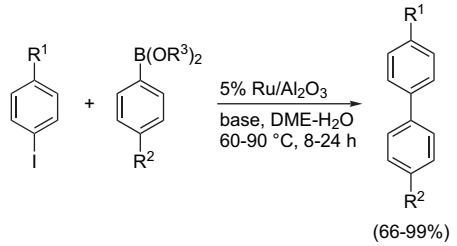
A highly effective catalyst for the coupling of aryl chlorides with phenylboronic acid was developed by Neumann et al., based on supported palladium nanoclusters (stabilised by a polyoxometalate) on KF–Al_2O_3.[133] Six out of seven aryl chlorides tested (with either electron-withdrawing or -donating moieties) furnished the corresponding products in >99% yield under solvent-free conditions (130 °C, 16 h) (Scheme 54). The whole procedure for the preparation of the catalyst is rather elaborate, although the catalyst could be re-used at least once with essentially no loss in activity.



Ar = H, 4-YC_6H_4 (Y = NO_2, CN, COMe), 2-MeC_6H_4, 2-pyridyl, 3-pyridyl

Scheme 54.

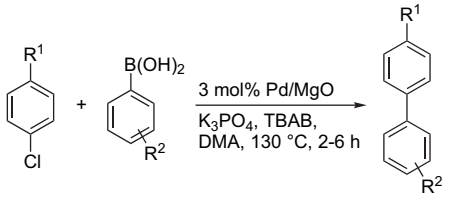
Chang et al. observed that the supported zerovalent ruthenium catalyst Ru–Al_2O_3 was superior to the homogeneous precursor [$RuCl_2$(*p*-cymene)]$_2$ in the Suzuki reaction of arylboronic acids and arylboronate esters with aryl iodides (see examples in Scheme 55).[134] A low catalyst loading was used either in a mono- or biphasic reaction medium at 60–90 °C, although bromo- and chloroarenes were unreactive under these conditions. The supported catalyst was quantitatively recovered at the end of the reaction by simple filtration, but no data on its possible recycling were given. It is worth noting that the Suzuki reaction could be scaled up to a few grams without any practical problems.



R^1 = H, Me, COMe, OMe, NO_2, CHO, CH_2OH
R^2 = H, Cl, OMe
R^3 = H, CH_2
base = NaOH, K_2CO_3, K_3PO_4

Scheme 55.

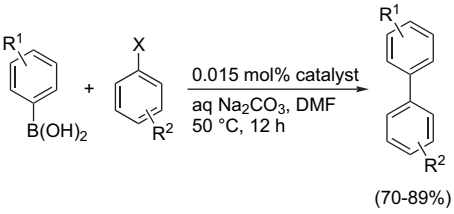
A nanocrystalline magnesium oxide-stabilised palladium(0) catalyst was found to be highly efficient in the coupling of some representative aryl bromides and iodides with several arylboronic acids in water at room temperature and in relatively short reaction times (5–6 h).[135] Very high yields (88–98%) of the biaryls were obtained with a variety of substituents on both coupling partners. Furthermore, chloroarenes with electron-withdrawing and -donating groups were also coupled in the presence of TBAB at 130 °C using DMA as the solvent in moderate-to-high yields (Scheme 56). Moreover, the catalyst could be re-used with only a slight decrease in the yield after five cycles.



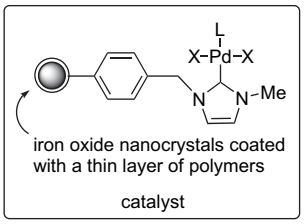
R^1 = H, Me, OMe, COMe, CN, NO_2
R^2 = H, 4-Me, 4-OMe, 3-NO_2, 4-F

Scheme 56.

Core–shell superparamagnetic nanoparticles consisting of a highly crystalline γ-Fe_2O_3 core and a very thin polymeric shell wall were used as soluble supports for immobilising an *N*-heterocyclic carbene–palladium complex.[136] This catalytic system exhibited a good performance in the coupling of aryl iodides and bromides with arylboronic acids under mild conditions, irrespective of the nature of the substituents (Scheme 57). The preparation of the catalyst does not seem to be



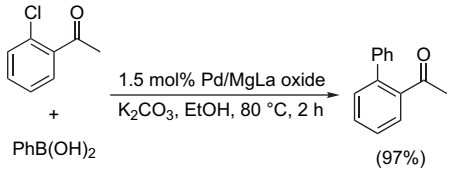
R^1 = H, 2-Me, 3-Me, 4-Me, 2-OMe, 3-OMe, 4-OMe, 4-COMe
R^2 = H, 2-Me, 3-Me, 2-OMe, 4-OMe, 2-COMe, 3-COMe, 4-CN, 1-naphthyl
X = Br, I



Scheme 57.

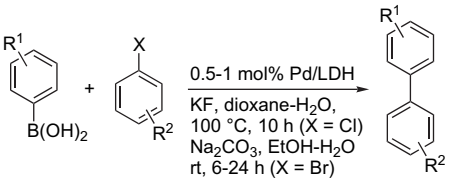
difficult, despite the multiple steps involved. Very interestingly, the nanoparticle-supported catalyst could be separated from the reaction mixture by applying a permanent magnet (>97% recovery), washed, air dried and used for five subsequent rounds without significant loss of catalytic activity.

A new air- and moisture-stable palladium on MgLa mixed oxide catalyst was prepared and applied to the Suzuki coupling of several aryl bromides and chlorides with phenylboronic acid at 80 °C in short reaction times.[137] This reaction was shown to be insensitive to steric hindrance, as bromo- and chlorobenzene having *ortho* substituents also gave excellent yields (see example in Scheme 58). The catalyst was re-used for two additional runs after filtering off, washing with water and drying at room temperature, with no significant loss of activity.



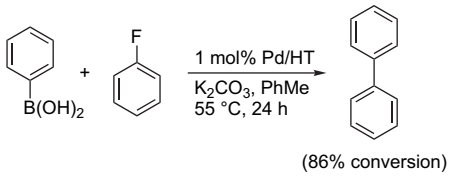
Scheme 58.

In recent years, layered double hydroxides LDHs (a major class of anionic clay materials) have received much attention, in view of their potential usefulness in catalysis and, in particular, in carbon–carbon coupling reactions as solid supports for palladium.[138] In 2002, the group of Choudary prepared an LDH-supported nanopalladium species as a highly effective catalyst for the Suzuki reaction of chloroarenes with arylboronic acids (Scheme 59).[139] In spite of the support not being commercially available, its recovery by simple filtration and re-use with consistent activity made it a good choice for the coupling of chloroarenes and arylboronic acids. More recently, this re-usable catalyst also showed a remarkable behaviour in the coupling of aryl bromides and iodides with arylboronic acids (both coupling partners bearing electronically different substituents) at room temperature (Scheme 59).[140]



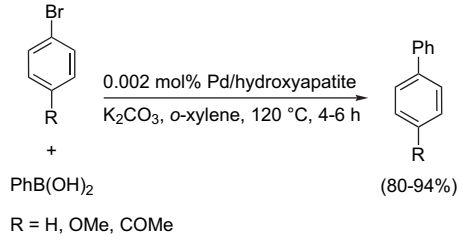
Scheme 59.

Hydrotalcite is a naturally occurring mineral of the layered double hydroxide family that has been recently used by the group of Ruiz and Jiménez-Sanchidrián as a solid support to immobilise palladium and the resulting supported catalysts have been applied to the Suzuki cross-coupling reaction. Among the various palladium-containing Mg–Al hydrotalcites prepared,[141] those obtained by supporting an acetate–pyridine complex were the most active in the coupling of bromobenzene and phenylboronic acid (1 mol % Pd, K_2CO_3, toluene, 55 °C, 0.25 h, 100% conversion). The catalyst, isolated by filtration, did not show any significant loss of activity after three more runs. Moreover, this catalyst allowed the less common coupling of fluorobenzene and phenylboronic acid under mild reaction conditions (Scheme 60).[142] It would be interesting to investigate about the substrate scope of this methodology, since the published work is practically almost limited to the simplest coupling partners.



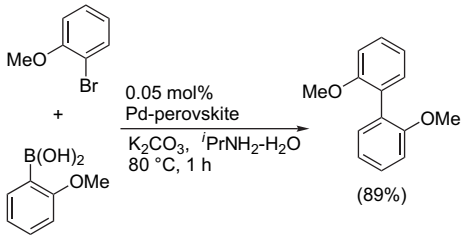
Scheme 60.

A hydroxyapatite-supported palladium complex was obtained by treatment of the non-stoichiometric Ca-deficient hydroxyapatite $Ca_9(HPO_4)(PO_4)_5(OH)$ with an acetone solution of $PdCl_2(PhCN)_2$.[143] The catalyst gave good yields at very low loading for three aryl bromides coupled with phenylboronic acid (Scheme 61). Hydroxyapatite, although not commercially available, was easily prepared by a precipitation method from $Ca(NO_3)_2 \cdot 4H_2O$ and $(NH_4)_2HPO_4$. Its possible re-use in the Suzuki reaction was not, however, studied.



Scheme 61.

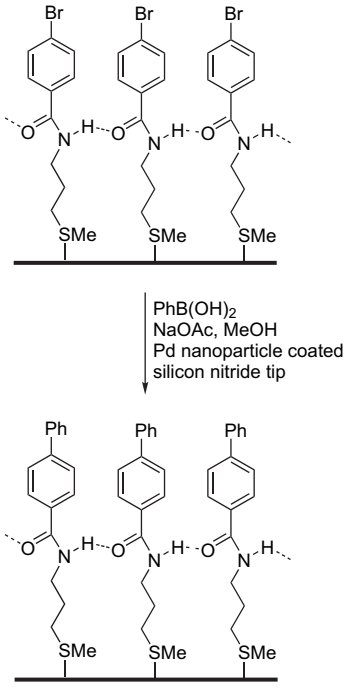
Palladium-containing perovskites ($LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$) were exploited by the groups of Ley and Tanaka as recoverable and re-usable catalysts in Suzuki coupling reactions.[144] Aryl bromides and iodides bearing different substituents reacted with a low catalyst loading at 80 °C in isopropylamine–H_2O, giving high yields of the biaryls (see example in Scheme 62). The addition of TBAB proved to be beneficial



Scheme 62.

in a few difficult cases. On the other hand, the coupling of aryl chlorides required microwave heating at 135 °C (4-nitrochlorobenzene was coupled with phenylboronic acid in 71% yield), deactivated aryl chlorides giving lower yields. The catalyst could be recovered and re-used for five runs without any apparent loss of activity. It was also demonstrated that this type of heterogeneous catalysts are pre-catalysts that operate by a solution-phase mechanism.[145]

It is worthwhile mentioning the first report of a catalytic coupling reaction controlled by atomic force microscopy (AFM).[146] Specifically, an aryl bromide-dialkyl sulfide-modified gold surface was mounted onto an AFM sample plate and the area was scanned with the catalytic probe, consisting of a silicon nitride tip coated with palladium nanoparticles (Scheme 63). During scanning, the probe and the substrate were incubated in a reagent bath comprising a millimolar methanolic solution of phenylboronic acid and sodium acetate. Obviously, this methodology has no application from the preparative point of view (i.e., synthesis of macroscopic amounts of biaryls), but it can be considered as a lithographic method capable of creating nanometre-scale patterns under flexible and controllable conditions.



Scheme 63.

4.2.3. Polymers

There is an ongoing interest in immobilising catalysts on polymeric supports in organic synthesis[147] and, in particular, in carbon–carbon coupling reactions.[148] The first applications of polymer-supported palladium catalysts to the Suzuki reaction can be attributed to Jang[149] and Le Drian and Fenger[150] in 1997 and 1998, respectively. The palladium catalysts were prepared from diphenylphosphino-polystyrenes (derived from the Merrifield resin) and shown to be stable in air as well as recyclable without any decrease in activity. In 1999, Uozumi et al. reported for the first time the successful use of amphiphilic PEG–PS resin-supported triphenylphosphane–palladium complexes in Suzuki coupling reactions in aqueous media under mild reaction conditions.[151] Since then, numerous polymer-supported catalysts have been prepared for the same purpose belonging to different compound families.

Phosphane-containing polymers are the most abundant supports, mainly for the palladium-catalysed Suzuki reaction. Hu et al. synthesised a new type of ferrocene-based monophosphane- and bisphosphane-containing polymers that were applied as ligands to the palladium(0)- and nickel(0)-catalysed Suzuki cross-coupling reaction, respectively (Chart 5).[152] Ligand **18** was shown to be efficient in the coupling of both activated and inactivated aryl chlorides with several boronic acids at room temperature, whereas ligands **19** and **20** were used in THF at reflux. Moreover, all the ligands were readily prepared in 3–4 synthetic steps and the ligands **19** and **20** could be recovered and re-used maintaining a good performance.

Chart 6 shows some phosphane-based ligands and catalysts used in the Suzuki reaction since 2003. Ikegami et al. developed a supramolecular complex prepared from a self-assembly of $(NH_4)_2PdCl_4$ and a non-cross-linked amphiphilic phosphine polymer, poly[(*N*-isopropylacrylamide)$_5$-*co*-(4-diphenylstyrylphosphine)] (**21**).[153] This catalyst was shown to be very effective in the coupling of electronically different aryl halides (bromides and iodides) and triflates with a variety of arylboronic acids. The reactions proceeded in water at 100 °C for 5–20 h, the yields being, in most cases, >90%. Very high TONs were reached (up to 1,250,000) and the complex could be recycled up to 10 times, still retaining its activity with only 5×10^{-5} mol equiv. The polymer is not commercially available and must be synthesised by radical copolymerisation of *N*-isopropylacrylamide and the expensive diphenyl(4-styryl)-phosphane, but this is compensated for by the effectiveness of the catalyst.

Polystyrene-supported palladacycle **22** was obtained in 20% overall yield after six steps from 4-methylacetophenone.[154] Initially, only the coupling of 4-bromoacetophenone and phenylboronic acid was studied in *o*-xylene at 130 °C for 5 h. The corresponding biphenyl was obtained in excellent yield, even after re-using the catalyst seven times. Interestingly, several *p*-terphenyls could be synthesised under similar reaction conditions, starting from a 1,4-benzenediboronic acid and various aryl bromides.

Plenio and Datta reported the synthesis of a polymer-enlarged catalyst formed from $(1\text{-Ad})_2$P-substituted poly(methylstyrene) (**23**) and a suitable palladium source [$Pd(OAc)_2$]. Polymer **23** was obtained by anionic polymerisation of 4-methylstyrene, bromination and reaction with $(1\text{-Ad})_2$PH. The catalyst (1.5 mol % Pd) was utilised in the high-yielding (83–95%) coupling of aryl bromides and chlorides with phenylboronic acid at 70 °C for 6–24 h (K_3PO_4 as base).[155] A particular mixture of solvents composed of cyclohexane and nitromethane was used in this case. The catalyst was suitable for separation over a solvent-resistant nanofiltration membrane with >99.95% retention and showed an unchanged catalytic

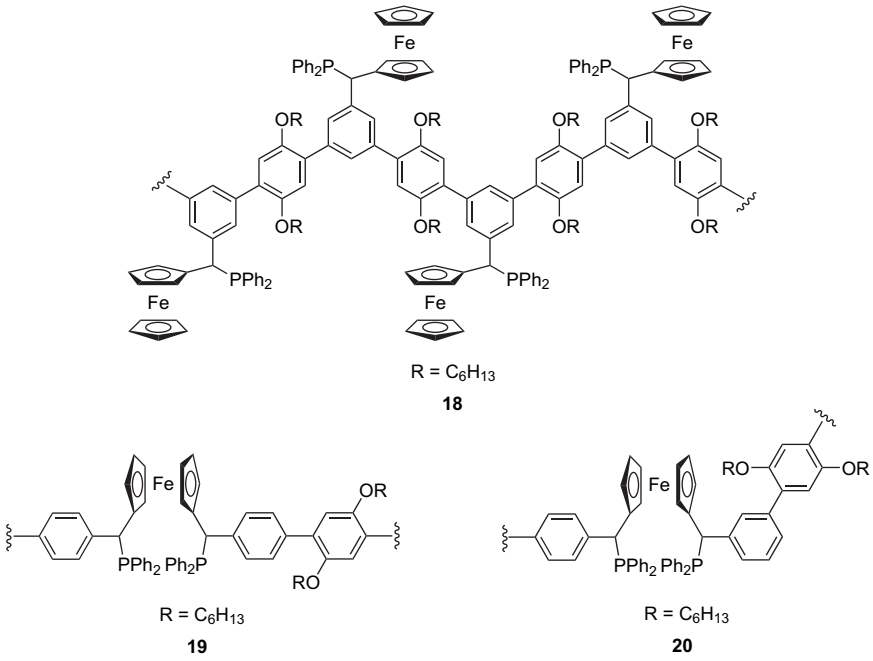


Chart 5.

activity.[156] Ligand **24** exhibited a similar performance to that of ligand **23**.[157]

A new polymeric solid-supported palladium catalyst (**25**) was obtained from high-density polyethylene resin plugs co-sintered with Merrifield resin, by cross-linking with divinylbenzene, substitution with Ph_2PLi and an exchange reaction with $Pd(PPh_3)_4$. The plugs were used in the synthesis of a small library of biaryl compounds from a representative variety of aryl iodides and arylboronic acids (0.05 equiv catalyst, Na_2CO_3, DMF, 80 °C, 24 h).[158] The plugs, which apparently are not difficult to prepare, showed a similar behaviour to the homogeneous analogue $Pd(PPh_3)_4$ with the advantages of being re-usable (92–85% coupling yield after four cycles) and easier to handle.

Parlow et al. developed a polymer-assisted solution-phase Suzuki protocol by employing a combination of anthracene-tagged catalyst, anthracene-tagged boronic acid and polymer-supported tetramethylammonium carbonate as base.[159] The anthracene-tagged catalyst allowed the easy removal of the palladium catalyst along with the dissociated phosphane ligand and phosphane oxide by-products by a Diels–Alder cycloaddition with polymer-bound maleimide followed by removal of the polymer-bound adducts by filtration. The formation of complex **26** through the Diels–Alder reaction was highly efficient, as no observable phosphorus or palladium was detected in solution after the sequestration process.

