Fast, easy, clean chemistry by using water as a solvent and microwave heating: the Suzuki coupling as an illustration

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Water is an excellent solvent for organic chemistry and microwave heating offers a very efficient way of heating reaction mixtures. In this article, by focusing on the Suzuki reaction, it is shown how these two methods, used alone or together, can impact modern synthetic chemistry, making reactions faster, easier and cleaner.

Introduction

Increasingly, chemists are looking for cleaner, more environmentally benign ways to make target molecules.[1] Two areas of current interest are the use of water as a solvent for organic synthesis and the application of microwave heating for efficient heating of reaction mixtures. It is the aim of this *feature article* to show the advantages of using these two techniques together. To illustrate this, I have focused on the Suzuki coupling, a reaction that attracts widespread interest within the synthetic chemistry community due to the many uses for the products and also because of the range of possible catalysts and reaction conditions that can be used. I look first at the use of water as a solvent for the reaction, then at the use of microwave heating followed by applications of the two together, reviewing the literature and discussing experiments we have undertaken in our laboratories.

Microwave-heating as a tool for synthetic chemistry

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories. Although people had been using microwaves in their homes for many years, it was not until 1986 that the first reports of microwave-heating in organic synthesis appeared in the literature.[2,3] The work was performed using a domestic microwave. Since these first papers, much has changed in terms of the apparatus available

for microwave-promoted synthesis and the technique has found a valuable place in the synthetic chemist's toolbox. This is evidenced by the large number of papers and reviews appearing in the literature in the last few years.[4–7] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Also, as the field matures, people are finding that they can perform chemistry using microwave heating that can not be achieved using 'conventional' heating methods, thus opening up new avenues for synthesis. These discoveries have also sparked a debate into the nature of microwave heating.[8]

Microwave-promoted chemistry is founded on the fact that materials, be they solvents or reagents, can absorb microwave energy and convert it to heat.[9] A good estimator for how well a particular material will absorb microwaves and convert the energy to heat is its dielectric loss factor, tan δ. Microwave synthesis is frequently performed using solvents and the tan δ values for a representative range of commonly used solvents are shown in Table 1. Polar solvents are often used for rapid, efficient heating by microwave irradiation although, since either the substrates or some of the reagents or catalysts are often polar, this is often not essential.

Much of the work in the field has been conducted using domestic microwave ovens. There are, however, problems associated with using a domestic system. It is hard to control reactions and this can be particularly hazardous when using flammable solvents and reagents. Also, accurate temperature and microwave power measurement is very difficult; this, at least in part, being the reason behind the poor reproducibility of reaction conditions published using domestic microwave apparatus. This has had the effect of giving microwave chemistry a bad name and it has been, by many, considered as a black art. With the advent of scientific microwave systems,

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Table 1 Dielectric loss factor (tan δ) values for a range of solvents[a]

Solvent	Tan δ	Solvent	Tan δ
Ethanol	0.941	Water	0.123
DMSO	0.825	Acetonitrile	0.062
1,2-Dichlorobenzene	0.280	THF	0.047
NMP	0.275	Toluene	0.040
DMF	0.161	Hexane	0.020

[a] Data taken from reference 6c.

these problems can be overcome.[10–13] It is possible to control the temperature, microwave power and reaction time very easily and perform reactions reproducibly. Temperature can be measured either using an IR probe located outside the reaction vessel or a fibre-optic probe inserted into the reaction vessel. Pressure is measured using a load cell. By using software available with the machines it is possible to heat a reaction mixture to a desired bulk temperature and hold it there for a predetermined period of time. Temperature, pressure and power profiles can be recorded for each reaction. Depending on the apparatus used, reactions can be run either in sealed vessels of varying volumes or in open vessels under atmospheric pressure.

There are two types of microwave reactor design; namely multimode and monomode (also known as single-mode). The multimode instruments are conceptually similar to a domestic oven. The microwaves enter the cavity and are reflected by the walls and the reaction vessel within a large cavity. In most instruments a mode stirrer ensures that the field distribution is as homogeneous as possible. The microwave power is variable with a maximum of around 1600 W. In the much smaller monomode cavities, the microwaves are directed through an accurately designed wave guide onto the reaction vessel mounted at a fixed distance from the magnetron, thus creating a standing wave. The power delivered from the magnetron is variable from 0–300 W. This is lower than in the multimode machines but, when using a monomode reactor, the microwaves are directed on the sample, leading to very efficient and rapid heating. A key point to be stressed in connection with all scientific microwave apparatus is that it is designed with safety in mind and it is possible to heat reaction mixtures to high temperatures and moderate pressures, although of course caution and common sense are required.

Water as a solvent for microwave-promoted synthesis

The concept of efficient and selective synthesis in water has been exemplified as the rates, yields and selectivities observed for many reactions in water have begun to match, or in many cases, surpass those in organic solvents.[14,15] In contrast to many other solvents, water not only provides a medium for solution chemistry but often participates in elementary chemical events on a molecular scale. Water also offers practical advantages over organic solvents. It is cheap, readily available, non-toxic and non-flammable. In addition to using water for chemistry at ambient pressure in open vessels there has been a growth of interest in the use of high-temperature water,[16] superheated water[17] and supercritical water.[18] High-temperature water is broadly defined as liquid water above 200 °C, superheated water as water between 200–300 °C and supercritical water as that above 374 °C and 218 atm. At these temperatures the water approaches properties more like those of polar organic solvents at room temperature, and can act as an acidic or basic catalyst. The use of water as a solvent for metal-mediated synthesis has attracted considerable research interest since it can be used to implement approaches combining the advantages of homogeneous and heterogeneous catalysis by distributing the reagents, products and catalysts between different phases, *pseudo*-phases or interface regions.[19]
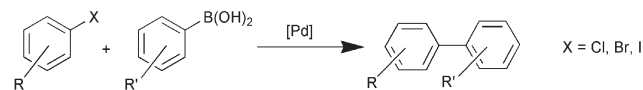
Three distinct types of approach can be taken based on phase transfer, phase separation or solubilization although most processes involve a combination of two or all three of these.

Due to its properties, water is an excellent solvent for microwave-promoted synthesis. Although it has a dielectric loss factor which puts it into the category of only a medium absorber, even in the absence of any additives it heats up rapidly upon microwave irradiation. Using a sealed vessel it is possible to heat water to well above its boiling point. At these elevated temperatures organic substrates become increasingly soluble and, even if they are not, addition of a phase-transfer agent can be used to facilitate solvation. Of course water can not be used as a replacement for organic solvents for every class of reaction and, at the high temperatures used in microwave reactions, competitive decomposition of starting materials or products can become an issue.
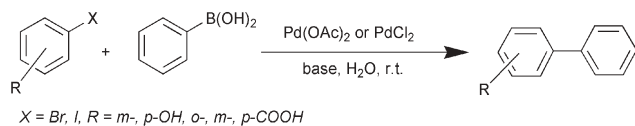
The Suzuki reaction using water as a solvent

The Suzuki reaction (palladium-catalysed cross-coupling of aryl halides with boronic acids) is one of the most versatile and utilised reactions for the selective construction of carbon–carbon bonds, in particular for the formation of biaryls (Scheme 1).[20] As the biaryl motif is found in a range of pharmaceuticals, herbicides and natural products, as well as in conducting polymers and liquid crystalline materials, development of improved conditions for the Suzuki reaction has received much recent attention. Indeed, in the last 10 years, there have been over 700 publications on the area of aryl–aryl bond formation.

A wide range of metal complexes have been used as catalysts in these coupling reactions, attention particularly being focused on palladium. Complexes bearing bulky phosphines,[21] N-heterocyclic carbenes[22,23] or palladacyclic complexes[24,25] have been found to be particularly active, and allow for the use of aryl chlorides as substrates rather than, with the majority of previous catalyst candidates, aryl bromides and iodides. Unlike other cross-coupling reactions involving transmetallation, the Suzuki reaction requires the use of a base. This forms a more electron-rich intermediate with the boronic acid which is more reactive than the original boronic acid towards attack of Pd(II) complexes. Generally, mineral bases such as alkali metal carbonates or K_3PO_4 are used as bases. The use of water either as a solvent or additive helps with the solvation of these organic-insoluble materials. Also, as organoboron compounds are often quite stable to protolytic decomposition by water, there is significant potential for development of methodologies using water or aqueous media as solvents. When using neat water as a solvent, it is possible to perform the reaction using simple palladium salts such as $PdCl_2$ or $Pd(OAc)_2$ in air. Beletskaya and co-workers showed that the reaction of arylboronic acids with water-soluble aryl halides can be performed at room temperature in the presence of the palladium
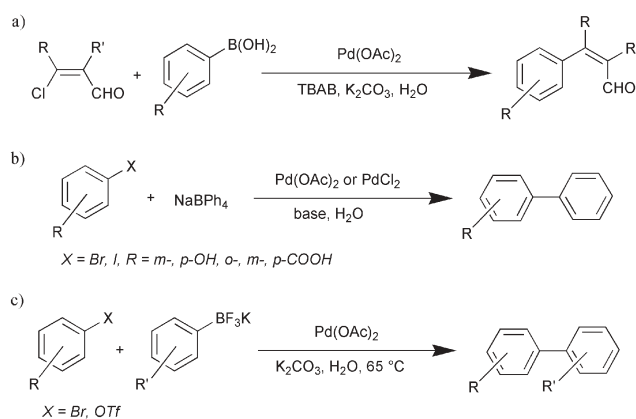

Scheme 1

Scheme 2

$X + B(OH)_2 \xrightarrow{\text{Pd(OAc)}_2 \text{ or PdCl}_2,\ \text{base, H}_2\text{O, r.t.}}$ biaryl

$X = Br, I, R = m\text{-}, p\text{-OH}, o\text{-}, m\text{-}, p\text{-COOH}$

Scheme 3

a)

β-chloroacrolein + $B(OH)_2 \xrightarrow{\text{Pd(OAc)}_2,\ \text{TBAB, K}_2\text{CO}_3, \text{H}_2\text{O}}$ product with CHO

b)

$ArX + NaBPh_4 \xrightarrow{\text{Pd(OAc)}_2 \text{ or PdCl}_2,\ \text{base, H}_2\text{O}}$ biaryl

$X = Br, I, R = m\text{-}, p\text{-OH}, o\text{-}, m\text{-}, p\text{-COOH}$

c)

$ArX + Ar'BF_3K \xrightarrow{\text{Pd(OAc)}_2,\ \text{K}_2\text{CO}_3, \text{H}_2\text{O, 65 °C}}$ biaryl

$X = Br, OTf$

salt and an inorganic base (Scheme 2).[26,27] This procedure can be modified to improve the substrate scope by using aqueous ethanol as the solvent.[28] This has led to the synthesis of a range of unsymmetrical biaryls. The reaction must be run in the absence of oxygen. The reaction of iodobenzene with phenyl-boronic acid has been performed in neat water by heating the mixture at reflux overnight using 10 mol% Pd(OAc)$_2$.[29] By running the reaction in neat ethanol it is possible to couple aryl bromides at room temperature in air using PdCl$_2$ or Pd(OAc)$_2$ at much lower catalyst loadings.[30]

Badone and co-workers have investigated the effects of solvent, including water, on the rate of the palladium acetate catalysed Suzuki reaction of a range of aryl bromides, iodides and triflates.[31] They reported that, when using water as a solvent, the addition of one equivalent of tetrabutylammonium bromide (TBAB) to the reaction mixture greatly accelerates the reaction. They find that activated aryl bromides can be coupled with phenylboronic acid to yield biaryls fairly rapidly (1 h) and in good yields, whereas with aryl iodides the reaction does not reach completion. The role of the ammonium salt is thought to be twofold. Firstly, it facilitates solvation of the organic substrates in the solvent medium. Secondly it enhances the rate of the coupling reaction by activating the boronic acid towards reaction by formation of a boronate complex $[ArB(OH)_3]^-[R_4N]^+$.

By using a high TBAB–water ratio in conjunction with palladium acetate as a catalyst, Bedford and co-workers have found that it is possible to couple three aryl chlorides with phenyl boronic acid.[32] Similar methodologies have been used by Zou and co-workers[33] and Arcadi and co-workers[34] but using alkylammonium tetrafluoroborates and cetyltrimethyl-ammonium bromide (CTAB) respectively in place of TBAB. With the alkylammonium salts, the Suzuki reaction between iodobenzene or bromobenzene and p-tolylboronic acid has been performed in water but the substrate scope not explored any further than this. When using CTAB, some aryl chloride substrates can be used in the coupling protocol. It is possible to couple β-chloroacroleins with boronic acids in water using Pd(OAc)$_2$ as the catalyst and TBAB as the additive (Scheme 3a).[35] Suzuki-couplings in water using simple palladium salts have been extended to include borates as substrates (Scheme 3b,c). Sodium tetraphenylborate has been coupled with aryl halides[36,37] and potassium aryltrifluorobo-rates have been coupled with aryl- or heteroaryl halides or triflates.[38] In the case of the latter, catalyst loadings in the region of 0.2–0.5 mol% can be used.

With all the couplings mediated by palladium salts there is the question of how the palladium, introduced as Pd(II), is reduced to Pd(0) where it enters the catalytic cycle. Palladium salts such as PdCl$_2$ or Pd(OAc)$_2$ are known to be quite strong oxidants but their oxidative properties are dependent on the solvent used. In water, the polymeric structure of these
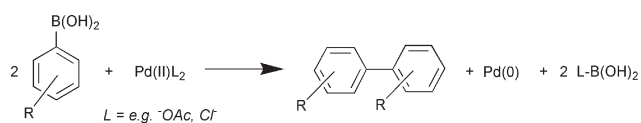
complexes is somewhat broken down as a result of solvation and the Pd(II) complexes are of significantly high oxidative power that they can attack electron-rich species in solution. In light of this, and other experimental observations, it has been suggested that in the Suzuki reaction, the boronic acid is oxidised by the Pd(II) salt leading to formation of the desired Pd(0) complex and the generation of a biaryl formed by concomitant homocoupling of the boronic acid (Scheme 4).[39,40]
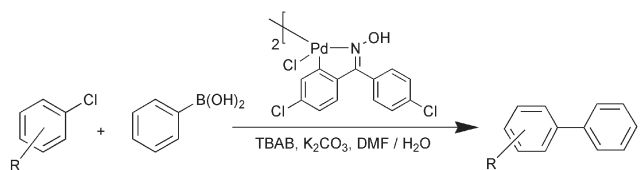
In addition to Suzuki couplings performed in neat water as the solvent, there have been a number of reports of the use of water as a co-solvent for the reaction, again focused in the main on the use of aryl iodides and activated bromides. Nájera and co-workers have used an oxime-derived palladacyclic com-plex as a catalyst for couplings of aryl chlorides in DMF–water mixtures with the use of TBAB as an additive (Scheme 5).[41]

By performing the coupling in aqueous acetone it is possible to couple aryl iodides with boronic acids using palladium acetate alone.[42] Also, benzyl halides can be used as substrates in the reaction with boronic acids, catalysed by PdCl$_2$, using a 1:3 water–acetone mix as solvent (Scheme 6a).[43] Acyl chlorides can be coupled with tetra-arylborates in aqueous acetone using Pd(OAc)$_2$ or PdCl$_2$ to give unsymmetric biaryl ketones (Scheme 6b).[44,45]
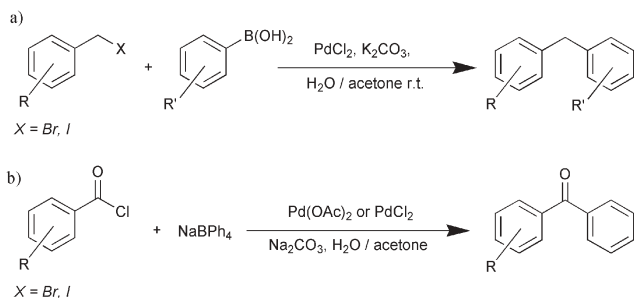
Di-(2-pyridyl)methylamine-based palladium complexes have been shown to be versatile catalysts for different types of cross-coupling reactions in water or aqueous solvents (Fig. 1).[46,47] The Suzuki reaction of arylboronic acids can be performed

Scheme 4

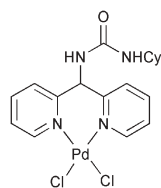$2\ ArB(OH)_2 + Pd(II)L_2 \longrightarrow$ biaryl $+ Pd(0) + 2\ L\text{-B(OH)}_2$

$L = e.g.\ {}^-OAc, Cl^-$

Scheme 5

$ArCl + B(OH)_2 \xrightarrow{\text{TBAB, K}_2\text{CO}_3, \text{DMF / H}_2\text{O}}$ biaryl (oxime palladacycle catalyst)

a)

b)

Scheme 6

Fig. 1

with bromoarenes in water at reflux using K_2CO_3 as base or at between room temperature and 60 °C in aqueous methanol using KOH as base. For aryl chlorides the couplings with arylboronic acids can be carried out in water at reflux with K_2CO_3 as base and TBAB as an additive. Arylboronic acids also react with benzylic chlorides and allylic substrates such as chlorides, acetates or carbonates in water at reflux or at room temperature in aqueous acetone, to give diarylmethanes and arylpropenes. Trimethylboroxine and alkylboronic acids can be coupled with bromo- and chloroarenes in water at reflux with TBAB as an additive to yield methyl- and butylarenes.