Polymer **27** was obtained for the first time by copolymerisation of a phosphaalkene with styrene and was utilised in the Suzuki coupling of bromobenzene with phenylboronic acid [5 mol % $Pd_2(dba)_3$, CsF, THF, 80 °C].[160] Up to 90% isolated yield of biphenyl was obtained (at an unspecified reaction time) after removal of the polymeric catalyst by precipitation with hexanes. The results, comparable with those using $Pd(PPh_3)_4$, and the avoidance of column chromatography, make this catalytic system advantageous. Further research dealing with the recycling of the catalyst would be welcome.

Two polyethylene-supported FibreCat palladium catalysts (**28**) were shown to be highly active in the microwave-accelerated Suzuki reaction of aryl chlorides, bromides and iodides with a wide range of electronically different arylboronic acids (3 mol % catalyst, aq K_2CO_3, MW, 110 °C, 10 min).[161] The catalysts are commercially available and in combination with a Si-carbonate plug, as a boronic acid scavenger, led to the corresponding biaryls in excellent yields and in very short reaction times. Even non-activated aryl chlorides reacted under these conditions in moderate yields (50–60%). Apparently, the catalysts could not be re-used.

Poly(dimethylsiloxane)-tagged phosphane ligand **29**, prepared from commercially available poly(dimethylsiloxane) in three steps, was heterogenised on silica and applied to the Suzuki coupling of 4-bromotoluene and 4-iodoanisole with phenylboronic acid.[162] Moderate yields (59%) were obtained when the reaction was performed in $scCO_2$ at 75 °C for 3 h. Most probably, the yields would be much better for activated aryl halides, but the study was rather limited as regards the substrate scope.

Biaryldicyclohexylphosphine **30**, based on polystyrene or on a copolymer PEG–PS, was synthesised in four steps from 2-bromoiodobenzene and was highly efficient in the coupling of three activated aryl chlorides with phenylboronic acid and 4-methyphenylboronic acid (K_3PO_4 or Na_2CO_3, PhMe or PhMe–EtOH–H_2O, 80–100 °C, 20 h, 90–96% yield). No decrease in activity was observed during four runs and only a slight decrease occurred in the fifth and the sixth runs (80 and 79%, respectively).[163]

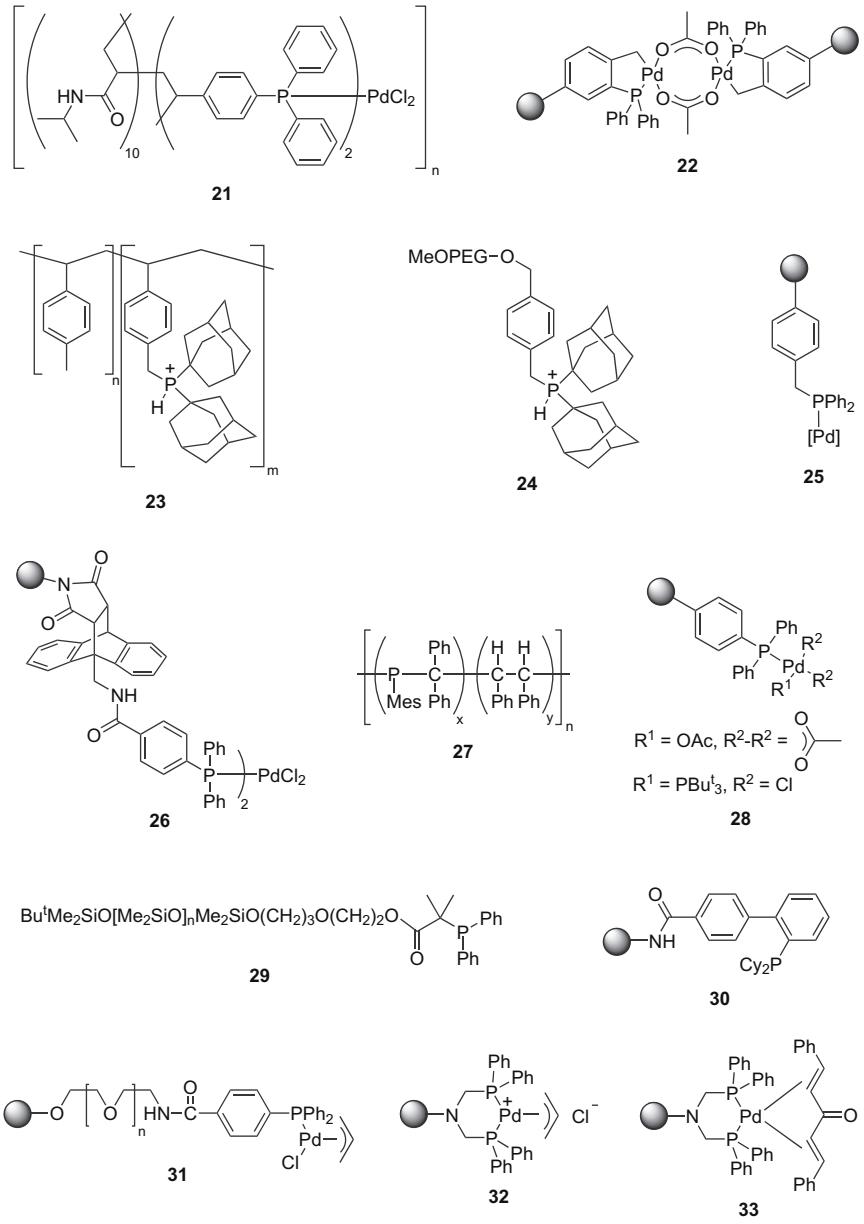


Chart 6.

Uozumi and Kikuchi developed an amphiphilic PS–PEG resin-supported palladium catalyst (**31**) for the selective monoarylation of dibromoarenes with arylboronic acids (1–2 mol % **31**, 8 mol % PPh_3, aq K_2CO_3, PhMe–H_2O, 105 °C, 12–24 h).[164] The precipitation of the resulting biaryls in the biphasic system could be the reason for retarding a successive cross-coupling, giving the corresponding teraryls. The latter were obtained by the addition of 1.5 equiv of the arylboronic acid to the reaction mixture and stirring for an additional 15 h. The recyclability of the catalyst (after recovery and rinsing) was successful, leading to 98–99% selectivity and 87–94% yield during three runs.

Polymer-supported bidentate phosphanes have also proved to be useful ligands for the palladium-catalysed Suzuki reaction. Catalyst **32**, prepared from an ArgoGelNH_2 resin and diallyldichlorodipalladium, was applied to the coupling of iodobenzene and phenylboronic acid (1 mol % catalyst, K_2CO_3, 50 °C, 12 h), giving biphenyl in 99% yield and purity.[165]

More interesting are the commercially available surface-modified (with Boc-protected primary amines) polyethylene sheets, in which a bis(diphenylphosphanyl)methyl ligand was introduced and complexed by treatment with $Pd_2(dba)_3$ (**33**).[166] Several aryl bromides and phenylboronic acids bearing electronically different substituents were coupled in moderate-to-good yields (0.16 mol % **33**, Cs_2CO_3, DMF, 120 °C, 24 h, 65–83%). The polyethylene sheets were easily separated from the product by removing them from the reaction mixture with tweezers. The conversions were high after five cycles.

A variety of polymer-bound catalysts have been developed in recent years, in which coordination to palladium takes place through nitrogen atoms (Chart 7). For instance, poly(*N*,*N*-dihexylcarbodiimide) (PDHC) is a relatively weak coordinating ligand (which results in a higher activity) that was found to be very effective to prepare and stabilise palladium nanoparticles.[167] The nanoparticles were prepared by $NaBH_4$ reduction of H_2PdCl_4 in a two-phase mixture of the ligand, toluene and water. The catalytic activity of PDHC–Pd in the Suzuki reaction led to nearly quantitative yields of the biphenyl products for various aryl bromides and iodides (K_2CO_3, dioxane, reflux, 18–24 h). The catalyst was easily recovered by precipitation and filtration and was shown to be active in the coupling reaction, even after five reaction-recovery cycles (97–90% yield). Alternatively, microwave heating could be applied, also with high conversions, but the recycled catalyst showed, in this case, a significant decrease in catalytic activity. A wider substrate scope study would be desirable including the effect of electronically different substituents and, apparently, aryl chlorides do not react under these conditions.

Chitosan or poly[β-(1–4)-2-amino-2-deoxy-D-glucan] is produced by deacetylation of chitin, a major naturally occurring biopolymer. Macquarrie et al. modified chitosan by the introduction of a palladium iminopyridyl complex.[168] The resulting complex **34** catalysed the reaction of several aryl bromides and iodobenzene with phenylboronic acid, but chlorobenzene was virtually inert under the same reaction conditions (K_2CO_3, xylene, 143 °C, 1 h). The presence of a nitro group was incompatible with these conditions. Despite the rather limited range of substrates studied, the catalytic system was shown to be more efficient than the corresponding homogeneous system and could be re-used (after filtration, washing and drying) five times without appreciable loss of activity.

Starch has also been used as a biomaterial support to bind Schiff bases for chelating palladium. Complex **35** catalysed the coupling of bromobenzene and phenylboronic acid, giving 100% of biphenyl with no side products (K_2CO_3, xylene, 140 °C, 7 h).[169] Unfortunately, the catalyst became deactivated with time, as shown in the decreased yields after re-use. The main disadvantage of this catalyst is the large amount of waste generated during its preparation, including solvents such as toluene, ethanol, acetone and acetonitrile.

A new palladium(II) complex **36** with a 2-pyridinealdoxime ligand was anchored to a cross-linked chloromethylpolystyrene–divinylbenzene resin (analogous to the Merrifield resin) and efficiently catalysed the cross-coupling of 4-bromoacetophenone and arylboronic acids in air (0.75–3 mol % catalyst, K_2CO_3, toluene, 110 °C, 91–99% yield).[170] The catalyst was recycled once, leading to a lower conversion (78%). 4-Chloroacetophenone could be coupled with phenylboronic acid under microwave irradiation in fair yield (3 mol % catalyst, Cs_2CO_3, TBAB, H_2O, 130 °C, MW, 8 min, 68% yield).

Another oxime-based palladacycle (**37**) was immobilised onto a polyvinylpyridine resin, affording a re-usable, air, moisture and thermally stable palladium precatalyst highly active in the Suzuki coupling of several activated aryl chlorides and 4-bromoacetophenone with a large variety of arylboronic acids.[171] 4-Chloroacetophenone was coupled (1 mol % **37**, K_2CO_3, PhMe, 110 °C, 0.75–5 h, air) in moderate-to-high yields (63–97%), the catalyst showing high conversions along 10 consecutive runs (100–80%). It is worthy of note that the immobilised catalyst **37** was more active than the corresponding unsupported soluble catalyst. Water as the solvent and Cs_2CO_3 as the base in the presence of TBAB were found to be the optimum conditions for the coupling of aryl chlorides. In this case, slightly better results were obtained by microwave

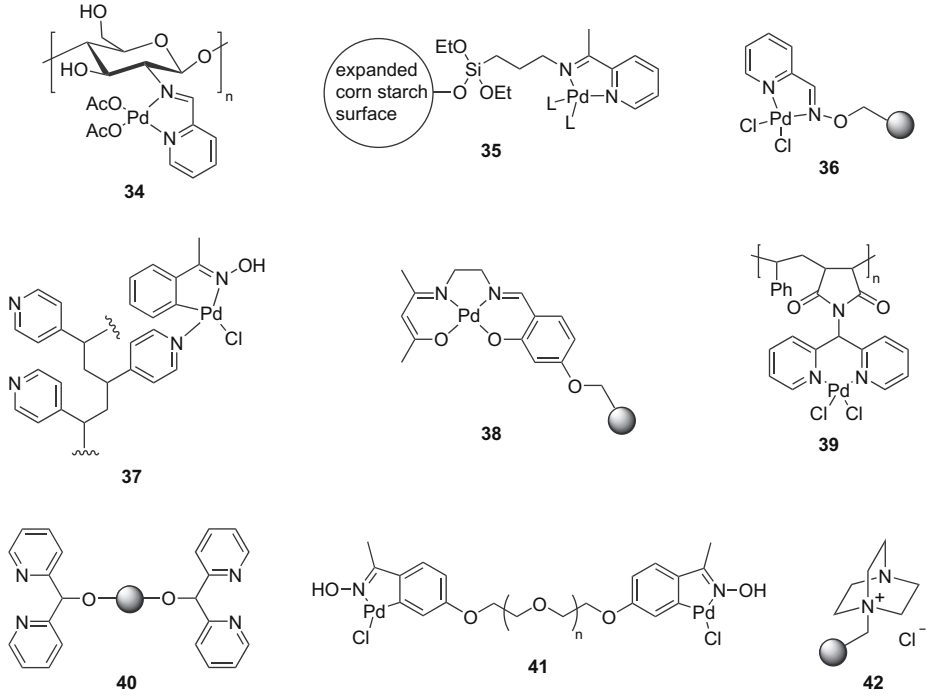


Chart 7.

heating in only a 3-min reaction time. Although a considerable number of biaryls were synthesised by varying the substitution on the arylboronic acid, a wider substrate scope in the aryl halide partner would be desirable.

A salen-type palladium(II) complex immobilised onto a Merrifield resin (**38**) was applied to the cross-coupling of aryl bromides containing electron-withdrawing and -donating groups with phenylboronic acid (0.5 mol % catalyst, K_3PO_4, DMF, 90 °C, 24 h).[172] Excellent conversions were achieved in most cases, whereas 4-bromonitrobenzene and 4-bromoaniline failed to react. The catalyst was recovered by filtration and washing and re-used for five consecutive runs with a gradual decrease in activity (90→60% conversion). In this case, the polymer-supported catalyst was considerably more active than the homogeneous analogue. This catalyst was also applied in a mini-continuous-flow reactor system (see Section 7.2).

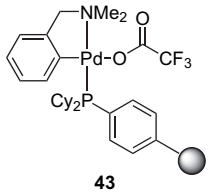
Nájera et al. reported the preparation of a polymer-supported di-(2-pyridyl)methylamine-based $PdCl_2$ complex covalently anchored to a poly(styrene-*alt*-maleic anhydride) resin (**39**).[173] The coupling of 4-bromoacetophenone, 4-bromophenol and 4-chloroacetophenone with phenylboronic acid furnished the corresponding biaryls in excellent GLC yields and short reaction times using water or MeOH–H_2O as the solvent (0.001–4.5 mol % Pd, K_2CO_3 or KOH, 60–100 °C, 0.5–7 h). The longer reaction times needed for the aryl chlorides were considerably shortened by applying microwave heating. Recycling experiments carried out in the same flask led to similar quantitative yields for 4-bromobenzene in 1–2.5 h, whereas longer reaction times were needed after polymer filtration. Longer reaction times and lower yields were observed in the recycling experiments for 4-chloroacetophenone, and the polymer could not be recycled after microwave heating. Unfortunately, the substrate scope of this catalytic system seems to be rather limited.

A PEG-supported dipyridyl ligand (**40**) was obtained in two steps from 2000 Da PEG (PEG-2000) and applied to the palladium-catalysed Suzuki reaction of electron-poor and -rich aryl bromides with a variety of arylboronic acids in PEG-2000 as the solvent [0.2 mol % $Pd(OAc)_2$–**40**, K_2CO_3, 110 °C, 15–24 h].[174] High yields of the coupled products were obtained (85–98%) without an inert atmosphere, even with sterically hindered substrates. The catalytic system was less effective for the reaction of aryl chlorides, needing a higher catalyst loading (3 mol %). Interestingly, the reaction proceeded much more smoothly with sodium tetraphenylborate, although recycling of the catalyst was better achieved in the case of the arylboronic acids (six times, 98–95% yield).

Corma et al. covalently anchored an oxime carbapalladacycle on a soluble PEG 6000 scaffold, the resulting polymer (**41**) being used as a soluble catalyst for the Suzuki reaction.[175] Several aryl bromides and activated aryl chlorides were cross-coupled with various arylboronic acids in modest-to-high yields (25–95%) using PEG 6000 as solvent and CsOAc as base. The reaction conditions were rather harsh (24 h at 150 °C), the catalyst decomposing during catalysis to form palladium nanoparticles, which were catalytically less active and curtailed the catalyst re-usability.

A wide variety of aryl and heteroaryl bromides were very efficiently coupled with phenylboronic acid, 4-methoxy- and 4-fluorophenylboronic acid using a polymer-supported DABCO–palladium complex under very mild reaction conditions (0.25 mol % Pd–**42**, K_2CO_3, EtOH–H_2O or DMF, rt to 40 °C).[176] Ligand **42** was easily prepared from DABCO and Merrifield resin, followed by treatment with $Pd(OAc)_2$ to afford the corresponding complex. Excellent yields of the coupled products were obtained in all cases (also with sterically hindered aryl bromides), even after filtering, washing, drying and re-using the catalyst seven times (a decrease in the reaction rate was observed after the second run). By increasing the temperature up to 80 °C, it was possible to react 1-chloro-4-nitrobenzene and 1-chloro-2,4-dimethoxybenzene with phenylboronic acid in good yields (95 and 86%, respectively).

The polystyrene-immobilised palladacyclic complex **43**, with a mixed nitrogen–phosphorus coordination to palladium, was applied to the coupling of several aryl chlorides (4-YC_6H_4Cl, Y=Me, OMe, COMe; 2-MeC_6H_4Cl) with phenylboronic acid, affording the corresponding biaryls in moderate-to-high conversions (0.72 mol % Pd, Cs_2CO_3, dioxane, 100 °C, 18 h).[177] Despite the catalyst being easily prepared, it exhibited poor recyclability, with essentially no activity observed on the second runs.



43

In recent years, *N*-heterocyclic carbene (NHC) complexes of Pd(II) and Pd(0) have emerged as potential alternatives to the widely used phosphane complexes, since the former are remarkably stable towards heat, oxygen and moisture.[178] The NHC ligands bind to both Pd(II) and Pd(0) centres substantially more strongly than the phosphane ligands, and are highly suitable for attachment to solid supports owing to the low level of metal leaching. Some polymer-supported palladium NHC complexes have been used as catalysts for Suzuki reactions (Chart 8).

The palladium complex supported on Tenta Gel® resin **44**, containing a pyridylbis (*N*-heterocyclic) carbene ligand derived from isonicotinic acid, could be recycled up to 14 times (by filtration, washing and drying) in the Suzuki coupling of iodobenzene and 4-methoxyphenylboronic acid.[179] The different cycles were carried out with 1 mol % Pd and K_2CO_3 in DMA at 165 °C for 48 h under an inert atmosphere to avoid Pd black formation. Very low levels of palladium leaching from the resin were detected. The reaction conditions are, however, still rather harsh (165 °C, sealed tube, 48 h) and the methodology seems to be practically restricted to the above-mentioned coupling partners, since a much lower yield was obtained for bromobenzene (95 vs 57%).

A polymer-supported imidazolium salt (**45**) was prepared from a bisimidazolium salt and cross-linked Merrifield resin

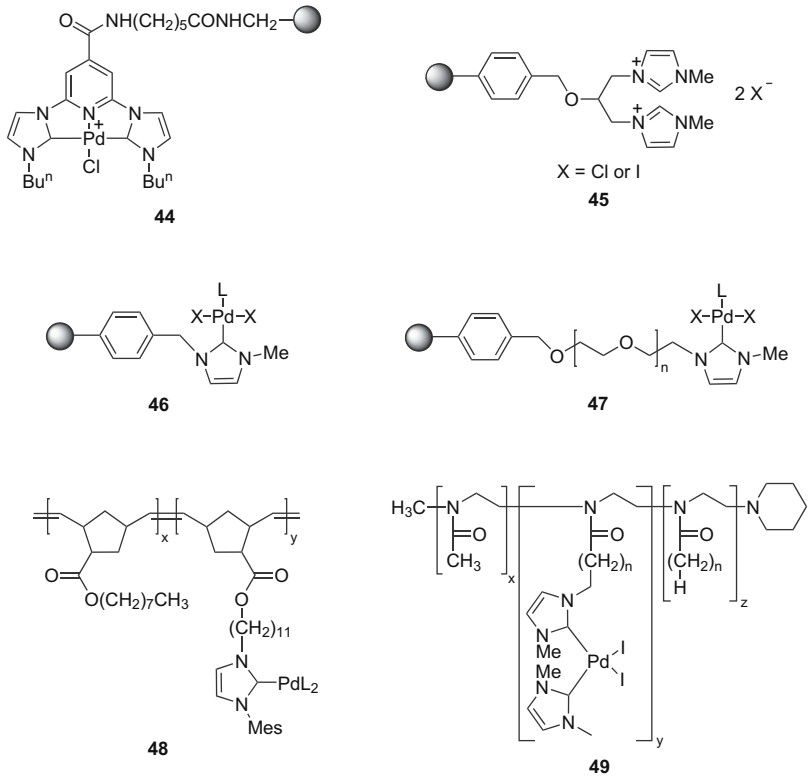


Chart 8.

and used for the generation of the corresponding NHC–palladium complex.[180] The catalyst was applied to the cross-coupling of all kinds of substituted arylsulfonyl chlorides with several arylboronic acids (2.4 mol % Pd, Na_2CO_3, THF, reflux, 13–24 h, 50–91% yield). The catalyst could be re-used after filtration, washing and drying, maintaining a good catalytic activity after five runs (88–81% yield). The disadvantages of using arylsulfonyl chlorides as substrates have already been commented above (see comments on Scheme 10).

Complex **46** was easily obtained from chloromethyl polystyrene resin, 1-methylimidazole and $Pd(OAc)_2$.[181] This catalyst provided good-to-excellent yields of biaryls from the coupling of several aryl iodides and bromides with phenylboronic acid (1.2 mol % Pd, Na_2CO_3, DMF–H_2O, 50 °C, 12 h, 69–98% yield). A slight decrease in the catalytic activity was observed in its second and third uses, due to partial palladium leaching (93→76% yield). A remarkable behaviour was exhibited by the same catalyst in which the resin was prepared by suspension polymerisation.[182] In this case, all the catalytic sites were located on the surface of the resin, greatly increasing the reaction rate and showing an outstanding re-usability (after filtering and washing) without any loss of the catalytic activity (95→92% along 10 cycles). A broad range of aryl iodides and bromides reacted with phenylboronic acid (1 mol % Pd, Na_2CO_3, DMF–H_2O, 50 °C, 1–6 h), as well as 4-iodoanisole with six different arylboronic acids (1–1.5 h), in excellent yields (91–98 and 93–95%, respectively).

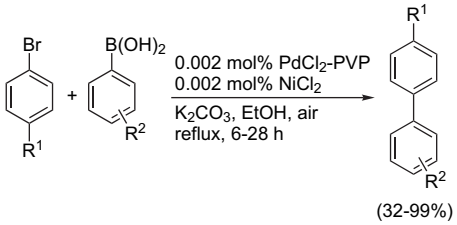
The same group synthesised an amphiphilic polymer-supported NHC precursor resin by loading PEG-containing imidazolium groups on the Merrifield resin.[183] This resin formed a stable complex with palladium (**47**) that showed a high catalytic activity in the cross-coupling of different aryl bromides and iodides with phenylboronic acid in water (2 mol % **47**, Cs_2CO_3, H_2O, 50 °C, 12 h, 76–99% yield). The catalyst continued to provide good catalytic activity after five cycles (91–82%), although it is not clear whether the catalyst was separated from the reaction medium after each cycle or the reactions were performed in the same flask.

Several poly(norbornene)-supported NHC–palladium complexes (**48**) were prepared by ring-opening metathesis polymerisation and utilised in the coupling of aryl chlorides and 2-bromopyridine with phenylboronic acid in short reaction times and very high yields (1 mol % **48**, Cs_2CO_3, dioxane, 80 °C, 0.5–3 h, 84–100% yield).[184] Aryl chlorides that were sterically hindered, as well as those bearing either electron-donating or -withdrawing groups, were successfully applied as substrates. Unfortunately, the polymeric residue obtained after the reaction became less soluble with a consequent and significant decrease in activity (44% conversion in the third cycle).

Catalysts **49** belong to a novel class of amphiphilic, water-soluble block copolymers based on 2-oxazoline derivatives with a pendant NHC–palladium complex.[185] These catalysts were tested in the coupling of iodobenzene, bromobenzene, 4-bromoacetophenone and 4-bromobenzaldehyde with phenylboronic acid in neat water (0.1–1 mol % Pd, KOH, H_2O, 50–110 °C, 0.3–5 h). Although high yields (84–95%) and TOFs (up to 5200 h^{-1}) were achieved, this study was focused on only a few substrates and no catalyst recycling experiments were carried out.

Polymeric materials have been used not only to immobilise transition metals through the formation of the corresponding complexes, but also to incarcerate, encapsulate and to stabilise metal(0) nanoparticles.[186] For instance, it is well known that PVP can disperse Pd(0) effectively preventing the formation of palladium black. In this context, El-Sayed and Narayanan studied in detail the Suzuki reaction between phenylboronic acid and iodobenzene (NaOAc, MeCN–H_2O, 100 °C, 12 h) catalysed by PVP–Pd nanoparticles in order to investigate the effect of catalysis, recycling and the different individual chemicals on the stability and catalytic activity of the nanoparticles.[187] It was found that the process of refluxing the nanoparticles for 12 h increased the average size and the width of the distribution of the nanoparticles. A loss of the catalytic efficiency was observed during the second cycle, as well as after the addition of biphenyl or excess of PVP, while the addition of iodobenzene had no effect and phenylboronic acid acted as stabiliser.

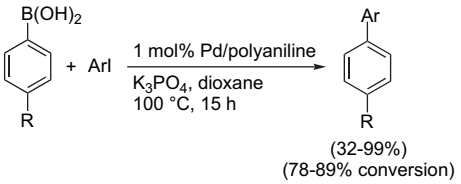
More recently, a synergistic effect of nickel(II) salts and PVP–Pd has been found, strongly promoting the Suzuki coupling of representative aryl bromides with several arylboronic acids.[188] Although aryl chlorides were practically inert, many different functional groups proved to be compatible with the reaction conditions tested, in the presence of air and at a low catalyst loading (Scheme 64). Even the more sterically hindered 2-bromotoluene was coupled with phenylboronic acid in 86% isolated yield.



R^1 = Me, OMe, CHO, COMe, CO_2Et, NO_2, OH
R^2 = H, 4-OMe, 3-NO_2

Scheme 64.

Palladium(0) nanoparticles were supported on polyaniline in a simple manner, the resulting nanocomposites catalysing the coupling of activated and non-activated aryl iodides with phenylboronic acid and 4-methylphenylboronic acid in good conversions and yields (Scheme 65).[189] Modest conversions were, however, observed for the coupling of aryl bromides. Although the reactions were performed under nitrogen, the process was tolerant to air. Unfortunately, the possibility of recycling the catalyst was not reported and modest conversions were observed for the coupling of aryl bromides.



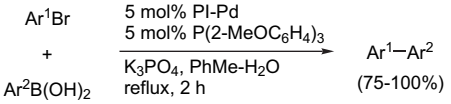
R = H, Me
Ar = 4-YC_6H_4 (Y = Me, CN, OMe), 2-naphthyl

Scheme 65.

More effective was the polymer-supported catalyst resulting from palladium nanoparticles captured on a PS–PEG resin after cross-linking.[190] The cross-linked resin-captured palladium (XL-RC Pd) catalysed the coupling of activated and deactivated aryl bromides with phenylboronic acid and 4-methoxyphenylboronic acid in water in moderate-to-excellent yields (10 mol % XL-RC Pd, K_2CO_3, 80 °C, 4–16 h, 63–99%). Furthermore, the catalyst could be recycled six times (after filtration and washing) without loss of catalytic activity and with no special precautions needed with respect to handling (in air). Under the reported conditions, however, low catalytic activity was observed for the coupling of aryl chlorides.

Similarly, a polymeric ammonium gel, obtained from the Merrifield resin and triethylamine, was shown to promote the formation of stabilised palladium nanoparticles during the Suzuki reaction of aryl and heteroaryl bromides with aryl- and heteroarylboronic acids (0.7 mol % Pd, $^iPr_2NH$, MeCN–H_2O, 85 °C, 6.5 h). The biaryls were obtained in high yields (76–96%) and the catalyst was recycled five times with almost constant activity.[191]

The group of Kobayashi developed a polymer incarcerated (PI) method for the immobilisation of $Pd(PPh_3)_4$ onto PS-based polymers. PI–Pd was shown to be highly active in the cross-coupling reaction of both electron-rich and -deficient aryl bromides with some representative arylboronic acids (Scheme 66).[192] It is noteworthy that the PI–Pd exhibited high activity also for sterically hindered substrates and even higher activity (TON of up to 53,600) than the homogeneous palladium catalysts. In addition, PI–Pd was recovered by simple filtration and re-used several times without loss of activity. Alternatively, the cross-coupling could be accomplished efficiently with a PI–Pd catalyst using polymer supports, which contain the diphenylphosphino group instead of adding external phosphane ligands. In general, the preparation of the catalysts is rather elaborate, although the latter methodology avoided the loss of the phosphane ligand during filtration of the catalyst.[193]



Ar^1 = 2-MeC_6H_4, 2,6-$Me_2C_6H_3$, 4-YC_6H_4 (Y = NO_2, MeCO, CN, CO_2Me, Bu^t), 2-HOC_6H_4, 4-pyridyl
Ar^2 = Ph, 4-YC_6H_4 (Y = OMe, MeCO), 2-MeC_6H_4

Scheme 66.

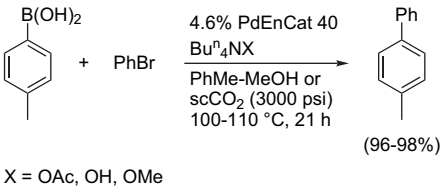
More recently, the same group prepared a polysilane-supported palladium catalyst from poly(methylphenylsilane) and $Pd(OAc)_2$.[194] This catalyst (5 mol %) was utilised in the coupling of 4-bromoacetophenone with phenylboronic acid in the presence of phosphane [5 mol % P(*o*-$MeOC_6H_4)_3$, K_2CO_3, EtOH, 80 °C, 2 h, 94% yield]. Although the catalyst could be recovered and re-used for other types of reactions,

the recyclability in the Suzuki reaction was not studied. It is assumed that the substrate scope of this methodology will be published in the near future.

A PS-microencapsulated palladium catalyst was prepared by the group of Toy by treating non-cross-linked PS-supported triphenylphosphane with Pd(OAc) in THF at 50 °C, followed by precipitation with cold hexane and washing with MeOH.[195] A range of aryl iodides and bromides, with both electron-donating and -withdrawing substituents, reacted with electron-rich arylboronic acids in the presence of 0.5 mol % catalyst at 70 °C in 1 h, giving good-to-excellent yields of the biaryl products (73–98%). The catalyst could be recovered and re-used, the yield dropping from 90 to 73% after four cycles due to some palladium leaching.

A polyurea-encapsulated $Pd(OAc)_2$ catalyst was discovered by Ley et al. in 2002, in which the microcapsules were prepared by an in situ interfacial polymerisation approach. The versatility of the so-called and now commercially available PdEnCat catalyst was demonstrated in the Suzuki coupling of different aryl bromides with various arylboronic acids (5 mol % PdEnCat, K_2CO_3, PhMe–H_2O–EtOH, 80 °C, 6–12 h, 71–97% yield).[196] The heterogeneous catalyst could be recovered by simple filtration and recycled up to four times without deterioration of the catalytic activity. Alternatively, the Suzuki coupling with PdEnCat could be performed in $scCO_2$, giving yields comparable to those obtained in organic solvents (0.4 mol % PdEnCat, $^nBu_4NOAc$, $scCO_2$, 100 °C).[197]

Ley's research group studied in detail the effect of different tetra-*n*-butylammonium salts on the PdEnCat 40-catalysed Suzuki reaction of bromobenzene and 4-tolylboronic acid in the batch mode (in PhMe–MeOH or $scCO_2$) and in a continuous-flow process (in PhMe–MeOH).[198] The tetra-*n*-butylammonium salts $^nBu_4NX$ (X=OAc, OMe, OH) provided the higher yields in the batch mode (Scheme 67), whereas a quantitative yield of 4-methylbiphenyl was obtained after a single pass through the PdEnCat stationary bed with $^nBu_4NOMe$.



Scheme 67.

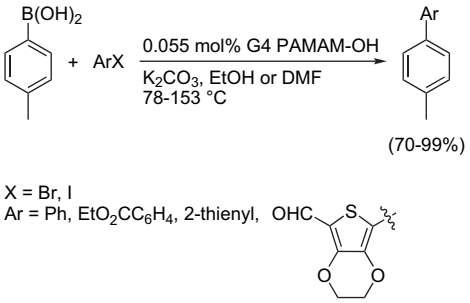
More recently, it has been demonstrated that PdEnCat systems behave as heterogeneous sources for soluble, catalytically active species during the course of Suzuki couplings. Although the reaction is not occurring only in solution, there is a solution-phase contribution to be taken into account in this type of reaction.[199] In spite of all the advantages of the PdEnCat systems (commercial availability, recyclability, high yield, etc.), their application to the Suzuki coupling of aryl chlorides seems to be rather limited. Nonetheless, 4-chloronitrobenzene was coupled with 4-tolylboronic acid in moderate yield in $scCO_2$ ($^nBu_4NOAc$, 100 °C, 60% yield).[197]

4.2.4. Dendrimeric systems

There has been extensive work to optimise the catalytic activity of functional dendrimers to mimic that of small molecules, but with the inherent retention ability that accompanies immobilisation on macromolecular supports. Such materials can be at the interface between homogeneous and heterogeneous catalyses and are particularly attractive hosts for catalytically active nanoparticles and to facilitate linking to surfaces and other polymers.[200] In comparison with the polymeric materials, dendrimers have been much less studied for the Suzuki reaction, mainly as soluble supports that enable the encapsulation of palladium nanoparticles.[201]

In 2001, El-Sayed and Li found that palladium nanoparticles stabilised by a G3 PAMAM [poly(amidoamine)] dendrimer could catalyse the Suzuki reaction between phenylboronic acid or 2-thienylboronic acid and iodobenzene (1.5 mol % dendrimer–Pd solution, Na_3PO_4, EtOH, 100 °C, 24 h, 71 and 90% yield, respectively).[202] The G4 PAMAM dendrimer led to a higher ratio of the yield of biphenyl formed in the second cycle to that in the first cycle in comparison with PVP–Pd nanoparticles.[203] This behaviour was attributed to the greater stability of the dendrimer–Pd nanoparticles and the increase in size during the reaction.

Christensen et al. studied the behaviour of palladium nanoparticles encapsulated in G4 PAMAM–OH terminated dendrimers in the Suzuki reaction of various aryl iodides and bromobenzene with 4-tolylboronic acid.[204] Aryl chlorides were completely unreactive, while aryl bromides reacted at much higher temperatures than aryl iodides (Scheme 68). The catalyst was used at a low loading and could be recycled in a bag of dialysis tubing, but gradually lost its reactivity, due to the formation of palladium black (99–80% yield in three runs).



Scheme 68.

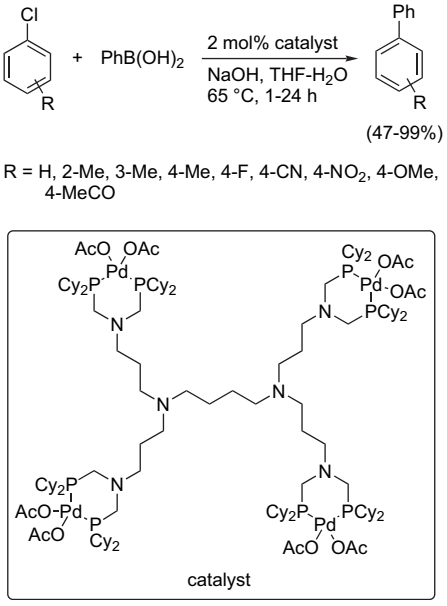
Following El Sayed's and Christensen's methods, five different generations of 1,4-diaminobutane (DAB) dendrimers were prepared and their catalytic activity was tested in the coupling of iodobenzene with phenylboronic acid in aqueous media (0.4–1 mol %, NaOAc, MeCN–H_2O, 100 °C, 1 h to 4 days).[205] The open structure of the low-generation dendrimers, DAB-G1, DAB-G2 and DAB-G3, favoured the formation of catalytically inactive Pd black. They exhibited, however, a higher catalytic activity (1–4 h, 90–100% yield) than the higher generation dendrimers, DAB-G4 and DAB-G5 (1 h to 4 days, 40–97% yield). This behaviour was

attributed to the lower accessibility of the catalytic sites for the substrate entering the dendrimer. The application to other substrates, as well as the recyclability, was not studied.