TBAB has also been used in conjunction with a palladium oxime catalyst for the coupling of aryl chlorides with phenylboronic acid in water (Scheme 7a).[48,49] Supported oxime carbapalladacyclic complexes have subsequently been prepared and used as catalysts for the reaction in water.[50,51] Aryl bromides and activated aryl chlorides have been coupled with phenylboronic acid using a cyclopalladated palladium complex as a catalyst (Scheme 7b).[52] The complex, prepared from an imine precursor, was used with and without the use of TBAB
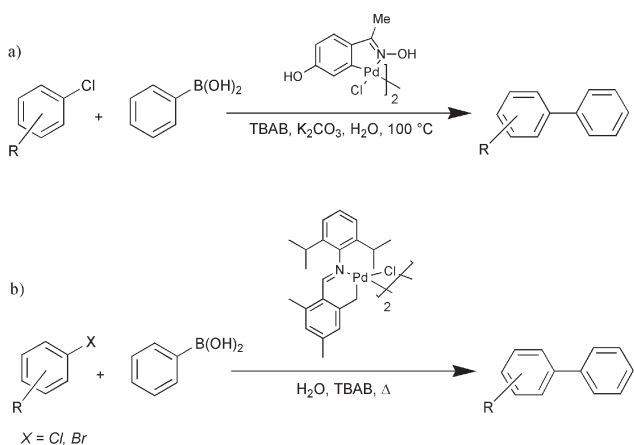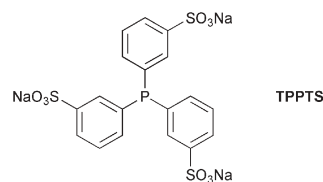

Scheme 7

Fig. 2

as an additive. Reactions were run for between 1 and 20 h depending on the substrate used; aryl chlorides requiring longer times, higher catalyst loadings and giving significantly lower yields than bromo- analogues.

Water soluble phosphines have been used as ligands for Suzuki couplings in aqueous media.[53] This is interesting in the light of a number of reports that have shown that the addition of phosphine ligands often leads to a substantial drop in catalytic activity in Suzuki coupling reactions in water[54] and can even result in significant by-product formation.[55] One of the best known phosphines for use in aqueous-phase catalysis is *m*-trisulfonated triphenylphosphine (TPPTS) as shown in Fig. 2. This has been used in conjunction with palladium acetate.[56,57] Interestingly, organic bases were found to be superior to the more frequently observed mineral bases, diisopropylamine being particularly effective. Water soluble calixarenes have been used as inverse phase-transfer agents, using a catalyst derived from $PdCl_2$ and TPPTS.[58] Reaction rates were significantly higher than in the absence of the additive. In related work, a range of cyclodextrins and calixarenes possessing extended hydrophobic host cavities have been used in conjunction with a palladium catalyst prepared from TPPMS, the mono-sulfonated analogue of TPPTS.[59] Again reaction rates were significantly higher than in the absence of the additive. The coupling of 4-iodoanisole with phenylboronic acid in water has been studied using immobilised detergents as additives. The reaction was performed using a palladium complex containing the potassium salt of TPPMS as a ligand and the detergents immobilised on a range of mesoporous silicas and aluminas.[60,61] A range of surfactants, including CTAB, have been used in conjunction with $Pd(PPh_3)_4$ as a catalyst for the reaction.[34]

Shaughnessy and Booth prepared two sterically demanding, water-soluble alkylphosphines based on P^tBu_3 and used them in Suzuki couplings of aryl bromides in water or water–acetonitrile and water–toluene mixtures at room temperature (Fig. 3).[62,63] They have also prepared sterically demanding, water-soluble analogues of TPPTS such as TXPTS and find that this ligand in particular, when combined with palladium acetate, forms a highly active catalyst for use in
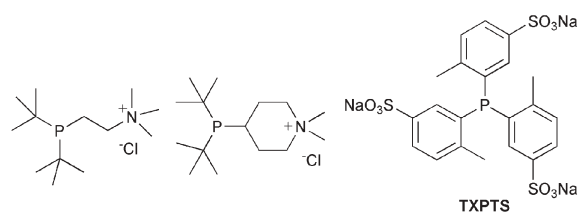

Fig. 3

Fig. 5

water–acetonitrile mixtures at between 50 and 80 °C.[64] The group have screened their alkyl and aryl phosphines, as well as TPPTS, in the aqueous-phase modification of unprotected halonucleosides. They find that TPPTS is superior to the alkylphosphines but that the palladium complex formed with TXPTS is particularly active.[65]

A number of carbohydrate-based phosphines have been used, in conjunction with palladium acetate, as catalysts. Those ligands derived from halo- and amino-sugars forming glycoside[66,67] and glycosamine[68,69] based phosphines have received most attention (Fig. 4). They show higher activities than TPPMS and TPPTS based analogues.

Self-assembly of amphiphilic rod-coil molecules in water has been used as a tool for Suzuki couplings catalysed by a complex formed from palladium acetate and triphenylphosphine.[70] The amphiphilic molecules, comprising hexaphenylene rod segments linked to poly(ethylene oxide) coil units self-assemble into micellar aggregates. The organic substrates for the Suzuki coupling can be entrapped in the rod-bundle that provides a nano-environment suitable for the confinement of aromatic substrates through hydrophobic and π–π interactions. Within this environment, the substrates may be forced into close proximity with one another thus giving a highly concentrated reaction site that lowers the energy barrier for the coupling reaction. The triphenylphosphine ligated palladium could also be held close to or within this environment. The coupling of aryl iodides and bromides can be effected in high yield at room temperature using this methodology. Aryl chlorides have also been screened. When using 4-chloronitrobenzene, a 74% yield of the desired biaryl is obtained after 12 h at room temperature with phenylboronic acid as the coupling partner. The yield drops to 17% when using 4-chloroanisole under the same conditions.

Cammidge and co-workers have prepared heterogeneous palladium phosphine catalysts and used these in Suzuki couplings in a 3:1 DME–water solvent mixture.[71] They prepared their supported catalysts by first ligating the palladium to a phosphine and a styrene functionalised monomer to give a *cis*-disubstituted square-planar complex. This was then polymerised with styrene, divinylbenzene and cyclohexanol (as a porogen). This methodology was chosen so that the preferred ligand geometry around the metal could be obtained in the final product. Yields of around 80% were obtained in the coupling of 4-bromoanisole with phenylboronic acid, as compared to around 50% when using a heterogeneous catalyst they prepared from polymer-supported triphenylphosphine, where the coordination environment around the metal would be more dictated by the polymer than the metal. Similar improved yields were obtained in couplings with 2-bromoanisole and 4-bromonitrobenzene.
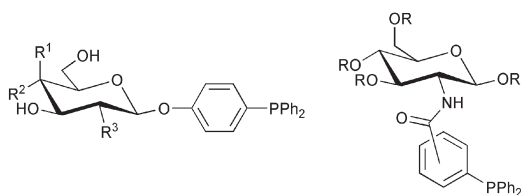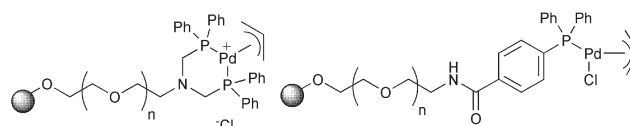
Amphiphilic polymer-supported phosphine-ligated palladium catalysts have also been prepared and used in the reaction using water as solvent (Fig. 5).[72] Using these catalysts, a 96-member library of biaryls was prepared. As well as boronic acids, sodium tetraphenylborate has been used as a substrate.

Ikegami and co-workers have used an assembled complex of palladium and a non cross-linked amphiphilic polymer as a catalyst (Scheme 8).[73,74] The material, denoted as PdAS, was prepared by reaction of $(NH_4)_2PdCl_4$ with poly[(*N*-isopropylacrylamide)-*co*-(4-diphenylstyrylphosphine)], itself made by random copolymerisation of 4-diphenylstyrylphosphine and *N*-isopropylacrylamide in the presence of AIBN. The catalyst can be used in very low loadings and with very high turnover numbers. For example, the coupling of iodobenzene with phenylboronic acid at 100 °C in neat water, using sodium carbonate as a base, can be achieved using a catalyst loading of 0.00008 mol% of PdAS. The reaction did however take 96 h to reach completion and required an excess of the boronic acid. If the catalyst loading is increased to 0.005 mol% it is possible to perform the same reaction in 24 h using the same conditions. It is also possible to reduce the excess of boronic acid required. The coupling works well for a range of aryl bromides using these conditions.

A polymer-assisted solution-phase methodology for the coupling in DMF–water mixtures has been reported for the easy isolation of the biaryl products (Scheme 9). It involves the use of an anthracene-tagged phosphine ligand attached to



PdAS

Scheme 8

Fig. 4
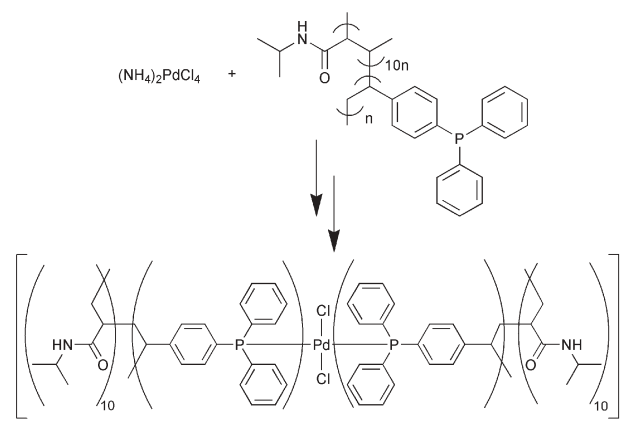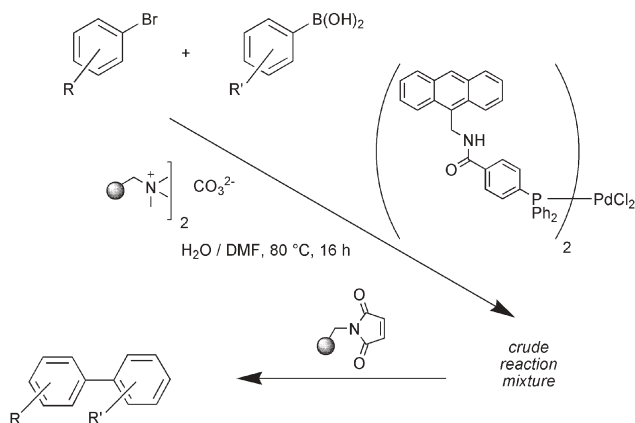
Scheme 9

the palladium catalyst. Thus, any dissociated phosphine and phosphine oxide is then sequestered from solution using a chemoselective Diels–Alder reaction with a maleimide resin. A supported carbonate base is used both in the Suzuki coupling and then at the end of the reaction to facilitate the removal of excess boronic acid and the boron containing by-products.

There has been significant interest in the use of palladium supported on inorganic materials as well as nanopalladium complexes as catalysts for the Suzuki coupling and other C–C bond forming reactions.[75,76] Some of this work has been applied to aqueous-phase chemistry.

A palladium(II) complex immobilised on sepiolite has been used for the coupling of 4-bromophenol and phenylboronic acid or sodium tetraphenylborate in neat water using sodium carbonate as a base.[77,78] The reaction did not work in organic solvents. Sepiolite is a natural clay mineral and the $Pd(NH_3)_4Cl_2$ was immobilised by an ion-exchange reaction. Incorporation of palladium into the cages of a zeolite (NaY) followed by reduction gives a Pd(0)–NaY material that is an active catalyst for the coupling of aryl bromides with phenylboronic acid or p-tolylboronic acid.[79] Water is essential but can not be used as the sole solvent. Instead, mixtures of organic solvents and water are used, DMF and dimethyl-acetamide (DMA) being the best. The palladium-containing perovskite $LaFe_{0.57}Co_{0.38}Pd_{0.05}O_3$ has been used as a catalyst for couplings involving aryl bromides and in particular cases iodides.[80] The reaction worked well in aqueous alcohols as solvents but was unsuccessful in non-aqueous solvent mix-tures. The addition of TBAB proved to be useful in difficult couplings such as that between 3,4,5-trimethoxyphenylboronic acid and 4-bromoanisole (Scheme 10).

The use of nanoparticulate palladium in the Suzuki coupling has been studied in both aqueous and non-aqueous[81] solvents.
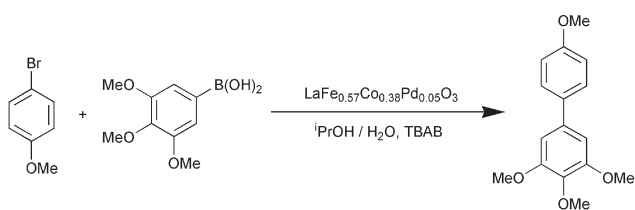
Scheme 10

Attention here will be focused on the former. Palladium nanoparticles stabilised by poly(N-vinyl-2-pyrrolidone) (PVP) in a colloidal aqueous solution have been shown to be active catalysts for couplings of aryl iodides.[82] The reactions are run in either 40% ethanol or in acetonitrile–water mixtures using sodium phosphate or sodium acetate as base. The nano-particles were prepared from H_2PdCl_4 and had a mean diameter of 3.6 nm, and 0.3 mol% of the colloidal solution was used in the coupling reactions. By using fluorescence spectroscopy, the authors found that the initial rate of the coupling reactions depends linearly on the concentration of the palladium catalyst. This, they suggest, points towards the fact that catalysis occurs on the surface of the palladium nanoparticles. Of note is that palladium metal precipitated over time during the reactions and, as a result, the catalytic activity of the colloidal solution decreased. The effects on catalytic activity of varying the size of the PVP stabilised nanoparticles have been studied.[83] Four different particle sizes have been used; 3.0, 3.9, 5.2 and 6.6 nm. The catalytic activity in the coupling of iodobenzene and phenylboronic acid in a 3:1 acetonitrile–water mixture was found to be in the order Pd (3.9 nm) > Pd (3.0 nm) ≈ Pd (5.2 nm) > Pd (6.6 nm). The authors suggest that the general trend of increased reactivity with the decrease in particle size indicates that the low-coordination number vertex and edge atoms on the nano-particle surface are the active sites for catalysis. The lower activity for the smallest nanoparticles is attributed to poison-ing of the surface by strong adsorption of substrate molecules, retarding the reaction rate. The same researchers have subsequently investigated the effect of different stabilisers on the catalytic activity and stability of palladium colloidal nanoparticles in the Suzuki coupling in aqueous solution.[84] They focused on three stabilisers, namely PVP, hydroxyl-terminated poly(amido-amine) (PAMAM) dendrimers and polystyrene-b-poly(sodium acrylate). All three give palladium colloidal solutions that are catalytically active in the coupling protocol with aryl iodides but palladium black precipitation is a problem in many of the cases studied. The reaction with aryl bromides is very slow and significant homocoupling of the boronic acid is observed. Of all the nanoparticles prepared, those with the PAMAM stabilisers were amongst the most robust but were the least catalytically active because the palladium particles are effectively encapsulated, thus limiting the access of reaction substrates. A further report of the use of PAMAM-stabilised nanoparticles has been published by another group.[85] These materials are active for the coupling of aryl iodides and, at elevated temperatures, bromides using aqueous ethanol or DMF as solvent. Around 0.055 mol% Pd is found to be sufficient for these reactions. The authors contradict themselves over whether or not deactivation due to palladium black is a problem. However, it is clear from the bulk of the nanoparticle literature that the formation of palladium black during the course of Suzuki reactions using stabilised nanoparticles is an issue. The stability of PVP-stabilised nanoparticles in the coupling of iodobenzene and phenylboronic acid has been investigated using transmission electron microscopy and the effects on catalytic activity studied using HPLC.[86] It was found that the process of refluxing the nanoparticles for 12 h increases the average size

and width distribution. Interestingly, if the nanoparticles are re-used, the average size decreases again. The effect of the components of the reaction have also been studied individually. The presence of biphenyl in the reaction mixture results in poisoning of the active sites and hence a decrease in catalytic activity and product yield. The boronic acid inhibits the nanoparticle growth process because it binds to the surface through the oxygen of the deprotonated B-OH functionality. The iodobenzene does not inhibit the particle growth and thus must not bind strongly to the surface. Similar studies have been performed on the PAMAM-stabilised nanoparticles.[87] Again the size increases on the first use but this time it does again on the second use. The yield of biaryl obtained on the second use is greater with the PAMAM-stabilised materials than the PVP-stabilised nanoparticles. This could be because the PAMAM-stabilised particles are larger or because a smaller proportion of palladium has precipitated out of solution during the first run. The effect of the individual components of the reaction mixture on the stability of the PAMAM-stabilised particles was found to be similar to that for the PVP-stabilised nanopalladium particles.

Cyclodextrin-capped palladium nanoparticles (CD-Pd) have been prepared and screened for catalytic activity in the Suzuki coupling using 1:1 water–acetonitrile as solvent.[88] Iodoarenes react faster than the corresponding bromides and also palladium precipitation is a problem when using aryl bromide substrates. A difference between the palladium nanoparticles prepared here as compared to those prepared using a PVP stabiliser is that, in CD-Pd, the cyclodextrin molecules are covalently attached to the palladium particles thus rendering approximately 50% of the surface inaccessible by substrates. This, not surprisingly, impacts on the turnover frequency observed when using CD-Pd. Another problem is the solubility mismatch between the hydrophilic CD-Pd particles and the hydrophobic reaction substrates. If water-rich solvent mixtures are used then substrate solubility becomes a real issue but the formation constants of cyclodextrin inclusion complexes are adversely effected by the presence of non-aqueous solvents.

Microgel-stabilised palladium nanoclusters have been prepared and screened in the coupling reaction of aryl bromides and chlorides with phenylboronic acid.[89] The microgels were prepared from (N,N-dimethylamino)ethyl methacrylate (DMAM) or 4-vinyl pyridine (VP), as the functional, metal-binding co-monomer, ethylene dimethylacrylate as the cross-linker and methyl methacrylate as the non-functional co-monomer. They were loaded with palladium by reaction with Pd(OAc)$_2$. Reduction of the resultant solution gave the microgel-stabilised nanoclusters. Both the non-reduced Pd(II) material and the reduced Pd(0) nanoclusters were screened for activity in the Suzuki coupling. The Pd(0) materials are more active than their corresponding Pd(II) precursors, presumably because the latter need to be reduced *in situ* before they can enter the catalytic cycle. The nanoclusters generated from VP-functionalised microgels are less active than those from DMAM due to nanocluster aggregation. Aryl chloride substrates are not activated, except slightly with the unreduced material prepared from the VP-functionalised microgel.

Palladium nanoparticles derived from a palladium substituted Keggin-type polyoxometallate, have been used for a range of C–C and C–N bond-forming reactions of bromoarenes using water–ethanol mixtures as solvent.[90] The catalytically active material was prepared by treatment of K$_5$[PPdW$_{11}$O$_{39}$] with hydrogen. The stabilisation of the nanoparticles is thought to be due to the high anionic charge of the polyoxymetallate support material. The material works well in the Suzuki couplings of a range of aryl bromides with phenylboronic acid. Interestingly, aryl chlorides react very slowly in the aqueous medium but, if the catalyst is modified by reaction with KF and impregnated on alumina, they couple with phenylboronic acid successfully in the absence of solvent.

A capillary microreactor has been developed and used for Suzuki couplings mediated by nanoparticulate palladium in water.[91] The microreactor consisted of a 0.4 mm internal diameter pyrex glass capillary connected to a power supply to apply a potential across the reaction mixture. A palladium loading of 5 mol% was used and the pH of the reaction mixture held at 12 by use of a phosphate buffer. The authors claim the role of the applied potential (5 kV at a constant current of 100 μA) is twofold. Firstly, the mobility of the analytes (reagents) is driven by electro-osmotic flow and, secondly, the potential could increase the interaction between the reagents and the nanoparticles. Whether the latter is true is debatable. The authors compare the results they obtain from their microreactor with those from conventionally run experiments although a number of parameters are different between the two sets of experiments.

Palladium on carbon (Pd/C) has been used as a catalyst for Suzuki couplings in aqueous media as well as in organic solvents.[92] Choice of co-solvent turns out to be very important, especially when using aryl chlorides as substrates.

The first report of the use of Pd/C for the coupling in aqueous media was by a group from Hoffmann La Roche.[93] They showed that aryl iodides and bromides can be effectively coupled in mixtures of water and organic solvents, primarily ethanol. However, homocoupling of the substrates can be a problem. By changing the co-solvent from ethanol to DMA, it is possible to favour the Suzuki cross-coupling as opposed to the homocoupling pathway, when using Pd/C with aryl chlorides as substrates.[94] Using 5 mol% Pd/C, a 20:1 mixture of DMA–water gives a 96% isolated yield of the desired biaryl in the coupling of 4-chloro-trifluoromethylbenzene with phenylboronic acid as compared with 11% when using a 5:1 ethanol–water mixture. The conditions are applicable to a range of aryl chloride substrates. With those bearing electron-withdrawing groups, yields of between 79–95% are obtained in 24 h. With those bearing electron-neutral or electron-donating functionalities, longer times (48 h) or higher catalyst loadings (15 mol% Pd/C) are required to obtain moderate yields of the desired products. The ratio of DMA to water is also important. High water concentrations result in increased homocoupling product being formed and, if the water is removed and the reaction run in neat DMA, then the conditions are selective to the cross-coupled product but the rate of reaction is very slow. Of note is that the addition of phosphines to the reaction mixture was found to inhibit the coupling. The authors attribute the high activity of the Pd/C in the Suzuki coupling using aryl chlorides, to a heterogeneous mechanism. They suggest that there are synergistic anchimeric

and electronic effects, the former enhancing the interaction of the C–Cl bond with a Pd site on the surface by way of the substrate being anchored to the surface by a separate but nearby Pd site, and the latter resulting from a net flow of electron density from the aryl group of the substrate to the Pd, the surface acting in essence as an electron-withdrawing group thus facilitating C–Cl bond activation.

Low catalyst loadings can be sufficient when using Pd/C in NMP–water mixtures.[95,96] The best Pd/C catalyst was found to have a high palladium dispersion (36%), a low-reduction degree [mainly Pd(II)] and a high water content ($\sim$55%). Using this, bromoarenes could be coupled with phenylboronic acid within 2 h at 120 °C in a sealed tube, using between 0.005 and 0.1 mol% catalyst and Na_2CO_3 as base. p-Chloroacetophenone could be coupled with phenylboronic acid in high yields in the same time, with 0.05–0.25 mol% Pd/C but using NaOH as base. The high activity is attributed to a dissolution–reprecipitation process, it being the dissolved Pd species at the elevated temperatures that are catalytically active. Interestingly, pre-reduction of the Pd/C led to significantly lower catalytic activity.

The idea of catalysis of the Suzuki reaction having a homogeneous component when using Pd/C, has been further examined by Conlon and co-workers as part of their synthesis of a potential drug candidate bearing a quinoline functionality attached to benzaldehyde (Scheme 11).[97]

Running the reaction using 2.6 mol% Pd/C at 80 °C, a 10:1 DMF–water mixture was optimum but, depending on the base used, the residual palladium levels in the isolated product vary. With K_2CO_3 as base, lower residual Pd levels were observed as compared to when using KF. Working first with K_2CO_3 as base, monitoring the reaction mixture for substrate consumption and Pd content showed that the palladium concentration reached a maximum at around 90% conversion and then decreased with time. By undertaking further experiments and by comparison with other work in the literature, the authors suggest that the oxidative addition step in the reaction mechanism is responsible for the desorption of the palladium from the Pd/C and that the consumption of the aryl halide slowed the rate of desorption. When using KF, similar rates of Pd desorption were observed but the maximum palladium concentration was higher and the time to achieve this point was longer. This taken in conjunction with the results using K_2CO_3, suggests that a step other than the oxidative addition of the aryl halide is the rate-determining step in the reaction. Based on other experiments, the authors suggest that trans-metallation is in fact the rate determining factor in the reaction.

A range of iodophenols and one example of a bromophenol have been coupled with boronic acids in neat water at room temperature using 0.3 mol% of 10% Pd/C and K_2CO_3 as base
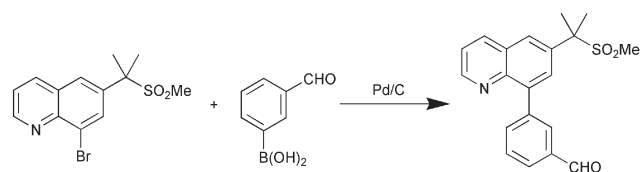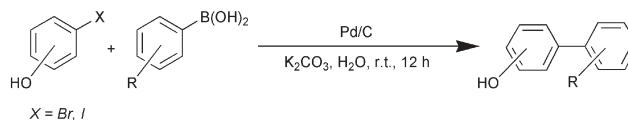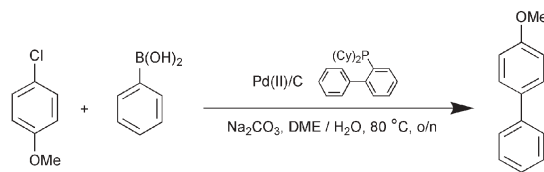

Scheme 12

(Scheme 12).[98] The Pd/C could be re-used although the catalytic activity slowly diminished.

In their synthesis of halopyridines and haloquinolines using Suzuki couplings in DME–water mixtures, Tagata and Nishida report that, when using Pd/C as a catalyst, a phosphine ligand was necessary in order to obtain reasonable yields of products with a wide range of substrates.[99] They studied two different types of Pd/C, one in which the level of palladium reduction is high, Pd(0)/C, and one where it is low, Pd(II)/C, and found significant differences. When using Pd(0)/C in the absence of any additives, bromopyridines could be coupled with phenylboronic acid in yields from 21–54%. They tried adding TBAB to the reaction mixture and yields improved but the quantity of TBAB required varied from substrate to substrate. Addition of triphenylphosphine instead of TBAB led to high yields of product with bromopyridines and also with chloropyridines, but not with those bearing an electron-donating group. When using Pd(II)/C in conjunction with PPh_3, some of these substrates could be coupled, reiterating the observation that Pd(II)/C is more active than Pd(0)/C when coupling aryl halides. As an extension to this work, the effect of addition of bis(diphenylphosphino)ferrocene (dppf) or 2-(dicyclohexyl-phosphino)biphenyl in the place of PPh_3 was studied using substrates deemed hard to couple. Using the sterically crowded 2-(dicyclohexylphosphino)biphenyl in conjunction with Pd(II)/C it was possible to couple 4-chloroanisole with phenylboronic acid in 80% yield (Scheme 13). The authors propose that the reason the phosphines enhance the catalytic activity is because any palladium dissociated into solution during the course of the reaction is coordinated and stabilised by the donor ligands. This would be expected to effect the reprecipitation of the palladium at the end of the reaction, as is supported by the fact that analysis of a product mixture showed that 80% of the Pd in the original Pd/C was recovered and 20% contaminated the crude reaction product. The increased activity of the electron-rich, sterically crowded phosphine over PPh_3 is attributed to the already known fact that these ligands facilitate oxidative addition and reductive elimination at a metal centre.

Palladium on carbon has been used for the large-scale synthesis of biphenylacetic acids.[100] Reactions were performed in aqueous isopropanol at 65 °C for 3 h using 5% Pd/C with sodium carbonate as base. Using this methodology, greater than 120 g of the acid can be prepared easily in one batch (Scheme 14). A similar methodology has been used by chemists

Scheme 11

Scheme 13

Scheme 14

Scheme 15

Scheme 16
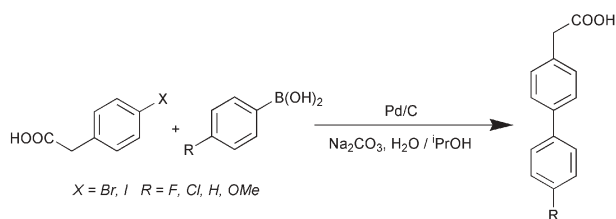
from SmithKline Beecham to prepare a key intermediate in the synthesis of SB-245570, a compound in development for the treatment of depression (Fig. 6).[101] The biaryl, SB-251475, was prepared on a greater than 6 kg scale using, as a step, a Suzuki coupling with Pd/C in a 1:1 water–methanol mixture.

In a variant of the Pd/C chemistry, palladium hydroxide on carbon has been used in a Suzuki coupling, this being selected because of its ease of handling.[102] The reaction of 4-bromonitrobenzene with phenylboronic acid and 4-methoxyphenylboronic acid has been studied using 1.1 mol% of 10% Pd(OH)$_2$ on carbon. A mixture of water and DME was used as solvent and Na$_2$CO$_3$ used as base. The Pd(OH)$_2$ on carbon turned out to be comparable in catalytic activity to Pd/C.

The Suzuki reaction using microwave promotion

(a) Using solvent-free conditions or in organic solvents

Microwave heating has been used extensively in homogeneous catalysis.[103] The first reports of Suzuki couplings using microwave promotion were by Larhed and Hallberg, 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.[104,105] With reaction times of only approximately 3–4 min, good yields of product were obtained, particularly with the solid-phase examples. The reactions were run in a scientific microwave. The same catalyst has been used for Suzuki couplings between halopyrimidines and phenylboronic acid using toluene–ethanol as a solvent mixture (Scheme 15). Reactions with bromo- and chloropyrimidines gave good yields of products after 10–15 min at 140 °C using a scientific microwave.

Using an (N-heterocyclic carbene)Pd(allyl)Cl complex it is possible to couple aryl chlorides with phenylboronic acid using a scientific microwave (Scheme 16).[106] Yields of products were similar to those obtained using conventional heating but the
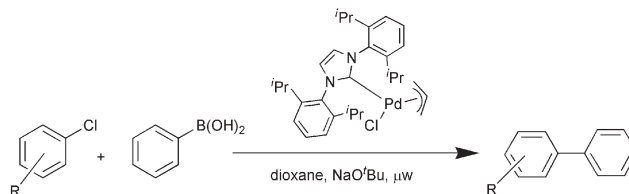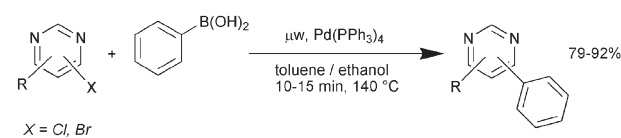
reaction temperature higher and time much shorter (90 s at 120 °C instead of 3 h at 80 °C).

Wang and Sauer have assessed a number of supported palladium complexes for their activity as catalysts for Suzuki couplings of aryl halides and triflates using a scientific microwave apparatus.[107] They focused attention on palladium complexes anchored on polyethylene-based supports known as FibreCat catalysts.[108] With FC1001 (Fig. 7), good yields were obtained with a range of substrates. Optimum conditions were 3 mol% of the supported catalyst, ethanol as solvent, potassium carbonate as base and microwave heating in a scientific apparatus at 110 °C for 10–15 min. An excess of boronic acid was used (1.4 equiv.), unreacted material then being removed at the end of the reaction by passing the crude product mixture through a carbonate-functionalised silica solid-phase extraction cartridge.

There have been a number of reports of microwave-assisted solvent-free Suzuki coupling protocols.[109] Using palladium-doped alumina, aryl iodides can be coupled with boronic acids in 2 min using a domestic microwave oven (Scheme 17a).[110,111] Aryl bromides couple in lower yields and aryl chlorides give only traces of the desired product. Reactions between arylboronic acids and alkyl or vinyl halides were unsuccessful but, only reported with conventional heating, those using allyl substrates did give moderate yields of the desired coupling products. Vinylboronic acids could be coupled with iodobenzene using both conventional and microwave heating (Scheme 17b). Vinyl halides could be coupled with arylboronic acids (Scheme 17c). Couplings with alkylboronic acids worked only when using conventional heating and only in low yield. The palladium-doped support used for the reactions was prepared by mixing commercially available Al$_2$O$_3$/KF with
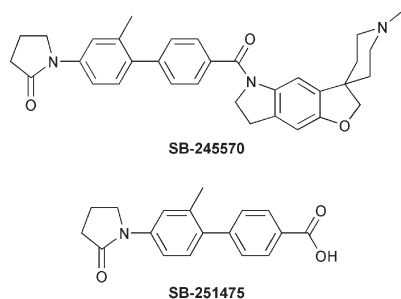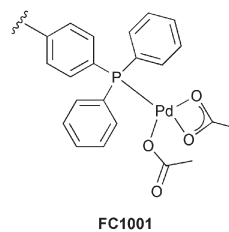
SB-245570

SB-251475
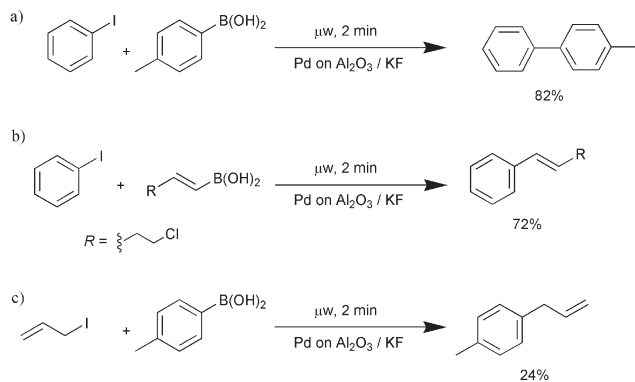
Fig. 6

**FC1001**

Fig. 7

Scheme 17

Scheme 19

palladium powder to give a 5% doped material which can be recycled at least six times.