A palladium-nanoparticle-cored dendrimer of generation 3 (Pd-G3) was prepared from K_2PdCl_4 and Fréchet-type dendritic polyaryl ether disulfide of generation 3, followed by reduction with $NaBH_4$.[206] The Pd-G3 was stable for several months, both as a powder and as a dilute solution in CH_2Cl_2. The catalyst was tested in the Suzuki reaction of bromo- and iodobenzene with phenylboronic acid in EtOH (0.002 mol % Pd-G3, NaOAc, 40% EtOH, reflux, 24 h). Since Pd-G3 is not soluble in EtOH, it acts as a heterogeneous catalyst in these reactions. Despite high TONs (23,300, 26,100) and TOFs (1942, 2175) being achieved, the yields of biphenyl were very modest (42 and 47%). The products were isolated by decanting the reaction mixture into water and extracting with hexane and the recovered catalyst, however, was not subjected to recycling experiments.

Phosphane dendrimer-stabilised palladium nanoparticles were synthesised from Fréchet-type polyaryl ether dendrons and were shown to be highly effective in the Suzuki coupling of aryl chlorides, bromides and iodides with a variety of arylboronic acids.[207] Excellent yields of the biaryls (86–100%) were obtained, both for aryl iodides and bromides with low catalyst loading (0.06 mol % catalyst, $K_3PO_4\cdot 7H_2O$, dioxane, reflux, 20 h). Interestingly, aryl chlorides (including halopyridines) gave yields >80% by increasing the catalyst loading and the reaction time (2 mol % catalyst, 48 h). Moreover, the catalyst could be precipitated by the addition of methanol and re-used at least eight times with a high performance.

A dendritic diphosphane–palladium(II) complex was found to catalyse the coupling of electron-rich, electron-poor and hindered aryl chlorides with phenylboronic acid in an aqueous medium under relatively mild reaction conditions (Scheme 69).[208] Moderate-to-excellent yields of the products



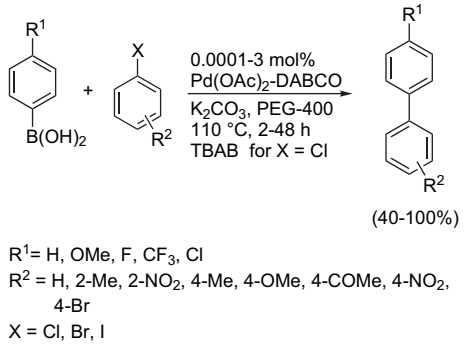
Scheme 69.

were achieved with the advantage that the catalyst could be stored in air at room temperature for months. A negative dendritic effect was observed by increasing the dendrimer generation. An important decrease in the reactivity was, however, found after three cycles (100–54% yield).

5. Solvents

Within the context of green and sustainable chemistry, the endeavour to replace volatile organic solvents in organometallic catalysis by alternative more practical and environmentally friendly solvents must be a priority.[209] Interesting approaches include catalysis based on aqueous systems, ionic liquids, supercritical media or fluorinated phases. Nevertheless, some Suzuki-type reactions under solvent-free conditions[210] have been studied (see Schemes 53 and 54),[131,133] mainly under microwave irradiation (see Section 6.1.1).

Much less common is a recyclable and re-usable catalytic system based on the use of an organic solvent. As an example, Li et al. reported a palladium catalyst [$Pd(OAc)_2$–DABCO] immobilised onto a liquid phase by dissolving it into a non-volatile and non-mixing liquid, such as PEG.[211] This catalytic system was applied to the coupling of aryl iodides, bromides and chlorides with a variety of arylboronic acids at 110 °C (Scheme 70). Excellent yields of the corresponding biaryls were obtained for aryl iodides and bromides with TONs of up to 960,000. The presence of TBAB was necessary for the aryl chlorides in order to improve the yields. After initial experimentation, the reaction mixture was extracted with dry diethyl ether, and PEG and $Pd(OAc)_2$-DABCO were solidified and subjected to a second run by charging with the same substrates. Consistent yields were obtained for the aryl iodide tested after five runs, whereas the addition of TBAB was necessary for recycling the catalyst in the case of aryl bromides. Unfortunately, the catalytic system could not be re-used for aryl chlorides.



Scheme 70.

5.1. Supercritical fluids

Only during the last decade have the special properties of supercritical fluids made them attractive solvents for modern synthetic chemistry.[212] Most of the attention has been directed towards the palladium-catalysed carbon–carbon

bond formation in $scCO_2$, which was mainly led by Holmes and Carroll.[213] On the other hand, highly fluorinated compounds were shown to have an unusually high solubility in $scCO_2$, and their incorporation into phosphane-based ligands was expected to improve the solubility of the corresponding metal complexes. In this context, Holmes and Carroll[213] and Tumas et al.[214] independently reported in 1998 the first palladium-catalysed carbon–carbon coupling reactions in $scCO_2$ using fluorinated ligands. Holmes and Carroll demonstrated that the Suzuki reaction of iodobenzene with phenyl- and 2-thienylboronic acid in $scCO_2$, with $(C_6F_{13}CH_2CH_2)_2PPh$ as the ligand, occurred in comparable yields to those achieved in conventional solvents.[213] Despite the work-up procedure being easy, the reaction time was considerably long (64 h) and the fluorous ligand had to be prepared from $C_6F_{13}CH_2CH_2MgI$ and $PhPCl_2$. The use of other fluorinated ligands in this kind of reaction was studied by other groups.[215]

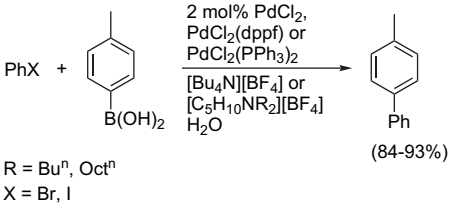
The group of Holmes also showed that a completely non-fluorous catalytic system, composed of $Pd(OAc)_2$ and $^tBu_3P$ in the presence of a base, also catalysed the Suzuki coupling of iodo- and bromobenzene with phenyl- and 4-tolylboronic acid in $scCO_2$.[216] Alternatively, a PS-supported phosphane resin facilitated this process in $scCO_2$.[217]

Other more recent applications of $scCO_2$ in the palladium-catalysed Suzuki reaction have already been discussed in this review.[162,197,198]

5.2. Ionic liquids

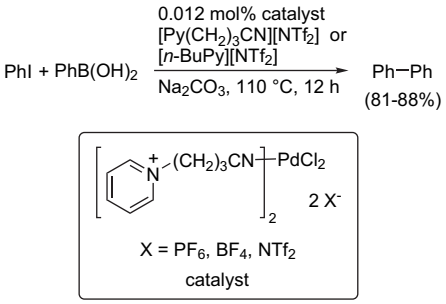
In recent years, ionic liquids (ILs) have captured the imagination of chemists as alternative solvents for synthesis and catalysis.[218] The effects of ILs on palladium-catalysed carbon–carbon bond formation have been briefly reviewed recently.[219] The first examples of palladium-catalysed Suzuki cross-coupling reactions in ambient temperature ILs were reported by Welton et al. in 2000.[220] A variety of aryl bromides and arylboronic acids were coupled in the IL, [bmim][BF_4], giving the corresponding biaryls in moderate-to-high yields [1.2 mol % $Pd(PPh_3)_4$, aq Na_2CO_3, 10 min, 110 °C]. The products could be isolated from the reaction mixture by extraction with diethyl ether, sublimation or precipitation by the addition of water, all of which did not give any apparent leaching of palladium species into the product. In addition, the catalytic solution could be re-used three times, after washing with water, without loss of activity. The in situ formation of mixed phosphane–imidazolylidene–palladium complexes was demonstrated in all the catalytically active solutions tested.[221] Since then, the Suzuki reaction in ILs has been extensively studied.[222]

In 2003, Zou et al. developed an aqueous–ionic liquid biphasic reaction medium for the ligandless-palladium-catalysed Suzuki coupling of iodo- and bromobenzene with 4-tolylboronic acid, based on high-melting-point hydrophobic alkylammonium tetrafluoroborates.[223] High yields of the expected biaryl were obtained in all cases, although a decrease in the catalytic activity was observed after three cycles (92–52%), possibly due to loss of palladium in the work-up (Scheme 71). Separation of the products was effected by extraction with hexane followed by filtration and removal of the solvents.



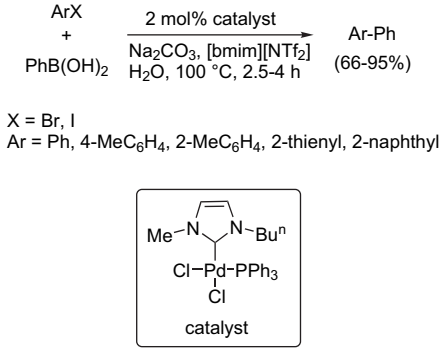
Scheme 71.

A series of nitrile-functionalised ILs based on *N*-butyronitrile pyridinium cation, $[Py(CH_2)_3CN]^+$, were synthesised and tested as suitable solvents for the palladium-catalysed biphasic Suzuki coupling reaction.[224] These ILs were reacted with $PdCl_2$ to give new palladium complexes that were air stable and that decompose in water or alcohols at room temperature only over prolonged periods of time. The palladium complexes and $PdCl_2$ were immobilised onto $[Py(CH_2)_3CN][Tf_2N]$ or onto the non-functionalised IL [*n*-BuPy][Tf_2N] and applied to the coupling of iodobenzene and phenylboronic acid (Scheme 72). It was shown that the nature of the palladium source did not have a major effect on the kinetics of the reaction. No significant loss of activity was observed in the functionalised IL after nine cycles, whereas the catalyst became completely inactive after the fifth cycle in [*n*-BuPy][Tf_2N]. The GLC yields of biphenyl were good, but not excellent, above all taking into account that the more reactive iodobenzene was used as a coupling partner and the reactivity of other aryl halides was not explored or not mentioned.



Scheme 72.

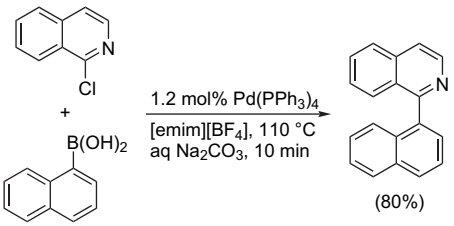
The low-viscosity IL, [bmim][NTf_2], exhibited a comparable efficiency to the frequently used high-viscosity ILs, such as [bmim][PF_6] and [bmim][BF_4], in the coupling of aryl iodides and bromides with phenylboronic acid using a palladium–carbene complex as catalyst (Scheme 73).[225] Water was added as a co-solvent, in order to solubilise the inorganic base. After separation of the product by a triphasic work-up (hexane–water–IL), the recovered IL containing the palladium catalyst was used in the next run by charging the reaction with fresh substrates to give the product in 92% yield. The reaction was, however, somewhat sluggish when aryl bromides were used as the substrates.



Scheme 73.

The ILs, [bmim][PF_6] and [bmim][NTf_2], were also shown to be the most active in the palladium-catalysed coupling of bromobenzene and 4-tolylboronic acid, especially in combination with a 1-phenylimidazole or 1-methylbenzimidazole ligand.[226] The palladium-catalysed cross-coupling of several aryldiazonium tetrafluoroborates with potassium phenyltrifluoroborate in ILs has already been described in this review (see Scheme 13).[32]

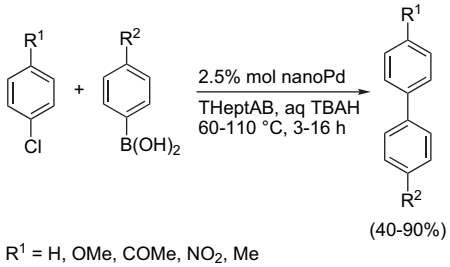
The IL, [emim][BF_4], was utilised as reaction medium for the Suzuki cross-coupling of chloroquinolines and chloroisoquinolines with naphthylboronic acids (see example in Scheme 74).[227] This methodology appeared to be advantageous in comparison with the use of conventional organic solvents; higher product yields in shorter reaction times being obtained with a simpler product isolation and re-usable ILs.



Scheme 74.

The activity of palladium nanoparticles [generated from $Pd(OAc)_2$ and TBAA in an IL] was tested for the Suzuki coupling of several aryl chlorides and bromobenzene with arylboronic acids in a biphasic medium composed of an IL and an aqueous solution of a source of hydroxide anions (*n*-tetrabutylammonium hydroxide, TBAH).[228] THeptAB exhibited better performance than TBAB as a stabilising agent for the palladium nanoparticles. Aryl chlorides bearing electron-donating substituents required higher temperatures providing lower conversions and yields of the corresponding biaryls (Scheme 75). The extracted cyclohexane phase had to be washed with dilute HCl to remove the trialkylamine derived from the IL decomposition. The catalytic system could be re-used for three runs with a slight decrease in the product yield, a noticeable decrease being observed in the fourth run.

New catalysts have recently been developed with the aim of increasing their ionophilicities by the introduction of an imidazolium group covalently attached to the rest of the palladium



Scheme 75.

complex. Corma et al. reported a four-step synthesis of the complex **50** (Chart 9), which was soluble in [bmim][PF_6] and was not extractable by ether.[229] Unfortunately, the catalytic activity of this palladium complex in [bmim][PF_6] was unsatisfactory, providing very low conversions (<10%) in the coupling of iodobenzene with *p*-tolylboronic acid (NaOAc as base at 130 °C). The low activity of complex **50** was attributed to the poor stability of imidazolium ILs to bases. Carbapalladacycle **51**[230] was shown to be stable upon extended heating in 1-*n*-butyl-2,3-dimethylimidazolium hexafluorophosphate and PEG.[231] The low catalytic activity in the former IL, however, made the development of a homogeneous and re-usable catalytic system based on **51** in ILs unpractical. In contrast, the in situ-generated palladium nanoparticles became stabilised by PEG, leading to higher product yields with potential recyclability.

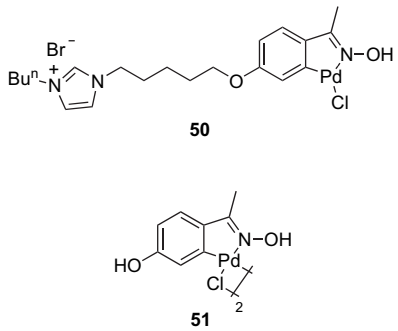
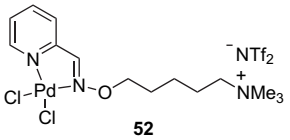
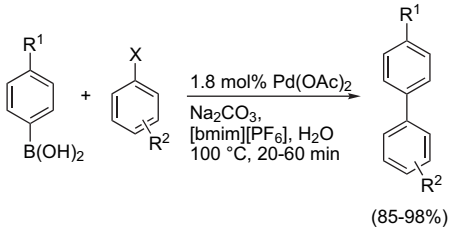


Chart 9.

Based on the above concept, a 2-pyridinealdoxime ligand was functionalised with an IL tag and treated with a palladium(II) salt to give the complex **52**.[170] The tag allowed the specific interaction with ILs and the insolubility in common organic solvents. This precatalyst could be recycled after extraction with toluene and water, and re-used up to four times in the coupling of several aryl bromides and arylboronic acids (1 mol % **52**, K_3PO_4, [bmim][PF_6], H_2O, 80–100 °C, 5–22 h) with a moderate decrease in the yields (97→77%). The yield dropped dramatically, however, in the fifth run (22%).



The catalytic system $Pd(OAc)_2$–[bmim][PF_6]–H_2O was demonstrated to be highly active, air stable and recyclable for the Suzuki reaction of aryl bromides and iodides in short reaction times in air.[232] A large variety of electronically different substituents were compatible with the reaction conditions, the corresponding biaryls being obtained in excellent yields (Scheme 76). The products were isolated by extraction with diethyl ether, although the salt by-products in the IL had to be removed by washing with water for successful catalyst recyclability. In fact, the catalytic system could be recycled seven times with a small decrease in activity. Unfortunately, the coupling of aryl chlorides was not too efficient, but this does not tarnish the merits of this catalytic system.



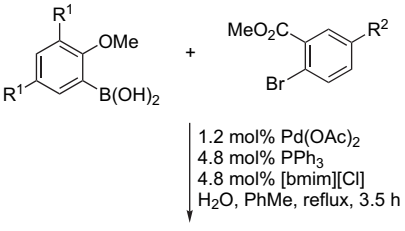
R^1 = H, OMe, CF_3
R^2 = H, 2-Me, 4-Me, 4-OMe, 4-COMe, 4-NO_2, 4-CN, 4-Cl, 4-NH_2, 3-OH
X = Br, I

Scheme 76.

A comparative study of the effect of ILs and organic solvents was carried out using the palladium-catalysed coupling of 4-bromoacetophenone and phenylboronic acid as a model reaction.[233] The following reaction conditions were applied: 0.05 mol % $Pd_2(dba)_3$–$CHCl_3$, PPh_3, aq K_3PO_4, solvent, 70 °C, 1 h. The study covered the following solvents: EtOAc, dioxane, cocosalkyl pentaethoxy methyl ammonium methosulfate, tetradecyltrihexylphosphonium chloride, [bmim][PF_6] and 1-methyl-3-octylimidazolium diethyleneglycolmonomethylethersulfate. It is noteworthy that nearly twice the yield of the desired product was obtained in the organic solvents compared to that in the ILs (74–77 vs 43–48%, respectively), albeit a large amount of palladium black being found for the former. In both imidazolium salt systems, however, the reaction produced none of the desired products, whereas the other ILs prevented palladium black formation. Mixtures of the non-imidazolium-based ILs (cocosalkyl pentaethoxy methyl ammonium methosulfate) with the organic solvents gave product yields as high as those in the pure organic solvent systems. These mixtures combine the beneficial effects of ILs on catalyst stability, while benefiting from the better transport properties of organic solvents. The reaction mixture was subjected to nanofiltration, the product staying in the permeate, while the IL and the palladium catalyst were retained by the membrane and recycled into subsequent consecutive reactions, maintaining a good performance.[234]

Based on the above concept, Kemperman et al. synthesised substituted benzo[*c*]chromen-6-ones by a Suzuki coupling and lactonisation sequence carried out in ILs.[235] The authors took advantage of the catalyst enhancement by the IL and of toluene as a solvent that facilitates the work-up. Two 2-methoxyphenylboronic acids were successfully coupled with differently substituted 2-bromobenzoates in a mixture of [bmim][Cl] (4.8 mol %), water and toluene (Scheme 77). The IL was extracted with toluene and washed with water to remove salts and for re-use subsequently. Unfortunately, the latter was not possible, as, during the work-up of these reactions, the catalyst was not recoverable.