Potassium fluoride on alumina has been used as a support for solvent-free Suzuki couplings in conjunction with palladium acetate as the catalyst precursor. Using 10 mol% Pd(OAc)$_2$, it is possible to couple 2-bromopyridine, 2-iodopyridine or aryl iodides with boronic acids in a scientific microwave oven, yields and reaction times varying from substrate to substrate.[112] Using 4 mol% Pd(OAc)$_2$, a number of polyarenes have been prepared from polyhaloaromatics and phenylboronic acid using a domestic microwave (Scheme 18a).[113] Potassium fluoride on alumina has also been used in conjunction with PdCl$_2$(PPh$_3$)$_2$ as a catalyst for phenylation of aryl halides with sodium tetraphenylborate (Scheme 18b).[114] The reactions are performed using DMF as a solvent and, in a domestic microwave oven, are complete in 10 min. Good yields of product are obtained not only with aryl iodide and bromide substrates but also with chlorobenzene and 4-chloronitrobenzene.

Barbarella and co-workers have reported a microwave-promoted solvent-free methodology for the synthesis of polythiophenes using Al$_2$O$_3$/KF as a support.[115] The catalyst of choice was PdCl$_2$(dppf)$_2$, this giving the highest yields of the desired products and the lowest yields of by-products which, in this type of chemistry, are inevitable. Using this catalyst, it was possible to effect not only Suzuki couplings between boronic acids and bromothiophenes but also prepare the boronic acids *in situ* and then react them directly. Thus, for example, quaterthiophene was prepared by reaction of 2-bromo-2,2′-bithiophene with bis(pinacolato)diboron (Scheme 19a). While the use of microwave heating proved to
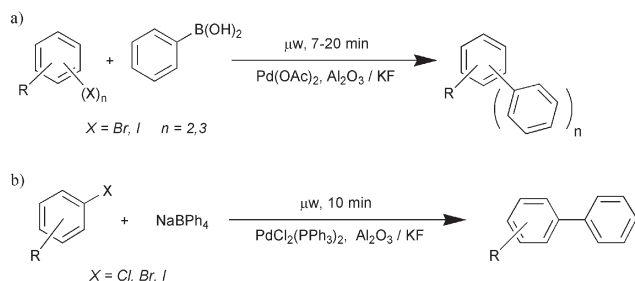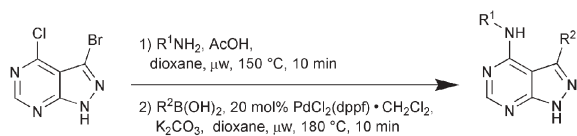

Scheme 18
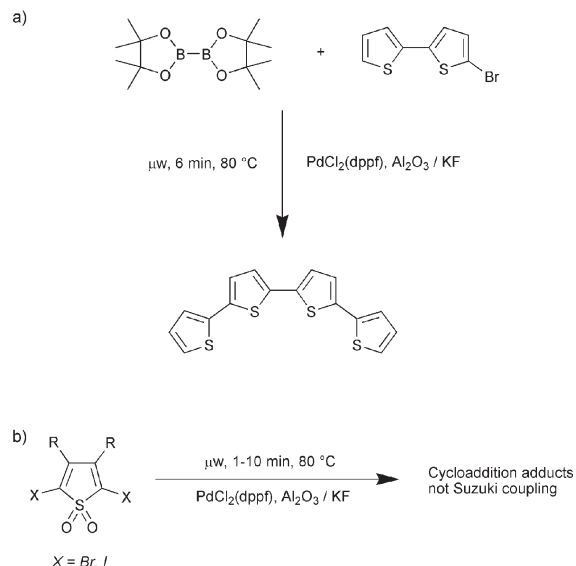
be very convenient for the coupling between conventional thienyl moieties, the same was not true for the coupling of thienyl rings to thienyl-*S,S*-dioxide moieties. Indeed, in this case, the desired product was obtained in low yields because of the competitive, accelerated, Diels–Alder reaction that affords a variety of condensation products (Scheme 19b). All reactions were performed using a scientific microwave apparatus.

One problem with the solvent-free methodology for the synthesis of polythiophenes is that, as the number of thiophene units increases, the solubility decreases to such a degree that sexithiophenes are essentially insoluble in common organic solvents. This makes their purification difficult since they cannot be separated from the alumina support. To overcome this problem, the same group have developed a solution-phase synthesis of unsubstituted and functionalised α-quinque- and sexithiophenes using microwave heating and the same PdCl$_2$(dppf)$_2$/KF catalytic system used in the solvent-free experiments.[116] Using a 1:1 toluene–methanol mix as solvent, α-quinquethiophene was prepared from diiodoterthiophene and 2-thienylboronic acid in 10 min at 70 °C using a scientific microwave apparatus. α-Sexithiophene was prepared from 5-bromoterthiophene and bis(pinacolato)diboron in a borylation–Suzuki coupling methodology. In both cases, methanol evaporation during the course of the microwave heating led to the formation of a fine suspension of the desired polythiophene which could easily be separated by centrifugation. The procedure was also applied to the synthesis of quinque- and sexithiophenes substituted at both terminal positions, α as well as β to sulfur.

The dichloromethane adduct of PdCl$_2$(dppf) has been used for part of a one-pot microwave-promoted synthesis of 4,5-disubstituted pyrazolopyrimidines from 4-chloro-5-bromopyrazolopyrimidine (Scheme 20).[117] In the first step of the reaction, microwave heating is used to facilitate an S$_N$Ar displacement of the C4-chloro substituent with various amines and anilines and then a Suzuki coupling is performed on the remaining bromo functionality. A catalyst loading of 20 mol%
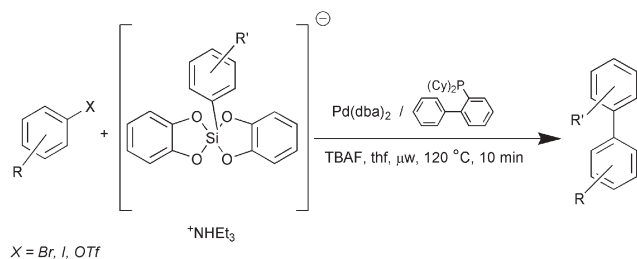
Scheme 20

is used for the Suzuki coupling step. Both steps of the reaction take only 10 min and the reactions are run in a scientific microwave.

In their assessment of poly(*N,N*-dihexylcarbodiimide) (PDHC) as a polymer for the stabilisation of palladium nanoparticles for use in the Suzuki reaction, Hu and co-workers show one example of a coupling using microwave heating.[118] The palladium nanoparticles were prepared by sodium borohydride reduction of H_2PdCl_4 in a two-phase mixture of PDHC, toluene and water. The resultant PDHC-Pd nanoparticles had an average size of 3 nm. Good yields of the desired product from the PDHC-Pd catalysed coupling of iodobenzene and phenylboronic acid were obtained after 40 min of microwave heating using a scientific apparatus. The reactions were run in toluene at 100 °C. To obtain the same product yield took 20 h at reflux in dioxane using conventional heating. Using the microwave conditions, the catalyst could be recycled several times but with a decrease in activity after each run. They attribute the diminishing activity to the intensive heating of the nanoparticles by the microwave irradiation, this leading to a fast rate of attrition.

Aryl triethylammonium bis(catechol)silicates have been used instead of boronic acids for Suzuki couplings with aryl halides and triflates (Scheme 21). Using conventional heating, aryl iodides and triflates couple well but aryl bromides give, at best, a 40% yield of the desired biaryl.[119] However, using microwave heating, a wide range of aryl bromides can be used as substrates with high yields of the product being formed.[120] The conditions optimised for the conventional heating experiments were directly transferred to the microwave, namely Pd(dba)$_2$ as the catalyst, 2-(dicyclohexylphosphino)biphenyl as a ligand, tetrabutylammonium fluoride as a promoter and THF as the solvent. Running the reactions in a scientific microwave for 10 min at 120 °C was sufficient.

(b) In aqueous media

Microwave heating has been used to facilitate the Suzuki coupling in both neat water and in mixtures of organic solvents and water. In this section, the latter will be discussed.
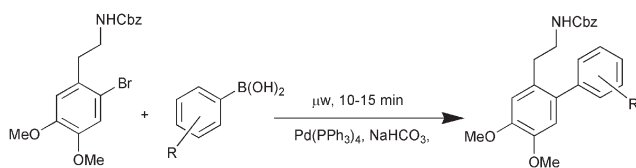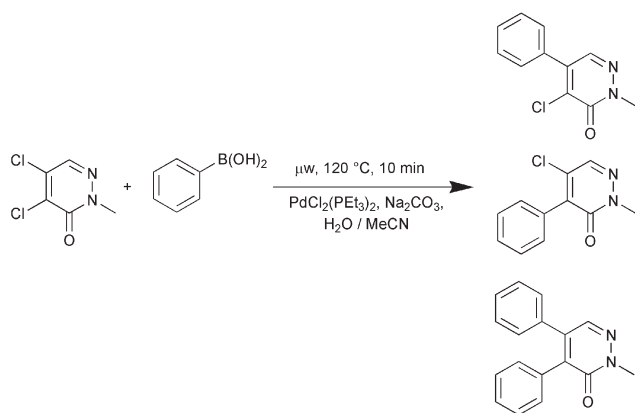

Scheme 21
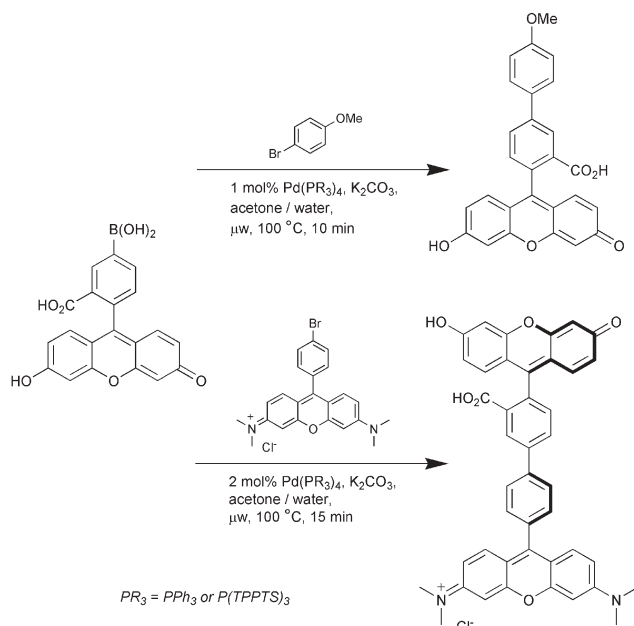
Scheme 22

A 1:1 mixture of water–acetone has been used for functionalisation of bromo-fluorescein and rhodamine derivatives by Suzuki and Sonogashira couplings (Scheme 22).[121] For the Suzuki couplings, Pd(PPh$_3$)$_4$ or Pd(TPPTS)$_4$ were used as catalysts and the reactions run for 10 or 15 min at 100 °C using a scientific microwave.

Microwave heating has been used for the synthesis of a small library of phenylethylamines, the diversity step being a Suzuki coupling with substituted boronic acids in DMF–water using 5 mol% Pd(PPh$_3$)$_4$ as the catalyst (Scheme 23).[122] The optimum base for the couplings was found to be sodium hydrogencarbonate, the optimum temperature between 120 and 150 °C, the reactions being performed for between 10–15 min in a scientific microwave. Using electron-donating, sterically hindered arylethylamines, the coupling works for a range of boronic acids including those bearing electron-withdrawing groups and heteroaromatic examples. It also works for sterically crowded examples with substituents in the *ortho*-position where hydrodeboronation is a problem when using conventional heating. Using 2-formylphenylboronic acid, yields were consistently 40–60% higher using microwave heating (15 min) as opposed to conventional heating (14 h) in a variety of solvent–water mixtures and in neat water.

Gong and He have used a scientific microwave apparatus to prepare 4-aryl phenylalanines as free amino acids from the Suzuki coupling of 4-boronophenylalanine with haloaromatics and heteroaromatics in 1:1 water–acetonitrile as solvent.[123] A
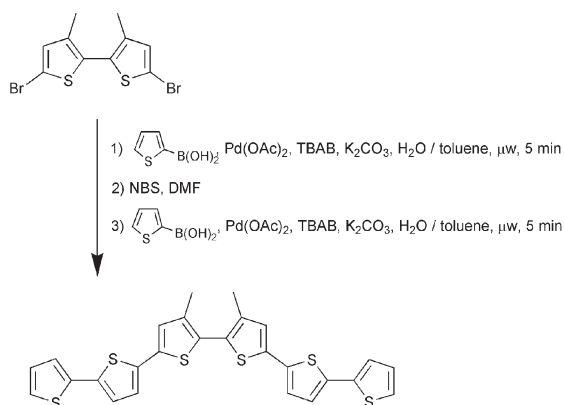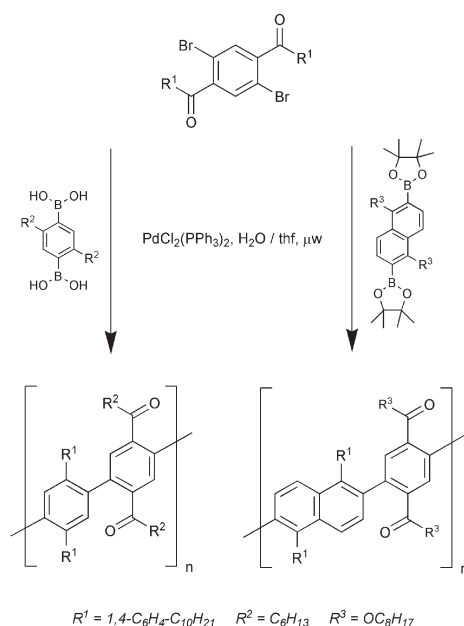

Scheme 23

Scheme 24

number of catalysts were screened and the best found to be $PdCl_2(PPh_3)_2$, the reactions being run at 150 °C for 5 min using sodium carbonate as base. The reaction works for chloro- and bromo-substituted heteroaromatics as well as iodo- and bromoarenes. A coupling involving a chiral boronic acid was also performed and no racemisation was observed.

The same authors have used a similar methodology for the rapid synthesis of 4-chloro-5-phenylpyridazinone from 4,5-dichloropyridazinone and phenylboronic acid (Scheme 24).[124] Other 4-aryl and 4,5-diaryl derivatives could also be prepared. The triethylphosphine ligated complex $PdCl_2(PEt_3)_2$ was found to be the best catalyst. The reactions were run for 10 min at 120 °C in acetonitrile–water mixtures. Further optimisation of reaction conditions in fact led to a methodology that worked at room temperature for some substrates.

A biphasic toluene–water mixture has been used for the preparation of a soluble sexithiophene by a Suzuki coupling methodology (Scheme 25).[125] Palladium acetate was used as the catalyst and TBAB as an additive. The desired seximeric product was prepared from 2,5′dibromo-3,3′-dimethyl-2,2′-bithiophene by reaction with 2-thiopheneboronic acid followed by NBS bromination of the product and then re-treatment under the Suzuki conditions. The authors compare their microwave-promoted synthesis of the polythiophene with an unsuccessful one using conventional heating. However, for the conventional heating methodology, $Pd(PPh_3)_4$ is used as the

Scheme 25

$R^1 = 1,4\text{-}C_6H_4\text{-}C_{10}H_{21}$ $R^2 = C_6H_{13}$ $R^3 = OC_8H_{17}$

Scheme 26

catalyst and THF as the solvent so it is hard to be able to make a real comparison.

Semiconducting polyketone-containing polymers have been prepared by Suzuki couplings in THF–water solvent mixtures using conventional and microwave heating (Scheme 26).[126] With microwave heating, a polyarene bearing a naphthalene unit was prepared in 12 min using a 4:1 THF–water mix as solvent and 4 mol% $PdCl_2(PPh_3)_2$ as catalyst. The mixture was irradiated with 150 W microwave power continuously for the duration of the reaction using a scientific apparatus. No comment is made regarding the final temperature of the reaction mixture. A polymer with similar polydispersity but a slightly higher number-average molecular weight (M_n) was formed as compared to an analogous reaction mixture heated at reflux for 3 days using an oil bath. The yield was 12% higher for the conventionally heated reaction. In the synthesis of the phenyl- rather than the napthyl-containing polyarylketone, the effects of microwave power on the molecular weight distribution of the product were examined. Continuous power settings of 70 W, 100 W and 150 W were used for a reaction time of 12 min and polymeric material with M_n values of 3,700, 4,200 and 12,600 respectively were obtained. In the light of this, the authors claim that the microwave power used in the reaction is an important factor. However, again there is no mention of the final temperature of the reaction mixture. A problem with comparing results from experiments undertaken at different power levels using constant microwave irradiation is that effects from power and bulk temperature are essentially impossible to separate. Therefore, the increased M_n values obtained with increased power could feasibly be due to the expected increased bulk temperature.

Using water–poly(ethylene glycol) (PEG) mixtures, 4-iodo-benzoic acid methyl ester has been coupled with a range of boronic acids in a domestic microwave.[127] The reactions are performed using 8 mol% $Pd(OAc)_2$ as the catalyst and potassium carbonate as base. The reactions were complete

within 4 min. Poly(ethylene glycol) has also been used as a reaction medium for microwave-promoted Suzuki couplings in the absence of added water.[128] Using 28 mol% $PdCl_2$, it is possible to couple aryl bromides and iodides with boronic acids in 50 s using a domestic microwave. The optimum amount of PEG was found to be 2 g per mmol of aryl halide substrate. The reactions can also be performed using conventional heating, taking 15 min at 100 °C.

Aryl perfluoro-octylsulfonates have been used in the place of aryl halides for Suzuki couplings using microwave heating (Scheme 27).[129] The advantage of these substrates is that excess starting material can be separated from the product easily by using the boronic acid component as the limiting reagent and fluorous solid-phase extraction as the product isolation step. Using these substrates and a 4:4:1 mixture of toluene–acetone–water as solvent, the best catalyst for the reaction was $PdCl_2(dppf)$, this being used at a loading of 10 mol%. Reactions were run at between 100–130 °C for 10 min in a scientific microwave apparatus giving product yields of 80–95%.

Suzuki couplings involving chloroarenes have been performed using microwave heating in conjunction with a $Pd(OAc)_2/PCy_3$ pre-catalyst mixture.[130] The reactions were run at 180 °C for 10 min using a 6:1 dioxane–water mixture as solvent.

The Suzuki reaction has been used to demonstrate the applicability of a microreactor and a flow-capillary reactor, both developed for use in conjunction with microwave heating. Two different microreactor designs were tested.[131] Both were made of glass and had linear channel designs in which a premixed reactant solution containing aryl halide, phenylboronic acid and K_2CO_3 in DMF–water could be pumped using a syringe pump from an input reservoir to a collection reservoir through a catalyst bed. Both had catalyst bed channels 1.5 mm wide and 15 mm long but they differed in depth, one being 80 μm and the other 60 μm. The catalyst material was deposited as a dry powder. In the wider channelled microreactor, it formed a monolayer throughout the whole catalyst bed whilst, in the narrower one, because the catalyst particles were too big, the mixture formed a plug in the catalyst bed. An area on the outside of the bottom plate of the microreactors corresponding to the region of catalyst packing, was sputter coated with gold to a thickness of 10–15 nm. The aim of this was to get efficient localised heating in the region of the catalyst bed during microwave heating. A series of reactions were run using a scientific microwave apparatus. To allow for comparison between data obtained for different reactions, the microwave apparatus was set to heat the microreactor to between 90–100 °C and then fluctuate the power to maintain this temperature. Using the catalyst plug reactor with 5 wt% Pd/Al_2O_3 as the catalyst and a solution–catalyst contact time

of 36 s it was possible to couple a number of aryl bromides and iodides with phenylboronic acid in good yield. Running reactions in a pre-heated oil bath led to lower product yields as did performing the reaction in an identical microreactor but without the gold coating, but yields were still reasonable. This indicates that absorption of microwave energy by both the catalyst material and the gold film are effective in heating the reaction chamber in the microreactor. The coupling reaction could also be performed effectively in the microreactor containing Pd/Al_2O_3 along the entire length of the catalyst bed. Much less microwave power was needed to heat it to 90–100 °C and maintain the temperature, this being attributed to the more efficient microwave absorption by the catalyst and also better heat transfer from the gold patch to the microreactor.

The methodology using a flow-capillary reactor was similar to that with the microreactor.[132] A U-shaped capillary of internal diameter 800 μm, outer diameter 1.2 mm and total length 138 mm, was inserted into the cavity of a scientific microwave apparatus. The catalyst was loaded into the bend of the U-tube and the area around this sputtered coated with gold. The reactants were flowed over the catalyst bed as a DMF–water solution using a syringe pump. Two catalysts (Pd on silica and Pd on alumina) and two bases (K_2CO_3 and NaOH) were screened for their effectiveness in the reaction. When Pd on silica was used, as the reaction temperature was increased from rt to around 70 °C so the product yield increased, but beyond this it then started to decrease. This is attributed to condensation of the silica at higher temperatures, leading to aggregation and hence deactivation of the supported catalyst. When palladium on alumina was used, catalyst deactivation was not an issue so it is the better choice. Study of the bases showed that NaOH led to significant dehalogenation of the aryl halide substrate whilst K_2CO_3 was effective in the coupling. As with the microreactor, when using the flow-capillary apparatus, reactions run in a pre-heated oil bath led to lower product yields as did those performed using microwave heating with an identical reactor but without the gold coating.

(c) In water as the only solvent

Conventional and microwave heating has been used to facilitate the Suzuki coupling of aryl boronic acids with the poly(ethylene glycol) esters of an aryl iodide, triflate, nonaflate and a bromothiophene in neat water under argon (Scheme 28).[127] Palladium acetate (10 mol%) was used as the catalyst for the reactions and potassium carbonate as base. When using PEG-bound substrates it is not necessary to add a phase-transfer agent such as TBAB. When using conventional heating, the aryl iodide and bromothiophene substrates could be coupled with a range of boronic acids at 70 °C in 2 h. There was some cleavage of the ester-functionality linking the support to the aryl halide substrate, but this generally comprised only 3–6% of the product mixture. Using a domestic microwave system, the reaction was complete within 1–2 min when running one reaction at a time, this needing to be extended to 4 min for parallel synthesis. Again cleavage of the ester linkage on the support was not a major issue. The effect
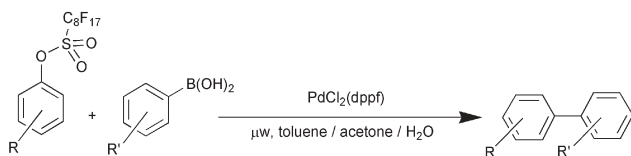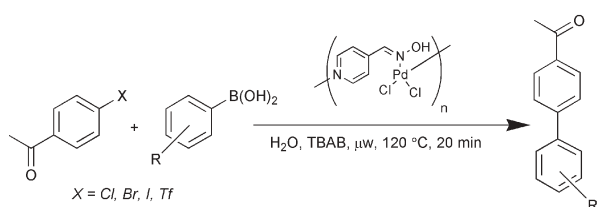

Scheme 27
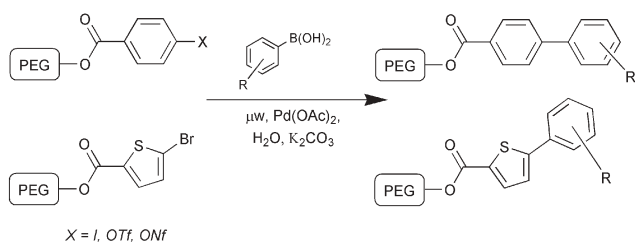
Scheme 28

Scheme 30

of varying the quantity of water on product yield was studied using the supported aryl iodide. Running the reaction under solvent-free conditions resulted in incomplete conversion of the supported substrate and also required high microwave power (400–900 W) in order to melt the starting materials. As water was added, so the yield of the product increased. A minimum quantity of 400 μl of water was found to be necessary for transforming 0.2 g of the starting polymer in quantitative yield to the desired biaryl but the reactions were best run using 1 mL water. A microwave power of 75 W was used. Coupling of the PEG-bound triflate with boronic acids could also be performed using these conditions, giving the desired products in good yield. The nonaflate worked moderately well but there were problems associated with the purity of the polymer-bound products.

Using microwave heating, Suzuki couplings can be performed in water using an insoluble palladium catalyst prepared from 4-pyridine-aldoxime and Na_2PdCl_4 (Scheme 29).[133] TBAB is used as a phase-transfer agent and the reaction mixtures heated to 120 °C for 20 min in a scientific microwave apparatus using 1 mol% of the Pd complex. A small library of biaryls have been prepared by coupling a number of boronic acids with 4-iodo-, bromo-, chloro- and triflylacetophenone and 4-bromoanisole. Good yields are obtained in each case. The catalyst can be recycled at least 14 times, yields fluctuating slightly. The reaction can also be performed using toluene as a solvent but water is superior.

Sodium tetraphenylborate has been used as a phenylation reagent for microwave-promoted synthesis of aryl-substituted heterocycles in water.[134] Using palladium acetate as a catalyst, the reaction can be performed in 8–12 min in a scientific microwave. All four phenyl groups from the $NaBPh_4$ can be transferred. The reaction also works in monomethylformamide and yields are slightly better in this solvent.

In our laboratory, we wanted to build on previous work and, in particular, to combine the advantages of using TBAB as a phase-transfer agent and activator for boronic acids in the Suzuki reaction, together with the ease of use and speed of
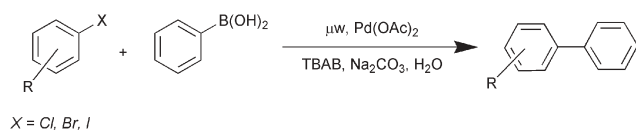
microwave heating. As already mentioned, an advantage of a scientific microwave is the ability to control reaction conditions very specifically. This meant that we were able to screen a wide range of parameters very fast and with close monitoring. As a result, we could optimise the reaction very easily. Our initial investigations were undertaken using 1 mmol of aryl halide and 1 mmol of boronic acid, the reactions being performed in 10 mL sealed tubes using 2 mL water as solvent (Scheme 30).[135] We used palladium acetate as the catalyst and sodium carbonate as base. There was no need to exclude air from the reaction mixture.

When using aryl iodides and bromides, the best yields of biaryl are obtained when the reaction is run at 150 °C for 5 min. For aryl chlorides it was necessary to increase the temperature to 175 °C in order to obtain reasonable yields of biaryl product. The optimum catalyst loading was 0.4 mol%. If higher catalyst loadings were used there was a problem with competitive hydrodeboronation of the boronic acid to generate the free arene. Although good yields of product were obtained using 0.5 equiv. TBAB, it is better to use 1 equiv. The optimum conditions for the reaction are summarised in Fig. 8. The conditions used are applicable to a wide range of substrates bearing different functional groups.

We subsequently showed that the reaction can be run equally as well using conventional heating.[136] We kept the quantities of catalyst, base, TBAB and water exactly the same as in the microwave heating reaction and performed the reaction in a sealed 10 mL microwave tube. We dipped the tube into an oil bath pre-heated to 150 °C and held it there for 5 min before removing it and cooling the reaction mixture. As well as showing that, in this reaction, the microwave irradiation simply provides an efficient heating method, the fact that the reaction can be performed so fast using conventional heating is interesting. Indeed, to our knowledge
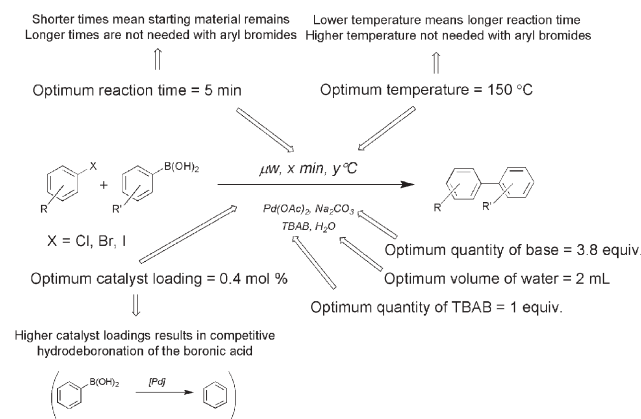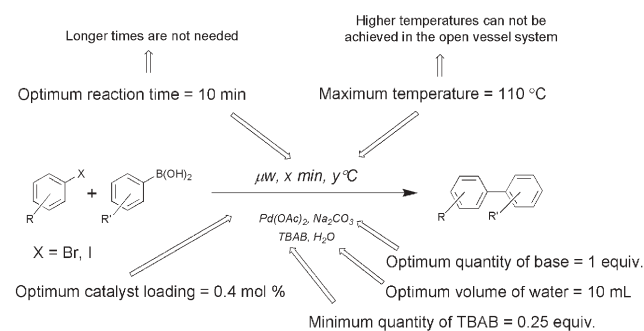

Scheme 29

Fig. 8 The optimum conditions for the Pd(OAc)₂-mediated Suzuki coupling in water on a 1 mmol scale using microwave heating.

these still represent the fastest Suzuki couplings with aryl bromides using conventional heating.

We wanted to scale up the reaction because, although performing the reaction on a 1 mmol scale produces around 200–300 mg of biaryl product, we wanted to increase the scope of the methodology to allow us to prepare grams of material. At that time, using our monomode microwave apparatus, the only sealed reaction vessels available to us were the 10 mL tubes. If we were going to scale up the reaction, we would have to do so in an open vessel. This meant that the maximum temperature we could obtain was around 110 °C. We kept all the other reaction parameters the same as for the sealed vessel work and ran a test reaction using 4-bromoacetophenone and phenylboronic acid on a 10 mmol scale in an open vessel and found that almost identical product yields were obtained. We then optimised the conditions for the larger scale reaction since we wanted to minimise the quantities of TBAB, base and water used in the reaction. It was possible to reduce the quantity of TBAB from 1 mmol to 0.25 mmol, base from 3.8 mmol to 1 mmol and water from 20 mL to 10 mL without any deleterious effect on the product yield. We increased the reaction time from 5 min to 10 min in order to ensure maximum conversion of starting material to product in all cases. The optimum conditions for the reaction are summarised in Fig. 9. Since the high temperatures needed to activate aryl chloride substrate can not be achieved using the open vessel apparatus, the methodology is limited to use with aryl bromides and, albeit in lower yield, aryl iodides. As with the smaller scale reactions, we find that it is possible to perform the open-vessel chemistry equally as well using either microwave or conventional heating.[137]

It was whilst probing the reaction in more detail that we made an interesting discovery.[138,139] We ran the coupling of 4-bromoacetophenone with phenylboronic acid but without the addition of any transition-metal catalyst. To our surprise we obtained a greater than 90% yield of the biaryl product. Based on this initial observation, we repeated the same reaction a further five times and obtained identical results on each occasion. The reaction was run using a 1:1.3 stoichiometric ratio of aryl halide to boronic acid, 3.8 mmol sodium carbonate as base, 1 mmol TBAB as an additive and the mixture was heated to 150 °C using microwave irradiation and held there for 5 min (Scheme 31).

We re-ran the reaction using new glassware, apparatus, reagents, and spatula, and analysed entire crude product
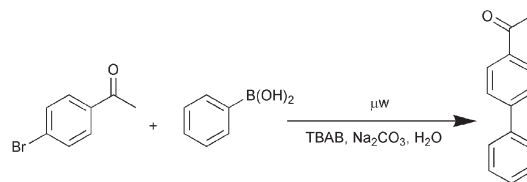
Scheme 31

mixtures from several reactions for palladium content. We found that there was no palladium in the reaction mixtures down to the level of detection of the analytical apparatus to which we had access (0.1 ppm). This was well below any reported levels for catalytic activity for Suzuki couplings or other related reactions in the literature at that time. Nickel,[140,141] platinum,[142,143] copper[143,144] and ruthenium complexes[143] have all been shown to act as catalysts for the Suzuki coupling, either individually or together. We screened our reaction mixtures for these and 27 other metals. All were present in levels less than 1 ppm which we believed was too low to be feasibly catalytically active.

The aryl halide substrate scope of the reaction was quite broad. Good product yields were obtained with a range of aryl bromides. Aryl iodides gave lower yields of the desired biaryl but aryl chlorides were unreactive. The boronic acid scope, when first explored, was much more limited. Indeed only three boronic acids seemed to be active in the coupling protocol, namely phenylboronic acid, 4-acetylphenylboronic acid and *p*-tolylboronic acid. All others reacted to give the deboronated arene rather than couple with the aryl halide.

Some interesting observations in connection with the reaction are worth highlighting:

• The coupling is totally regioselective, giving just the biaryl of choice.

• The only base that works effectively in the reaction is sodium carbonate. Other metal carbonates give significantly lower product yields, if any.

• The only solvent in which the reaction works is water. Organic solvents such as DMF, NMP, DMSO and methanol are ineffective, as are mixtures of them with water.

• The coupling of 4-bromoacetophenone with phenylboronic acid can be performed conventionally by placing a sealed tube containing the reaction mixture into a pre-heated oil bath. However with unactivated and deactivated aryl bromide substrates it is not possible to perform the reaction so efficiently (and in many cases not at all) using conventional heating.

• The reaction can occur without TBAB. Replacement by poly(ethylene glycol) as a phase-transfer agent results only in a slight decrease in product yield. Using water soluble aryl halide and boronic acid components, no phase-transfer agent is required.

We tried to rationalise all these findings and propose a mechanism for the reaction. Plausible mechanisms for the reaction in the absence of palladium also formed part of a discussion of the chemistry by Li.[145] These, and other options include σ-bond metathesis of a borate complex, an S_NAr mechanism, a base catalysed pathway or the formation and reaction of a diradical. We performed a wide range of
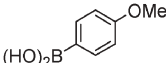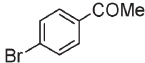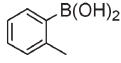
Fig. 9 The optimum conditions for the Pd(OAc)$_2$-mediated Suzuki coupling in water on a 10 mmol scale using microwave heating.
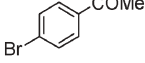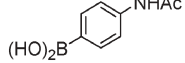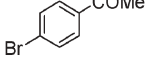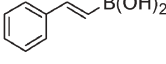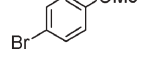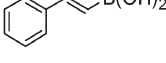
experiments to probe each of these options but our results were inconclusive.