Shreeve and Xiao synthesised a wide range of di- and monoquaternised 2,2′-biimidazolium-based ILs, the majority of the monoquaternary products being room-temperature ILs.[236] In particular, the monoquaternary product derived from 2,2′-biimidazole and 1-iodobutane was an IL that could act both as a solvent and as a ligand in the palladium-catalysed Suzuki reaction. The palladium complex **54** (Chart 10), preformed from the IL **53** and $PdCl_2$, gave high yields in the coupling of different 4-substituted aryl bromides with



R^1 = H, F
R^2 = H, Me, OMe, Cl, NO_2

Scheme 77.

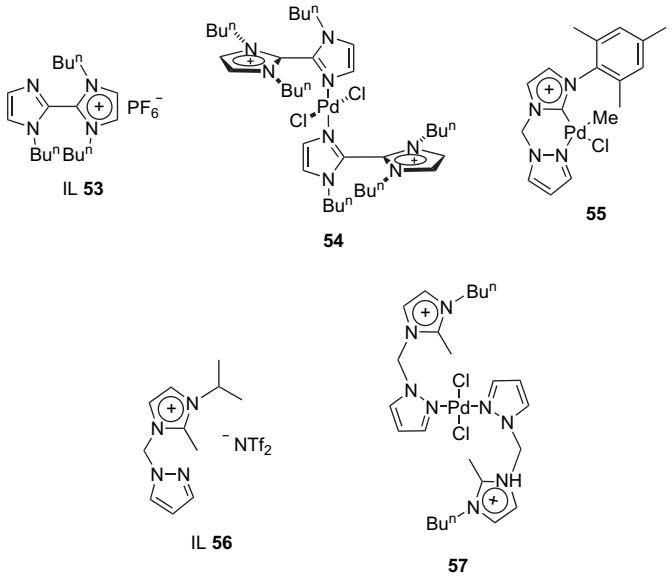


Chart 10.

phenylboronic acid (2 mol % $PdCl_2$, Na_2CO_3, IL **53**, 100 °C, 24 h). The products were easily separated from the reaction mixture by simple extraction and decantation with ether. The catalyst–IL could be recovered by washing with water, to remove the sodium salt, and drying under vacuum before use. Despite very low yields being obtained with chlorobenzene as the substrate, the high performance exhibited by the catalytic system, even after 15 runs, must be highlighted.

The pyrazolyl-functionalised NHC–palladium complex **55** (2 mol %) (Chart 10) could be also recycled five times using different aryl iodides and phenylboronic acid in [bmim][PF_6] and H_2O as co-solvent at 110 °C for 1 h, with no detectable loss of activity (90→87% yield).[237] Under similar reaction conditions, complex **57** in the IL **56** catalysed the coupling of a variety of aryl bromides with phenylboronic acid. The palladium(II)-containing catalytic solution was recycled 14 times without loss of catalytic activity.[238]

5.3. Fluorous media

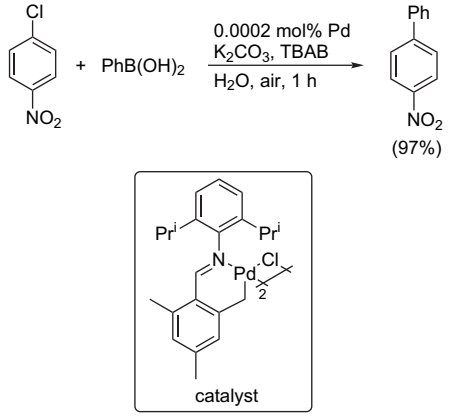
Fluorous chemistry can be considered as a complementary type of liquid-phase synthetic and separation methodology involving the use of fluorine-containing reagents and solvents, the advantages of which are well known.[239] In particular, the fluorous biphasic concept has been successfully applied in stoichiometric and catalytic chemical reactions utilising organic, inorganic or organometallic fluorous-soluble reagents.[240] This concept, however, has found very little application in the Suzuki reaction and has been recently reviewed.[241] For some examples of perfluoro-tagged palladium catalysts immobilised onto a fluorous solid support, which have been reported in this review, see Chart 4[119] and Scheme 46.[120]

5.4. Water

In recent decades, the use of water as a reaction solvent or co-solvent has received much attention in synthetic organic chemistry because of many potential advantages such as cost, safety, environmental concern, easier isolation of organic products and recycling of water-soluble catalysts and other reagents. As a result, the use of aqueous media for carbon–carbon bond formation,[242] including transition-metal catalysis, has been extensively studied and reviewed.[242b,243] The general beneficial effect of water in the Suzuki reaction is well known, and consequently, many publications have emerged combining its use with an organic solvent[242b,243] (e.g., DMF, MeCN, dioxane, PEG, acetone, THF, EtOH; some examples have already been shown in this review). The use of neat water as a solvent for the Suzuki reaction is, however, less common. The pioneering work in this field was carried out by Beletskaya et al., in 1989,[244] who coupled arylboronic acids with water-soluble aryl halides at room temperature in the presence of a palladium salt and an inorganic base in water. The Suzuki reaction using water as a solvent has been recently reviewed by Leadbeater, mostly until 2004.[245] Some more recent examples involving the use of neat water as a solvent will now be discussed.

One of the known protocols uses neat water as a solvent in the presence of a conventional phase-transfer agent. In this context, phenylboronic acid was coupled with 4-methoxyiodobenzene and 4-acetylbromobenzene in water in the presence of CTAB and 1% $Pd(OAc)_2$ at 100 °C to give the corresponding biaryls in high yields (84 and 90%, respectively). The reactions were fast (1–3 h) with high TOFs.[246]

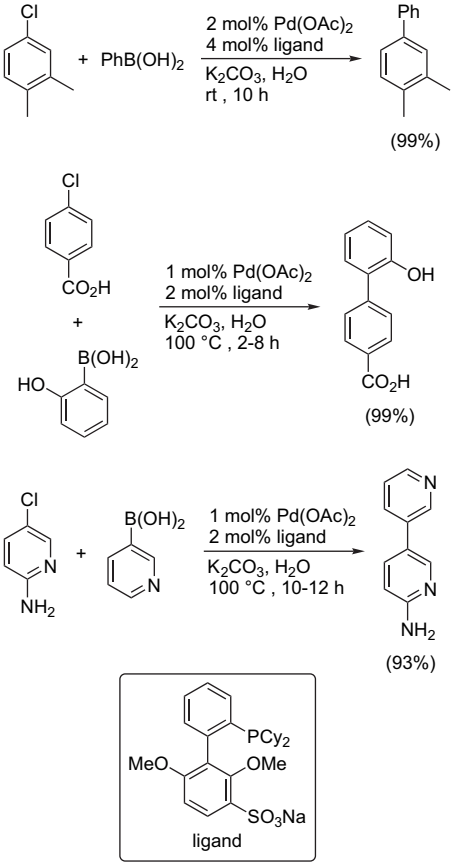
A cyclopalladated complex, derived from 2,4,6-trimethylbenzaldehyde and 2,6-diisopropylaniline, was found to catalyse the cross-coupling of activated aryl chlorides with phenylboronic acid in water under air, in the presence of TBAB.[247] High TONs were achieved in relatively short reaction times, the expected biaryls being obtained in modest-to-excellent yields (see example in Scheme 78). The conversion observed for the deactivated substrates and chlorobenzene was, however, rather poor.



Scheme 78.

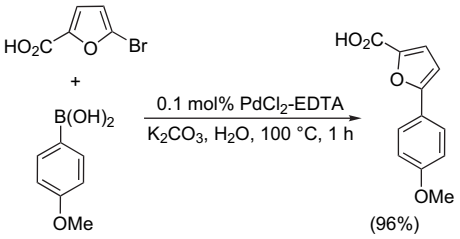
A highly effective catalytic system was developed by Buchwald and Anderson, based on the use of a water-solubilising sulfonate group-bearing ligand, for the Suzuki coupling of aryl chlorides and bromides with arylboronic acids in water.[248] A large variety of both hydrophobic and hydrophilic substrates, including heterocyclic compounds, could be coupled in excellent yields and even at room temperature in some cases (see examples in Scheme 79). The catalyst exhibited high thermal stability, allowing microwave heating (150 °C) in order to shorten some reaction times. As a requirement, degassed water must be used in all the experiments.

The air-stable and easy-to-prepare complex, $PdCl_2$–EDTA, catalysed the coupling of water-soluble and -insoluble aryl and heteroaryl iodides with differently substituted arylboronic acids in water in short reaction times and at room temperature in many cases.[249] This simple catalytic system could also be applied to the coupling of aryl bromides, which required higher reaction temperatures (50–100 °C) and the presence of 1 mol % TBAB for the water-insoluble aryl bromides (see example in Scheme 80). It is worthy of note that the catalytic system is highly tolerant to a broad range of functional groups, such as CHO, COMe, CO_2H, NH_2 and OH. For a preparative-scale synthesis, the catalyst amount could be reduced to 0.001 mol % without a noticeable decrease in activity. Apparently, aryl chlorides did not react under the reported conditions.



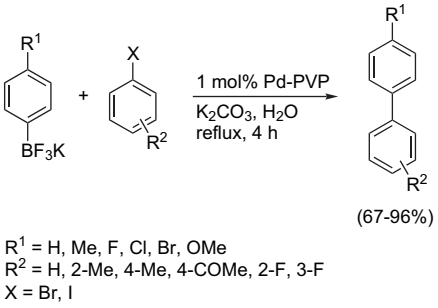
Scheme 79.

The same group developed an improved protocol for the ligandless Suzuki coupling in water, based on the reverse order of addition of the reagents (i.e., addition of base after arylboronic acid, aryl halide, water and catalyst).[250] With a similar substrate scope to that mentioned above, good-to-excellent yields of the expected biphenyls were obtained with a simple catalytic system composed of 0.1 mol % $Pd(OAc)_2$, KOH, H_2O, with gradual heating from 20 to 75 °C.



Scheme 80.

None of the previously mentioned catalytic systems in this section were re-used. In contrast, potassium aryltrifluoroborates were applied as alternative coupling partners to arylboronic acids in the reaction with electron-neutral and activated aryl bromides and iodides in water, using Pd–PVP as a re-usable catalyst (Scheme 81).[251] After completion of the reaction, the product was extracted with ether, Pd–PVP and the inorganic salts precipitating at the bottom of the flask. After decantation of the reaction solution, additional K_2CO_3 was added and the reaction was repeated with a minor decrease in the yield after eight cycles. Alternatively, the product could be distilled directly from the reaction mixture, the remaining components being re-used without purification.



Scheme 81.

The combination of neat water in a re-usable catalytic system is a topic of increasing interest that has led recently to the development of new ligands which fulfill this property (Chart 11). Uozumi et al. synthesised a 3D-palladium-network complex by the self-assembly of $PdCl_2$ and C_3-trisphosphane **58**.[252] The network complex catalysed 27 combinations of 6 varieties of aromatic halides (bromides and iodides) and 6 varieties of arylboronic acids under atmospheric conditions in water (0.05 mol % Pd–**58**, Na_2CO_3, 100 °C, 3 h). Both electron-deficient and -withdrawing aryl halides with different substitution patterns led to the corresponding biaryls in 80–99% yield. Despite the ligand synthesis from 2,4,6-tris(bromomethyl)mesitylene being not very straightforward, the recovered catalyst could be re-used four times without any loss of catalytic activity.

Catalyst **59** (Chart 11) (prepared in four steps from citrazinic acid) was utilised in the coupling of electronically different aryl bromides and arylboronic acids in neat water at 100 °C, leading to the corresponding biphenyls in >99% yield and in a short reaction time (0.1 mol % Pd, K_2CO_3, H_2O, 100 °C, 2 h).[253] It is worthwhile mentioning that the reaction worked efficiently, even for a catalyst loading of 10^{-7} mol % Pd. The products could be separated from the hydrophilic catalyst by extraction with ether, the remaining aqueous layer being re-utilised, without any further treatment, up to five times with no loss of catalytic activity. Apparently, aryl chlorides did not react under the described reaction conditions.

Palladium(II)-cationic 2,2′-bipyridyl catalyst **60** (Chart 11), which was shown to be soluble in water and air stable, catalysed the Suzuki coupling of representative aryl bromides with varied arylboronic acids in water and aerobic conditions (0.1 mol % Pd–**60**, K_2CO_3, H_2O, 100 °C, 40–99% yield).[254] The product was separated by filtration and the aqueous filtrate containing the catalyst was re-utilised in five consecutive runs with >90% yield. Furthermore, aryl chlorides with electron-withdrawing groups, as well as 2-chlorophenol, also gave excellent yields in the presence of 50 mol % TBAB at 100–140 °C. Chlorobenzene, however, gave only 50% of the corresponding biphenyl after 48 h at 140 °C with 1 mol % catalyst.

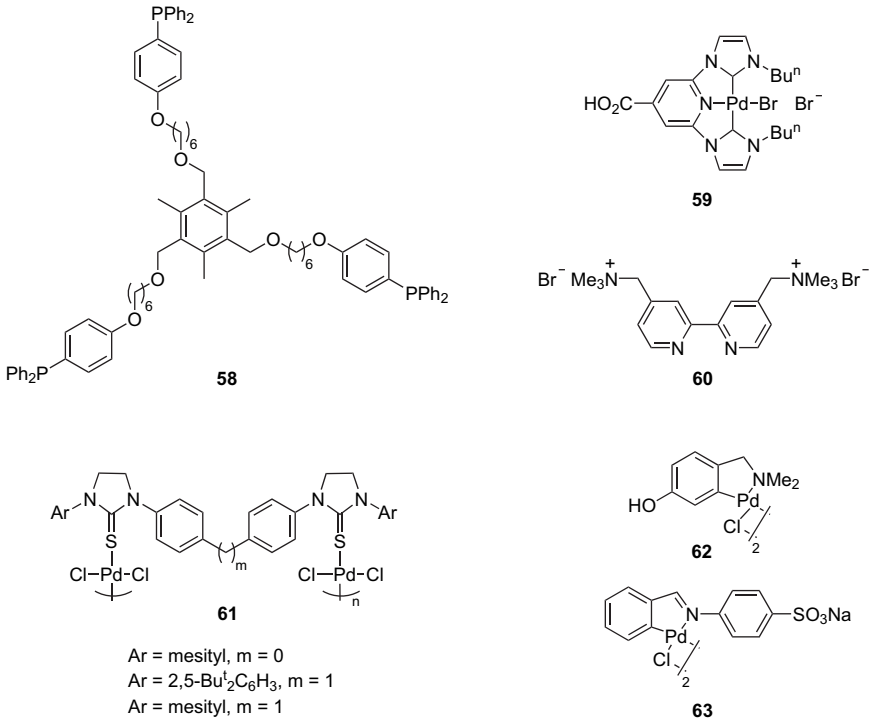


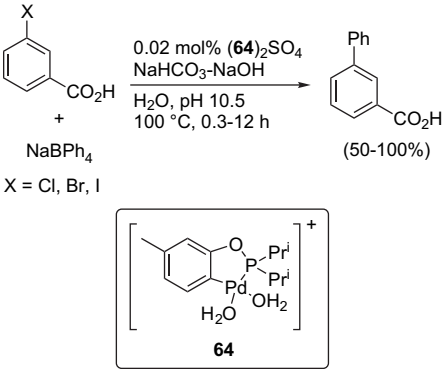
Chart 11.

Under the same reaction conditions applied for aryl bromides, high yields of the biphenyls were obtained with the self-supported thiourea–palladium complexes **61**.[255] In this case, quantitative yields were obtained after six runs in 1 h. Unfortunately, aryl chlorides were unreactive with this catalytic system.

The water-soluble palladacycles **62** and **63** (Chart 11) were demonstrated to be active catalysts in the Suzuki coupling of different aryl bromides and activated aryl chlorides with phenylboronic acid in combination with (2-di-*tert*-butylphosphinoethyl)trimethylammonium chloride (1 mol % **62** or **63**, 2 mol % phosphane ligand, H_2O, 80 °C, 4 h, 51–95% yield).[256] The reaction conditions were milder than those in the above-described publications, albeit with the help of an external phosphane ligand. The catalyst derived from **63**–phosphane could be used for 12 reaction cycles in the coupling of 4-bromotoluene, before a significant loss of catalyst activity was observed.

Electron-poor, electron-rich and sterically hindered both aryl bromides and arylboronic acids were coupled in excellent yields and in a fast manner under the catalysis of the commercially available complex, $PdCl_2$(dppf), in water [0.1 mol % $PdCl_2$(dppf), K_2CO_3, H_2O, 80 °C, 1 h, 81–99% yield].[257] The catalyst could be re-used (after product extraction with pentane and addition of fresh reagents) by using a 20% aq PEG-2000 solution as the reaction medium for a total of three runs with almost consistent yields. Apparently, aryl chlorides did not react under the reported conditions.

A series of water-soluble palladacyclic aqua complexes were synthesised from the reaction of the corresponding palladacyclic chloro complexes with silver salts in water and their activity tested in the pH-dependent Suzuki reaction.[258] Among them, complex **64** exhibited the highest catalytic activity for the coupling of sodium tetraphenylborate with 3-halocarboxylic acids in water at pH 10.5 (Scheme 82). The reactions could be carried out under an air atmosphere, leading to the corresponding biphenyl in excellent yields for the bromide and iodide, and moderate yield for the chloride. A strong dependence on the reaction pH was observed, the TOF decreasing drastically with increasing the pH to show no catalytic activity at pH 13. No catalyst recovery studies were carried out in this case.



Scheme 82.

6. Reaction conditions

6.1. Physical activation

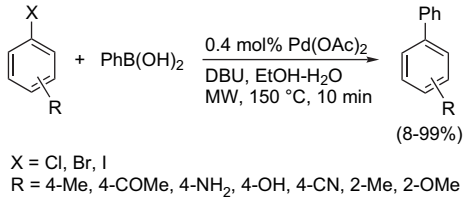
6.1.1. Microwave

Microwave-assisted organic synthesis has experienced a spectacular development in the last few years, as evidenced

by the large number of papers, books and reviews that have recently appeared in the literature.[259] In particular, the Suzuki reaction under microwave promotion has been recently reviewed in detail by Leadbeater[245] and, therefore, we will deal only with the more recent publications that have appeared in this field.