It was possible to expand the substrate scope of the reaction to include sodium tetraphenylborate as a phenylating agent[136] and to couple a range of aryl bromides with NaBPh$_4$, using a stoichiometric ratio of the two reagents of 4:1, respectively. The reaction was performed using the same conditions as for the couplings of aryl halides with boronic acids except that no TBAB is used. If TBAB is added to the reaction mixture there is a reaction with the boronic acid *in situ* to form [Bu$_4$N]$^+$[BPh$_4$]$^-$ and NaBr, the former of which precipitates out of solution and is inactive in the coupling reaction. We also used KBPh$_4$ in the place of NaBPh$_4$ but found that this results in a significant decrease in product yield.

During 2003 and 2004 a number of reports appeared in the literature suggesting that C–C coupling reactions can be catalysed by trace quantities of palladium complexes.[146] de Vries and co-workers have shown that the Heck reaction can be run with the addition of what they term 'homeopathic' quantities of palladium acetate, but find that when using very low metal concentrations the rate of reaction is too slow to be practical.[147,148] Köhler and co-workers have studied the Heck reaction using a range of solid catalysts prepared by co-precipitation of palladium hydroxide on a metal oxide support (TiO$_2$, Al$_2$O$_3$) or incorporation into the cages of a zeolite (NaY).[149] Their results suggest that there is *in situ* generation of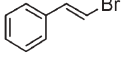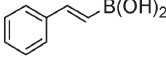 highly active dissolved palladium species and thus that the catalysis is in effect homogeneous, with palladium dissolution and reprecipitation being crucial and inherent parts of the catalytic cycle. Ikegami and co-workers have used a modified version of their PdAS assembled catalyst of palladium and a non-crosslinked amphiphilic polymer ligand in Heck couplings involving aryl iodides. The use of as little as 0.00008–0.005 mol% of the supported complex gave good yields of products with turnover numbers in excess of 1 million.[150,151] Very high turnover numbers have also been reported for Suzuki coupling reactions, mostly involving the use of ligated palladium complexes such as those bearing N-heterocyclic carbene ligands[152] or bulky phosphines[153] as well as Ikegami's PdAS supported material.[73,74] In 2003 de Vries and de Vries published a paper showing that palladium loadings as low as 0.05 mol% could be effective in Suzuki couplings.[154] They used a high-throughput experimentation methodology as a fast way to determine the effect of varying reaction parameters. They found that NMP–water mixtures (19:1 ratio), toluene– and isopropanol–water mixtures were especially good solvent systems for the reaction between 4-bromoacetophenone and phenylboronic acid. The palladium source is not very important when using NMP–water mixtures but is when using toluene. This is attributed to solubility issues. Shen and co-workers published a methodology based on using PdCl$_2$ in pyridine as a solvent. It is possible to use low catalyst loadings (0.2–0.3 mol%) and the methodology works well for a range of aryl bromide substrates.[155] As already discussed, Suzuki couplings have been performed using solid catalysts where again small quantities of *in situ* generated dissolved palladium species are suggested as the active catalyst. These bodies of work made us critically reassess our transition-metal free protocol in 2004.[156]

We first wanted to determine why the boronic acid scope of our methodology was so limited. We found that the success of the reaction is dependent on the purity of the boronic acid used. Impurities in the boronic acid, even in very small amounts, can effectively shut down the reaction. The purity of boronic acids, we found, varied from supplier to supplier, regardless of the information provided on the label. We felt that it may be the case that our previous screening of the boronic acids may have led to 'false negatives' and that the boronic acid substrate scope may not be as limited as we first thought. We obtained some boronic acid samples of high quality and purity and found that indeed they did work in our coupling protocol. We also used three ways to purify less pure commercially available boronic acids so that they too could be used in the coupling methodology. Examples of the substrate scope of the coupling methodology when using purified boronic acids are shown in Table 2. As well as aryl boronic acids, it is also possible to use alkenylboronic acids and it is possible to couple these with alkenyl halides to prepare dienes. Only the *trans*-isomer of the products is obtained and sometimes they are not particularly stable in the hot basic aqueous medium and hence yields can be low.

Table 2 Selected examples of the boronic acid scope in the coupling methodology once purified

Halide component	Boronic acid	Product yield (%)
		99
		99
		63
		99
		46
		26
		77

We then decided to probe the effects of purity of the other reagents on the coupling reaction. In particular, we wanted to re-analyse reagents and whole product mixtures for sub-ppm concentrations of palladium. We did this using ICP-MS analysis to enable us to measure palladium levels to concentrations well lower than previously possible in both solid and liquid samples. Perhaps the most obvious source of palladium would be the water used in the reaction. However we always used ultra-pure water, purified to a specific resistance of >16 mΩ cm. Analysis of this for palladium showed a Pd concentration of 0.24 ppb. Our attention focused on the sodium carbonate used in the reaction because this was essentially the only reagent that we could not purify prior to use. Analysis of solutions of this in ultra-pure water at a concentration equal to half that used in the reaction showed a palladium level of between 10 and 24 ppb. Therefore, the expected palladium concentration in our reaction vessels would be from 20 to 50 ppb. We have subsequently found that these levels of palladium are found in many commercially available sources of sodium carbonate but, interestingly, not potassium carbonate. Analysis of aqueous solutions of potassium carbonate showed levels of palladium corresponding to 0.09 ppb in the concentrations used in our couplings. We wondered whether this was why, as reported in our earlier papers, when the coupling is performed using sodium carbonate as a base the reaction works well, but with the potassium analogue it does not and the reaction was in fact palladium mediated but only required sub-ppm concentrations of the metal.

To study this, we used potassium carbonate as a base for the coupling reaction since we knew this was essentially palladium free and thus we could dope it with predetermined quantities of palladium so we knew the exact Pd concentration in each reaction. We found that whilst the coupling does not work with the "palladium-free" potassium carbonate, addition of 50 ppb Pd results in a 75% yield of product in the coupling of 4-bromoacetophenone and phenylboronic acid, this corresponding to a palladium loading of 0.0000008 mol% and a turnover number of 1,250,000. This, and a series of other experiments we undertook, confirmed that when the Suzuki reaction is performed without the addition of a transition metal catalyst but using sodium carbonate as a base, palladium contaminants down to a level of 50 ppb found in the commercially available base are responsible for the generation of the biaryl rather than, as previously suggested, an alternative non-palladium mediated pathway. We therefore want to rename the original methodology "*no catalyst added*" as opposed to "*transition-metal free*" (Scheme 32).

To develop a reliable new methodology, we screened a wide range of parameters and found a set of optimum general conditions as summarised in Fig. 10. Although the reaction will work without the addition of a catalyst because sodium
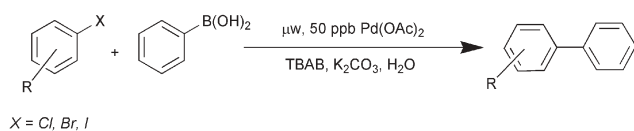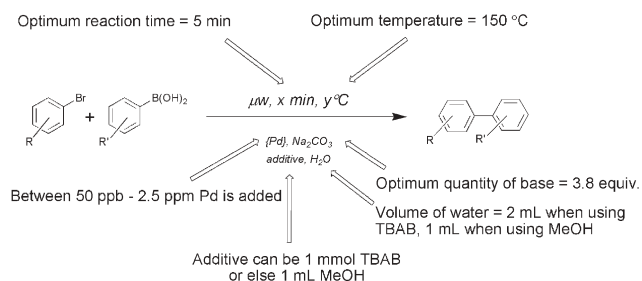

Fig. 10 The optimum conditions for the Pd(OAc)$_2$-mediated Suzuki coupling in water on a 1 mmol scale using microwave heating.

carbonate often contains palladium, this does not offer a totally reliable methodology. Therefore the reaction is best run with between 50 ppb and 2.5 ppm Pd. The reaction can be run equally as well using water with TBAB as a phase-transfer additive or using a 1:1 mixture of water and ethanol. When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is avoided by using an acid stabilised stock solution such as that purchased as an ICP standard for palladium. This can be diluted accordingly to give solutions of the desired concentrations. For low concentrations, a couple of drops of HCl can be added to avoid precipitation of the palladium from solution.

The reaction is actually very fast. We performed the coupling between 4-bromoacetophenone and phenylboronic acid for different palladium loadings and microwave heating times. The reaction reaches completion within a total microwave irradiation time of 90 s. The reaction mixture hardly reaches 150 °C. This corresponds to turnover frequencies of 28,000,000, 47,000,000 and 50,000,000 for palladium loadings of 100 ppb (0.0000016 mol% Pd), 250 ppb (0.000004 mol% Pd) and 2.5 ppm (and 0.00004 mol% Pd) respectively. We performed the same reaction using conventional heating and find that lower turnover numbers are obtained. In December 2004, de Vries and co-workers published data on Suzuki and other aryl–aryl couplings in NMP–water mixtures, using palladium acetate as the catalyst and conventional heating, but report higher catalyst loadings and lower turnover numbers than in our methodology.[157] Admittedly they say that they have not attempted to discover the exact boundaries of the reaction under their conditions. They suggest that, when using ligand-free sources of palladium, it is possible only to effect couplings such as the Suzuki and Heck reactions when the palladium–substrate ratio is kept low since once the palladium is reduced to Pd(0) it forms nanoclusters which have limited stability and eventually form palladium black. By lowering the palladium concentration it is possible for the oxidative addition of the aryl halide substrate to the Pd(0) formed, to compete with nanocluster formation. This has also been suggested by others.[158–161] The problem with using low palladium concentrations is that, when using conventional heating, there comes a point where the reactions can be so slow as to become impractical. We believe that it is the combination of low metal concentrations, use of water as the solvent and very importantly use of microwave heating that allows us to perform the Suzuki couplings so easily and so rapidly.
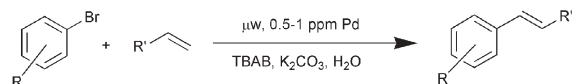

Scheme 32

General discussion

Our reassessment of the Suzuki-type coupling methodology and discovery that the coupling does need a catalyst but that it can be performed with sub-ppm levels of palladium has implications on other recent publications suggesting catalyst-free methodologies for other traditionally Pd-mediated reactions.

A catalyst-free Heck coupling of iodobenzene and styrene has been reported, using supercritical water as the reaction medium.[162,163] The reaction is run at 377 °C and 25 MPa and up to 55% yields of the desired stilbene product are formed within a reaction time of 10 min. As well as the Heck product, a number of by-products are also formed, the quantities and proportions of which depend on the reaction conditions (Scheme 33). Essentially, four competing processes take place during the reaction, namely hydrogenation, polymerisation of styrene, the Heck coupling and hydrolysis of iodobenzene to phenol. The choice of base has the greatest effect on the rate and product distribution of the reaction. Potassium acetate was the best base for obtaining the Heck product. Use of stronger bases led to the hydrolysis product predominating. With triethylamine or in the absence of base, polymerisation of styrene occurred with little or no coupling products being obtained.

Although feasible mechanisms for the formation of each of the products found in the reaction have been put forward, in the light of our results from the Suzuki coupling there is perhaps an issue relating to residual palladium in either the base used for the reactions or in the reactor vessels themselves. The couplings were performed in either an iron-base stainless steel or nickel-base alloy reactor. The authors state that they analysed product mixtures for Ni, Fe, Cr and Mo using inductively-coupled plasma atomic absorption spectroscopy (ICP-AES) and found none of these to be present to the level of detection of their apparatus. However they do not comment on whether they analysed reaction mixtures for palladium. Clearly we could not reproduce the conditions applied in these couplings using our microwave apparatus but all the same we wanted to study the Heck coupling in water under microwave irradiation using TBAB as a phase-transfer agent, both to see if a catalyst-free coupling was possible in our case or if ultra-low palladium concentrations could be used to catalyse the coupling.[164] We found that it was not possible to effect the
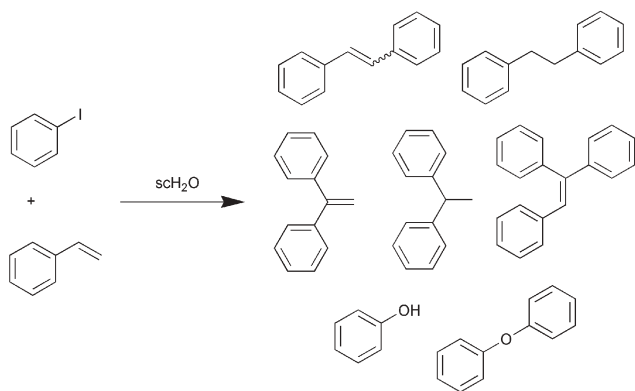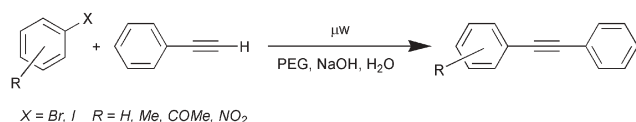

Scheme 34

coupling in the absence of a catalyst using water as a solvent and microwave heating, regardless of the temperature, reaction time, base or substrate ratio used. However, addition of between 500 ppb and 1 ppm palladium to the reaction mixture resulted in good yields of the Heck product within 10 min at 170 °C (Scheme 34). The reaction works only in water or water–DMF mixtures and not in neat organic solvents such as DMF and NMP. The fact that the reaction works at such low palladium concentrations is perhaps not that surprising in the light of the results from our Suzuki couplings and also the increasing number of reports in the literature of Heck couplings using low catalyst loadings. The reaction times however are much shorter in our methodology than in others in the literature using these low catalyst loadings, this again showing the advantages of the combination of water as a solvent and microwave heating.

In 2003, we published a report of a Sonogashira coupling without the need for addition of a transition-metal catalyst (Scheme 35).[165] The reaction is traditionally performed using a palladium catalyst with a copper co-catalyst added to activate the alkyne substrate. Our methodology again involved the use of water as a solvent and microwave irradiation as the method of heating. Sodium hydroxide was found to be the best base for the reaction and poly(ethylene glycol) used as the phase-transfer agent rather than TBAB. The reactions are run at 170 °C for 10 min. The methodology was somewhat limited in substrate scope. We are currently probing this reaction in more detail.

Van der Eycken and co-workers have independently published a catalyst-free methodology for the reaction, the difference being that sodium carbonate and TBAB are used as the base and phase-transfer agent combination.[166] A number of palladium[167] or copper[168] free coupling protocols for the Sonogashira reaction have also appeared in the literature, some of these using microwave heating[169] and/or water as the solvent[170] or a co-solvent.[171]

The amination of halopyridine and chloropyrimidine has been performed in the absence of a metal catalyst using microwave heating (Scheme 36a).[172] The reaction works best using solvent-free conditions, reaching completion after 30 min at 130 °C in a scientific microwave apparatus. Amination of aryl halides can be performed without a metal catalyst using microwave heating (Scheme 36b).[173] With DMSO as a solvent and KO^{t}Bu as a base, the reactions are performed in a domestic microwave, taking 5–20 min to reach completion. The reaction works best for electron-rich aryl bromides.

$X = Br, I$ $R = H, Me, COMe, NO_2$
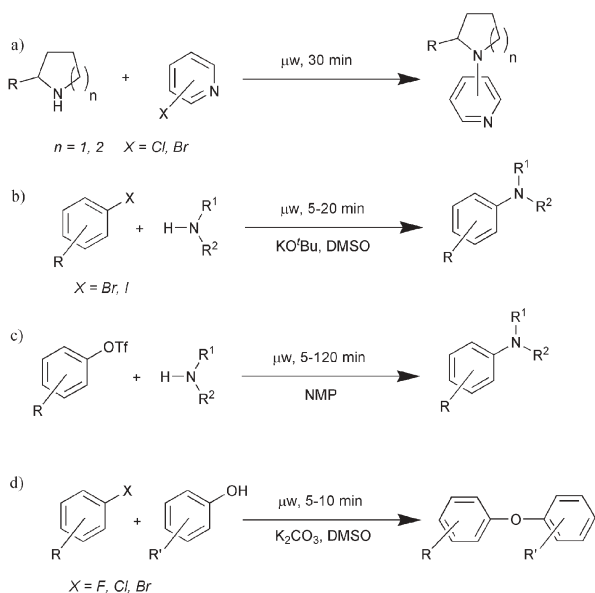
Scheme 35

Scheme 33

Scheme 36

Evidence for a mechanism involving the generation of a benzyne intermediate is presented. Amination of aryl triflates has also been achieved using microwave heating without the need for a catalyst or a base (Scheme 36c).[174] The reaction works best in NMP as a solvent under reflux (200 °C) and, using a scientific microwave, are complete in 5 min–2 h depending on the substrates used. An S_NAr mechanism is proposed for this reaction. Another coupling that is proposed to occur *via* an S_NAr mechanism is the catalyst-free reaction between phenols and electron deficient aryl halides to give diaryl ethers (Scheme 36d).[175] The reaction is performed in a domestic microwave with DMSO as solvent and potassium carbonate as a base. The reactions are complete in 5–10 min.

Concluding remarks

Nature has used water as a medium for chemical and biochemical reactions since the start of time. Chemists are increasingly using it for their chemical transformations in the laboratory. There is little doubt that interest will continue to grow, with more reports of reactions that work in water but not in common organic solvents being seen in the literature. Also, within the chemical industry, there are financial benefits of using water as a solvent, especially given the more stringent environmental laws that are being passed every year.[176,177] Microwave heating offers a very efficient way of heating reaction mixtures and again is an area that will see increased research effort. In this article, by focusing on the Suzuki reaction, I have tried to illustrate how these two methods, used alone or together, can impact modern synthetic chemistry significantly.

Acknowledgements

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References

1 For an introduction to green chemistry, see: (*a*) M. Lancaster, *Green Chemistry: An Introductory Text*, Royal Society of Chemistry, Cambridge, 2002; (*b*) A. S. Matlack, *Introduction to Green Chemistry*, Marcel Dekker, New York, 2001; (*c*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, Oxford, 1998.
2 R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279.
3 R. J. Giguere, T. L. Bray, S. M. Duncan and G. Majetich, *Tetrahedron Lett.*, 1986, **27**, 4945.
4 For a recent review, see: C. O. Kappe, *Angew. Chem. Int. Ed.*, 2004, **43**, 6250.
5 For other reviews on the general area of microwave-promoted organic synthesis, see: (*a*) P. Lidström, J. P. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225; (*b*) S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
6 (*a*) A number of books on microwave-promoted synthesis have been published recently: *Microwave-Assisted Organic Synthesis*, ed. P. Lidström and J. P. Tierney, Blackwell, Oxford, 2004; (*b*) *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2002; (*c*) B. L. Hayes, *Microwave Synthesis: Chemistry at the Speed of Light*, CEM Publishing, Matthews, NC, 2002.
7 A number of reviews on the use of microwaves in combinatorial chemistry have been published. Selected examples include: (*a*) H. E. Blackwell, *Org. Biomol. Chem.*, 2003, **1**, 1251; (*b*) A. Lew, P. O. Krutzik, M. E. Hart and A. R. Chamberlain, *J. Comb. Chem.*, 2002, **4**, 95; (*c*) P. Lidström, J. Westman and A. Lewis, *Comb. Chem. High Throughput Screening*, 2002, **5**, 441; (*d*) K. M. K. Swamy, W.-B. Yeh, M.-J. Lin and C.-M. Sun, *Curr. Med. Chem.*, 2003, **10**, 2403.
8 See for example: (*a*) N. Kuhnert, *Angew. Chem. Int. Ed.*, 2002, **41**, 1863; (*b*) C. R. Strauss, *Angew. Chem. Int. Ed.*, 2002, **41**, 3589.
9 For a review on the concepts of microwave heating, see: C. Gabriel, S. Gabriel, E. H. Grant, B. S. Halstead and D. M. P. Mingos, *Chem. Soc. Rev.*, 1998, **27**, 213–233.
10 For an overview of scientific microwave apparatus for use in synthetic chemistry, see: D. Stuerga and M. Delmotte, in *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2002, ch. 1.
11 Scientific microwave manufacturers include: Anton-Paar [www.anton-paar.com], Biotage (formally Personal Chemistry AB) [www.biotage.com], CEM corporation [www.cem.com] and Milestone Inc. [www.milestonesci.com].
12 For articles recently published by three of the microwave manufacturers, see: (*a*) J. D. Ferguson, *Mol. Diversity*, 2003, **7**, 281 (CEM); (*b*) L. Favretto, *Mol. Diversity*, 2003, **7**, 287 (Milestone); (*c*) J.-S. Schanche, *Mol. Diversity*, 2003, **7**, 293 (Biotage).
13 For a review article discussing some aspects of microwave technology, see: M. Nuchter, B. Ondruschka, W. Bonrath and A. Gum, *Green Chem.*, 2004, **6**, 128.
14 For a general introduction to organic synthesis in water, see: (*a*) *Organic synthesis in water*, ed. P. A. Grieco, Blackie Academic and Professional, London, 1997; (*b*) C.-J. Li and T.-H. Chan,

Organic Reactions in Aqueous Media, Kluwer Academic Publishers, Dordrecht, 1997.

15 S. Kobayashi, *Adv. Synth. Catal.*, 2002, **344**, 219.

16 For a recent review, see: N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725.

17 For a recent review, see: (*a*) M. Siskin and A. R. Katritzky, *Chem. Rev.*, 2001, **101**, 825; (*b*) A. R. Katritzky, D. A. Nichols, M. Siskin, R. Murugan and M. Balasubramanian, *Chem. Rev.*, 2001, **101**, 837.

18 For a recent review, see: D. Broll, C. Kaul, A. Kramer, P. Krammer, T. Richter, M. Jung, H. Vogel and P. Zehner, *Angew. Chem. Int. Ed.*, 1999, **38**, 2999.

19 For an introduction to the use of organometallic catalysts in aqueous-phase catalysis, see: B. Cornils and W. A. Herrmann, *Aqueous-Phase Organometallic Catalysis, Concepts and Applications*, Wiley-VCH, Weinheim, 1998.

20 For recent reviews, see: (*a*) F. Bellina, A. Carpita and R. Rossi, *Synthesis*, 2004, 2419; (*b*) P. J. Pershichini, *Curr. Org. Chem.*, 2003, **7**, 1725; (*c*) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359; (*d*) S. Kotha, S. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633.

21 For recent representative examples, see: (*a*) R. C. Smith, R. A. Woloszynek, W. Z. Chen, T. Ren and J. D. Protasiewicz, *Tetrahedron Lett.*, 2004, **45**, 8327; (*b*) T. J. Colacot and H. A. Shea, *Org. Lett.*, 2004, **6**, 3731; (*c*) J. E. Milne and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 13028; (*d*) A. Tewari, M. Hein, A. Zapf and M. Beller, *Synthesis*, 2004, 935; (*e*) N. Kataoka, Q. Shelby, J. P. Stambuli and J. F. Hartwig, *J. Org. Chem.*, 2002, **67**, 5553; (*f*) J. H. Kirchhoff, C. Y. Dai and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 1945.

22 For reviews, see: (*a*) E. Peris and R. H. Crabtree, *Coord. Chem. Rev.*, 2004, **248**, 2239; (*b*) C. M. Crudden and D. P. Allen, *Coord. Chem. Rev.*, 2004, **248**, 2247–2273; (*c*) A. C. Hillier, G. A. Grasa, M. S. Viciu, H. M. Lee, C. L. Yang and S. P. Nolan, *J. Organomet. Chem.*, 2002, **653**, 69; (*d*) L. Jafarpour and S. P. Nolan, *Adv. Organomet. Chem.*, 2001, **46**, 181–222.

23 For recent representative examples, see: (*a*) H. M. Lee, J. Y. Zeng, C. H. Hu and M. T. Lee, *Inorg. Chem.*, 2004, **43**, 6822; (*b*) K. Arentsen, S. Caddick, F. G. A. Cloke, A. P. Herring and P. B. Hitchcock, *Tetrahedron Lett.*, 2004, **45**, 3511; (*c*) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *Angew. Chem. Int. Ed.*, 2003, **42**, 3690; (*d*) C. W. K. Gstottmayr, V. P. W. Bohm, E. Herdtweck, M. Grosche and W. A. Herrmann, *Angew. Chem. Int. Ed.*, 2002, **41**, 1363.

24 For reviews, see: (*a*) R. B. Bedford, C. S. J. Cazin and D. Holder, *Coord. Chem. Rev.*, 2004, **248**, 2283; (*b*) R. Chincilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667; (*c*) R. B. Bedford, *Chem. Commun.*, 2003, 1787.

25 For recent representative examples, see: (*a*) D. A. Alonso, L. Botella, C. Nájera and C. Pacheco, *Synthesis*, 2004, 1713; (*b*) Z. C. Xiong, N. D. Wang, M. J. Dai, A. Li, J. H. Chen and Z. Yang, *Org. Lett.*, 2004, **6**, 3337; (*c*) F. X. Roca and C. J. Richards, *Chem. Commun.*, 2003, 3002.

26 N. A. Bumagin, V. V. Bykov and I. P. Beletskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 2394, Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.), 1989, 38, 2206.

27 The reaction using Pd(OAc)₂ as a catalyst has also been performed using organic solvents. See for example: D. Zim, A. L. Monteiro and J. Dupont, *Tetrahedron Lett.*, 2000, **41**, 8199.

28 E. M. Campi, W. R. Jackson, S. M. Marcuccio and C. G. M. Naeslund, *J. Chem. Soc., Chem. Commun.*, 1994, 2395.

29 S. Venkatraman, T. Huang and C.-J. Li, *Adv. Synth. Catal.*, 2002, **344**, 399.

30 Y. Deng, L. Gong, A. Mi, H. Liu and Y. Jiang, *Synthesis*, 2003, 337.

31 D. Badone, M. Baroni, R. Cardamone, A. Ielmini and U. Guzzi, *J. Org. Chem.*, 1997, **62**, 7170.

32 R. B. Bedford, M. E. Blake, C. P. Butts and D. Holder, *Chem. Commun.*, 2003, 466.

33 G. Zou, Z. Wang, J. Zhu, J. Tang and M. Y. He, *J. Mol. Catal. A: Chem.*, 2003, **206**, 193.

34 A. Arcadi, G. Cerichelli, M. Chiarini, M. Correa and D. Zorzan, *Eur. J. Org. Chem.*, 2003, 4080.

35 S. Hesse and G. Kirsch, *Synthesis*, 2001, 755.

36 N. A. Bumagin, V. V. Bykov and I. P. Beletskaya, *Metalloorg. Khim*, 1989, **2**, 1200.

37 N. A. Bumagin and V. V. Bykov, *Tetrahedron*, 1997, **53**, 14437.

38 G. A. Molander and B. Biolatto, *Org. Lett.*, 2002, **4**, 1867.

39 M. Moreno-Mañas, M. Pérez and R. Pleixats, *J. Org. Chem.*, 1996, **61**, 2346.

40 L. M. Klingensmith and N. E. Leadbeater, *Tetrahedron Lett.*, 2003, **447**, 765.

41 D. A. Alonso, C. Nájera and M. C. Pacheco, *J. Org. Chem.*, 2002, **67**, 5588.

42 F. E. Goodson, T. I. Wallow and B. M. Novak, *Org. Synth.*, 1998, **75**, 61.

43 B. P. Bandgar, S. V. Bettigeri and J. Phopase, *Tetrahedron Lett.*, 2004, **45**, 6959.

44 N. A. Bumagin and D. N. Korolev, *Russ. Chem. Bull.*, 2004, **53**, 364.

45 N. A. Bumagin and D. N. Korolev, *Tetrahedron Lett.*, 1999, **40**, 2057.

46 C. Nájera, J. Gil-Moltó, S. Karlström and L. R. Falvello, *Org. Lett.*, 2003, **5**, 1451.

47 C. Nájera, J. Gil-Moltó and S. Karlström, *Adv. Synth. Catal.*, 2004, **346**, 1798.

48 L. Botella and C. Nájera, *Angew. Chem. Int. Ed.*, 2002, **41**, 179.

49 L. Botella and C. Nájera, *J. Organomet. Chem.*, 2002, **663**, 46.

50 C. Baleizao, A. Corma, H. Garcia and A. Leyva, *J. Org. Chem.*, 2004, **69**, 439.

51 C. Baleizao, A. Corma, H. Garcia and A. Leyva, *Chem. Commun.*, 2003, 606.

52 C.-L. Chen, Y.-H. Liu, S.-M. Peng and S.-T. Liu, *Tetrahedron Lett.*, 2005, **646**, 521.

53 For a review containing a discussion of the use of water soluble phosphines, see: J.-P. Genet and M. Savignac, *J. Organomet. Chem.*, 1999, **576**, 305.

54 (*a*) T. I. Wallow and B. M. Novak, *J. Org. Chem.*, 1994, **59**, 5034; (*b*) D. F. O'Keefe, M. C. Dannock and S. M. Marcuccio, *Tetrahedron Lett.*, 1992, **33**, 6679.

55 F. E. Goodson, T. I. Wallow and B. M. Novak, *J. Am. Chem. Soc.*, 1997, **119**, 12441.

56 C. Dupuis, K. Adiey, L. Charruault, V. Michalet, M. Savignac and J.-P. Genet, *Tetrahedron Lett.*, 2001, **42**, 6523.

57 J.-P. Genet, A. Lindquist, E. Blart, V. Mouries, M. Savignac and M. Vaultier, *Tetrahedron Lett.*, 1995, **36**, 1443.

58 M. Baur, M. Frank, J. Schatz and F. Shildbach, *Tetrahedron Lett.*, 2001, **57**, 6985.

59 F. Hapiot, J. Lyskawa, H. Bricout, S. Tilloy and E. Monflier, *Adv. Synth. Catal.*, 2004, **346**, 83.

60 E. Paetzold, I. Jovel and G. Oehme, *J. Mol. Catal. A: Chem.*, 2004, **214**, 241.

61 E. Paetzold, G. Oehme, H. Fuhrmann, M. Richter, R. Eckelt, M.-M. Pohl and H. Kosslick, *Microporous Mesoporous Mater.*, 2001, **44–45**, 517.

62 K. H. Shaughnessy and R. S. Booth, *Org. Lett.*, 2001, **3**, 2757.

63 R. B. DeVasher, L. R. Moore and K. H. Shaughnessy, *J. Org. Chem.*, 2004, **69**, 7919.

64 L. R. Moore and K. H. Shaughnessy, *Org. Lett.*, 2004, **6**, 225.

65 E. C. Western, J. F. Daft, E. M. Johnson, P. M. Gannett and K. H. Shaughnessy, *J. Org. Chem.*, 2003, **68**, 6767.

66 M. Beller, J. G. E. Krauter and A. Zapf, *Angew. Chem. Int. Ed.*, 1997, **36**, 772.

67 M. Beller, J. G. E. Krauter, A. Zapf and S. Bogdanovic, *Catal. Today*, 1999, **48**, 279.

68 S. Parisot, R. Kolodziuk, C. Goux-Henry, A. Iourtchenko and D. Sinou, *Tetrahedron Lett.*, 2002, **43**, 7397.

69 R. Kolodziuk, A. Penciu, M. Tollabi, E. Framery, C. Goux-Henry, A. Iourtchenko and D. Sinou, *J. Organomet. Chem.*, 2003, **687**, 384.

70 M. Lee, C.-J. Jang and J.-H. Ryu, *J. Am. Chem. Soc.*, 2004, **126**, 8082.

71 A. N. Cammidge, N. J. Bates and R. K. Bellingham, *Chem. Commun.*, 2001, 2588.

72 Y. Uozumi, H. Danjo and T. Hayashi, *J. Org. Chem.*, 1999, **64**, 3384.

73 Y. M. A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, *Org. Lett.*, 2002, **4**, 3371.

74 Y. M. A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, *J. Org. Chem.*, 2003, **68**, 7733.

75 For reviews of the use of nanopalladium species in catalysis, see: (*a*) M. Moreno-Mañas and R. Pleixats, *Acc. Chem. Res.*, 2003, **36**, 638; (*b*) A. Roucoux, J. Shultz and H. Patin, *Chem. Rev.*, 2002, **102**, 3757.

76 For a key article on the use of nanopalladium species in Pd-catalysed C–C bond forming reactions, see: B. M. Choudary, S. Madhi, N. S. Chowdari, M. L. Kantam and B. Sreedhar, *J. Am. Chem. Soc.*, 2002, **124**, 14127.

77 K. Shimizu, R. Maruyama, S. Komai, T. Kodama and Y. Kitayama, *J. Catal.*, 2004, **227**, 202.

78 Palladium incorportaed into sepiolite has also been used for Suzuki couplings in organic solvents. See: (*a*) A. Corma, H. Garcia, A. Leyva and A. Primo, *Appl. Catal., A*, 2004, **257**, 77; (*b*) K. Shimizu, T. Kan-no, T. Kodama, H. Hagiwara and Y. Kitayama, *Tetrahedron Lett.*, 2002, **43**, 5653.

79 L. Artok and H. Bulut, *Tetrahedron Lett.*, 2004, **45**, 3881.

80 M. D. Smith, A. F. Stepan, C. Ramarao, P. E. Brenan and S. V. Ley, *Chem. Commun.*, 2003, 2652.

81 For representative examples, see: (*a*) K. R. Gopidas, J. K. Whitesell and M. A. Fox, *Nano Lett.*, 2003, **3**, 1757; (*b*) C. Rocaboy and J. A. Gladysz, *New J. Chem.*, 2003, **27**, 39; (*c*) N. Kim, M. S. Kwon, C. M. Park and J. Park, *Tetrahedron Lett.*, 2004, **45**, 7057; (*d*) S.-W. Kim, M. Kim, W. Y. Lee and T. Hyeon, *J. Am. Chem. Soc.*, 2002, **124**, 7642; (*e*) A. Pathak, M. T. Greci, R. C. Kwong, K. Mercado, G. K. S. Prakash, G. A. Olah and M. E. Thompson, *Chem. Mater.*, 2000, **12**, 1985; (*f*) M. T. Reetz, R. Breinbauer and K. Wanniger, *Tetrahedron Lett.*, 1996, **37**, 4499.