The first examples of Suzuki reactions promoted by microwave heating were conducted by the group of Larhed in 1996 in a single-mode cavity in septum-sealed Pyrex vessels, using $Pd(PPh_3)_4$ as a catalyst, homogeneous and polymer-supported aryl iodides and bromides as substrates, and a mixture of water, ethanol and DME as solvent.[260] They showed that microwave irradiation accelerated the homogeneous palladium-catalysed reaction, affording faster and cleaner chemical conversions.

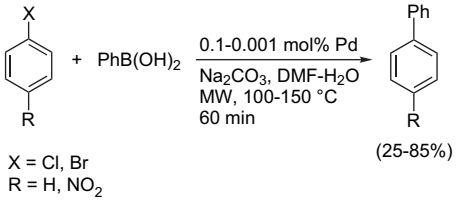
Some applications of microwave heating to the Suzuki reaction have already been shown in the present report.[33–35,38,61,73,78,81b,82,85,131,132,161,170] Other contributions of interest are those provided by Leadbeater's group in an aqueous medium. This group demonstrated that mineral bases were not essential for the success of the palladium-catalysed Suzuki coupling of aryl halides and phenylboronic acid in the presence of water under microwave irradiation. In fact, aryl bromides and iodides bearing electronically different substituents led to the corresponding biaryls in good-to-high yields using DBU as a base in 1:1 water–ethanol, heating to 150 °C and holding at this temperature for 10 min using microwave heating (Scheme 83).[261] Only 2-bromophenol and 2-bromoanisol gave low product yields, whereas 4-chloroacetophenone could be coupled in 58% yield. It is noteworthy that under the same conditions, but applying conventional heating for 13 min, the product yield for a model reaction dropped from 99 to 79%, the latter being a reasonable result taking into account that the heating time was short and that it might be improved by prolonged heating. The reaction with other arylboronic acids was not explored.



Scheme 83.

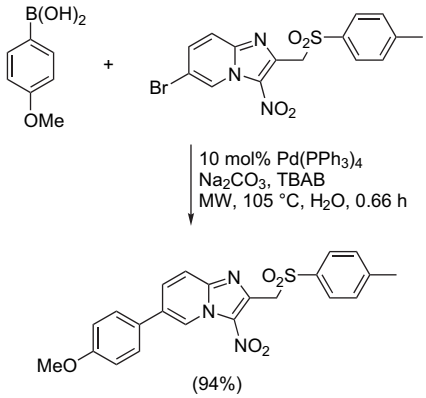
Leadbeater and Smith also discovered that the progress of the above-mentioned reactions could be monitored using in situ Raman spectroscopy. It was possible to know if the reaction occurred or reached completion, although the product yield could not be quantified. In addition, the monitoring confirmed that when working in aqueous media, the coupling is in competition with the deboronation of the boronic acid.[262] Interestingly, low palladium concentrations (1–5 ppm) provided high biaryl yields in open reaction vessels using microwave heating with a mixture of water and ethanol as solvent (80–83 °C, Na_2CO_3 as base, 20 min).[263] The reactions could be increased up to a molar scale using a multimode microwave apparatus.

Kostas et al. synthesised, in two steps, a new air- and moisture-stable palladium complex derived from salicylaldehyde, *N*(4)-methyl-*N*(4)-phenylthiosemicarbazide and cycloheptylamine.[264] In contrast to other palladium complexes with thiosemicarbazones, this complex was inactive towards the Suzuki coupling under aerobic conditions by conventional heating. On the other hand, microwave irradiation promoted the coupling of bromobenzene, 4-bromo- and 4-chloronitrobenzene with phenylboronic acid in DMF–H_2O under aerobic conditions (Scheme 84). The GC yield was good for bromobenzene (85%), but rather low for 4-bromo- and 4-chlorobenzene (37 and 25%, respectively), in all cases applying relatively high temperatures and long reaction times. Due to the limited substrate scope studied, it is difficult to gauge about the potential application of this catalytic system.



Scheme 84.

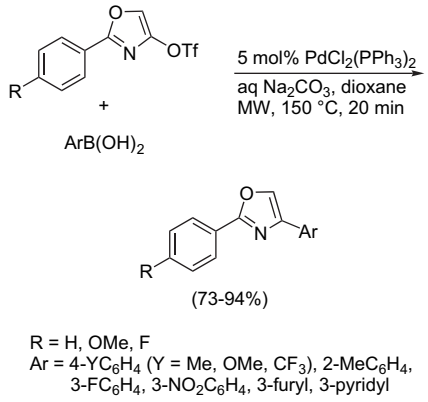
A series of 6-aryl-2-arylsulfonylmethyl-3-nitroimidazo[1,2-*a*]-pyridines were obtained by coupling eight different arylboronic acids with the corresponding bromoaryl partners using microwave irradiation in an aqueous medium in the presence of $Pd(PPh_3)_4$ and TBAB (see example in Scheme 85).[265] Arylboronic acids with both electron-donating and -withdrawing groups led to the corresponding biaryls in good-to-high yields. In some cases, however, the reaction times did not practically differ from those obtained under conventional heating, some reaction yields being even higher in the latter case.



Scheme 85.

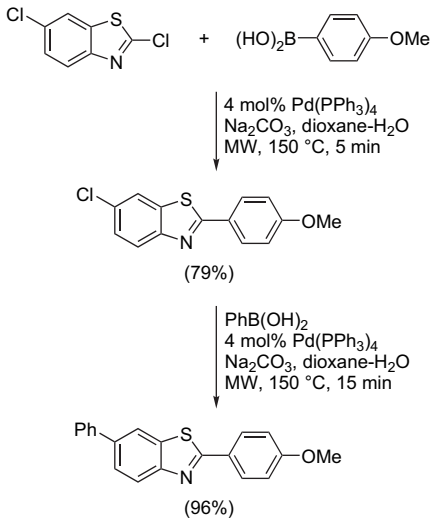
A series of 2-aryl-4-trifloyloxazoles underwent rapid microwave-assisted coupling with a range of aryl- and heteroarylboronic acids in good-to-excellent yields under palladium catalysis (Scheme 86).[266] Good reactivity was observed for

electron-deficient, -rich or *ortho*-substituted arylboronic acids, as well as for heteroaromatic pinacol boronic esters. The methodology was similarly effective by using 2-chloro-4-phenyloxazole as coupling partner.



Scheme 86.

A general and highly regioselective methodology has been developed for the synthesis of 2-aryl-6-chlorobenzothiazoles based on the Suzuki reaction of 2,6-dichlorobenzothiazole with arylboronic acids under similar conditions to those shown in Scheme 86.[267] These processes produced the coupling products in moderate-to-good yields irrespective of the electronic nature of the substituent on the arylboronic acid. Moreover, the remaining chlorine atom could be used for a further Suzuki coupling reaction under the same conditions (Scheme 87).



Scheme 87.

1-Bromo-2-naphthol, 2-bromophenol and 2-chlorophenol were reacted with phenylboronic acid and 1-naphthylboronic acid in moderate-to-excellent yields (48–98%) using some phosphane–$Pd(OAc)_2$ catalytic systems [2.5–5 mol % $Pd(OAc)_2$, 5 mol % **65**–**69**] with moist K_3PO_4–toluene or moist CsF–dioxane and microwave heating (20 min at 105 °C to 3 h at 100–120 °C).[268] Among the different ligands tested (Chart 12), ligand **65** was the most efficient in the coupling of

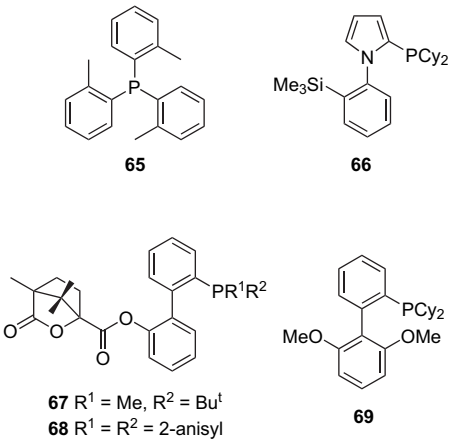
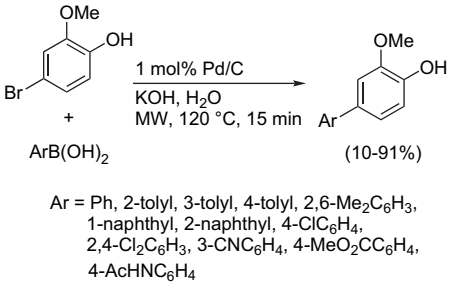


Chart 12.

bromophenols, whereas ligand **69** allowed the cross-coupling with chlorophenols. It would be interesting to study the performance of these ligands when different substituents are introduced in the coupling partners.

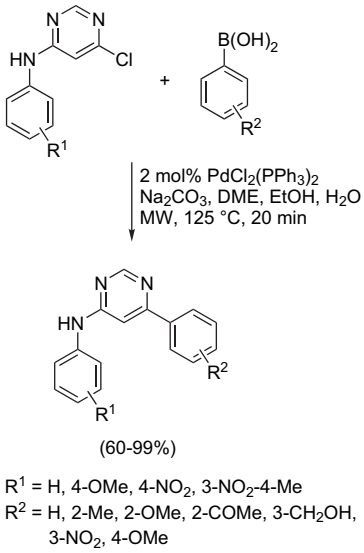
Freundlich and Landis developed a variant of Hirao's protocol for aryl iodides,[269] incorporating the benefit of microwave-reactor technology, which was applied to the aqueous Suzuki reaction of bromophenols and arylboronic acids (see example in Scheme 88).[270] It is worthy of note that the same results were obtained under the optimum reaction conditions using microwave as in the reaction conducted in a pre-equilibrated oil bath. Low product yield was obtained for sterically encumbered, heteroatom-containing, electron-rich and -poor arylboronic acids. Potassium phenyltrifluoroborate was less reactive than phenylboronic acid in this reaction. Although aryl bromides were used as substrates in this report, Hirao's method was milder, much higher yielding and the catalyst could be recovered and re-used at least five times with little decrease in activity.



Scheme 88.

4-Aminoaryl-6-aryl-substituted pyrimidines were prepared, by combined microwave-assisted amination and Suzuki–Miyaura cross-coupling reactions, using 4,6-dichloropyrimidine as substrate.[271] The microwave-assisted Suzuki cross-coupling of the amination products with arylboronic acids, bearing electron-withdrawing and -donating groups, led to the expected products in good-to-excellent yields (Scheme 89). Alternatively, the Suzuki and subsequent amination reactions could be conducted in a one-pot procedure

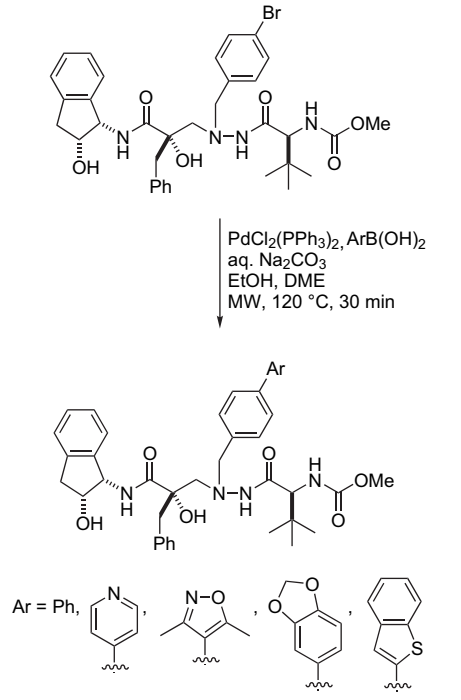
with overall comparable yields to those of the stepwise procedure.



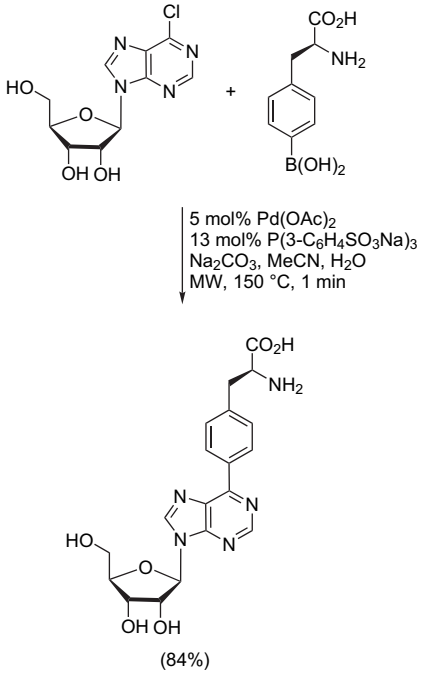
Scheme 89.

Under the same reaction conditions, two series of P1′-extended HIV-1 protease inhibitors were synthesised through the microwave-accelerated palladium-catalysed cross-coupling reaction of a 4-bromoaryl moiety in the starting material with several arylboronic acids (Scheme 90).[272] The product yield ranged from low to moderate, the P1′ benzyl group elongated with a 4-pyridyl substituent showing high cellular antiviral potencies.

Shaughnessy's method[273] for Suzuki reactions in aqueous media was further optimised and applied to the synthesis of novel purine–amino acid conjugates.[274] A single-step synthesis of optically pure (adenin-8-yl)phenylalanines and (purin-6-yl)phenylalanines was elaborated using both classical and microwave heatings. Classical heating was shown to be more efficient for the synthesis of 8-substituted nucleosides and more labile nucleotides, whereas microwave heating was shown to be more efficient for purine bases and 6-substituted nucleosides (see example in Scheme 91). The reactions were fast under microwave irradiation in the presence of a water-soluble ligand.

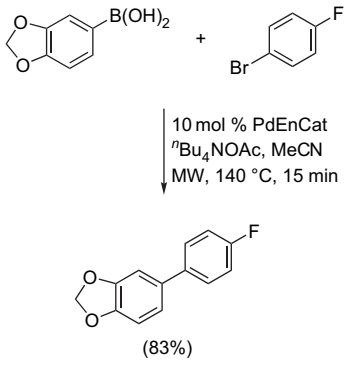


Scheme 90.



Scheme 91.

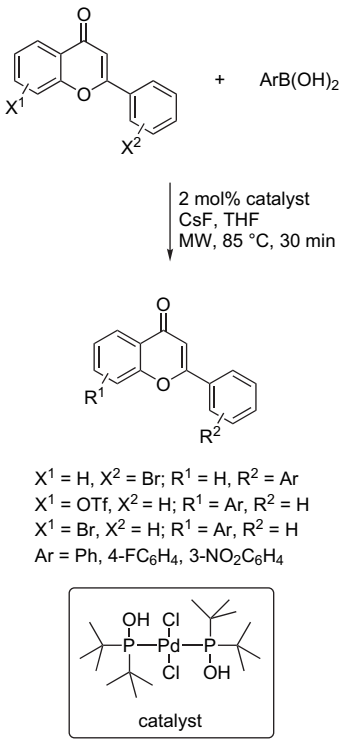
Microwaves have also been applied to the Suzuki reaction in non-aqueous media. Ley et al. carried out a complete study on the application of PdEnCat, in conjunction with TBAA, to the microwave-assisted Suzuki reaction of aryl halides and arylboronic acids.[275] Seven different arylboronic acids were efficiently coupled with activated aryl bromides in MeCN at 140 °C for 15 min (see example in Scheme 92). A small library of biaryl compounds was generated using this protocol in EtOH, 38% of the reactions leading to products with



Scheme 92.

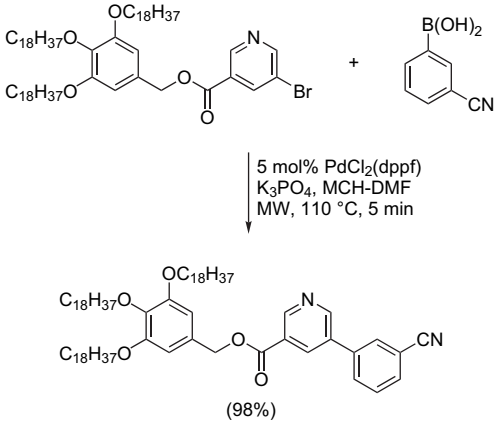
>98% purity. In addition, the yields and purities could be improved when simultaneous cooling was employed while microwave irradiation was being supplied to the reaction system. Furthermore, the same Suzuki reactions could be performed in a flow-type process by using a glass U-tube packed with the heterogeneous catalyst and inserted into the microwave cavity. Several grams of the pure product could be obtained in a continuous operation without having to regenerate or replace the catalyst. The application to aryl chlorides was restricted to two examples.

The group of Caddick utilised Li's catalyst[276] with CsF for the coupling of a range of flavone bromides and triflates with several arylboronic acids under microwave heating (Scheme 93).[277] The best yields were obtained for the more electron-poor bromides. It is noteworthy that the use of microwave heating at 85 °C reduced the reaction time from 5 h to 15 min, with respect to conventional heating, improving the yield from 83 to 98%. Attempts to selectively monoarylate the bishaloflavones were unsuccessful, leading to inseparable mixtures of mono- and bisarylated products.



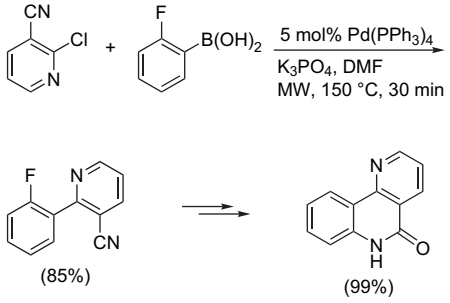
Scheme 93.