82 Y. Li, X. M. Hong, D. M. Collard and M. A. El-Sayed, *Org. Lett.*, 2000, **2**, 2385.

83 Y. Li, E. Boone and M. A. El-Sayed, *Langmuir*, 2002, **18**, 4921.

84 Y. Li and M. A. El-Sayed, *J. Phys. Chem. B.*, 2001, **105**, 8938.

85 M. Pittelkow, K. Moth-Poulsen, U. Boas and J. B. Christensen, *Langmuir*, 2003, **19**, 7682.

86 R. Narayanan and M. A. El-Sayed, *J. Am. Chem. Soc.*, 2003, **125**, 8340.

87 R. Narayanan and M. A. El-Sayed, *J. Phys. Chem. B*, 2004, **108**, 8572.

88 L. Strimbu, J. Liu and A. E. Kaifer, *Langmuir*, 2003, **19**, 483.

89 A. Biffis and E. Sperotto, *Langmiur*, 2003, **19**, 9548.

90 V. Kogan, Z. Aizenshtat, R. Popovitz-Biro and R. Neumann, *Org. Lett.*, 2002, **4**, 3529.

91 C. Basheer, F. Shahitha, J. Hussain, H. K. Lee and S. Valiyaveettil, *Tetrahedron Lett.*, 2004, **45**, 7297.

92 For a representative example of the use of non-aqueous solvent mixtures, see: G. W. Kabalka, V. Namboodiri and L. Wang, *Chem. Commun.*, 2001, 775.

93 G. Marck, A. Villiger and R. Buchecker, *Tetrahedron Lett.*, 1994, **35**, 3277.

94 C. R. LeBlond, A. T. Andrews, Y. Sun and J. R. Sowa, *Org. Lett.*, 2001, **3**, 1555.

95 R. G. Heidenreich, K. Köhler, J. G. E. Krauter and J. Pietsch, *Synlett.*, 2002, 1118.

96 M. Gruber, S. Chouzier, K. Koehler and L. Djakovitch, *Appl. Catal., A*, 2004, **265**, 161.

97 D. A. Conlon, B. Pipik, S. Ferdinand, C. R. LeBlond, J. R. Sowa, B. Izzo, P. Collins, G.-J. Hom, J. M. Williams, Y.-J. Shi and Y. Sun, *Adv. Synth. Catal.*, 2003, **345**, 931.

98 H. Sakurai, T. Tsukuda and T. Hirao, *J. Org. Chem.*, 2002, **67**, 2721.

99 T. Tagata and M. Nishida, *J. Org. Chem*, 2003, **68**, 9412.

100 D. Gala, A. Stamford, J. Jenkins and M. Kugelman, *Org. Process Res. Dev.*, 1997, **1**, 163.

101 D. S. Ennis, J. McManus, W. Wood-Kaczmar, J. Richardson, G. E. Smith and A. Carstairs, *Org. Process Res. Dev.*, 1999, **3**, 248.

102 Y. Mori and M. Seki, *J. Org. Chem.*, 2003, **68**, 1571.

103 For reviews, see: (*a*) M. Larhed, C. Moberg and A. Hallberg, *Acc. Chem. Res.*, 2002, **35**, 717; (*b*) K. Olofsson, A. Hallberg and M. Larhed, in *Microwaves in Organic Synthesis*, ed. A. Loupy, Wiley-VCH, Weinheim, 2002, ch. 11.

104 A. Hallberg and M. Larhed, *J. Org. Chem.*, 1996, **61**, 9582.

105 A. Hallberg, G. Lindeberg and M. Larhed, *Tetrahedron Lett.*, 1996, **37**, 8219.

106 O. Navarro, H. Kaur, P. Mahjoor and S. P. Nolan, *J. Org. Chem.*, 2004, **69**, 3173.

107 Y. Wang and D. R. Sauer, *Org. Lett.*, 2004, **6**, 2793.

108 For a general introduction to FibreCats and their application to the Suzuki reaction, see: T. J. Colacot, E. S. Gore and A. Kuber, *Organometallics*, 2002, **21**, 3301.

109 For a review on solvent-free microwave-promoted chemistry, see: R. S. Varma, *Green Chem.*, 1999, **1**, 43.

110 G. W. Kabalka, R. M. Pagni, L. Wang, V. Namboodiri and C. M. Hair, *Green Chem.*, 2000, **2**, 120.

111 G. W. Kabalka, L. Wang, R. M. Pagni, C. M. Hair and V. Namboodiri, *Synthesis*, 2003, 217.

112 D. Villemin and F. Caillot, *Tetrahedron Lett.*, 2001, **42**, 639.

113 B. Basu, P. Das, M. M. H. Bhuiyan and S. Jha, *Tetrahedron Lett.*, 2003, **44**, 3817.

114 J.-X. Wang, Y. Yang and B. Wei, *Synth. Commun.*, 2004, **34**, 2063.

115 M. Melucci, G. Barbarella and G. Sotgiu, *J. Org. Chem.*, 2002, **67**, 8877.

116 M. Melucci, G. Barbarella, M. Zambianchi, P. Di Pietro and A. Bongini, *J. Org. Chem.*, 2004, **69**, 4821.

117 T. Y. H. Wu, P. G. Schultz and S. Ding, *Org. Lett.*, 2003, **5**, 3587.

118 Y. Liu, C. Khemtong and J. Hu, *Chem. Commun.*, 2004, 398.

119 W. M. Seganish and P. DeShong, *J. Org. Chem.*, 2004, **69**, 1137.

120 W. M. Seganish and P. DeShong, *Org. Lett.*, 2004, **6**, 4379.

121 J. W. Han, J. C. Castro and K. Burgess, *Tetrahedron Lett.*, 2003, **44**, 9359.

122 P. Appukkuttan, A. Orts, R. P. Chandran, J. L. Goeman, J. Van der Eycken, W. Dehaen and E. Van der Eycken, *Eur. J. Org. Chem.*, 2004, 3277.

123 Y. Gong and W. He, *Org. Lett.*, 2002, **4**, 3803.

124 Y. Gong and W. He, *Heterocycles*, 2004, **62**, 851.

125 G. Sotgiu, M. Zambianchi, G. Barbarella and C. Botta, *Tetrahedron*, 2002, **58**, 2245.

126 B. S. Nehls, U. Asawapirom, S. Füldner, E. Preis, T. Farrell and U. Scherf, *Adv. Funct. Mater.*, 2004, **14**, 352.

127 C. G. Blettner, W. A. Konig, W. Stenzel and T. Schotten, *J. Org. Chem.*, 1999, **64**, 3885.

128 V. V. Namboodiri and R. S. Varma, *Green. Chem.*, 2001, **3**, 146.

129 W. Zhang, C. H.-T. Chen, Y. Lu and T. Nagashima, *Org. Lett.*, 2004, **6**, 1473.

130 R. B. Bedford, C. P. Butts, T. E. Hurst and P. Lidström, *Adv. Synth. Catal.*, 2004, **346**, 1627.

131 P. He, S. J. Haswell and P. D. I. Fletcher, *Lab Chip*, 2004, **4**, 38.

132 P. He, S. J. Haswell and P. D. I. Fletcher, *Appl. Catal., A*, 2004, **274**, 111.

133 W. Solodenko, U. Schön, J. Messinger, A. Glinschert and A. Kirschning, *Synlett*, 2004, 1699.

134 D. Villemin, M. J. Gómez-Escalonilla and J.-F. Saint-Clair, *Tetrahedron Lett.*, 2001, **42**, 635.

135 N. E. Leadbeater and M. Marco, *Org. Lett.*, 2002, **4**, 2973.

136 N. E. Leadbeater and M. Marco, *J. Org. Chem.*, 2003, **68**, 888.

137 Another group has subsequently published an almost identical protocol for microwave-promoted Suzuki couplings in water: L. Bai, J. X. Wan and Y. M. Zhang, *Green Chem.*, 2003, **5**, 615.

138 N. E. Leadbeater and M. Marco, *Angew. Chem. Int. Ed.*, 2003, **42**, 1407.

139 N. E. Leadbeater and M. Marco, *J. Org. Chem.*, 2003, **68**, 5660.

140 For nickel complexes as catalysts, see: (*a*) V. Percec, G. M. Golding, J. Smidrkal and O. Weichold, *J. Org. Chem.*, 2004, **69**, 3447; (*b*) D. Zim and A. L. Monteiro, *Tetrahedron Lett.*, 2002, **43**, 4009; (*c*) C. Griffiths and N. E. Leadbeater, *Tetrahedron Lett.*, 2000, **41**, 2487; (*d*) N. E. Leadbeater and S. M. Resouly, *Tetrahedron*, 1999, **55**, 11889.

141 For elemental nickel as a catalyst, see: (*a*) B. H. Lipshutz, S. Tasler, W. Chrisman, B. Spliethoff and B. Tesche, *J. Org. Chem.*, 2003, **68**, 1177; (*b*) B. H. Lipshutz, *Adv. Synth. Catal.*, 2001, **343**, 313; (*c*) B. H. Lipshutz, J. A. Sclafani and P. A. Blomgren, *Tetrahedron*, 2000, **56**, 2139.

142 (*a*) C. H. Oh, Y. M. Lim and C. H. You, *Tetrahedron Lett.*, 2002, **43**, 4645; (*b*) R. B. Bedford, S. L. Hazelwood and D. A. Albisson, *Organometallics*, 2002, **21**, 2599.

143 M. B. Thathagar, J. Beckers and G. Rothenberg, *J. Am. Chem. Soc.*, 2002, **124**, 2159.

144 (*a*) Y. Na, S. Park, S B Han, S. Ko and S. Chang, *J. Am. Chem. Soc.*, 2004, **126**, 250; (*b*) X. X. Liu and M. Z. Deng, *Chem. Commun.*, 2002, 622; (*c*) C. Savarin and L. S. Liebeskind, *Org. Lett.*, 2001, **3**, 2149.

145 C.-J. Li, *Angew. Chem. Int. Ed.*, 2003, **42**, 4856.

146 For a review focusing on the Heck reaction, see: M. T. Reetz and J. A. G. de Vries, *Chem. Commun.*, 2004, 1559.

147 A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org. Lett.*, 2003, **5**, 3285.

148 For background, see also: A. H. M. de Vries, F. J. Parlevliet, L. Schmieder-van de Vondervoort, J. H. M. Mommers, J. H. W. Henderickx, M. A. M. Walet and J. G. de Vries, *Adv. Synth. Catal.*, 2002, **344**, 996.

149 S. S. Prockl, W. Kleist, M. A. Gruber and K. Köhler, *Angew. Chem. Int. Ed.*, 2004, **43**, 1881.

150 Y. M. A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, *Tetrahedron Lett.*, 2003, **44**, 2379.

151 Y. M. A. Yamada, K. Takeda, H. Takahashi and S. Ikegami, *Tetrahedron*, 2004, **60**, 4097.

152 H. Palencia, F. Garcia-Jimenez and J. M. Takacs, *Tetrahedron Lett.*, 2004, **45**, 3849.

153 (*a*) W.-M. Dai, Y. Li, Y. Zhang, K. W. Lai and J. Wu, *Tetrahedron Lett.*, 2004, **45**, 1999; (*b*) A. Zapf, R. Jackstell, F. Rataboul, T. Riermeier, A. Monsees, C. Fuhrmann, N. Shaikh, U. Dingerdissen and M. Beller, *Chem. Commun.*, 2004, 38.

154 J. G. de Vries and A. H. M. de Vries, *Eur. J. Org. Chem.*, 2003, 799.

155 X. Tao, Y. Zhao and D. Shen, *Synlett*, 2004, 359.

156 R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados and R. S. Singer, *J. Org. Chem.*, 2005, **70**, 161.

157 A. Alimardanov, L. Schmieder-van de Vondervoort, A. H. M. de Vries and J. G. de Vries, *Adv. Synth. Catal.*, 2004, **346**, 1812.

158 M. R. Eberhard, *Org. Lett.*, 2004, **6**, 2125.

159 A. F. Schmidt and V. V. Smirnov, *J. Mol. Catal. A: Chem.*, 2003, **203**, 75.

160 Q. Yao, E. P. Kinney and Z. Yang, *J. Org. Chem.*, 2003, **68**, 7528.

161 Inhibition of palladium black generation has also been achieved by addition of chromate salts to the reaction mixture. See: N. A. Bumagin and V. V. Bykov, *Dokl. Akad. Nauk*, 1995, **340**, 775.

162 R. Zhang, F. Zhao, M. Sato and Y. Ikushima, *Chem. Commun.*, 2003, 1548.

163 R. Zhang, O. Sato, F. Zhao, M. Sato and Y. Ikushima, *Chem. Eur. J.*, 2004, **10**, 1501.

164 R. K. Arvela and N. E. Leadbeater, *J. Org. Chem.*, 2005, **70**, 1786.

165 N. E. Leadbeater, M. Marco and B. Tominack, *Org. Lett.*, 2003, **5**, 3919.

166 P. Appukkuttan, W. Dehaen and E. Van der Eycken, *Eur. J. Org. Chem.*, 2003, 4713.

167 Palladium-free coupling: (*a*) D. W. Ma and F. Lu, *Chem. Commun.*, 2004, 1934; (*b*) M. B. Thathagar, J. Beckers and G. Rothenberg, *Green Chem.*, 2004, **6**, 215; (*c*) M. Wang, P. H. Li and L. Wang, *Chem. Commun.*, 2004, 514; (*d*) S. Cacchi, G. Fabrizi and L. M. Parisi, *Org. Lett.*, 2003, **5**, 3843; (*e*) I. P. Beletskaya, G. V. Latyshev, A. V. Tsvetkov and N. V. Lukashev, *Tetrahedron Lett.*, 2003, **44**, 5011; (*f*) R. K. Gujadhur, C. G. Bates and D. Venkataraman, *Org. Lett.*, 2001, **3**, 4315; (*g*) K. Okuro, M. Furuune, M. Enna, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 4716.

168 Copper-free coupling, for recent examples see: (*a*) M. Feuerstein, H. Doucet and M. Santelli, *Tetrahedron Lett.*, 2004, **45**, 8443; (*b*) S. Rau, K. Lamm, H. Gorls, J. Schoffel and D. Walther, *J. Organomet. Chem.*, 2004, **689**, 3582; (*c*) R. A. Gossage, H. A. Jenkins and P. N. Yadav, *Tetrahedron Lett.*, 2004, **45**, 7689; (*d*) J. C. Hierso, A. Fihri, R. Amardeil, P. Meunier, H. Doucet, M. Santelli and V. V. Ivanov, *Org. Lett.*, 2004, **6**, 3473; (*e*) S. Urgaonkar and J. G. Verkade, *J. Org. Chem.*, 2004, **69**, 5752; (*f*) J. Cheng, Y. H. Sun, F. Wang, M. J. Guo, J. H. Xu, Y. Pan and Z. G. Zhang, *J. Org. Chem.*, 2004, **69**, 5428; (*g*) K. Heuze, D. Mery, D. Gauss, J. C. Blais and D. Astruc, *Chem. Eur. J.*, 2004, **10**, 3936; (*h*) A. Soheli, J. Albaneze-Walker, J. A. Murry, P. G. Dormer and D. L. Hughes, *Org. Lett.*, 2003, **5**, 4191; (*i*) N. E. Leadbeater and B. J. Tominack, *Tetrahedron Lett.*, 2003, **44**, 8653; (*j*) Y. D. Ma, C. Song, W. Jiang, Q. S. Wu, Y. Wang, X. Y. Liu and M. B. Andrus, *Org. Lett.*, 2003, **5**, 3317; (*k*) D. A. Alonso, C. Nájera and M. C. Pacheco, *Tetrahedron Lett.*, 2002, **43**, 9365.

169 Palladium-free coupling using microwave heating: (*a*) M. Wang, P. H. Li and L. Wang, *Synth. Commun.*, 2004, **34**, 2803; (*b*) J. C. Yan, Z. Y. Wang and L. Wang, *J. Chem. Res.*, 2004, 71.

170 Copper-free coupling using water as a solvent and conventional heating: (*a*) S. Bhattacharya and S. Sengupta, *Tetrahedron Lett.*, 2004, **45**, 8733; (*b*) L. Djakovitch and P. Rollet, *Tetrahedron Lett.*, 2004, **45**, 1603.

171 Palladium-free coupling using water as a co-solvent and conventional heating: S.-K. Kang, S.-K. Yoon and Y.-M. Kim, *Org. Lett.*, 2001, **3**, 2697.

172 S. Narayan, T. Seelhammer and R. E. Gawley, *Tetrahedron Lett.*, 2004, **45**, 757.

173 L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang and Y.-Q. Tu, *Org. Lett.*, 2003, **5**, 3515.

174 G. Xu and Y.-G. Wang, *Org. Lett.*, 2004, **6**, 985.

175 F. Li, Q. Wang, Z. Ding and F. Tao, *Org. Lett.*, 2003, **5**, 2169.

176 S. Bell and D. McGilvray, *Environmental Law*, Oxford University Press, Oxford, 6th edn., 2005.

177 J. C. Warner, A. S. Cannon and K. M. Dye, *Environ. Impact Assess. Rev.*, 2004, **24**, 775.