Microwave-promoted Suzuki coupling of two aryl bromides and one aryl iodide, attached to a cycloalkane-soluble platform, with a variety of arylboronic acids (most of them bearing electron-withdrawing groups), was accomplished in a cycloalkane-based thermomorphic biphasic system.[278] The biphasic system was composed of methylcyclohexane (MCH) and DMF, a palladium catalyst and K_3PO_4 as base (degassed under argon). After cooling the reaction mixture and phase separation, the cycloalkane-soluble platform-bound coupled products could be recovered in the upper MCH phase. Further work-up involving solvent evaporation, MeOH addition and filtration was required in order to obtain the cycloalkane-soluble platform-bound coupled products (see example in Scheme 94). Treatment of the coupled products with a catalytic amount of NaOMe in an MeOH–MCH solution afforded the corresponding biaryls in excellent yields. It is noteworthy that so high product yields (all the examples except one are in the range 94–98%) could be obtained after so many work-up steps, based on a substrate scale of only 0.05 mmol. This methodology, however, is not so advantageous taking into account that: (a) many steps are needed to attach the substrates to the platform and for the work-up, (b) an ester functionality must be present in the reagents and is also present in the products, (c) the catalytic system was not recycled and (d) the behaviour of this methodology at a larger scale is unknown.



Scheme 94.

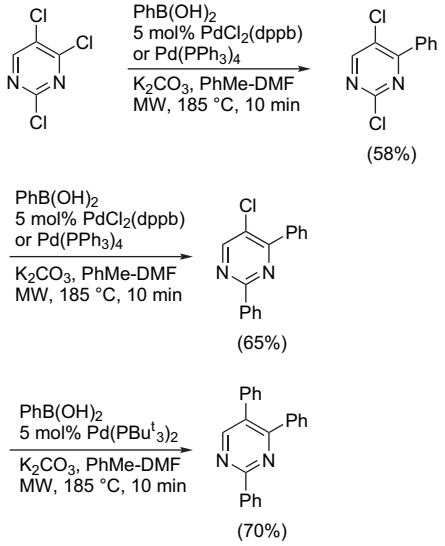
As an application of the Suzuki reaction, 2-fluorophenylboronic acid was coupled with all the *ortho*-chlorocyanopyridine isomers in good yields using a standard catalytic system under microwave irradiation (see example in Scheme 95).[279] An excess of 2-fluorophenylboronic acid (2 equiv) was used in order to compensate for protodeboronation as a side reaction. The resulting biaryls could be transformed in two steps into the corresponding benzonaphthyridin-5-ones in high yields.



Scheme 95.

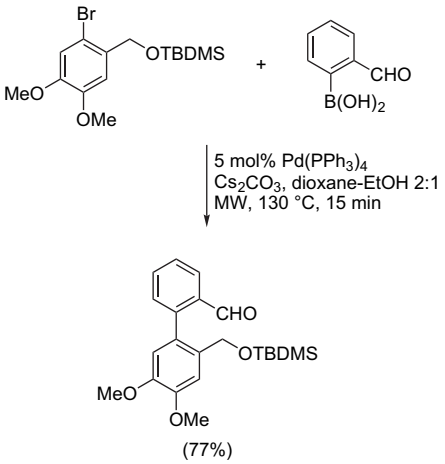
The microwave-assisted palladium-catalysed cross-coupling reaction of 2,4-di- and 2,4,5-trihalopyrimidines with phenylboronic acid allowed the selective introduction of phenyl groups in the 2-, 4- or 5-position of the pyrimidine system, depending

upon the choice of the halopyrimidine and the catalyst employed.[280] The commercially available 2,4,5-trichloropyrimidine was stepwise coupled with phenylboronic acid to give the mono-, di- or triphenylated product in moderate yields by combining different palladium catalysts (Scheme 96). These reactions proceeded much faster when compared with those under conventional conditions [$Pd(OAc)_2$, Na_2CO_3, PPh_3, DME–H_2O, 70 °C, 18–24 h], albeit the temperature in the latter case being much lower and the yields being higher (88, 88 and 93%, respectively).



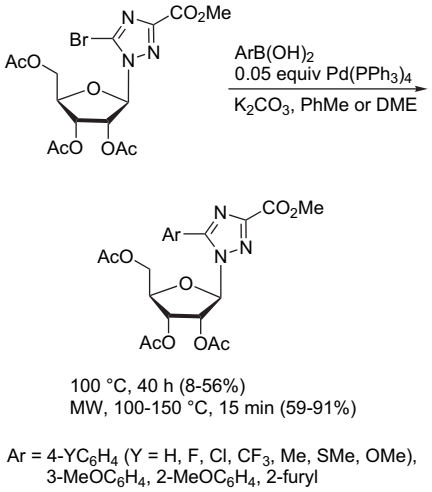
Scheme 96.

The cross-coupling reaction of 2-formylphenylboronic acid with a dimethoxy-substituted aryl bromide was found to be the key step in the synthesis of (−)-steganacin and (−)-steganone.[281] The optimised reaction conditions involved microwave heating at 130 °C in dioxane–ethanol for 15 min (Scheme 97). In contrast, the reaction performed under conventional heating resulted in a lower yield (42%) at 102 °C for 3 h, where benzaldehyde (the protodeboronation product) was the major product.



Scheme 97.

Microwave irradiation was also shown to be much superior to conventional heating in the Suzuki coupling of 5-bromotriazole nucleosides with a series of differently substituted arylboronic acids (Scheme 98).[282] The starting material was almost completely consumed in the reaction under microwave irradiation, which simplified the product separation and purification steps.

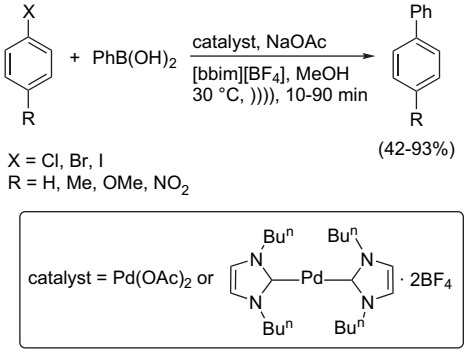


Scheme 98.

As an interesting application of microwave-promoted Suzuki reactions, a powerful microwave-enhanced multiple Suzuki coupling methodology has been developed and applied to the synthesis of highly luminescent six-arm monodispersed macromolecules, based on triazatruxene and fluorine units. The reactions were performed in the presence of 0.6 equiv $Pd(PPh_3)_4$ and aq K_2CO_3 (15 equiv) in THF under microwave irradiation (150 °C, 15–30 min).[283]

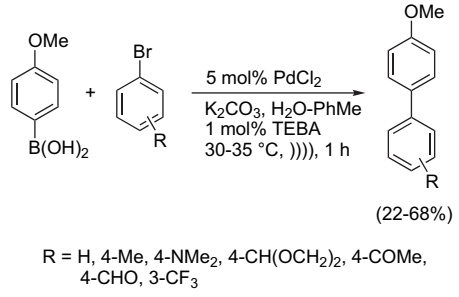
6.1.2. Ultrasound

It is well known that ultrasound has a beneficial effect on reaction acceleration with minimum decomposition of thermally labile products, both in homogeneous and in heterogeneous conditions.[284] The ultrasound-promoted Suzuki reaction has been very little studied, the first example being reported by the group of Srinivasan in 2002.[222a] The sonochemical reactions were carried out in a thermostatted ultrasonic cleaning bath of frequency 50 kHz. A number of halobenzenes were reacted with phenylboronic acid in the IL, [bbim][BF_4], with methanol as co-solvent, using $Pd(OAc)_2$ as catalyst and NaOAc as base (NaOMe for chlorobenzenes) under ultrasonic irradiation at 30 °C. Complete conversion for iodobenzenes was achieved in 20–30 min, 82–85% conversion in 10–45 min for bromobenzenes and 42–52% in 1–1.5 h for chlorobenzenes (Scheme 99). In a modified process, a Pd–biscarbene complex was preformed, giving similar yields, but with the advantages of being recycled, the reaction being carried out in air (instead of argon) and no palladium black being formed. Recovery of the IL from the aqueous layer after work-up required, however, extraction with dichloromethane.



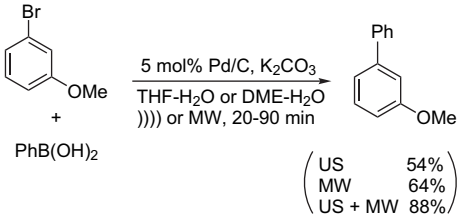
Scheme 99.

More recently, the groups of Toma and Palmisano reported, independently in the same year, their investigations on the ultrasound effect on Suzuki reactions.[285,286] The first group studied the heterogeneous reaction of aryl iodides with different arylboronic acids catalysed by Pd–C and KF as base in a methanol–water mixture at 30–35 °C for 1 h sonication.[285] Good yields were obtained for the reaction of substituted iodoarenes with phenyl- or 4-methoxyphenylboronic acid (62–95%). On the other hand, low yields of products were obtained for the reaction of phenylboronic acid with iodobenzene (21%) or when the arylboronic acid bore a strong electron-withdrawing group (23%). In the case of the reaction of aryl bromides with 4-methoxyphenylboronic acid, the best, but modest, results were achieved for bromobenzene and bromoarenes with electron-withdrawing groups in the presence of TEBA as phase-transfer catalyst, $PdCl_2$ as catalyst and K_2CO_3 as base (Scheme 100). Although sonication reduced the reaction time from 4 h (conventional conditions) to 1 h, the catalyst could, apparently, not be recycled.



Scheme 100.

Similar results in the coupling of aryl iodides with phenylboronic acid were obtained by Palmisano's group under similar reaction conditions (5 mol % Pd–C, K_2CO_3, THF–H_2O or DME–H_2O 1:1,)))) or MW, 45 °C, 20–90 min).[286] Interestingly, a notable improvement in the yield was observed by combining the action of ultrasound (US) and microwave in the coupling of an aryl iodide, bromide and chloride with phenylboronic acid (see example in Scheme 101). A novel reactor prototype had to be developed by this research group in order to combine US and MW irradiation. Low yields were obtained when the reactions were carried out under conventional



Scheme 101.

conditions (reflux, 4 h) and, as in the above reactions, recycling experiments were not reported.

6.2. Physicochemical activation: micellar solutions

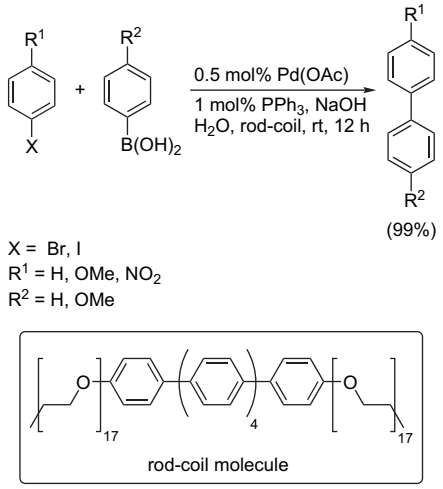
It is well known that the rates and pathways of all kinds of chemical reactions can be altered by performing the reactions in micellar media instead of pure bulk solvents.[287] Triblock copolymers of poly(ethylene oxide) $[(EO)_n]$ and poly(propylene oxide) $[(PO)_n]$, with the block sequence $(EO)_n$–$(PO)_n$–$(EO)_n$, are non-ionic amphiphilic molecules, which are both surface active and able to form micelles in aqueous solutions. They are commercially available and their application to the Suzuki reaction has already been reviewed.[288] Some other micellar systems for the Suzuki reaction have been described in Section 5.4.

Nevertheless, a more recent and interesting contribution to this field deserves more attention, because of its peculiarity and effectiveness. Lee et al. investigated supramolecular reactors for the Suzuki reaction by using the self-assembly of amphiphilic rod–coil molecules based on poly(ethylene oxide) coils.[289] The rod–coils synthesised were shown to self-assemble in aqueous solution into discrete micelles consisting of aromatic rod bundles encapsulated by hydrophilic poly(ethylene oxide) coils, which can entrap solvophobic aromatic molecules. The Suzuki coupling reactions can take place within the aromatic bundles in aqueous media at room temperature, because this confined environment would lead to a highly concentrated reaction site that lowers the energy barrier of the reaction. When the extended rod segments without side groups were used as a reaction template, the coupling reactions of aryl iodides and bromides with phenyl- and 4-methoxyphenylboronic acid were conducted in excellent yields (99%) (Scheme 102). The coupling reaction of electron-poor aryl chlorides was also achieved in 72% yield, although low yields were obtained for other aryl chlorides. Interestingly, the reaction takes place at very low palladium loading (200 ppb) for a wide range of aryl halides.

7. Miscellaneous non-conventional techniques

7.1. Nanofiltration

The main drawback of homogeneous catalysis is the loss of the active catalyst during the isolation of products. Membrane technology offers the possibility of continuously separating catalysts from the product in a non-destructive way and



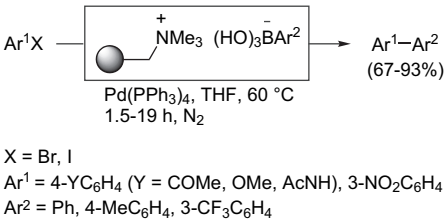
Scheme 102.

re-feeding the catalyst into the process. Recently, solvent-stable ultra- and nanofiltration membranes have been introduced, showing high retentions for medium-sized soluble molecules.[290] This technique has, however, been very little applied to the Suzuki reaction, the only two more recent examples already being described in this review.[156,234]

7.2. Microreactors

Microreactor research for organic synthesis is a rapidly growing field following the realisation of the benefits of microfluidic technology over conventional chemical synthesis, including improved temperature control, selectivity, yield, reaction time and both environmental and safety issues resulting from the use of small quantities of reagents and solvents.[291]

Since the first experiments in 2000,[291,292] increasing interest has been shown in the application of microreactors to the Suzuki reaction. In the more recent literature, Kirschning et al. developed a continuous-flow microreactor with an interior monolithic glass–polymer composite containing a quaternary ammonium ion suitable for the loading of various anions and applied to the Suzuki reaction.[293] First, the arylboronic acid was immobilised onto the anion-exchange resin, the rest of the components [aryl bromide or iodide, 2–5 mol % $Pd(PPh_3)_4$, THF] being circulated at 60 °C through the reactor to give the products in good yields (Scheme 103). The use of anhydrous THF and degassed solutions under nitrogen was mandatory. The reactor could be re-used more than 20 times after washing successively with 2 M HCl, 1 N NaOH and



Scheme 103.

water. The reaction could also be performed without preliminary immobilisation of the boronic acid on the anion-exchange resin with comparable yields. Alternatively, the reactor was loaded with palladium nanoparticles, prepared by ion exchange followed by reduction, the cross-coupling being effected in an H_2O–DMF solvent system with KOH as base at 100 °C. The re-utilisation of the palladium catalyst in these experiments remains unclear.

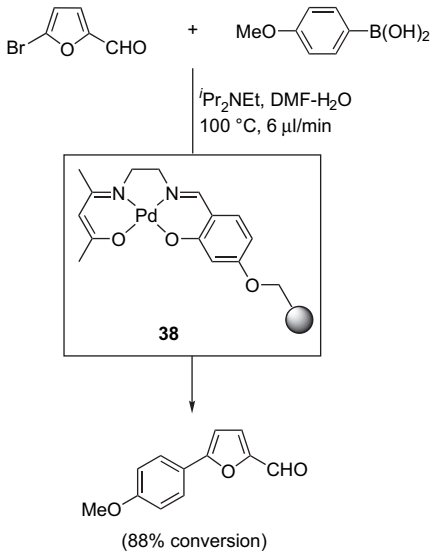
The oxime-based palladacycle **37** immobilised onto polyvinylpyridine resin (Chart 7) was loaded in a microreactor containing a monolithic composite material composed of megaporous glass rods covered with the same polyvinylpyridine matrix.[171] The apparatus was used in a continuous-flow Suzuki reaction of 4-bromoacetophenone and phenylboronic acid under homogeneous conditions (CsF, DMF–H_2O, 100 °C), leading to the coupling product in 84% yield after 24 h. The behaviour of other substrates or the possible re-utilisation of the catalyst was not reported.

A Pyrex glass capillary (0.4 mm internal diameter) microreactor was loaded with palladium nanoparticles (prepared from palladium acetate and PVP), which interacted with Suzuki substrates under an applied potential.[294] The optimum reaction conditions (pH 12, rt, 40 min, 5 kV, 100 μA, 5 cm length capillary) provided much higher yields (78–89%) in the coupling of phenylboronic acid with 4-bromophenol, 4-bromoacetonitrile and chlorobenzene than the conventional method (NaOAc, MeCN–H_2O, 80 °C, 11–23%). The authors believed that the applied potential increased the electron density on the surface of the palladium nanoparticles, enhancing the rate of the reaction and the product yield. Despite many parameters needing to be adjusted, this is one of the few examples in which the electronically neutral chlorobenzene could be coupled in good yield (83%).

Polymer monoliths with high loadings of chloromethyl groups were prepared in granular and cubic forms, and used in the synthesis of biaryls by Suzuki coupling under batch and flow-through conditions.[295] High yields of the pure biaryls were obtained in the coupling of three different boronic acids with resin-bound 4-iodobenzoic acid (73–93%). The highest yield of the biaryl was obtained using the cubic form of the support and 4-methoxyphenylboronic acid. Under identical flow-through conditions (PTFE tube in a parallel synthesiser), the monolith was found to be a much more efficient form of support material than permanently porous beads.

The salen-type palladium(II) complex **38** immobilised onto a Merrifield resin[172] was shown to be catalytically active in the cross-coupling reaction of a wide range of aryl and heteroaryl bromides with phenyl- and 4-methoxyphenylboronic acid in a mini-continuous-flow reactor system (bed size 25×3 mm).[296] The reactions were run for 5 h at a flow rate of 6 μl/min at 100 °C. Electron-deficient substrates were more reactive, although the reaction of 4-bromonitrobenzene failed. It is worthy of note that many functional groups were compatible with the reaction conditions (CHO, COMe, COPh, CO_2Me, CN, NHCOMe, SO_2Me) and that a variety of bromopyridines, bromothiophenes and bromofurans were also coupled in modest-to-high conversions (see example in

Scheme 104). The residence/space time on the reactor was 10.5 min, compared to 24 h in the batch mode. In general, the reaction in the minireactor was more selective than the reaction in the batch mode. It would be more interesting to ascertain about some isolated yields rather than conversions.

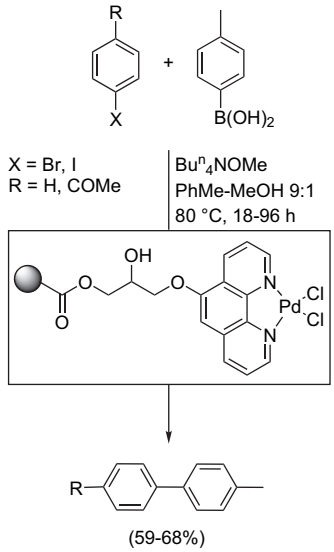


Scheme 104.

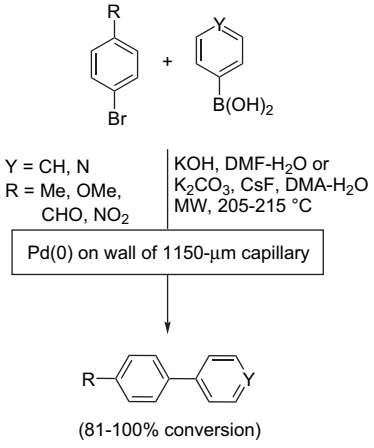
The internal surface of fused silica capillaries (250 μm internal diameter; outer surface coated with polyimide) was modified to covalently anchor the monolith, poly(glycidylmethacrylate-*co*-ethylene dimethacrylate), followed by covalent attachment of a phenanthroline ligand (by ring opening of epoxide groups) and complexation with $PdCl_2(MeCN)_2$.[297] A solution of iodobenzene or *p*-bromoacetophenone, *p*-tolylboronic acid and $^nBu_4NOMe$ as base in toluene–methanol was passed through the capillary heated at 80 °C with a column heater at a flow rate of 0.05 μl/min (Scheme 105). The yield of the products (59–68%) remained consistent over time, even when the process was continued uninterrupted for 4 days. A 15–20% palladium leaching was observed after 4 days, although this seemed to occur at the early stages of the reaction. Similar yields (62–75%) were obtained in the conventional batch process mode with the solid macroporous monolith. Although larger amounts of substrates than normal could be used (50 mmol aryl halide), the GLC yields were only moderate for the long reaction times applied (18–96 h).

Haswell et al. developed in 2004 a microwave-based technique capable of delivering heat locally to a solid palladium-supported catalyst located within a continuous-flow capillary reactor.[132,298] The flow capillary consisted of a U-shaped glass capillary of inner diameter 800 μm, outer diameter 1.2 mm and total length 138 mm. The capillary was mounted within the cavity of a Discover microwave system and connected to an external syringe pump. An infrared sensor was fitted into the microwave cavity to monitor the temperature. This reactor gave the best performance in the coupling of electron-deficient aryl bromides with phenylboronic acid when using a catalytic system composed of $Pd-Al_2O_3$, K_2CO_3, $DMF-H_2O$, 15 s contact time, 50±5 °C, with a gold film situated on the outside of the capillary, in the region of the catalyst zone, for additional microwave absorption (54–74% yield). Surprisingly, aryl iodides gave rather low yields (30–32%). Although heating the capillary reactor by immersion in an isothermal oil bath at 65 °C produced almost no product, the set up of the microwave-based system was rather sophisticated to achieve only low-to-moderate yields.

In this context, Organ et al. prepared thin palladium films on the inner face of capillaries by flowing a solution of $Pd(OAc)_2$ into 1150-μm capillaries, capping the ends and heating at 150 °C for 30 min.[299] Premixed solutions containing the arylboronic acid, aryl bromide, base and solvent were flowed through the metal-coated capillary, while being subjected to microwave irradiation. Both electron-rich and -poor aryl bromides, including hindered substrates, were coupled in moderate-to-excellent conversions at high temperatures, but, apparently, in only a few seconds (see example in Scheme 106). In contrast, the batch reaction scarcely proceeded. A special capillary reactor design was needed including eight inlets,



Scheme 105.



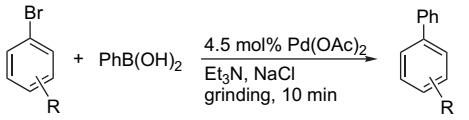
Scheme 106.

a stainless-steel mixing chamber with machined channels, four 10-cm length capillary tubes, a microwave chamber and collection tubes, in order to carry out the microwave-assisted, continuous-flow reactions. Interestingly, no palladium was liberated from the film during prolonged heating, strongly suggesting that the reaction occurred at the metal surface with a high re-utilisation capability.

7.3. Ball-milling conditions

Mechanically induced solid-state reactions are of interest because of the mild conditions under which they operate and also because of the absence of any solvent and easy work-up.[300] Grinding allows mixing of the reagents to occur thoroughly and rapidly, which, together with an induced localised heating of the reaction mixture, can accelerate the reaction. In particular, grinding methods using a ball mill have, however, been scarcely applied in synthetic organic chemistry and in particular to the Suzuki reaction.

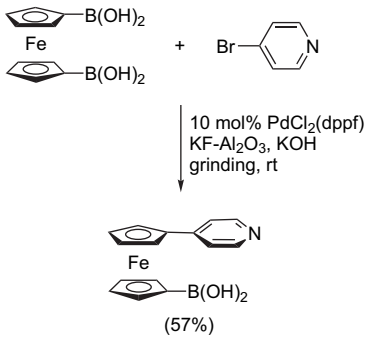
To the best of our knowledge, the first Suzuki reaction using ball-milling conditions was reported in 2000, under solvent-free conditions with $Pd(PPh_3)_4$ as catalyst and NaCl to render the mixture sufficiently powdery.[301] The product was often accompanied by a significant amount of biphenyl, resulting from the homocoupling of phenylboronic acid. Later, Leadbeater and Klingensmith described the coupling of 10 different aryl bromides with phenylboronic acid in the presence of only the catalyst and the base (Scheme 107).[302] NaCl also had to be added to form a damp paste. The reactions were fast and there was no need to use dry reagents or anaerobic conditions, the conditions being compatible with a variety of functional groups.



R = H, 4-Me, 4-CO_2Me, 4-NO_2, 4-OMe, 4-CHO, 3-Me, 3-OMe, 2-OMe

Scheme 107.

Finally, mono- and disubstituted pyridine- and pyrimidine-ferrocenyl complexes were prepared by mechanical treatment of ferrocene-1,1′-diboronic acid with the corresponding heteroaryl bromides under Suzuki conditions.[303] All the reactions were carried out in the air at room temperature using KF–Al_2O_3 as a solid support and KF or KOH as a base with a few drops (1.1–0.2 ml) of methanol. The amount of palladium catalyst used was relatively large (10–20 mol %) to afford low-to-moderate yields of the coupled products (see the best result in Scheme 108), following a very specific experimental procedure that aims to make the mixture as homogeneous as possible. Nonetheless, and in contrast, the solution process required prolonged heating that could only be accelerated by microwave heating.



Scheme 108.

8. Conclusions

The Suzuki reaction has been one of the most studied reactions in organic chemistry since its discovery in 1981, due to its potential in the construction of biaryl moieties. Mostly in the 21st century, new methodologies have been developed in order to make the processes more efficient from the economical, energetic, ecological and chemical point of view. This report has dealt with some recent advances in the Suzuki reaction that utilise non-conventional substrates, catalytic systems, solvents, reaction conditions or work-up, in order to pursue some of the above objectives.

In this sense, a variety of alternative electrophilic coupling partners to the classical aryl halides have been described, which present some disadvantages: aryl fluorides need special activation with electron-withdrawing groups; aryl tellurides and/or their precursors are toxic; aryl alkyl thioethers exhibit good behaviour, especially in the coupling of heteroaromatic compounds, but the presence of a Cu(II) salt is necessary; aryltriazenes react fast at room temperature, but require stoichiometric amounts of BF_3 and arylsulfonyl chlorides are moisture sensitive. In addition, almost all these reagents are not commercially available and have to be prepared by increasing the total number of synthetic steps and the amount of waste.

As regards alternative boron-containing nucleophilic coupling partners, aryltrifluoroborates (which are easily prepared) have emerged as potential substitutes of arylboronic acids, allowing the coupling of aryl chlorides or triflates in the presence of a suitable ligand. On the other hand, the use of sodium tetraarylborates is practically restricted to sodium tetraphenylborate, which is light sensitive and toxic, and lacks atom economy by transferring only one phenyl group.

The use of supported substrates in the Suzuki reaction facilitates the separation of the biaryl products from the reagents and soluble by-products. There are some inherent inconveniences and limitations that can, however, curtail the whole efficiency of the process, e.g., (a) additional synthetic steps are needed to support the substrate and release the product (most of the linkers are not traceless and rather sophisticated linkers are used sometimes) with the consequent drop in the overall yield, (b) a large excess of the boronic acid and/or the base is required (loss of atom efficiency), (c) longer reaction times are applied, (d) the resulting resins are washed with large amounts of solvent with the consequent increase of waste

and (e) the support is not normally recovered. Some common general inconveniences of using supported substrates are discussed in Section 4.2 of Part 1 (our previous report).[1]

In general, the inorganic supported catalysts reported here were demonstrated to be very advantageous from the point of view of catalyst recycling and product purification. Among them, a variety of silicas, sepiolites, alumina, layered double hydroxides and perovskites showed a good performance. Nonetheless, no information was reported in many cases about the catalyst recycling ability.

Some polymeric ligands tested in the Suzuki reaction offer high effectiveness with easy separation of the products and recycling, despite the fact that they have to be synthesised. They can be combined with microwave heating to shorten the reaction times, but their application to aryl chlorides is rather limited. As occurred with the inorganic supports, recycling studies are missing in some reports.

Dendrimeric systems have been scarcely used for the Suzuki reaction, despite the easy separation of the catalyst by precipitation in a suitable solvent being very advantageous from a re-utilisation point of view. The preparation of the catalysts, especially those of higher generations, is, however, not straightforward in most cases, involving sometimes non-commercially available substrates and different synthetic steps with the concomitant generation of waste.

Concerning the solvents, $scCO_2$ and fluorous chemistry have found little application in the Suzuki reaction to make it possible to extract some firm conclusions, except the general trends found for other reactions, i.e., an expensive stainless-steel reactor with sapphire windows is needed to perform reactions in $scCO_2$ media and the CO_2 used must be of a very high purity, and the preparations of perfluorinated ligands in most cases involve long synthetic pathways from relatively expensive starting materials.

In principle, the use of ILs should be clearly advantageous from the point of view of product separation and re-use of the catalytic system. In the Suzuki reaction, however, re-usability is somewhat limited for many of the catalytic systems reported, the salt by-products needing to be removed by washing with water and drying in vacuo in order to return the IL to its original state. Moreover, the ILs are rather expensive solvents and this can curtail their use on a larger scale. The non-flammability of ILs is often highlighted as a safety advantage over volatile organic compounds. Recently, however, it has been demonstrated that a large group of ILs are combustible, due to the nature of their positive heats of formation, oxygen content and decomposition products.[304]

To use water to replace totally or partially an organic solvent is, without any shadow of a doubt, beneficial from the environmental point of view. In the case of the Suzuki reaction, there is an additional beneficial effect affecting the reactivity. In fact, many catalytic systems have been developed that proceed in neat water. These have also been found to be advantageous in the sense that they are simpler, they allow the coupling of water-soluble and -insoluble substrates and they permit some reactions to be performed at room temperature and/or in air. Nonetheless, further research into the Suzuki reaction is needed to improve and combine the use of neat water together with a recoverable and re-usable catalyst.

Microwave has been extensively applied to the Suzuki reaction with the main aim of shortening the reaction times. In fact, good results have been observed even in the synthesis of heterobiaryl compounds and natural products. In some cases, however, the results are comparable, or even better, when performed under conventional heating. Unfortunately, most of the reactions were carried out under homogeneous catalysis with no catalyst recycling. On the other hand, the health hazards of microwave radiation are still under investigation and it is not yet known whether a low-level exposure is detrimental. Another potential hazard is the formation of electric arcs in the microwave cavity so that closed vessels sealed under an inert gas atmosphere to reduce the risk of explosions are generally recommended. There is also a clear need to develop larger-scale, microwave-assisted organic synthesis techniques. In this sense, the continuous-flow microwave-assisted Suzuki reaction seems promising, despite the special apparatus design required.

The little work that has been published on ultrasound applied to the Suzuki reaction makes difficult to balance its advantages and disadvantages. The main general features are that the reactions occur in short reaction times and very mild reaction conditions, with the possibility of using aqueous solvents either under homogeneous or heterogeneous conditions. On the other hand, more attention must be focused on catalyst recycling using this technique.

Microreactor technology has experienced remarkable progress in recent years, with a concomitant increasing interest in its application to the Suzuki reaction. In general, shorter reaction times and better selectivity were observed, compared to batch experiments. A rather sophisticated apparatus, however, has to be utilised in some cases in order to obtain acceptable results.

Grinding of a Suzuki reaction mixture in a ball mill is still an underdeveloped technique that has given interesting and promising results. The reactions proceed in air at room temperature in the absence of solvent and offer an easy work-up. It is worthy of note that better results than those obtained in solution have been achieved.

Besides the above specific conclusions, there are also some general issues that need to be addressed, which are similar to those previously mentioned for the Heck reaction,[1] namely: (a) a wider substrate scope, including the more reluctant-to-react aryl chlorides, is desirable, (b) only highly selective reactions are worthwhile, the formation of by-products (e.g., homocoupling or protodeboronation products) being a procedural and economical problem, (c) whenever possible, commercially available starting materials, reagents, ligands, catalysts or solvents must be used, (d) the catalyst and/or ligands must be recyclable (in the strict sense) and/or display high TONs, in this sense, heterogeneous catalysts with no leaching are preferable, (e) the catalytic system must be as simple as possible (e.g., ligandless, single solvent or solventless, etc.), (f) although many Suzuki reactions proceed under mild conditions, room-temperature reactions or reactions

below 50 °C, are preferable, (g) in general, reproducible, as well as atom-economy, low-cost, scalable and practical procedures are needed to extend the methodologies from the academic laboratory to the industrial plant and (h) expensive and sophisticated equipment or reaction medium must be avoided, above all when little or no improvement is observed with respect to the conventional methodologies.

In short, more research must be directed to improve the eco-efficiency of the products and to optimise the use of resources and minimise waste and environmental impact in the terms described by the mnemonic, PRODUCTIVELY,[305] which captures the spirit of the 12 principles of green chemistry:[306] prevent waste, renewable materials, omit derivatisation steps, degradable chemical products, use safe synthetic methods, catalytic reagents, temperature, pressure ambient, in process monitoring, very few auxiliary substances, *E*-factor, maximise feed in product, low toxicity of chemical products, yes, it is safe.

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Biographical sketch

Miguel Yus was born in Zaragoza (Spain) in 1947, and received his B.Sc. (1969), M.Sc. (1971) and Ph.D. (1973) degrees from the University of Zaragoza. After spending 2 years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr he returned to Spain to the University of Oviedo, where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he moved to a chair in Organic Chemistry at the University of Alicante, where he is currently the head of the Organic Synthesis Institute (ISO). Professor Yus has been a visiting professor at different institutions and universities, such as ETH-Zentrum, Oxford, Harvard, Uppsala, Tucson, Okayama, Paris, Strasbourg and Kyoto. He is co-author of more than 400 papers, mainly in the field of the development of new methodologies involving organometallic intermediates, and three patents. Professor Yus is member, among others, of the Advisory Board of the journals Tetrahedron, Tetrahedron Letters, Chemistry Letters, European Journal of Organic Chemistry, Trends in Organic Chemistry and Current Chemical Biology, being also Regional Editor of Letters in Organic Chemistry. He has given more than 100 lectures, most of them abroad, and has supervised 43 Ph.D. students. Among others, he has received twice the Japan Society for the Promotion of Science Prize (Okayama, 1999; Kyoto, 2007), the French-Spanish Prize of the Societé Française de Chimie (Paris, 1999), the C.A. Stiefvater Memorial Lecture Award (Nebraska, 2001), the Nagase Science and Technology Foundation fellowship (Kyoto, 2003), the Cellchem Lectureship (Sheffield, 2005), the Singenta Lectureship (Basel, 2007) and the Fundeun-Iberdrola Prize (Alicante, 2007). His current research interest is focused on the preparation of very reactive functionalized organometallic compounds and their use in synthetic organic chemistry, arene-catalyzed activation of different metals, preparation of new metal-based catalysts, including metallic nanoparticles, for homogeneous and heterogeneous selective reactions, and asymmetric catalysis. A few years ago, he and other members of the ISO founded the chemical company MEDALCHEMY, S.L. to market fine chemicals.

Irina Beletskaya received her Diploma degree in 1955, her Ph.D. degree in 1958, and her Doctor of Chemistry degree in 1963 from Moscow State University. She became a Full Professor in 1970 and in 1974 a Corresponding Member of the Academy of Sciences (USSR), of which she became a full member (Academician) in 1992. She is a Professor at Moscow State University since 1971 to present and Head of the Laboratory of Organometallic Chemistry at this University since 1989. Irina Beletskaya is a Chief Editor of the Russian Journal of Organic Chemistry. She was a President of the Organic Chemistry Division of IUPAC from 1989 to 1991. She was a recipient of many awards and distinctions, including: the Lomonosov Prize (1979), the Mendeleev Prize (1982), the Order of Red Banner (1984), Doctor Honoris Causa of the University of Cordova (Argentine, 1987), the Nesmeyanov Prize (1991), Honorary Member Academy of Science Bashkortostane (1994), Doctor Honoris Causa of the Technical University (Saint Petersburg, 1997), 'Women in the Engineering Science' Award in TFR's Program (1998), Honored Professor of Moscow State University (1999), Mendeleev Reader (2001), Prize for the best publication in Russian Journal of Organic Chemistry (2002), the Demidov Prize for Research (2003), the State Prize (2004), Tarrant foundation Prize (2004), Honored Doctor of KTH (Sweden, 2006) and International Arbusovs Prize (2007). She is the author of more than 1000 articles (200 in international journals), 4 monographs and 30 reviews. She is active in the research at the boundary of organoelement compounds in organic synthesis and catalysis. Her current scientific interests are mainly focused on transition metal catalysis in organic synthesis.

Francisco Alonso was born in Villena (Alicante, Spain) in 1963. He received his B.Sc. (1986), M.Sc. (1988) and Ph.D. (1991) degrees in Chemistry from the University of Alicante. After a postdoctoral stay (1992–1994) as a Fleming fellow at the University of Oxford (UK), with Professor S. G. Davies, he moved back to the University of Alicante where he joined the research group of Professor M. Yus. He became Associate Professor in 1998, and his research interest is focused on the development of new synthetic methodologies involving active transition metals (especially metal nanoparticles) and the application of organometallic intermediates to the synthesis of naturally occurring molecular structures. He was awarded the Ph.D. Extraordinary Prize in 1992.